Sleep-deprived individuals appear to have decreased psychological and physical capabilities. Studies have shown how major psychological aspects, such as alertness, complex mental performance, and memory, are strongly affected by sleep deprivation. Military use of psychostimulants dates back many years, especially in units that operate over long hours and deprive soldiers of sleep. During prolonged military operations, pilots are regularly kept awake for hours and days without fulfilling their biological sleep requirements. This consequently affects their natural circadian rhythm. This article deals with both the benefits and the side effects of two kinds of psychostimulants, namely, dextroamphetamine, which is more popular and is most widely used, and modafinil, which is a relatively newer type. There is growing evidence that modafinil has fewer side effects, in comparison with its predecessor dextroamphetamine, while still maintaining all of the latter's beneficial characteristics.

**Introduction**

Sleep is defined as a state of unconsciousness from which a person can be awoken by appropriate environmental sensory stimuli or internal signals. Sleep is critical for maintaining alertness, attention, motivation, short-term memory, mood stability, and the ability to complete routine tasks and/or physical performances. Adequate sleep is essential for the proper functioning of the human body. However, the reason for sleep is still unclear. Some authors postulate that sleep is an adaptive response that improves the organism's chances of survival. Those with proper sleeping habits, which match their environmental requirements, are most likely to survive. Another theory, the "energy conservation" theory, states that fast-moving animals with high rates of metabolism sleep more, thereby conserving their energy by maintaining low energy expenditure. Finally, others claim that sleep may help the body to restore itself; neurotoxins, which accumulate during the day, are neutralized and growth hormones are released.

Prolonged military operations are classified into two categories, namely, continuous and sustained operations. Continuous operations last >24 hours and are divided into shifts. Sustained operations are characterized by continuous performance (>24 hours) until the required goal is reached. Both types may be associated with fatigue; however, a sustained operation can result in a great amount of sleep loss and may affect the soldier's circadian rhythm, thus impairing judgment or even operational capabilities. In general, military operations are known to last from hours to days; therefore, the state of consciousness of soldiers is a major concern in the performance of sustained operations. There are several factors that determine operational effectiveness at both the individual level and the group/unit level, including experience, training, fitness, morale, leadership, and physiological factors (backload, hydration, nutrition, and alertness).

Modern warfare is not limited to daylight or comfortable climates as in the past. Around-the-clock operations are mandatory in combat and may last for hours, days, and even weeks without cessation. For these reasons, soldiers who are required to stay awake for days while maintaining high levels of alertness may suffer from mental and physical strain, which can lead to operational failure. The conflict between operational demands and human sleep deprivation is best observed in the Air Force. Although an aircraft can mechanically function effectively throughout long hours, pilots cannot. This "human-machine conflict" represents a major issue for military operations. There have been reports of pilots falling asleep during operational flights and friendly fire, resulting in catastrophic accidents or a change in the operational goal.

Lack of sleep, in combination with physical activity, eventually leads to fatigue. This, in turn, can lead to exhaustion. The literature differentiates between two categories of fatigue, physical and mental. The former results from excessive physical strain and leads to temporary loss of muscle power, whereas the latter occurs during states of continuous mental stress with no rest periods. Physical fatigue is further divided into acute and chronic fatigue according to the duration of symptoms. Acute fatigue is a result of temporary sleep loss, which occurs in prolonged military operations, whereas chronic fatigue results from medical disorders that do not allow the person to sleep the required amount needed to restore energy. These disorders include insomnia, sleep apnea, and other diseases such as arthritis.

Acute fatigue can cause an upheaval in the body's biological rhythm. Circadian rhythm is defined as the human biological clock and is determined by environmental factors such as food, drink, social activities, and, most importantly, the balance between sleep and consciousness. Circadian rhythm regulates body temperature, hormone levels, heart rate, cognitive performance, and other vital functions. Chronic loss of sleep may impair the proper functioning of such mechanisms. Circadian rhythm performances peak between the hours of 5:00 a.m. and 7:00 a.m. and fall to the minimum between the hours of 2:00 a.m. and 6:00 a.m. Moreover, there is a sudden decline in the degree of alertness during mental performance in the early and middle afternoon hours (1:00 p.m. to 3:00 p.m.). The fall in the circadian rhythm represents two periods, that is, when the body is mostly prone to sleep and when there occurs a decrease in mental capacity because of lack of sleep.

It has been demonstrated that sleep deprivation (<3 hours of sleep at night) can affect coordination, reaction time, and judgment. Moreover, the British Medical Association has warned that there are problems associated with sleep deprivation apart from its effects on alertness and performance.
from impaired motor skills. People who get too little sleep may have higher levels of stress, anxiety, and depression and may take unnecessary risks.\textsuperscript{3,11} Sleep deprivation in military scenarios can lead to accidental errors, with catastrophic results, during operational activities. This was demonstrated during the Persian Gulf War when U.S. soldiers, observing enemy territory, noticed a hot spot approaching on their thermal eye gear during a firefight.\textsuperscript{9,10} Unfortunately, concentration on the approaching spot was lost, and guns were fired at their fellow soldiers. Investigation of the incident concluded that the soldiers were suffering from the effects of sleep deprivation, which resulted in confusion and impaired judgment.\textsuperscript{1,9} It was also found that individuals suffering from sleep deprivation attempt to compensate for failed performance long before falling asleep.

If the sleep deprivation period is long enough, then rhythm can be affected in such a way that a change in the cycles eventually leads to desynchronization between biological cycles (such as body core temperature and cognitive performance) and environmental cycles.\textsuperscript{5,7} The result may be impairment of cognitive and motor skills. The ability to perform cognitive tasks is reduced by \textasciitilde{25}\% for every 24 hours of full wakefulness.\textsuperscript{1,2} This state can result in fatigue that is much more difficult to manage, known as "operational fatigue."\textsuperscript{5,7,11} Furthermore, operational fatigue may express itself in two main behavioral effects, namely, susceptibility to falling asleep in a nonstimulating environment while performing monotonous tasks and impairment of high-order mental operations, especially those that are not routine or familiar or that require imaginative solutions in a stimulating environment.\textsuperscript{1,3,14} Interestingly, sleep-deprived individuals are themselves poor judges of their own cognitive performance (brain areas that are involved in self-assessment may be impaired by sleep deprivation).\textsuperscript{1,5,7,9,11}

**Pharmacological Strategies for Improving Alertness and Complex Mental Performance**

During forced sleep deprivation, alertness and performance can be improved through the administration of psychostimulants, which are capable of releasing excitatory neurotransmitters such as dopamine and norepinephrine from storage vesicles in the central nervous system or peripheral nervous system or having a sympathomimetic mode of action. \textsuperscript{2,15-21} This chemically heterogeneous drug group includes amphetamines, amphetamine-like drugs, caffeine, and nicotine (although nicotine and caffeine are considered nutritional supplements rather than drugs).\textsuperscript{2,15,18,21}

The potential of psychostimulants to reduce fatigue was recognized and introduced into military use during World War II.\textsuperscript{20} Nazi scientists used concentration camp inmates to test the "wonder drug," to discover whether it could enhance the performance of German troops. The United States initiated studies in the late 1940s and 1950s to determine the military significance of psychostimulants. The psychostimulants were administered to military personnel to help maintain alertness and to diminish drowsiness and were used by German, Japanese, and English troops.\textsuperscript{1,2,9,20,22,23}

**Dextroamphetamine**

The most abundant subtype of amphetamine is dextroamphetamine.\textsuperscript{15,16,19,20,22} Dextroamphetamine has been widely used for the treatment of a variety of physical (obesity, congestion narcolepsy, attention-deficit/hyperactivity disorder, and some types of Parkinson's disease) and mental disorders.\textsuperscript{15,20,22,24} Pharmacokinetically, the drug is administrated orally or through intravenous injection. Effects are experienced within 30 minutes after oral doses. Slow metabolism takes place in the liver.\textsuperscript{8} It was revealed that, within a short time, increased doses of the drug were required to maintain the same effects.\textsuperscript{15,16,23,25} The possible side effects are mentioned in Table I. The efficacy of dextroamphetamine for sustaining performance was evaluated in experiments with helicopter aviators in a placebo-controlled, double-blind study during 64 hours of prolonged wakefulness.\textsuperscript{26} Data included electroencephalographic (EEG) activity and subjective mood ratings. Dextroamphetamine, in comparison with the placebo, improved aviator simulator control on descents, straight and level flight, standard-rate turns, and left descending turns. Performance was facilitated most remarkably in the early morning and in the afternoon (after 22, 26, and 34 hours of continuous wakefulness). EEG and mood data showed that, when dextroamphetamine was administered, alertness was sustained significantly, slow-wave EEG activity was reduced, and levels of energy and fatigue were improved.\textsuperscript{26}

Caldwell et al.\textsuperscript{27} evaluated the flight performance, mood, and alertness of 10 helicopter pilots during sleep deprivation peri-

**TABLE I**

**COMPARISON OF DEXTROAMPHETAMINE AND MODAFINIL SIDE EFFECTS**

<table>
<thead>
<tr>
<th>Category</th>
<th>Dextroamphetamine</th>
<th>Modafinil</th>
</tr>
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<tbody>
<tr>
<td>Central/peripheral nervous system</td>
<td>Headaches, nervousness, dizziness, depression, anxiety, cataplexy, insomnia, confusion, amnesia, abnormal vision, distortions of nocturnal sleep, tremors, dry skin, increase in core body temperature</td>
<td>Nervousness, depression, anxiety, insomnia, vertigo, increase in core body temperature</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypotension/hypertension, vasodilation, arrhythmia</td>
<td>Hypotension/hypertension, arrhythmia</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Lung disorder, dyspnea, asthma</td>
<td></td>
</tr>
<tr>
<td>Urinary/sexual</td>
<td>Urinary retention, abnormal ejaculation</td>
<td>Low potential for abuse and addiction (current data)</td>
</tr>
<tr>
<td>Abuse, tolerance, and addiction potential</td>
<td>High potential for abuse and addiction</td>
<td></td>
</tr>
</tbody>
</table>

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The effects were not found to be clearly dose dependent. In one experiment, hypotension/hypertension, and depression while increasing feelings of vigor. No significant side effects occurred, although dextroamphetamine has been associated with mild symptomatic increases in heart rate and blood pressure.

Cardiovascular side effects with therapeutic doses of dextroamphetamine were also investigated. Pilots were exposed to two periods of continuous wakefulness. Thirty milligrams of dextroamphetamine (divided into 10-mg doses) were administered at midnight, 4 a.m., and 8 a.m. The dextroamphetamine group, in comparison with the placebo group, demonstrated elevated heart rate, increases in systolic blood pressure, and, to a minor extent, increases in diastolic blood pressure. It was concluded that dextroamphetamine appeared to be effective for sustaining pilots' performance during short periods of sleep loss, while producing adverse side effects in some susceptible subjects.

Modafinil

Modafinil is an amphetamine-like drug that is biochemically and pharmacologically distinct from prototypical stimulants such as dextroamphetamine. This agent is used to improve daytime wakefulness in patients suffering from narcolepsy. Modafinil produces psychoactive effects and alterations in mood, perception, thinking, and feelings typical of other central nervous system stimulants. Baranski et al. found that, among young healthy subjects, in terms of self-assessments of cognitive performance, both the placebo group and the modafinil group showed neither marked overconfidence nor underconfidence. Unlike amphetamines, modafinil is associated with minimal peripheral side effects when administered in therapeutic doses. Reported side effects include nervousness, depression, anxiety, insomnia, vertigo (mentioned by a few subjects in one experiment), hypotension/hypertension, and arrhythmia. Overall, current data imply that modafinil has a low potential for addiction, does not interfere with normal sleep, and does not seem to promote tolerance.

Cognitive effects of modafinil were investigated in 60 healthy, young, adult male volunteers who received a placebo or modafinil before performing a variety of tasks designed to test memory and attention. Results indicated that modafinil significantly enhanced performance in tests of digit span, visual pattern recognition memory, spatial planning, and stop-signal reaction time. These performance improvements were complemented by a slow onset in three tests, i.e., delayed matching to sample, decision-making, and spatial planning. Subjects reported feeling more alert, attentive, and energetic when given modafinil. The effects were not found to be clearly dose dependent.

The potential of modafinil as a psychostimulant was evaluated in 80 healthy volunteers subjected to 60 hours of sleep deprivation. Self-assessment questionnaires, visual tasks, and EEG recordings evaluated wakefulness. Subjects were given either modafinil or a placebo every 8 hours for 3 days. The modafinil group demonstrated higher performance test results because of a satisfactory level of vigilance, compared with the placebo group. Moreover, volunteers who were administered modafinil showed a total absence of micro-sleep episodes, which occurred under placebo conditions.

A double-blind, placebo-controlled, crossover study was conducted with six helicopter pilots by using a flight simulator. The pilots were exposed to two 40-hour periods of continuous wakefulness, separated by one night of recovery sleep. In one of the sleep deprivation periods, three doses of modafinil were administered. In the other sleep deprivation period, a placebo was given. Testing included flight maneuvers, EEG tests, mood questionnaires, and cognitive evaluations. Results indicated improvement in performance of all tasks with modafinil, compared with placebo. Reported side effects included nausea, and one subject reported vertigo indicated by nervousness.

Dextroamphetamine versus Modafinil

The most noticeable difference between dextroamphetamine and modafinil is in the observed side effects summarized in Table I. A human study included 41 military subjects who received modafinil, dextroamphetamine, or placebo on three separate occasions during 64 hours of continuous cognitive work and sleep deprivation. Subjective estimates of mood, fatigue, and sleepiness, as well as objective measures of reaction times, logical reasoning, and short-term memory, clearly showed better performances with both modafinil and dextroamphetamine, in comparison with the placebo group. Both drugs maintained or increased body temperature, compared with the natural circadian cycle observed in the placebo group. At the end of the study, modafinil elicited fewer side effects than did dextroamphetamine but more than in the placebo group.

In another study, modafinil administration showed relatively restricted patterns of changes in regional metabolic activity in the brain, whereas dextroamphetamine altered glucose utilization in a wide variety of brain regions. Both drugs increased glucose utilization in all subregions of the hippocampus responsible for creating new memory. Increased utilization of glucose was well demonstrated in the amygdala (responsible for fear condition) after modafinil administration. The latter finding suggests that, although both drugs promoted wakefulness, they acted through distinctly different mechanisms; modafinil acted on specific brain pathways that regulate sleep/wakefulness, whereas dextroamphetamine affected a greater number of cerebral structures involved in the regulation of behavioral states, including alertness. Modafinil lacked any effect on the extrapyramidal motor system; therefore, its effects were not mediated by the dopaminergic system. This result implies a selective increase in wakefulness with fewer side effects of the peripheral nervous system, in comparison with dextroamphetamine.

Recently, Wesensten et al. demonstrated improvement in executive function tasks with administration of modafinil and dextroamphetamine to healthy young subjects. Twenty milligrams of dextroamphetamine and 400 mg of modafinil were compared in two tested groups during 85 hours of total sleep deprivation, to determine the extent to which the two agents restored performance on simple psychomotor tasks, objective

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alertness, and tasks of executive functions. All subjects in both groups remained awake for this period. Dextroamphetamine and modafinil improved psychomotor vigilance speed and objectively measured alertness, relative to placebo. Effects on executive function tasks were mixed, with improvement on some tasks with modafinil, and apparent decrements with dextroamphetamine. The doses tested showed that dextroamphetamine caused a dose-dependent impairment of sleep maintenance, whereas modafinil did not. The use of classic stimulants, such as dextroamphetamine, resulted in reduced total sleep time and rapid eye movement (REM) sleep time. This ultimately means that larger doses will be required, creating a devastating “positive feedback mechanism” cycle. In contrast, modafinil was not shown to interfere with nighttime sleep, which clearly indicates that the two compounds act through different mechanisms.

Two double-blind control studies compared the effects of modafinil and dextroamphetamine on sleep. In both studies, 12 people were given either 100 mg or 200 mg of modafinil, 10 mg or 20 mg of dextroamphetamine, or a placebo. All drugs were administered orally, and evaluation of sleep scales and the quality of waking procedures, together with psychometric tests, were completed in the morning. The outcomes of both tests showed that dextroamphetamine caused a dose-dependent impairment of sleep maintenance, whereas modafinil did not. The use of classic stimulants, such as dextroamphetamine, resulted in reduced total sleep time and rapid eye movement (REM) sleep time. This ultimately means that larger doses will be required, creating a devastating “positive feedback mechanism” cycle. In contrast, modafinil was not shown to interfere with nighttime sleep, which clearly indicates that the two compounds act through different mechanisms.

Sleep Recovery

The effects of sleep deprivation in sleep recovery were investigated in 37 volunteers who were exposed to 64 hours of continuous work while taking dextroamphetamine, modafinil, or placebo. Sleep recovery was recorded for 2 days after the sleep deprivation period. The second recovery night served to indicate whether drug-induced sleep disturbances on the first recovery night would carry over to the second night of sleep. Sleep recovery for the placebo group demonstrated a deficit in slow-wave sleep and maintenance of REM sleep period during the first recovery night, although REM sleep was distributed in episodes. Throughout this period, sleep recovery for the dextroamphetamine group was also consistent with longer sleep periods, together with intermediate periods of wakefulness, a decrease in total continuous and efficient sleep, and changes in the order of sleep stages. For that group, increased REM sleep was observed only during the second recovery night. Results for the modafinil group exhibited a reduction in total sleep time, suggesting a smaller requirement for sleep recovery than for the other two groups. That group showed fewer disturbances during the first recovery night than did the dextroamphetamine group. In particular, there were no REM sleep and slow-wave sleep deficits in the modafinil group. Moreover, the increase in REM sleep episodes observed with dextroamphetamine was not observed with modafinil. However, those results are controversial; a comparison study between dextroamphetamine and modafinil revealed no effect on recovery sleep and postrecovery sleep performance.

References

Psychostimulants and Military Operations
