Modafinil, Sleep Deprivation, and Cognitive Function in Military and Medical Settings

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Military personnel of many professions, including health care workers, are routinely challenged with performing their duties during hours when the circadian rhythm is at its trough, namely, late night and early morning. Studies have shown that cognitive performance declines significantly during these hours. Although many pharmacologic agents have been studied in an attempt to find a safe medication to enhance alertness and cognitive function, no safe nonaddictive options have been identified. Modafinil is a novel wakefulness-promoting agent that has been shown to improve cognitive performance and promote wakefulness among shift workers. This article reviews the studies on modafinil administration and cognitive performance as they relate to military operations and the provision of health care by sleep-deprived individuals.

Introduction

Pharmacologic agents promoting wakefulness have long attracted the attention of those in charge of military operations worldwide. Sustained military operations demand the maintenance of wakefulness and intact cognitive function for prolonged periods of time, often longer than average human subjects can tolerate while maintaining effectiveness. Many other professionals also regularly perform “sustained operations” that require vigilance and intact cognitive function; examples include transportation workers, emergency services providers, and medical personnel.

The relationship of cognitive performance to the circadian rhythm has been well established.1–3 Our biologic, or circadian, rhythm operates in 24-hour repetitions. This rhythm is matched, or entrained, to the environment through specific timing clues. One timing clue is the light/dark cycle of day and night, which is specifically tied to the sleep/wake cycle for humans. Humans have an increased tendency to sleep and a diminished capacity to function cognitively during the trough hours of the circadian cycle, from 2:00 a.m. to 7:00 a.m.4 For many professions, wakefulness and cognitive function must be sustained during the circadian trough, posing unique challenges for the human body.

Sleep Deprivation

There are two types of sleep deprivation, i.e., total and partial. Total sleep deprivation occurs when an individual gets no sleep during the normal sleep/wake cycle. Episodes of total sleep deprivation most often occur in acute or emergency situations. Partial sleep deprivation is defined as “a night of reduced or interrupted sleep.” How individuals respond to sleep deprivation of any kind is variable and depends on a number of factors, including age, previous sleep amount, and sleep distribution.5 In addition, there are many “arousal influences” that can often successfully counter isolated episodes of total or partial sleep deprivation. These influences include activity, bright light, noise, temperature, posture, drugs, interest, motivation, and history of exposure to sleep loss.

Acute episodes of total sleep deprivation tend to be followed by a few nights of recovery sleep. Shift work, however, produces a cumulative sleep loss, or chronic partial sleep deprivation.6 Although most people can recover easily from an isolated night of partial sleep deprivation, recurrent episodes of partial sleep deprivation tend to have a negative cumulative effect on cognitive and psychomotor performance.7 Unfortunately, many of the individuals who regularly perform shift work or experience recurrent episodes of total sleep deprivation are at risk for developing shift work sleep disorder. Shift work sleep disorder is defined by the American Academy of Sleep Medicine as a disorder characterized by extreme sleepiness, insomnia, headaches, and difficulty concentrating.

Multiple studies have been done on the occurrence of sleep deprivation among military personnel and health care providers. These individuals routinely participate in rotating shift work and serial night shifts, often while performing tasks that are cognitively very challenging. The performance decrements among sleep-deprived military personnel are significant; one night of sleep deprivation tends to decrease cognitive performance by 30 to 40%, whereas two nights of sleep deprivation can result in 60 to 70% declines in performance.8 The negative effects of sleep deprivation on the quality of patient care have been well studied.9–12 Physicians engaged in patient care during episodes of sleep deprivation tend to make more errors and perform procedures more slowly. A 2002 Journal of the American Medical Association article on sleep deprivation asserted that “patient care may be compromised if a fatigued, sleep-deprived clinician is allowed to operate, administer an anesthetic, manage a medical crisis or deal with an unusual or cognitively demanding clinical presentation” (p 957).9 Overall, cognitive function is impaired and operational and patient safety is at risk when we perform our duties in a sleep-deprived state. Although many studies have demonstrated the occurrence of this dilemma, no practical solutions have been found.

Drugs and Wakefulness

Some pharmacologic approaches to excessive sleepiness are well known. Amphetamines, for example, have been used by military personnel as a countermeasure to the fatigue of sustained operations. However, the sleep and psychiatric disturbances, cardiovascular side effects, and addictive properties of

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amphetamines make them less than ideal. Even caffeine, which is used worldwide as a wakefulness agent, is not without negative side effects. Although caffeine has less potential for dependence, it does cause irritability, tremors, and diuresis. The ideal wakefulness-producing agent would be safe, easy to use, free of side effects, affordable, and accessible. The perfect agent would not interfere with the natural circadian rhythm when ingested.

**Modafinil**

Many have asserted that modafinil (Provigil) comes closest to being the ideal wakefulness-producing agent. Modafinil, manufactured by Cephalon, Inc. (West Chester, Pennsylvania) was initially developed for the treatment of narcolepsy and was approved by the Food and Drug Administration for this indication in December 1998. On January 26, 2004, the Food and Drug Administration approved expanded labeling of modafinil to include indications for the treatment of shift work sleep disorder and excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome.

Modafinil is a unique wakefulness-promoting medication. It is nonaddictive and has a superb safety profile. Although the precise mechanism of action of modafinil is unknown, numerous human and animal studies have elucidated many of its characteristics. Modafinil has site-specific central nervous system activity13,14 and acts on a specific subset of brain pathways that regulate sleep and wakefulness. However, it does not bind to many receptors that are normally involved in sleep/wake regulation, including those for norepinephrine, serotonin, dopamine, and \( \gamma \)-aminobutyric acid. It does not have the effects on the extrapyramidal motor system that other stimulants exhibit, such as restlessness, hyperactivity, and irritability. This suggests that modafinil has the potential to increase wakefulness without the accompanying side effects possessed by other wakefulness-promoting agents.15

Modafinil is a racemic compound with the molecular formula of \( \text{C}_{15}\text{H}_{15}\text{NO}_{2}\text{S} \). It is available for oral administration in 100- and 200-mg tablets. Modafinil is readily absorbed; it reaches peak plasma concentrations 2 to 4 hours after administration and reaches a pharmacokinetic steady state after 2 to 4 days. Current recommendations are that the medication be administered 3 times per day for wakefulness and 1 hour before the beginning of an overnight shift for shift work sleep disorder. The majority of modafinil elimination occurs through hepatic metabolism, and the elimination half-life is 12 to 15 hours. There are few drug-drug interactions with modafinil. However, coadministration of modafinil with diazepam, phenytoin, propranolol, tricyclic antidepressants, or selective serotonin reuptake inhibitors may increase the circulating levels of those drugs. Furthermore, modafinil may decrease the levels of steroid contraceptives, cyclosporine, and theophylline, and drug dosage adjustments may be necessary.16

Since its discovery, modafinil has been studied as a wakefulness-producing agent for fatigue states associated with sleep deprivation among healthy volunteers.17-20 In 1989, Michel Jouvet, one of the original modafinil researchers, asserted that modafinil “could keep an army on its feet and fighting for three days and nights with no side effects.”21 Although this specific assertion has yet to be tested, the military has given much research time and attention to the drug in the years since Dr. Jouvet made his claim.

Military studies have repeatedly demonstrated that modafinil has the ability to promote wakefulness and improve cognitive performance during sustained periods of sleep deprivation associated with military operations. In a study conducted by the U.S. Army, volunteer helicopter pilots were given 600 mg of modafinil or placebo during two 40-hour periods of sleep deprivation. The results of that study showed that modafinil attenuated sleep deprivation effects during simulated flight maneuvers and lessened subjective problems with mood and alertness, compared with placebo. The most frequently observed side effects were vertigo, nausea, and dizziness, although investigators thought some of the side effects could be attributed to the motion of a simulator and the use of >400 mg of modafinil. Because modafinil works at site-specific areas in the central nervous system, use of the medication does not prevent sleep if opportunities are available.22 Researchers have also discovered that, unlike other stimulants, modafinil does not produce a paradoxical sleep rebound.23-25

Modafinil has an excellent safety profile. Long-term studies of >10 years among patients with narcolepsy failed to demonstrate any serious side effects.26 Studies of healthy volunteers revealed that modafinil is very well tolerated at the recommended daily dose of 200 mg. At doses of >800 mg, increased blood pressure and heart rate were observed.27,28 The most common side effects associated with modafinil administration are headache (10%), nausea (9%), runny nose and sore throat (3%), and nervousness (3%). In addition, a study with healthy volunteers showed that the administration of modafinil did not alter the plasma levels of melatonin, cortisol, or growth hormone.29

Modafinil is considered to have a very limited potential for abuse. The physiologic effects of modafinil differ from those of addictive central nervous system stimulants in that modafinil does not produce sympathomimetic or anxiogenic effects.30,31 A study of the subjective effects of modafinil, compared with amphetamines and placebo, showed that modafinil did not produce amphetamine-like subjective effects among healthy volunteers.32 Long-term studies of patients with narcolepsy who were administered daily doses of modafinil revealed that patients did not develop tolerance or dependence.33 Also, researchers have found that, because modafinil is essentially insoluble in water and is unstable at high temperatures, the potential for abuse as an intravenously administered or inhaled agent does not exist.34

Modafinil has largely proved to be an effective wakefulness-promoting agent, with a very favorable side effect profile. The drug has not formally been studied in civilian occupational settings, however. Cephalon completed a clinical study in 2002, looking at the use of modafinil for patients with an International Classification of Sleep Disorders-confirmed diagnosis of shift work sleep disorder.35 However, patients in the study participated in simulated night shifts, rather than performing their real occupations. The January 26, 2004, announcement about the expanded indication for modafinil to treat shift work sleep disorder indicated that patients who suffer from this disorder should take 200 mg of the drug 1 hour before the start of their shifts. Paul Blake, Senior Vice President of Clinical Research and Regulatory Affairs for Cephalon, Inc., stated, “The favorable safety profile of Provigil in studies involving more than 3,500 patients should allow physicians to confidently prescribe the drug.”36

**Ethical Considerations**

The use of modafinil in some military and medical settings raises significant ethical issues. Those in charge of military operations must carefully consider who will be appropriate can-
didates for the use of modafinil. For those involved in the delivery of health care, questions have been raised about whether the use of modafinil might compromise patient safety by hindering decision-making ability. For example, when an article in the Residency Program Director’s Alert in November 2003 suggested that modafinil “might be a good solution to the demands of long hours and irregular shifts for [medical] residents (p 103),”36 a flurry of letters to the journal ensued. Dr. Irene Rosen, Associate Program Director for the Internal Medicine Residency at the University of Pennsylvania, stated, “There is no role for modafinil use by resident physicians. It is unethical and irresponsible for physicians to use a stimulant drug while performing duties related to patient care.”36 A follow-up disclaimer article, published in the December 2003 issue (p 113), stated, “...we do not recommend the drug for residents.”37 Included in the article was a quote from Paul Blake, Senior Vice President of Clinical Research and Regulatory Affairs for Cephalon. He stated, “Provigil is a schedule IV prescription medicine and is not intended for use in helping residents work longer hours. Nor is the drug intended to help healthy people forego sleep.”37

Research on sleep deprivation and modafinil administration to date has been conducted in simulated environments, and no studies have been published about the safety and efficacy of modafinil for those performing their actual jobs in any capacity. Therefore, it is difficult to argue that military or medical personnel can safely take modafinil and engage in their regular duties. Conversely, given the drug’s excellent safety profile and low abuse potential, coupled with the documented impairment caused by sleep deprivation, it could be argued that modafinil is likely to improve professional judgment and performance, compared with those not taking the medication.

Obviously, we have an ethical obligation to study the use of modafinil by those engaged in sustained operations of many types. It is imperative to determine whether this medication will improve our abilities or endanger them.

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