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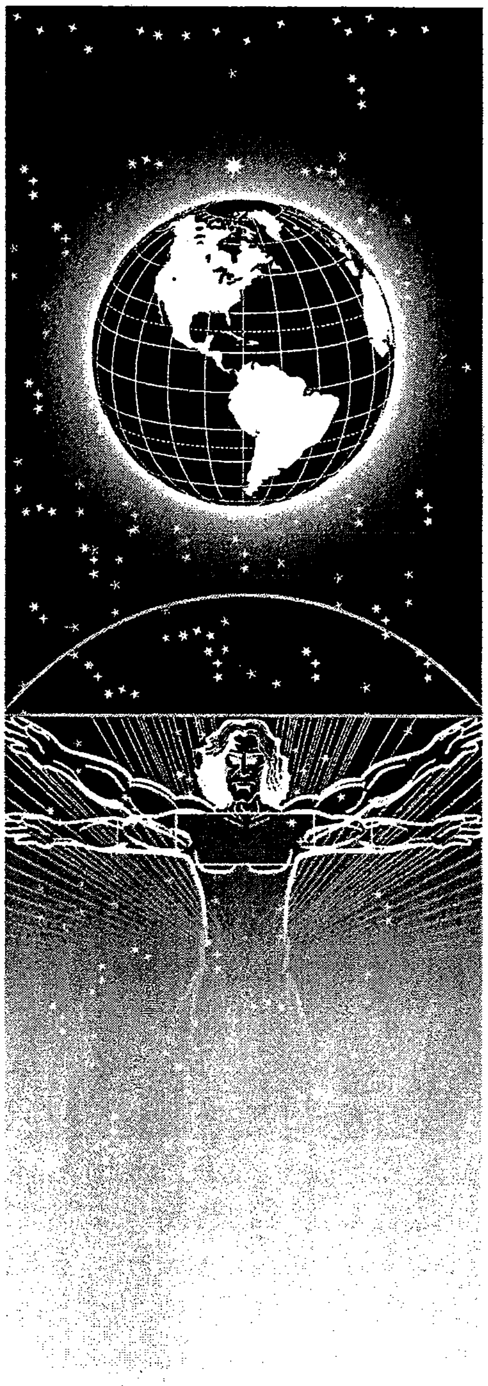

UNITED STATES AIR FORCE RESEARCH LABORATORY

AN OVERVIEW OF THE UTILITY OF STIMULANTS AS A FATIGUE COUNTERMEASURE FOR AVIATORS

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14. ABSTRACT
Sleepiness and fatigue are common in the aviation environment even during peacetime, but during combat, fatigue can reach critical levels due to the necessity for sustained operations and the consequent requirement for lengthy duty schedules. Effective nonpharmacological countermeasures are often difficult to implement in these settings due to the situational demands and the unpredictable nature of war. Thus, during combat, pharmacological countermeasures (stimulants or Go Pills) may represent the only feasible alternative for the maintenance of aviator performance when sleep deprivation is inevitable. Caffeine is a first line choice, but might not be sufficiently effective for long durations or for those who are heavy caffeine users. Modafinil is a new alertness-promoting compound that appears to hold promise for use in military aviation, but is not yet recommended because of a lack of field-oriented aviation research. Dextroamphetamine has been successfully used by the military in past conflicts, and its effectiveness and safety are well established. Commanders, flight surgeons, and individual aviators may wish to examine what has been determined from past research in order to make the best possible decision concerning the appropriateness of Go Pills for future aviation sustained operations.

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BACKGROUND

Aviator sleepiness and fatigue are common even during peacetime (Caldwell, Gilreath, and Norman, 1999; Caldwell et al., 2001), but in combat, the situation is exacerbated by operational demands that can lead to dangerous levels of sleep deprivation. Most aviators attempt to get sufficient sleep, but job demands, anxiety, uncomfortable sleep environments, and other problems can interfere. Personnel who have been deployed know about the "real world" causes of fatigue and the problems associated with being overly tired, but possessing this knowledge doesn't always lead to operationally-useful solutions. Even when there are solutions available, concise information about various strategies can be difficult to find.

This report will provide a brief aviator-oriented overview of fatigue in intense military operations and summarize information about a fatigue countermeasure that has recently received a great deal of attention (i.e., stimulants). Although numerous opinions exist about the wisdom of using stimulants to maintain alertness and performance in combat aviation, facts concerning the military's historical use of these medicines, and the research which forms the foundation of stimulant-use guidance, can be difficult to obtain. If the past is any predictor of the future, stimulants will continue to be used in specific types of operational scenarios not only by the U.S. Air Force (where a policy is already in place), but by the other services as well. Once Command authorization has occurred, aviators will be faced with a personal decision about whether or not they will use stimulants in the operational environment. This report may help them make an informed decision when the time comes.

Military Sustained Operations are a Necessity, but are not without Drawbacks

Military doctrine requires that units be capable of sustained operations during times of conflict because U.S. superiority on the battlefield stems in part from our ability to maintain pressure on the enemy by making them fight around the clock. In fact, the Air Force Chief of Staff recently noted that persistent and sustained operations "24 hours a day, seven days a week..." are essential to attaining U.S. victory in today's battlespace (Elliot, 2001). By keeping up a 24-hour-a-day operational tempo, enemy forces can be placed at significant risk for the severe sleepiness that can lead to slower reactions, a loss of battlefield awareness, and a general inability to maintain a coherent representation of the tactical environment (Belenky, 1995). This provides us with a tactical advantage, but only if U.S. forces guard against severe sleepiness in themselves. Unfortunately this is difficult to do because fully staffing three 8-hour work shifts with well-rested personnel around the clock for seven days a week in combat is a daunting task, especially since substantial force reductions have occurred. Since 1990, there has been an overall 37.7 percent reduction in military personnel, and the number of active Air Force tactical wings has fallen from 24 to 12 (Congressional Research Service, 2002). Meanwhile, contingency deployments have increased by as much as 400 percent (Correll, 1998).

In sustained operations, prolonged work bouts are common, shorter-than-normal sleep periods are unavoidable, and fatigue from both of these factors threatens to impact operational readiness (Department of the Army, 1994). It is well established that sustained wakefulness and the resulting cumulative sleep debt increase the likelihood that personnel will briefly (and uncontrollably) nod off on the job, even during flights (Dinges, 1995). The longer someone remains awake, the more likely these involuntary sleep lapses become. In addition, sleepiness takes a heavy toll on reaction time, motivation, attention, memory, endurance, and judgment (Krueger, 1989). Naitoh and Kelly (1993) warn that sleep deprivation in extended operations quickly leads to motivational decrements, impaired attention, short-term memory loss, carelessness, reduced physical endurance, degraded verbal communication skills, and impaired judgment.

The time course of various decrements is fairly well established. Angus and Heslegrave (1985) found that cognitive abilities suffer 30 percent reductions after only 1 night without sleep and 60 percent reductions after a second night. Belenky et al. (1994) estimates a 25 percent decline in the ability of personnel to perform useful mental work with each 24-hour period of sleep loss. In a Norwegian military field study, Roussel (1995) found that the fighting capability of soldiers was reduced by 80 percent across 4 consecutive days of sleep deprivation. Thus, significant sleep loss, without the introduction of appropriate countermeasures, ultimately will result in virtual incapacitation of personnel in the operational environment. In light of the significant reductions in the numbers of military personnel, this could become a serious issue as attempts are made to fulfill Air Force doctrine emphasizing the tactical necessity of sustained and overwhelming application of air and space power in modern warfare (Department of the Air Force, 1997).

The Body's Circadian Clock Influences Fatigue Levels throughout the Day

Anyone who has worked nights knows that sleepiness and fatigue are worse in the early morning (from 0200-0500) than at other times. This is because the body's internal rhythms are programmed to "wind down" at night (when we are usually asleep) and "rev up" during the day (when we are usually awake) (Monk, 1990). It takes several days to adjust to a new working and resting schedule, and many people never fully adjust to night work no matter how long they stay on the night shift (Czeisler, 1990). People who aren't adjusted to their duty schedule suffer in terms of their feelings (tired, upset stomach, poor mood, etc.), their alertness (slow and drowsy), and their performance (reduced accuracy, poor vigilance, and slow reactions). Such problems have been labelled "shift lag" because the body's clock is not synchronized with environmental time cues due to shift work.

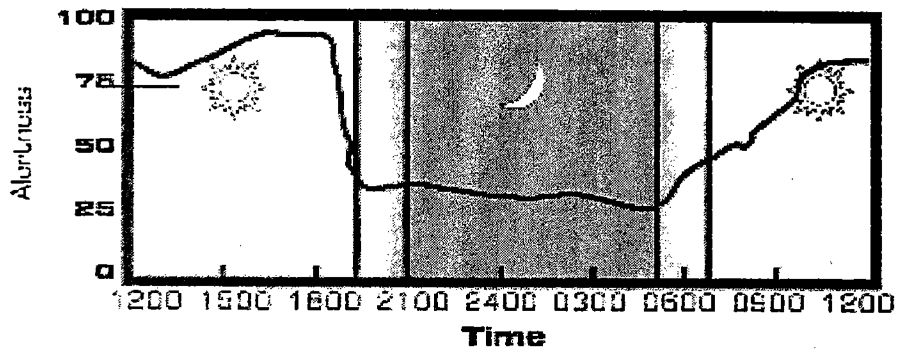

Figure 1. How alertness and performance change throughout a 24 hour period.

The phenomenon of "jet lag" produces similar problems because the body's clock becomes out of phase with a new environmental light/dark cycle that results after rapidly crossing numerous time zones. Shift lag and jet lag compound the fatigue associated with long hours of wakefulness so that someone who, for instance, is working early in the morning (after being awake since the previous day) is suddenly vulnerable to involuntary brief laspses into sleep even though they felt fine just a few hours before. These same people might deceive themselves into thinking they've overcome fatigue after the sun comes up even though they haven't slept. Unfortunately, this kind of thinking leaves them unprepared for even greater problems later in the day, and since they don't expect this subsequent drop in alertness and performance, their safety may be even more at risk than it was initially.

An Example of the Effects of Fatigue

An example of the performance decline associated with sleep loss and circadian factors is shown below. This graph was produced by a computer model (the Air Force Fatigue Avoidance Scheduling Tool™) that predicts performance efficiency based on the amount of sleep obtained and the circadian phase. As shown (based on a schedule from a recent military exercise), serious deficits in effectiveness were predicted on the morning of the second day of the exercise (Tuesday) after 18-22 hours of continuous wakefulness. At this point, effectiveness was expected to fall below 75% of optimal levels (down to approximately 67%). Due to the subsequent lack of sleep (with only a 2-hour nap on Days 2 and 3), performance likely would have continued to decline until it degraded to less than 50% of optimal levels. Decrements of this magnitude could create serious problems in the operational environment unless a proven fatigue countermeasure is implemented. Note that the greatest decrement on Tuesday was predicted to occur after nearly 24 hours without sleep at approximately 0300 (during the circadian trough), a time associated with basic fatigue-induced performance losses similar to those produced by blood alcohol concentrations (BACs) of .05 to .10 (Dawson and Reid, 1997).

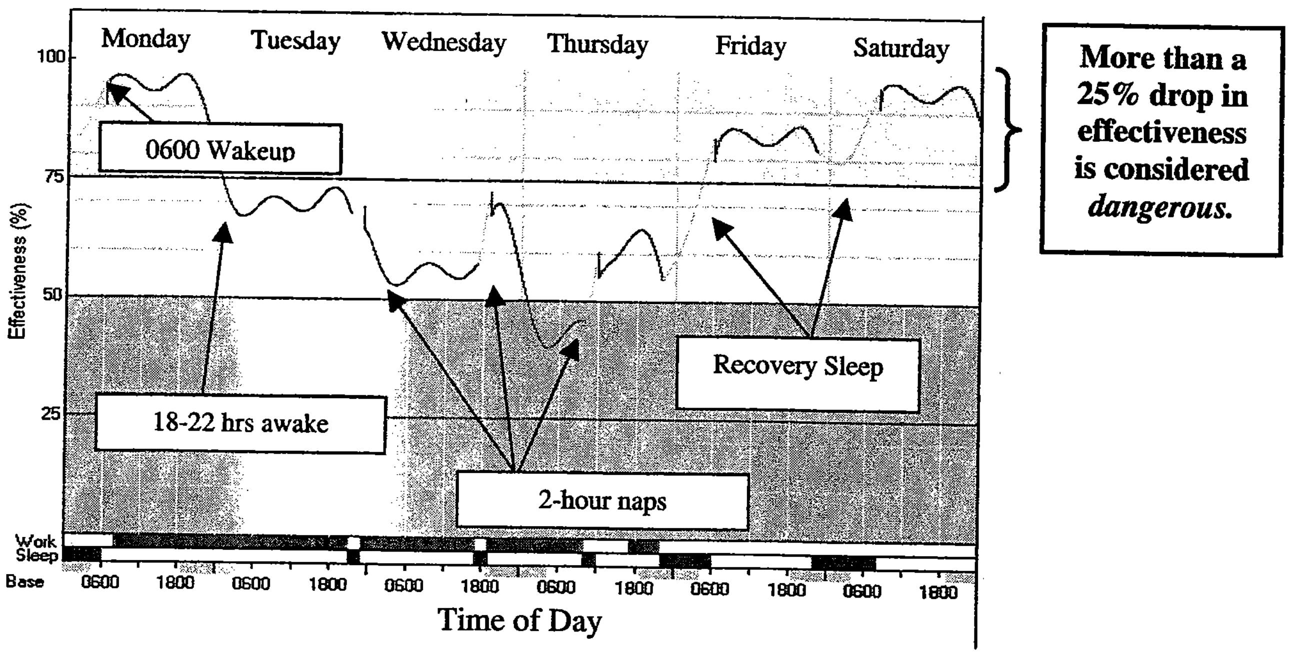

Figure 2. Computer model prediction of Operational Performance Based on the Schedule Proposed for a Recent Field Exercise.

Clearly, fatigue is an important issue in the training environment. It therefore would be expected to create even greater problems in the real-world operational environment. It is for this reason that proven countermeasures must be implemented.

DEALING WITH OPERATIONAL FATIGUE

A number of fatigue remedies have been proposed for field settings (Babkoff and Krueger, 1992). Nonpharmacological (non-drug) strategies include the establishment of optimal duty schedules, and the use of napping, rest breaks, exercise, and environmental stimulation. One other non-drug countermeasure has been to ensure the physical fitness of personnel. Pharmacological (drug) strategies primarily include the administration of stimulants.

Nonpharmacological Strategies

Emphasizing proper work/rest management is one strategy that the military has rightfully focused upon. However, when the intensity of combat reaches a certain point, it can be very difficult to properly control sleep periods, and this can lead to a substantial problem with on-the-job fatigue (Cornum, 1994; Angus, Pigeau, and Heslegrave, 1992). Even during peacetime, a recent survey of Army pilots revealed that 26 percent complained of poor sleep while in the field or while traveling away from home compared to only 5 percent complaining of poor sleep at their home post (Caldwell et al., 2001). Similar difficulties are no-doubt present in the U.S. Air Force.

Strategic naps can help alleviate sleep-deprivation-related performance decrements in situations where naps are feasible (Dinges et al., 1988). However, scheduling naps is not a simple matter in that operational constraints can make it very difficult to ensure proper control over nap timing (placement of naps at optimal points in the sleep-deprivation period), nap duration (ensuring sufficient sleep time), and nap scheduling (placing naps at appropriate points in the circadian cycle) (Caldwell, 2001). In addition, it can be difficult to establish a restful and isolated environment in which effective naps can take place.

Brief periods of exercise may offer some benefit in situations where full sleep periods and naps are not possible, but this strategy only temporarily reduces the impact of sleep loss (LeDuc et al., 1998; Horne and Reyner, 1995a; and Angus et al., 1992). Also, there is some indication that the short-term benefits of exercise are not sufficiently robust to outweigh the alertness decrements that it produces later on.

Exposure to environmental stimulation such as cold air or noise is another strategy that has been tried in laboratory studies of driver fatigue. Results have shown that such measures are virtually ineffective for maintaining alertness (Horne and Reyner, 1995b).

Finally, high levels of physical fitness, while good for sustaining physical endurance, has been found to have little impact on the ability to maintain cognitive performance (Angus et al., 1992).

Pharmacological Strategies

Pharmacological countermeasures (stimulants) may be the only reliable method for maintaining the performance of personnel, especially aviators, in sustained operations. Stimulants are effective and easy to use, and their feasibility is not dependent upon environmental manipulations or scheduling modifications. This explains why pharmacological compounds such as the amphetamines have been used extensively in several military conflicts (Cornum, Caldwell, and Cornum, 1997). Despite debate on this topic, dextroamphetamine remains one of the best stimulant choices because its actions are well understood and its effectiveness in sleep-deprived personnel is well known. However, there are other possible alternatives that will be briefly discussed here before the utility of dextroamphetamine is summarized.

Caffeine

Caffeine is easy to acquire and socially acceptable. It appears suitable for sustaining alertness in relatively short (i.e., 37 hour) rather than long (i.e., 64 hour) periods of continuous wakefulness (Lagarde and Batejat, 1995). Caffeine is considered by some to be preferable to amphetamine for promoting alertness in sleep-deprived individuals, but others have concluded that caffeine is less effective than amphetamine and more prone to produce unwanted side effects (Weiss and Laties, 1967). The effectiveness of caffeine may be less than optimal in individuals who normally consume moderate to high amounts in coffee, soft drinks, nutritional supplements, and/or food products, but this has not been firmly established. However, it is known that tolerance to the sleep-disrupting effects of caffeine can occur in as little as 7 days in individuals given high doses (1200 mgs per day), and although the majority of adults consume far less than 1200 mgs per day, it is estimated that about 80 percent of the U.S. adult population does regularly consume a behaviorally active dose of caffeine on a daily basis (Griffiths and Mumford, 1995). Note that a typical single serving of coffee (smaller than a Starbucks™ short) contains 60-150 mg caffeine, tea contains 20-50 mg, chocolate contains 5-35 mg, and Coke contains 46 mg of caffeine (Lieberman, 1992). Thus, some degree of tolerance is inevitable, and this may mean that more than the minimum recommended dose of 200 mg caffeine would be required to noticeably improve wakefulness in sleep-deprived pilots. However, all of this not withstanding, it has been established that caffeine will significantly improve the performance of sleep-deprived people who do not normally consume high doses of this compound. Given the safety and the ready availability of this stimulant, caffeine administration should be considered a "first line" pharmacological approach to sustaining the performance of sleep-deprived aviators.

Figure 3. Two Over-the-Counter Caffeine Preparations.

<u>Modafinil</u>

Modafinil is a new stimulant that may eventually prove efficacious for sustaining performance in prolonged periods of total sleep loss (Lagarde and Batejat, 1995). This substance only recently became available in the United States (it was FDA approved for the treatment of excessive daytime sleepiness in patients with narcolepsy in December, 1998). Testing in militarily-relevant contexts is at this point, insufficient. The one aviator performance study that exists (with 600 mg modafinil given in three divided 200 mg doses) indicated modafinil was capable of sustaining simulator flight performance at near rested levels despite over 30 hours of sleep loss (Caldwell et al., 2000), but this study also produced evidence of side effects (nausea, vertigo, and dizziness) which may have been modafinil-related in some pilots. It may be possible to eliminate the side effects by adjusting the dosage, but this has not yet been established in aviation-related research efforts. Studies focusing on ground-based performance have produced more promising results. Lagarde et al.

(1995) and Lagarde and Batejat (1995) found that modafinil reduced the frequency of involuntary sleep lapses and maintained cognitive performance during 60 continuous hours of wakefulness, and Pigeau et al. (1995) reported that modafinil (300 mg) was as effective as dextroamphetamine (20 mg) for maintaining mood, alertness, and performance throughout 64 hours of sleep deprivation. Eddy et al. (2001) reported that modafinil eliminated fatigue-related performance decrements on a vigilance task in people kept awake for 22 hours. Wesensten et al. (2002), from a study conducted at the Walter Reed Army Institute for Research (WRAIR), indicated that modafinil (200 mg and 400 mg) restored response speed and throughput which had degraded after 41.5 hours without sleep (a similar effect was observed with 600 mg of caffeine).

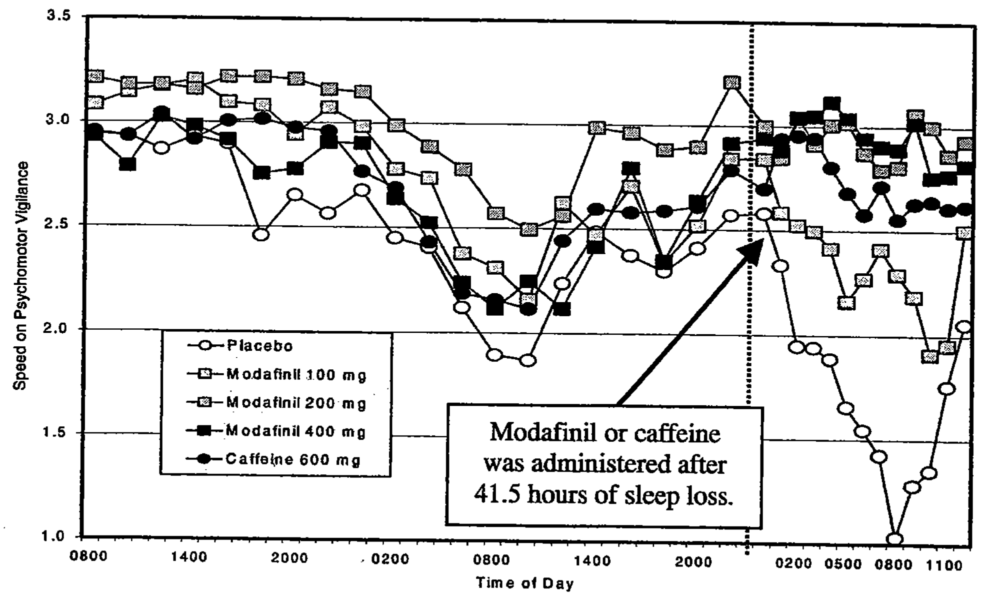

Figure 4. Data from WRAIR Demonstrating the Efficacy of 200 and 400 mg of Modafinil Compared to Placebo and 600 mg Caffeine.

It may be that modafinil will ultimately become an approved alertness-enhancing compound for Air Force aviation sustained operations, but at present, more aviation-oriented studies are needed. Until these studies are performed, dextroamphetamine is a better choice in terms of what is known about the drug and it's proven potential for sustaining alertness for relatively long periods in sleep-deprived people.

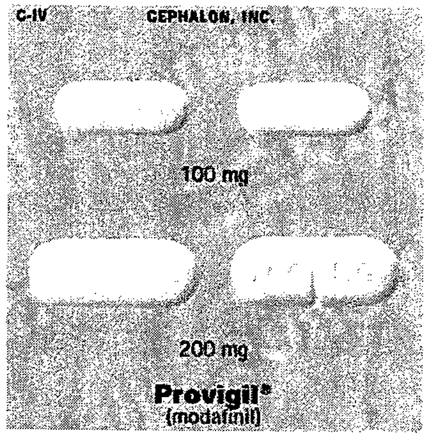

Figure 5. Modafinil Comes in 100-mg and 200-mg Tablets.

Amphetamines

Amphetamines have been on the market in the U.S. since 1937 and have been widely used to treat the symptoms of medical conditions such as narcolepsy (with excessive daytime sleepiness) and hyperactivity/attention deficit disorder (Cornum, Caldwell, and Cornum, 1997). In the 1940s and 1950s, the military began exploring the significance of stimulants, and the general consensus was that they were capable of restoring or maintaining the performance of sleep-deprived people to nondeprived levels. Recently, their beneficial effects have been overshadowed by the recognition that they have significant abuse potential, but there is clear evidence that the military has successfully used amphetamines (under certain conditions, at the direction of the commander and the flight surgeon) for years. The Air Force authorized the use of amphetamines to sustain the performance of sleep-deprived pilots as early as 1961, and dextroamphetamine (marketed under the brand name Dexedrine®) continues to be authorized under Air Force policy for certain situations today (i.e., in specific single-seat and dual-seat aircraft operations). Dextroamphetamine was authorized under Army policy as an anti-fatigue drug as recently as during Desert Storm, and dextroamphetamine is presently considered a waiverable medication for Army aviators.

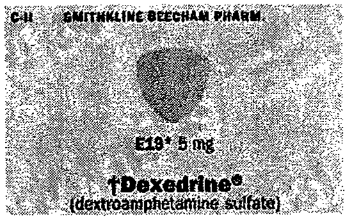

Figure 6. Dextroamphetamine, or Dexedrine, comes in 5-mg Tablets.

Dextroamphetamine--laboratory studies. In the laboratory, single doses (20 mg) of dextroamphetamine have been shown to return alertness and cognitive performance to near baseline levels and maintain this recovery for 7 to 12 hours after 48 hours of total sleep deprivation (Newhouse et al., 1989). In addition, a single 20 mg dose has been found to temporarily prevent performance decrements in subjects kept awake for approximately 34 hours, and to restore the performance of volunteers deprived of sleep for 48 hours (Pigeau et al., 1995). Multiple 10-mg doses of dextroamphetamine, administered prophylactically, are known to sustain the performance of helicopter pilots throughout 40 hours of continuous wakefulness (Caldwell et al., 1995; Caldwell, Caldwell, and Crowley, 1996; Caldwell and Caldwell, 1997). A study completed at the U.S. Army Aeromedical Research Laboratory (USAARL) extended these results by showing that dextroamphetamine continues to work well in pilots deprived of sleep for up to 64 hours (Caldwell et al., 1999).

In each of these dextroamphetamine studies, unwanted side effects were minimal (most often consisting of increased blood pressure rather than psychological or cognitive disturbances) and of little or no consequence in healthy young adults. In addition, although there is a widely held view that amphetamines lead personnel to become reckless and overconfident, the studies cited above indicated no increases in risk-taking behaviors or overestimation of performance capabilities associated with dextroamphetamine. This finding has been confirmed elsewhere (Higgins et al., 1975; Baranski and Pigeau, 1997). Thus, laboratory studies indicate dextroamphetamine is a logical choice for maintaining the performance of healthy personnel who are deprived of the opportunity to sleep in sustained military operations. This is especially true for aviators because a high level of medical oversight is possible in aviation settings.

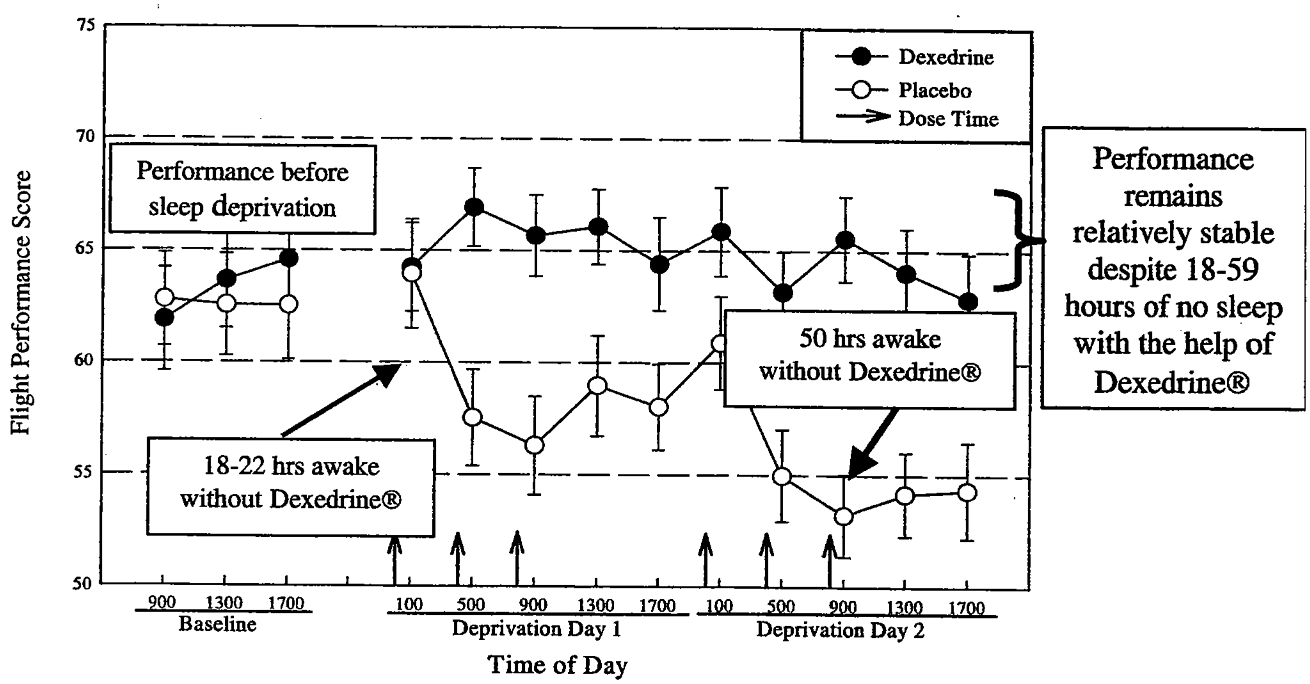

Figure 7. Data from USAARL Demonstrating the Efficacy of 10-mg Doses of Dexedrine®.

<u>Dextroamphetamine--field studies</u>. Although dextroamphetamine has not been well-studied in ground-based personnel in the field environment, evaluations from the aviation community have been favorable. Dextroamphetamine (5 mg) administered to EF-111A Raven jet crews during an Air Force strike on Libya in April of 1986, enabled crews to overcome the fatigue of the mission itself and the sleep deprivation which occurred during earlier preparation for the mission (Senechal, 1988). There were no in-flight or landing

problems, and all of these aircraft returned safely to base.[1] When Dexedrine was administered to F-15C pilots flying lengthy combat air patrol missions during Operation Desert Shield/Storm, it enabled flight crews to overcome the fatigue from sleep deprivation and circadian disruptions (Cornum, 1994). (In practice, the aviators self-administered 5-mg doses at a frequency of 1 tablet approximately every 2-3 hours as directed). The unit commander concluded that this strategy contributed to the safety of air operations. There were no reported adverse effects, even in personnel who took 10 mg at a time, and no aviators reported a need to continue the drug once proper work/sleep schedules were reinstated. This agrees with the results of a survey of Air Force pilots conducted at the conclusion of the Gulf War. This survey indicated that dextroamphetamine was helpful in maintaining mission performance during sustained operations without inducing unwanted side effects (Emonson and Vanderbeek, 1993).

In part, because of such reports, the U.S. Air Force recently approved the use of dextroamphetamine for sustaining the performance of pilots in single- and dual-pilot flight operations. Under this policy, 10 mg doses have been authorized. No explicit dosing regimen was specified in the policy, but an Air Force Fatigue Countermeasures working group recommended that the longest period during which personnel should be kept awake on dextroamphetamine is 72 hours (because this is the longest duration that has been evaluated in a controlled study). Of course, the ultimate decision about whether or not dextroamphetamine will be used in any given air operation rests with the pilot. The Air Force does not mandate the use of any stimulant for any type of operation.

[1] Although one of the strike F-111's involved in this mission was taken out by a surface-to-air missile, all of the EF-111's and the remaining F-111's returned safely.

SUMMARY AND CONCLUSIONS

Fatigue will probably always be a concern in combat operations because of the intensity and unpredictability of wartime missions. There are solutions for operational fatigue, but the best choice depends on several factors which, when taken together, can be complex.

Obviously, the best way to prevent fatigue on the job is to ensure that everyone gets enough sleep before the mission ever starts (sleep experts recommend 8 hours of sleep per day to maintain top-notch performance). If possible, it is best for this sleep to occur during the normal nighttime sleep period because this is the time at which the body is naturally better able to sleep. It also is important to provide personnel with a comfortable place to sleep that is dark and free of disruptive noise and activity. *Remember, proper sleep is the only sure way to keep fatigue in check!*

If a full 8-hours of sleep is impossible, naps are a good compromise. Each individual nap should be long enough to provide at least 45 continuous minutes of sleep, although longer naps (2 hours) are better. In general, the shorter each individual nap is, the more frequent the naps should be (the objective remains to acquire a daily total of 8 hours of sleep). Once again, to promote the most restorative sleep, the same rules about environmental comfort apply to them as they do to the longer sleep episodes.

Physical exercise, work breaks, and physical fitness are not particularly effective for managing fatigue in the operational aviation environment. In particular, being physically fit apparently offers no benefit for sustaining mental alertness.

When it's impossible to obtain any sleep, stimulants are the only realistic alternative to being drowsy in the cockpit for any significant period of time. Although stimulants cannot replace the need for sleep, they can temporarily postpone it. This is especially important in sustained aviation operations because sleepiness in the cockpit is a serious problem which cannot be overcome through motivation, training, or experience. Once the body reaches a certain point, involuntary lapses into sleep will occur, and these can last anywhere from a few seconds to several minutes each. Compounding the problem is the fact that people often aren't aware that they are lapsing into sleep until the lapses sometimes stretch into periods of a minute or longer. Stimulants can stave off the effects of fatigue for several hours if used correctly.

If stimulants are to be used, the basic choices are caffeine or dextroamphetamine. Herbal remedies are not advisable, and modafinil is not currently an approved option. Of the available choices, caffeine is the only one that an aviator can take advantage of without explicit flight surgeon and command authorization. Caffeine is beneficial, but its effectiveness may be degraded in people who normally consume moderate to high amounts of caffeine. Also, longer durations of sleep loss may require a more powerful stimulant. Dextroamphetamine should be considered for intense cases of fatigue since its efficacy has been repeatedly demonstrated in longer-term aviation-relevant settings. Controlled experiments have established that dextroamphetamine can maintain performance at rested levels for over 55 hours. However, dextroamphetamine is a controlled prescription medication that can be used only under flight-surgeon supervision (after Command approval).

Exact stimulant administration guidance is beyond the scope of this paper, but factors to consider include the amount of sleep deprivation (fatigue increases with sleep loss), the time of day (fatigue is worse in the circadian trough), the predicted time of the next sleep period (wake-promoting agents may interfere with recovery sleep), and the health of the pilot (identified cardiovascular problems may prohibit stimulant use). It should be recognized that sleep postponed with stimulants will need to be repaid. At least one full 8-hour period of sleep is necessary to recover from each 24-hour period of continuous wakefulness. A longer period of recovery sleep may be necessary after repeated bouts of sleep deprivation.

The bottom line is that stimulant use is often appropriate for situations where the mission simply must be accomplished despite the fact that total sleep deprivation is inevitable. When such a situation arises, commanders, flight surgeons, and individual aviators can make informed decisions by considering what laboratory and field research have revealed about nonpharmacological and pharmacological fatigue-management strategies. Dextroamphetamine has been well-tested in a variety of situations, and while it should not be used as a replacement for sound crew-scheduling practices, it's ability to postpone the need for sleep can make the difference between life and death in situations where high levels of fatigue are simply unavoidable.

NOTE

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