Fatigue in Military Aviation: An Overview of U.S. Military-Approved Pharmacological Countermeasures

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Uncomfortable working and sleeping environments, high operational tempos, sustained operations, and insufficient staffing make fatigue a growing concern. In aviation, where a single mistake can cost millions of dollars, it is essential to optimize operator alertness. Although behavioral and administrative fatigue countermeasures should comprise the "first line" approach for sustaining aircrew performance, pharmacological fatigue countermeasures are often required. Various components of the U.S. military have authorized the use of specific compounds for this purpose. Hypnotics such as temazepam, zolpidem, or zaleplon can mitigate the fatigue associated with insufficient or disturbed sleep. Alertness-enhancing compounds such as caffeine, modafinil, or dextroamphetamine can temporarily bridge the gap between widely spaced sleep periods. Each of these medications has a role in sustaining the safety and effectiveness of military aircrews. The present paper provides a short overview of these compounds as well as factors to be considered before choosing one or more to help manage fatigue.

Keywords: hypnotic, stimulant, aviation, fatigue, sustained operations.

IN THE MILITARY aviation community, "24/7" schedules are often essential for effective mission completion. The Air Force Chief of Staff notes that persistent and sustained operations "24 h a day, 7 d a week. . ." are essential to attaining U.S. victory in today's battlespace (41). Fighting and maneuvering around the clock is intended to wear down the enemy by minimizing or eliminating their recuperative rest breaks, thereby impairing effectiveness via the onslaught of severe fatigue. This fatigue-induction strategy has proven to work extremely well, but it can backfire unless U.S. military personnel manage to effectively guard against sleep loss themselves.

Aircraft and other equipment can function for extended periods without adverse effects, but human operators need periodic sleep for the restoration of both body and brain (48). Prolonged periods of wakefulness produce attentional lapses and slower reaction times which are associated with poor performance (13,39,56). Sleep-deprived personnel lose approximately 25–30% of their ability to perform useful mental work with each 24-h period of sleep loss (4,10). In fact, a recent study on the impact of fatigue on F-117 pilots revealed that 27–33 h of sleep deprivation (1 night of sleep loss) degrades basic piloting skills by more than 40% below normal (23). A near-total loss of operational readiness can result from 2 to 3 d without sleep, especially in aviation and other demanding sectors where a high level of cognitive functioning and vigilance are required to perform complex tasks. Several researchers have warned that insufficient sleep can lead to motivational decrements, impaired attention, short-term memory loss, carelessness, reduced physical endurance, degraded verbal communication skills, and impaired judgment (39,68,106). Increased operator drowsiness and lapses into sleep are thought to underlie many serious accidents/incidents that typically have been attributed to "insufficient operator attention." In the aviation arena, such episodes are no doubt the result of the fatigue that has been associated with almost 8% of the Air Force's reportable Class A mishaps between 1972 and 2000 (62) and approximately 4% of the Army's Class A-C accidents between 1990 and 1999 (28).

Today's military seems to be particularly at risk for fatigue-related problems compared with the military of the past. One of the reasons for this is that operational demands have increased substantially while manpower and other resources have declined. Between 1992 and 2000, military funding was curtailed by 16%, and the number of personnel was cut by 28%. Meanwhile, the pace of deployments increased 16 times over the nominal pace at the end of the Cold War. Between 1960 and 1991, the U.S. Army and Marines conducted 25 operations outside their typical training and alliance commitments; in 1998, the number of operations was 88, a 352% increase (94). Since September 11, 2001, the Air Force's operational tempo has increased dramatically, largely as a result of combining a full-scale war on terrorism at home with missions in Iraq, North and South Korea, and the Balkins, in addition to a number of other significant tasks (101). This high operational tempo is directly responsible for long duty cycles, chronically shortened sleep periods, increased hours of shift work and night operations, and exacerbated jet lag due to an increase in rapid time-zone transitions.

Several strategies have attempted to mitigate the fa-

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tigue associated with such factors. These include limiting time on task, ensuring high levels of physical fitness, and providing brief periods of exercise, but none of these have proven particularly effective (5,49,60). Controlled activity breaks are helpful for short durations (15–25 min), but are not effective for longer periods (69). A couple of particularly successful counter-fatigue strategies have been used to facilitate full-length sleep periods with optimal sleep hygiene (1,55) and/or to augment inadequate daily/nightly sleep with strategic napping (38,95,98,99). However, sleep of any duration is often difficult to accomplish in the operational context because cockpits, command posts, and other military work settings, as well as living arrangements, are not conducive to sleep (22,58). To make matters worse, sometimes there are no opportunities for sleep at all due to mission requirements. In such situations, pharmacological fatigue-management techniques can be of assistance.

The remainder of this paper briefly discusses several of the pharmacological approaches: 1) for optimizing sleep opportunities when such opportunities are available; and 2) for sustaining alertness in the face of unavoidable sleep deprivation. In aviation settings where there is a high degree of medical oversight, such drug-based avenues can be used in a manner that is both safe and effective. In fact, the U.S. military has approved particular hypnotics and stimulants for pilot use, and there are specific guidelines concerning the manner in which these compounds are to be employed in efforts to manage fatigue in military aviation operations. Although numerous potentially useful sleep-promoting and alertness-enhancing compounds are currently on the market (and many new ones are being developed), the present report will focus only on the medications currently approved for widespread U.S. operational military use.

The primary aim of this report is to provide flight surgeons and other military personnel in the field with a basic overview of factors to be considered when implementing pharmacological solutions to fatigue-related problems in the military aviation context. By necessity, the scope of this report is far from an exhaustive review of each of the currently approved compounds. There are literally hundreds of published reports detailing aspects related to the basic pharmacology, safety, and efficacy of these medications in a wide array of settings and populations. Thus, the present overview is not intended to supersede official Department of Defense policy nor is intended to substitute for the sort of sound medical judgment that is a routine part of formulating and managing any type of drug-based therapy. However, it is a starting point for selecting the best solution to certain operationally relevant fatigue problems.

Sleep-Promoting Compounds

Sleep is often difficult to obtain in operational contexts, even in situations where efforts have been made to ensure the existence of adequate sleep opportunities. There are a number of reasons for this, but generally speaking, the difficulties are due to one or more of the following: 1) the sleep environment is less than optimal (too noisy, hot, and/or uncomfortable); 2) the state of the individual is incompatible with the ability to sleep (too much excitement, apprehension, or anxiety); or 3) the sleep opportunity occurs at a time that is not biologically conducive to rapid sleep onset and/or sufficient sleep maintenance due to circadian physiological rhythms associated with time of day variations and even from shift lag or jet lag. For such circumstances, the U.S. Air Force and Army have approved the limited use of temazepam, zolpidem, and zaleplon*. These hypnotics can optimize the quality of crew rest in circumstances where sleep is possible, but difficult to obtain. The choice of which compound is best for each circumstance must take several factors into account, including time of day, half-life of the compound, length of the sleep period, and the probability of an earlier-than-expected awakening, which may risk more sleep inertia effects.

Temazepam: Temazepam (Restoril®, 15–30 mg) has been recommended in military aviation populations in Great Britain since the 1980s (73–75). Given the pharmacodynamics of this substance, it may be the best choice for optimizing 8-h sleep periods that are out-of-phase with the body's circadian cycle because, under these circumstances, sleep is often easy to initiate, but difficult to maintain due to the circadian rise in alertness. Personnel who work at night generally find that they can easily fall asleep after the work shift since sleep pressure is high from their previous night (and often day) of continuous wakefulness. Also, in the early morning, the circadian drive for wakefulness is typically low, so the body's natural rhythms do not interfere with sleep onset. However, once daytime sleep has begun, night workers are frequently plagued by late-morning or noontime awakenings that result from the increased prominence of circadian-based alerting cues. The net result is that the day sleep of night workers often is 2 or more hours shorter per day than their typical night sleep (1,100).

For these individuals, the longer half-life of temazepam is desirable because the problem usually is one of sleep maintenance and not sleep initiation. In addition to temazepam's known facilitation of nighttime sleep (66,67), this compound, particularly in the 30-mg dose, has been shown to objectively and subjectively improve daytime sleep as well (30,76,84). Temazepam's intermediate half-life of approximately 9 h provides a sufficiently lengthy hypnotic effect to mitigate the disruptive arousals that often lead to sleep deprivation in personnel suffering from shift lag or jet lag. The pharmacokinetic disposition of temazepam is affected by the time of administration; the absorption of the drug is

* Note that at one time, the U.S. Air Force and Army both approved the use of triazolam (Halcion®), but that at present, only the U.S. Army continues to authorize the limited use of this medication for pre-deployment rest or sustained operations. Triazolam's association with adverse effects, particularly on memory, has curtailed its use in many clinical settings. Therefore, a detailed discussion of triazolam will be omitted from the present paper in favor of concentrating on the more frequently used hypnotics (temazepam, zolpidem, and zaleplon).

faster and the half-life and distribution are shorter for daytime administration compared with nighttime administration (67). Furthermore, in studies involving simulated night operations, temazepam has been shown to improve nighttime performance by optimizing daytime sleep (84). A study using U.S. Army pilots who worked and flew at night in a simulated shift-work environment demonstrated that temazepam-induced improvements in daytime sleep led to better nighttime pilot performance (relative to placebo) as well as improvements in psychomotor vigilance and self-reported alertness (30).

Thus, temazepam appears to be a good choice for maximizing the restorative value of daytime sleep opportunities. However, caution should be exercised prior to using temazepam in certain operational settings since the compound does have a relatively long half-life. Although residual effects were not reported in a military study in which personnel were able to gain suitable sleep before reporting for duty (16), nor in some other situations in which 30–40 mg of temazepam were given prior to a full sleep opportunity (88,111), residual post-dose drowsiness has been reported elsewhere. Paul et al. (79) observed that drowsiness was noticeable within 1.25 and 4.25 h of a midmorning 15-mg dose. They also noted that psychomotor performance was impaired within 2.25 h post-dose (plasma levels were still elevated at 7 h post-dose). These data emphasize that there is certainly a possibility of sleep inertia hangover effects from temazepam's long half-life; however, the potential for this drawback must be weighed against the potential for impairment from sleep truncation in the event that temazepam therapy is withheld. Along these lines, it should be noted that Roehrs et al. (86) found that just 2 h of sleep loss produces the same level of sedative effect as the consumption of $0.54\ g \cdot kg^{-1}$ of ethanol (the equivalent of 2–3 12-oz bottles of beer), whereas the effects of 4 h of sleep loss are similar to those of $1.0\ g \cdot kg^{-1}$ of ethanol (5–6 12-oz beers).

The same qualities that make temazepam desirable for maintaining the daytime sleep of shift workers make it a good choice for temporarily augmenting the nighttime sleep of personnel who are deployed westward across as many as nine time zones (72,96). On arrival at their destination, these travelers are essentially facing the same sleep/wake problems as the night worker. Namely, they are able to fall asleep quickly since their local bedtime in the new time zone is much later than the one established by their circadian clock (from the origination time zone); however, they generally are unable to sleep throughout the night. The reason for this is demonstrated by the following example: a 6-h westward time zone change places bed time at 23:00 local time, which is 05:00 origination time; this is followed by a wakeup time of 06:00 local, which corresponds to a "body-clock time," still adjusted to the origination time, of 12:00. Based on a readjustment rate of 1.5 d per time zone crossed (54), it could take up to a week for adjustment to the new time zone to occur. Until this adjustment is accomplished, temazepam can support adequate sleep maintenance despite conflicting circadian signals, and the obvious benefit will be less performance-degrading sleep restriction. While the problem with daytime alertness due to circadian disruptions will not be alleviated, the daytime drowsiness associated with increased homeostatic sleep pressure (from sleep restriction) will be attenuated.

Thus, temazepam is a good choice when a prolonged hypnotic effect is desired as long as there is relative certainty that the hypnotic-induced sleep period will not be unexpectedly truncated. This compound is especially useful for promoting optimal sleep in personnel suffering from premature awakenings due to shift lag or jet lag since the hypnotic effect helps to overcome circadian factors that can disrupt sleep immediately following a time zone or schedule change. However, temazepam should not be used longer than is necessary to facilitate adjustment to the new schedule. Depending on the circumstances, temazepam therapy probably should be discontinued after 3 to 7 d either to prevent problems associated with tolerance or dependence (in the case of night workers) or because adaptation to the new time zone should be nearly complete (in the case of travelers or deployed personnel) (72). When discontinuing temazepam after several continuous days of therapy, it is recommended that the dosage be gradually reduced for 2–3 d prior to complete discontinuation in order to minimize the possibility of rebound insomnia (89,104).

Zolpidem: Zolpidem (Ambien®, 5–10 mg) may be the optimal choice for sleep periods less than 8 h, and zolpidem would be a better choice than temazepam if there were a possibility that the hypnotic-induced sleep period is likely to be unexpectedly shortened. This compound is especially useful for promoting short- to moderate-length sleep durations (of 4–7 h) when these shorter sleep opportunities occur at times that are not naturally conducive to sleep. As noted above, daytime naps would fall into this category because, just like daytime sleep in general, daytime naps are typically difficult to maintain (37,59,100), especially in non-sleep-deprived individuals. Furthermore, unless the naps are placed early in the morning or shortly after noon, they can be extremely difficult to initiate without some type of pharmacological assistance (44). Zolpidem is a good choice for facilitating such naps because its relatively short half-life of 2.5 h provides short-term sleep promotion while minimizing the possibility of post-nap hangovers. Thus, it is feasible to take advantage of a nap without significantly lengthening the post-nap time needed to ensure that any drug effects have dissipated. However, as with temazepam, there should be a reasonable degree of certainty that there will not be an early interruption of the sleep period followed by an immediate demand for performance.

The efficacy of zolpidem as a nighttime sleep promoter has been clearly demonstrated in clinical trials (with up to 1 yr of administration) in normal, elderly, and psychiatric patient populations with insomnia (12). Rebound insomnia, tolerance (treatment over 6–12 mo), withdrawal symptoms, and drug interactions are absent, and the dependence/abuse potential is low (9). Overall, zolpidem is a clinically safe and useful hypnotic drug (78,90).

Zolpidem has been proven to possess utility in militarily relevant circumstances. An Army study (21) demonstrated that zolpidem-induced prophylactic naps enhanced the alertness and performance of sleep-deprived pilots (relative to placebo) during the final 20 h of a 38-h period of continuous wakefulness without producing significant hangover effects. Since these naps were placed at a time during which sleep is often difficult to obtain (59), the benefits in terms of sleep promotion and sleep quality were clear. Thus, zolpidem is an effective way to promote short naps, and a better nap (relative to a placebo comparison) is associated with improved subsequent alertness.

Zolpidem may also be helpful for promoting the sleep of personnel who have traveled eastward across three to nine time zones (97). Unlike westward travelers who experience sleep maintenance difficulties, eastward-bound personnel suffer from sleep initiation problems. For example, a 6-h time zone change in the eastward direction creates difficulty with initiating sleep because a local bedtime of 23:00 translates to a body clock time of only 17:00, and it has been well established that such early sleep initiation is problematic (73,96,107). Thus, eastward travelers need something that will facilitate early sleep onset and suitable sleep maintenance until the normal circadian-driven sleep phase takes over; however, they do not need a compound with a long half-life. This is because, in this example, any residual drug effect would only exacerbate the difficulty associated with awakening at a local time of 07:00 that corresponds to an origination time (or body-clock time) of only 01:00 in the morning. As stated above, sleep difficulties are only part of the jet-lag syndrome, but alleviating sleep restriction or sleep disruption will help to attenuate the alertness and performance problems associated with jet lag.

Thus, zolpidem is a good compound for facilitating naps of moderate durations (4–7 h), even when these naps occur under less-than-optimal circumstances and/or at the "wrong" circadian time. Zolpidem is also appropriate for treating sleep-onset difficulties in eastward travelers. However, as is the case with any hypnotic, this medication normally should be used only when necessary, i.e., prior to circadian adaptation to a new work or sleep schedule. More chronic zolpidem administration may be essential for promoting naps that occur under uncomfortable conditions or naps that are "out of phase" since, by definition, these generally are difficult to initiate and maintain, but zolpidem probably should not be used for more than 7 d to counter insomnia from jet lag. After this time, most of the adjustment to the new time zone should be accomplished (96,107).

Zaleplon: Zaleplon (Sonata®, 5–10 mg) may be the best choice for initiating very short naps (1–2 h) during a period of otherwise sustained wakefulness or for initiating early sleep onsets in personnel who are trying to ensure sufficient sleep prior to a very early start time the next morning. With regard to facilitating early report times, zaleplon is an alternative to zolpidem, but both compounds are important for the same reason. As noted earlier, it is extremely difficult for most people to initiate sleep 1–4 h prior to their typical bedtimes unless they are severely fatigued (2,45,59). Since these individuals are unable to fall asleep early, the total length of their sleep period is truncated by the early rise time even if, once they finally go to sleep, they sleep relatively well. Personnel who are required to report to duty in the predawn hours can easily suffer 2–3 h of sleep deprivation because of physiologically based sleep initiation difficulties. This is why short-haul pilots attribute a substantial percentage of their fatigue-related problems to early report for duty times (15). Sleep truncation of this amount has been shown to significantly impair both alertness and performance (11,86,106). Similar to zolpidem (which has a 2.5-h half-life), zaleplon can overcome this sleep-initiation problem, and its ultra-short 1-h half-life is less likely to pose hazards in terms of residual drug effects that can exacerbate the drowsiness associated with the predawn awakening dictated by the early start time.

Clinical trials of the hypnotic efficacy of zaleplon have shown improvement in sleep initiation, particularly with the 20-mg dose (33,40,43). In people diagnosed with primary insomnia, the latency to sleep onset decreased significantly compared with placebo (33). After zaleplon exerts its initial effects, the drug is subsequently (and quickly) eliminated in time for more natural physiological mechanisms to take over and maintain the remainder of the sleep period. There is evidence that there are no hangover problems as early as 6–7 h later (33). The rapid initiation of sleep at an earlier-than-normal time permits a full sleep period despite the requirement for an early awakening, and thus bolsters subsequent performance. Paul et al. (79) found that 10 mg zaleplon increased drowsiness for 2 to 5 h after dosing, with plasma drug levels equal to placebo by 5 h post-dose. These authors recommend zaleplon for times when an individual may have to awaken no earlier than 3 h after drug ingestion.

Thus, zaleplon (10 mg) is a good hypnotic for promoting short naps (2–4 h) which would otherwise be difficult to initiate and maintain, as well as for hastening the early-to-bed sleep onset of personnel who are faced with an acute demand to report for duty in the early morning (i.e., at 04:00–05:00). In addition, as was the case with zolpidem, zaleplon can be considered useful for the treatment of sleep-onset insomnia in eastward travelers who are experiencing mild cases of jet lag. For instance, those who have transitioned eastward only 3–4 time zones can use this short-acting drug to initiate and maintain what the body believes to be an early sleep period. As with any hypnotic, the course of treatment should be kept as short as is reasonably possible to minimize drug tolerance and dependence (72). **Table I** summarizes some of the characteristics of each of the hypnotics discussed.

General Precautions for Hypnotic Therapy

Sleep-promoting compounds can be useful in operational contexts where there are problems with sleep initiation or sleep maintenance. However, it should be noted that, like all medications, there are both benefits and risks associated with the use of these compounds.

TABLE I. LIST OF HYPNOTICS AND THEIR USES.

Generic name	Brand name	Dosage	Average Half-life	Recommended Use	Cautions
Temazepam	Restoril® (Mallinckrodt Inc.)	15–30 mg	9 h	Sleep maintenance; daytime sleep; prolonging sleep to avoid early morning awakenings from jet lag/shift lag	Need an 8-h sleep period; not recommended if on-call
Zolpidem	Ambien® (Sanofi-Synthelabo Inc.)	5–10 mg	2.5 h	Sleep initiation; intermediate-length naps; assisting early sleep onset due to early bedtimes from shift or time zone change	Need to have at least 4–6 h of sleep; not recommended if on call
Zaleplon	Sonata® (Jones Pharma Incorporated)	5–10 mg	1 h	Sleep initiation; short naps; assisting early sleep onset due to early bedtimes from shift or time zone change	Not recommended if on call

These should be considered by the prescribing flight surgeon, the aviation safety officer, and the individual pilot before the decision to use hypnotic therapy is finalized (U.S. military pilots are never required to use hypnotics of any type). An hypnotic of any type probably should not be used if a person is on call and may be awakened for immediate duty at any time. Although temazepam, zolpidem, and zaleplon are widely recognized as being both safe and effective, personnel should be cautioned about potential side effects and instructed to bring these to the attention of the unit flight surgeon should they occur. Potential problems may include morning hangover, which may cause detrimental effects on performance, dizziness and amnesia that may be associated with awakenings that are forced before the drug has been eliminated, and various idiosyncratic effects (6,64,72,89). If any difficulties occur, it may be necessary to discontinue the specific compound or to abandon hypnotic therapy altogether. However, it is likely that significant side effects can be reduced or eliminated by using an alternate compound or by modifying dosages or dose intervals (72). For these reasons, military personnel are required to experience a test dose of the hypnotic of interest under medical supervision before using the medication during operational situations. Even after the test dose yields favorable results and it is clear that operationally important side effects are absent, hypnotics should be used with particular caution when the aim is to aid in advancing or delaying circadian rhythms in response to time-zone shifts. Reviews by Waterhouse and associates (107), Nicholson (72), and Stone and Turner (96) offer detailed information on this rather complex issue.

Alertness-Enhancing Compounds

For those situations in which, despite the best intentions, adequate sleep opportunities are simply nonexistent, stimulants or alertness-enhancing drugs represent a viable option for temporarily staving off the deleterious effects of fatigue. Unavoidable manpower constraints, hostile environmental circumstances, extremely high workloads, and/or unexpected enemy attacks all may require a postponement of sleep until a break in the operational tempo permits rest and recuperation. Although stimulants should not be viewed as a substitute for proper staffing or adequate work/rest cycles, they can be life saving in circumstances in which sleep deprivation is unavoidable (35). Stimulants offer the advantages of being effective and easy to use, and because their feasibility is not dependent on environmental manipulations or scheduling modifications, their usefulness, especially for short-term applications, can be significant (53). These advantages explain why pharmacological compounds such as amphetamines have been used extensively when fatigue was unavoidable in several past military conflicts.

Caffeine, modafinil, and dextroamphetamine are approved for certain aviation operations by the U.S. Air Force. Caffeine and dextroamphetamine are approved for limited use by the U.S. Army and Navy[†]. Each of these compounds will be briefly discussed below.

Caffeine: Caffeine is a good choice for situations where medical oversight of drug administration is not available. This is because caffeine is not a controlled substance and, therefore, prescriptions are not required. Also, since caffeine is already in widespread use and is generally viewed as quite safe, there is little concern that there will be adverse physiological consequences associated with its ingestion that will require medical intervention. Caffeine (50–300 mg) is available in a number of forms to include 100- and 200-mg tablets (i.e., Vivarin® and NoDoz®), 50- and 100-mg chewing-gum preparations (i.e., Stay Alert™), and even 15- and 20-mg candies (i.e., Penguin™ peppermints, iFive brand, Seattle, WA, and Moovitz™ candies, Moovitz, Madison, WI). Of course caffeine also is a component in a wide variety of beverages as well as in some food products. An 8-oz cup of drip-brewed coffee contains an average of 135 mg of caffeine, an 8-oz cup of brewed tea contains approximately 50 mg of caffeine, and a 12-oz cola drink contains an average of 44 mg caffeine,

[†] Note that such approvals are generally "Service wide" rather than location specific. For instance, Air Force policy authorizes the use of modafinil for dual-seat bomber missions longer than 12 h in duration, and authorizes dextroamphetamine on a wider basis for similar circumstances. Although individual units or bases can choose not to use these compounds, they are not permitted to authorize the use of medications that have not been officially sanctioned by the Air Force, Army, or Navy without obtaining a waiver from higher headquarters.

ranging from 23 to 58 mg, depending on the drink. An 8-oz cup of Starbucks™ contains 250 mg of caffeine (31).

Decades of research have shown that caffeine's effects range from those that are virtually undetectable, to those that are actually detrimental, to those that are desirable, depending on the dose administered and the task measured (50,61,114). Side effects can include increased heart rate, elevated BP, nervousness, anxiety, restlessness, nausea, and frequency of urination, as well as reductions in fine motor control (34,92). In general, caffeine improves reaction time and cognitive performance, elevates mood, and reduces sleepiness in fatigued subjects (34,61,80). A recent study by Wyatt et al. (113) found that frequent low-dose caffeine administration (0.3 mg · kg^{-1} administered every hour) is effective for boosting performance following extended wakefulness. Subjects were placed on a 42.85-h sleep/wake cycle, with wake periods of 28.57 h, and sleep periods of 14.28 h over a period of 25 regular 24-h days. Hourly administration of caffeine during each of the 28.57-h wake periods attenuated the decline in cognitive performance and the number of accidental sleep episodes; however, slow eye movements and subjective sleepiness were not affected by caffeine. A study which compared caffeine to naps (14) found that a single 400-mg dose of caffeine preserved performance for approximately 24 h, and that repeated doses of 150 or 300 mg (every 6 h) preserved performance better than the large single dose. However, none of these dosing schedules produced beneficial effects beyond 24 h. Another analysis from this data set indicated that 300 mg of caffeine was effective for maintaining alertness on a single daily measure of the Maintenance of Wakefulness Test throughout the deprivation period; however, subjects maintained alertness on the Multiple Sleep Latency Test for only 24 h (52).

Militarily focused studies at the Walter Reed Army Institute of Research have shown that 600-mg single-dose caffeine is beneficial for sustaining the performance and alertness of sleep-deprived personnel kept awake for over 50 continuous hours (110). Other researchers have found that 150–300-mg bolus doses of caffeine are sufficient to increase performance over placebo when the sleep deprivation period is short, for example less than 24 h (80). Wesensten et al. (110) stated that 600 mg of caffeine is "the only dose that is effective for both improving and maintaining performance and alertness after 48 h of sleep deprivation compared with dosages of 150 and 300 mg, whose efficacy is not maintained beyond several hours post-administration" (p. 245) (in this study, the caffeine dose was not administered until after 48 h of continuous wakefulness).

Despite these and other positive findings, wholesale dependence on caffeine to mitigate the effects of sleep deprivation in the military operational environment is controversial since the effects of tolerance have not been adequately studied (113). Rogers and Dernoncourt (87) went so far as to conclude that there is little consistent evidence that regular caffeine use improves mood or performance; but instead, its effects appear to result from the alleviation of caffeine withdrawal in habitual users. The relevance of this assessment within the context of sleep deprivation is unclear since the effects of habitual caffeine consumption on the efficacy of caffeine as a fatigue countermeasure have not been studied. However, despite a recent report suggesting that doses of 200–800 mg of caffeine should be considered a first-line remedy for the drowsiness associated with insufficient sleep in operational military settings (34), further research on the tolerance issue is required for the following reasons: 1) over 80% of adults in the United States daily consume behaviorally active doses of caffeine; 2) complete tolerance to caffeine's subjective effects has been shown to occur within 18 d of chronic dosing; and 3) tolerance to caffeine's sleep-disrupting effects has been observed after 7 d of consistent caffeine administration (46). Together, these facts suggest the possibility that the already-widespread use of caffeine may diminish its effectiveness as a wake-promoting agent in severely fatigued individuals. Nonetheless, caffeine should be considered a "first line" approach to pharmacologically based alertness enhancement because caffeine has been shown to exert a number of positive effects. Although there is some indication that caffeine's short half-life of only 4–6 h may make it undesirable for situations in which a long-term boost is needed, this same quality may make caffeine optimal for situations in which there is the possibility that an unexpected sleep opportunity may arise shortly after the dose administration time.

Modafinil: For those concerned with the possibility that caffeine tolerance may limit the positive benefits of caffeine in habitual users, modafinil may be a better choice for sustaining alertness in operational contexts. However, prior to making the decision to use this prescription medication, it should be established that sufficient medical support is available to ensure that modafinil (a Schedule IV drug) is properly controlled and administered. Although modafinil (Provigil®, 100–200 mg) is a relatively new alertness-enhancing substance, there is substantial evidence that it is useful for sustaining performance during continuous and/or sustained military operations. After administering 200-mg doses every 8 h to volunteers who were kept awake for 60 continuous hours, Lagarde and Batejat (57) found that the drug reduced episodes of microsleeps and permitted subjects to maintain more normal (i.e., rested) mental states than placebo without inducing the anxiety that is sometimes associated with psychostimulant administration. Modafinil attenuated decrements in reaction time, math, memory-search, spatial-processing, grammatical-reasoning, letter-memory, and tracking tasks. Generally, modafinil maintained performance at well-rested levels for approximately 44 h, but not the full 60 h studied in this experiment. Wesensten et al. (110) found 200–400-mg doses of modafinil to be effective for restoring the performance and alertness of sleep-deprived research volunteers; however, it was concluded that modafinil did not offer benefits above and beyond those obtained with a 600-mg dose of caffeine. Another study from this laboratory (109) indicated that a single 400-mg dose of modafinil was as effective as 600 mg of caffeine and 20 mg of d-amphetamine for sustaining the simple psychomotor and cog-

nitive performance of sleep-deprived volunteers for 12 h post-dose. Thus, in terms of efficacy alone, the Walter Reed Army Institute of Research suggests modafinil's effects are similar to those of high-dose caffeine and dextroamphetamine.

Despite the previously noted findings, modafinil has not been as widely assessed as caffeine and amphetamine in normal, sleep-deprived people engaged in real-world tasks (3). However, there have now been two aviation-oriented studies which have demonstrated the efficacy of modafinil for sustaining pilot performance in flight simulators. Caldwell et al. (27) found that 200 mg of modafinil every 4 h maintained the performance of Army pilots at near-well-rested levels despite 40 h of continuous wakefulness. However, there were reports of nausea and vertigo that were attributed to the large cumulative dose (600 mg within a 24-h period). A more recent study with Air Force F-117 pilots indicated that 100-mg doses of modafinil administered every 5 h sustained flight control accuracy to within 27% of baseline levels, whereas performance under the no-treatment condition degraded by over 82% during the latter part of a 37-h period of continuous wakefulness (26). Similar beneficial effects were seen on measures of alertness and cognitive performance. Furthermore, the lower dose produced these positive effects without causing the side effects noted in the earlier study (27).

Although doses in the range of 200–800 mg have been observed to increase anxiety, insomnia, headaches, palpitations, BP, and resting pulse rate (18), generally speaking, the frequency of adverse side effects is low. In addition, there appears to be little or no drug tolerance with modafinil even after weeks of continuous use, and the abuse liability is limited (32). As a result, modafinil is a Schedule IV medication, making it easier to dispense compared with dextroamphetamine. Another advantage of modafinil is that it appears to have a relatively small adverse effect on recovery sleep even when given fairly close to the time of sleep onset (17). Thus, modafinil may be an optimal choice for use in sustained military operations in which there is a moderate possibility that a short break in the operational tempo could provide an unexpected sleep opportunity. Initial concerns that modafinil administration could cause overconfidence in sleep-deprived people (8) have not been substantiated by more recent research (7).

Due to positive effects on alertness and performance, modafinil is gaining popularity as a way to enhance the alertness of sleepy personnel, largely because it is considered safer and less addictive than older types of alertness-enhancing compounds such as amphetamines. Since modafinil does not significantly stimulate the cardiovascular system (at doses of 100 or 200 mg), it is preferable for promoting wakefulness in personnel who suffer from hypertension or cardiac rhythm anomalies (problems that are fairly rare in military pilots). Lastly, modafinil may offer an advantage over amphetamine for use in situations where unexpected napping or sleep opportunities may arise because, despite modafinil's half-life of approximately 12–15 h (82,85), the drug's impact on sleep architecture is minimal. However, it should be kept in mind that modafinil has not been thoroughly tested in real-world military environments, its efficacy for the long-term sustainment of wakefulness (i.e., beyond 40 h) in sleep-deprived subjects has not been well established, and work with clinical populations suggests that modafinil is less effective than amphetamine (65).

It should be noted that the use of modafinil for sustaining the alertness of military pilots is considered an "off-label" application of this medication. Modafinil can only be used operationally after an informed consent agreement has been signed showing that the pilot has voluntarily chosen to use this medication. In addition, both U.S. Army and U.S. Air Force policy require that aviators be administered a test dose under flight surgeon supervision before in-flight use of modafinil is authorized.

Amphetamine: Dextroamphetamine (Dexedrine®, 5–10 mg) has been researched for many years, and several studies have provided evidence that this compound is effective for maintaining alertness and performance in sleep-deprived people in a variety of settings. In comparison to caffeine, it appears to offer a more consistent and prolonged alerting effect (65,108). In comparison to modafinil, some reports suggest it is more efficacious (57,65). However, three other reports have suggested that dextroamphetamine is equivalent to modafinil for sustaining the performance of sleep-deprived normal individuals in sleep-deprivation periods of up to 40 h (19,83,109). Real-world operational comparisons of dextroamphetamine to caffeine or modafinil are currently nonexistent.

Although dextroamphetamine can produce side effects such as palpitations, tachycardia, elevated BP, restlessness, euphoria, and dryness of mouth (81), the properly controlled administration of this compound remains a viable (and fairly routine) strategy for the sustainment of combat performance in select military aviation operations where sleep is difficult or impossible to obtain. The U.S. Navy's guide for flight surgeons and the U.S. Army's guide for leaders both discuss the use of dextroamphetamine for the sustainment of aviator performance in continuous flight operations (103,105), and the U.S. Air Force has authorized the use of dextroamphetamine in certain types of lengthy (i.e., 12 or more h) single-seat and dual-seat flight missions. A recent NATO Research and Technology Organization publication discusses amphetamine's significant value as an anti-fatigue measure for aviation personnel (77).

With regard to the efficacy of dextroamphetamine in sleep-deprivation paradigms, Newhouse et al. (71) studied d-amphetamine (5, 10, or 20 mg) in people deprived of sleep for over 48 h. The 20-mg dose of d-amphetamine produced marked improvements in cognitive functioning, e.g., addition/subtraction (lasting for over 10 h), a gradual improvement in logical-reasoning (significant between 5.5 and 7.5 h post-dose), a long-lasting improvement in the speed of responding during the choice reaction-time task (10 h), and an increase in alertness for 7 h. The 10-mg dose exerted fewer effects, and those that were seen (addition/sub-

traction performance and alertness) were shorter in duration than was the case with the 20-mg dose. The observed performance enhancements with 20 mg continued even after the subjects' subjective feelings of increased vigor had subsided. The 5-mg dose did not affect any of the measures, and was barely distinguishable from placebo. Overall, amphetamine improved performance without impairing judgment.

In addition to basic laboratory studies, numerous studies have been conducted with amphetamine in military-relevant environments. In two studies, U.S. Army aviators were kept awake for 40 continuous hours (24,25). Performance on standard cognitive tasks as well as in a flight simulator were measured, and subjective mood was evaluated. During this time, repeated 10-mg doses of dextroamphetamine (given at midnight, 04:00, and 08:00) were administered to mitigate the fatigue-related decrements in the performance of these aviators. In both studies, dextroamphetamine maintained performance and alertness close to well-rested levels even though significant fatigue from sleep loss was present. These effects were especially noticeable between 03:00 and 11:00, when fatigue-related problems were most severe due to the circadian trough. These results were later confirmed in an actual in-flight study in which 10 pilots completed a series of 1-h flights in a specially instrumented UH-60 helicopter throughout 40 h of continuous wakefulness (20). In a follow-on investigation, Caldwell et al. (29) exposed Army aviators to 64 h of continuous wakefulness while providing 10-mg doses of dextroamphetamine (vs. placebo) at midnight, 04:00, and 08:00 on 2 successive nights. Results indicated that flight performance was maintained close to well-rested levels even through the last flight of the study (after 58 h of continuous wakefulness). It was concluded that while dextroamphetamine was not a replacement for adequate work/rest scheduling or restful sleep, it attenuated the performance, alertness, and mood degradations associated with significant sleep loss.

In addition to militarily relevant laboratory studies, there are also evaluations of amphetamine's effects in field settings. Early studies indicated that administration of amphetamines to various military populations was effective for reducing the impact of fatigue during periods without sleep (63,102,112). Subsequently, there have been numerous reports indicating that dextroamphetamine was used successfully in a number of combat situations such as Viet Nam (35), the 1986 Air Force strike on Libya (91), and Operation Desert Shield/Storm (35). Emonson and Vanderbeek (42) found that pilots who were administered dextroamphetamine during Operation Desert Shield/Storm were better able to maintain acceptable performance during continuous and sustained missions, and that the medication contributed to both safety and effectiveness. A recent analysis of stimulant use during B-2 combat missions indicated that pilots chose to use dextroamphetamine 97% of the time on shorter missions that were devoid of suitable napping opportunities, while they chose to use dextroamphetamine 58% of the time on long-duration missions during which naps were more feasible. To date, no major side effects or other problems have been reported from the medical use of dextroamphetamine in several military settings (36,42,53,91).

Despite the positive effects of amphetamines in sleep-deprived personnel, concerns have been raised that amphetamine-treated subjects will experience overconfidence, and by implication, poor judgment. In addition, the potential for amphetamine-related psychotic reactions has been cited as a serious contraindication for the operational use of dextroamphetamine. However, experimental evidence that either concern should limit the use of this compound in operational contexts is not evident from a comprehensive examination of the peer-reviewed scientific literature.

Regarding the potential of amphetamine to impair judgment, Newhouse et al. (70) reported that amphetamine reversed a sleep-loss-induced liberal response bias to normal pre-sleep-deprivation levels. Baranski and Pigeau (8) found that subjects who were administered either placebo or 20-mg doses of dextroamphetamine were consistently able to monitor their own performance status (i.e., did not express unwarranted overconfidence) throughout a period of sleep deprivation, whereas subjects given 300 mg modafinil were less able to accurately assess themselves. Finally, Shappell et al. (93) reported that a group of Marine flight students chose an increasingly risky response strategy (higher speed with lower accuracy) under placebo during a simulated sustained-operations mission, but that administration of 10 mg $\cdot$ 70 kg^{-1} of dextromethamphetamine did not demonstrate this problem. Thus, although it is likely that amphetamine abuse tends to promote risky behavior in normally alert people who inappropriately use the drug, similar problems are not consistently seen in those who take amphetamine to prevent fatigue or to recover from the effects of sleep loss. To date, there has never been a flight mishap in which amphetamine administration was implicated (Luna T. U.S. Air Force Safety Center, Personal communication, 2003) despite occasional inaccurate media implications to the contrary.

Regarding the potential of amphetamine to produce psychotic or other serious adverse reactions, such as the suspiciousness and over-sensitivity about being watched, generalized paranoid behavior, ideas of reference, auditory hallucinations, feelings that bizarre experiences are normal, and/or other problems characteristic of "amphetamine psychosis" as described by Janowsky and Risch (51), it should be noted that well-controlled studies with normal volunteers are virtually non-existent. According to the office of the U.S. Air Force Surgeon General (Michaud V. Personal communication, March 2003), there has never been a documented case in which an Air Force pilot has experienced such problems associated with amphetamine administration. From a clinical (i.e., non-military) perspective, Guilleminault (47) searched the 487 patients comprising the Stanford database in an effort to clarify the effects of long-term amphetamine treatment (well beyond what would normally be used in military aviation operations). He found there were 42 patients who had been maintained on more than 100 mg amphetamine per day for at least 18 mo (with a prior history of some level of the drug for approximately 10 yr) and 45

TABLE II. LIST OF STIMULANTS/ALERTNESS-ENHANCERS AND THEIR USES.

Generic name	Brand name	Dosage	Average Half-life	Recommended Use	Cautions
Caffeine	Vivarin® (GlaxoSmithKline); NoDoz® (Key Pharmaceuticals); Stay Alert™ (Wrigley Corporation for military use)	50–300 mg	5 h	Short-term maintenance of alertness (up to 24 h)	Tolerance exists in regular users so may not obtain the needed benefit as naïve users
Modafinil	Provigil® (Cephalon)	100–200 mg	15 h*	Intermediate-term maintenance of alertness (up to 40 h)	Lacking operational research studies; needs medical oversight; off-label use
Dextroamphetamine	Dexedrine® (GlaxoSmithKline)	5–10 mg	10 h	Long-term maintenance of alertness (up to 64 h)	History of abuse; should not be used in persons with high blood pressure or cardiac problems; needs medical oversight; off-label use

*Short-term modafinil administration is characterized by a 10- to 12-h half life. Chronic administration is characterized by a longer 15-h half life.

patients who had been receiving 60–100 mg amphetamine for approximately 9 yr. Interviews with the families of these patients revealed that few patients were troubled by serious adverse reactions, and only three of the patients (0.6%) had ever experienced an amphetamine-related psychosis. Yoshida (115) points out that such psychotic symptoms, if they appear at all, can take from 2–4 wk to years to develop. In addition, these symptoms have been observed primarily in individuals who are intravenously injecting large doses of amphetamines rather than those taking reasonable oral doses (as would be the case in U.S. military operations).

In summary, documented evidence of serious amphetamine-related problems in operational personnel is nonexistent, whereas peer-reviewed published information on the operational benefits associated with the administration of dextroamphetamine to fatigued pilots is readily available. Dextroamphetamine doses of 10–20 mg (not to exceed 60 mg $\cdot$ d^{-1}) should be considered for situations in which military personnel simply must complete the mission despite dangerous levels of fatigue, especially when the period of sleep deprivation is expected to extend beyond 40 continuous hours. Like caffeine and modafinil, dextroamphetamine's effects are most clearly observed in fatigued or sleep-deprived personnel suffering from degraded alertness and performance. Dextroamphetamine is the only prescription stimulant currently authorized under U.S. Army policy, and it is the primary alertness-enhancing compound authorized under U.S. Air Force policy for combating fatigue in certain types of aviation missions. In both cases, these policies are service-wide and not idiosyncrasies of particular units or air bases.

Thus, dextroamphetamine is a safe and viable counter-fatigue medication; however, it is a Schedule II compound that possesses significant abuse potential, and as such, it should only be used under proper medical supervision. As with modafinil, the use of dextroamphetamine to counter the effects of fatigue in healthy individuals is an off-label use of this drug. Prior to operational use, an informed consent which indicates voluntary use is required. In addition, all three U.S. military services require a ground-based test dose supervised by a flight surgeon prior to in-flight use of this compound (42,53). **Table II** summarizes some of the characteristics of each of the stimulants discussed.

General Precautions for Stimulant Therapy

As noted above, alertness-enhancing compounds can be useful for temporarily mitigating the impact of sustained wakefulness in operational contexts where sleep opportunities are severely limited. However, like all medications, there are both benefits and risks associated with the use of these compounds. These benefits and risks should be considered by the prescribing flight surgeon, unit safety officer, and the individual pilot before a decision is made to use caffeine (in forms other than foods or beverages), modafinil, or dextroamphetamine. It should be noted that U.S. military pilots are never required to use stimulants of any type. Although these compounds are widely recognized as being both safe and effective when used under proper medical supervision, personnel should be cautioned about potential side effects that may arise. Potential problems include irregular heartbeats, accelerated heart rate, elevated BP, dry mouth, diarrhea, constipation, loss of appetite, restlessness, dizziness, light-headedness, tremor, headaches, nausea, and/or reduced libido (81,82). On rare occasions, persons have experienced psychotic episodes associated with high doses of amphetamines (but not caffeine and modafinil) (51). If any of these difficulties occurs, the dosage may need to be modified, the specific compound may need to be changed, or the alertness-enhancement therapy may need to be discontinued altogether.

Summary and Conclusions

Fatigue is a known risk factor in the operational environment, and it warrants treatment with scientifically validated fatigue countermeasures. Since a large percentage of operator fatigue stems from insufficient sleep, the best countermeasure would be to avoid sleep deprivation by: 1) ensuring adequate manpower levels to properly staff all work periods; 2) consider scheduling of naps or taking advantage of opportunities for

naps; and 3) establishing work/rest schedules that enable personnel to gain sufficient restorative sleep in their off-duty hours. However, if real-world demands disrupt or prevent sleep, and behavioral or administrative counter-fatigue strategies are found to be insufficient or impractical, pharmacological adjuncts can help to safely sustain alertness.

In the event that sleep opportunities are available but compromised due to operational factors that prevent the onset and/or maintenance of restful sleep, the hypnotics temazepam, zolpidem, and zaleplon should be considered. Temazepam is best for maintaining sleep for relatively long periods during the night and/or for optimizing daytime sleep, while zolpidem and zaleplon are better for promoting an earlier-than-usual sleep onset or for inducing and maintaining short naps. Also, as discussed earlier, these compounds can help to minimize sleep disruptions associated with circadian factors (jet lag and shift lag). In this regard, the choice of compound depends on when the new sleep opportunity is offered and the probability that the sleep period will be unexpectedly truncated. An effort should be made to balance the need to improve sleep with the need to avoid residual effects, taking into account the effects of sleep restriction vs. any residual effects which may occur from hypnotically aided sleep.

The duration of hypnotic therapy should be kept as short as possible, usually for only a few days, to help with jet lag symptoms, or intermittently to help with shift lag symptoms. While the modern hypnotics are much safer and shorter acting than the hypnotics of years past, caution is still needed with prolonged use of any hypnotic. Continued use of hypnotics for several weeks or months may lead to tolerance or dependence, but the extent of these problems remains an issue of debate (64,89). In addition, sudden withdrawal after several weeks of therapy may lead to rebound insomnia (64,72).

In the event that sleep opportunities are scarce or almost non-existent due to a high operational tempo, the alertness-enhancing compounds should be considered. Although direct comparisons of caffeine, modafinil, and dextroamphetamine are non-existent with the exception of the Walter Reed study (109), basic recommendations can be made based on the studies that have examined the effects of these compounds. Caffeine appears best for temporarily sustaining the alertness of personnel in situations where a high level of medical oversight is not practical (caffeine is a non-prescription stimulant). Although debate remains on the effects of tolerance in habitual caffeine users, there is evidence that caffeine is more likely to produce the desired alertness enhancement in personnel who normally do not consume heavy doses of caffeine in their daily lives. Modafinil appears best for prolonging wakefulness (for up to 40 h), particularly in situations where there is some possibility that a sleep opportunity may unexpectedly arise (since modafinil has minimal sleep-disrupting effects). Modafinil also appears to be a better choice for personnel with high BP or other medical factors that may preclude the use of caffeine or dextroamphetamine. Dextroamphetamine is often the drug of choice for sustaining operator alertness during prolonged periods of sustained wakefulness (i.e., 30–70 h) based on the extensive laboratory and real-world data on both safety and efficacy in these circumstances.

The maximum duration of stimulant therapy in operational personnel has not been established in controlled studies. Although reports from the field (42,53) indicate dextroamphetamine has been used successfully for brief sorties, this issue needs further study. Data from Operation Iraqi Freedom (53) showed that pilots were administered only 6 10-mg tablets or 12 5-mg tablets prior to each sortie, with the unused portion returned to the flight surgeon. The data did not detail how frequently the pilots ingested the medication over a period of time, or the number of sorties in which the compound was used, so little is known about the extended use of this medication. The combined use of stimulants and hypnotics has not been researched. Therefore, caution should be exercised when considering prolonged combined use of alertness-enhancing and sleep-promoting drugs. In the event that such a polypharmaceutical approach to fatigue management is undertaken, close medical oversight is clearly warranted.

When considering the use of medications for aid in operational contexts, the following points should be kept in mind: 1) drugs are not a substitute for good work/rest scheduling; 2) sleep-promoting and alertness-enhancing compounds should not be administered to personnel indiscriminately or in the absence of proper medical oversight; and 3) with regard to situations devoid of sleep opportunities, there has not been a drug of any description that has been found capable of indefinitely postponing the basic physiological need for 8 h of restful daily sleep. However, clearly there are circumstances that warrant the operational use of pharmacological fatigue countermeasures, and in these situations, properly administered, appropriately supervised medication therapies can enhance both the safety and effectiveness of military aviation personnel.

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