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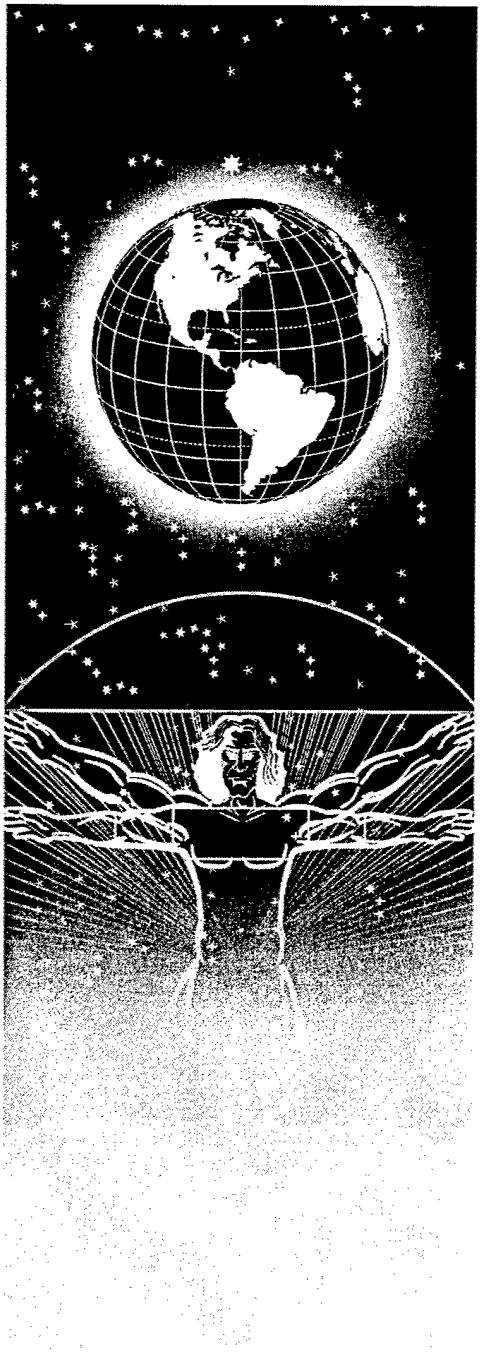

# UNITED STATES AIR FORCE RESEARCH LABORATORY

## CRITICAL KNOWLEDGE GAPS CONCERNING PHARMACOLOGICAL FATIGUE COUNTERMEASURES FOR SUSTAINED AND CONTINUOUS AVIATION OPERATIONS

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The purpose of this literature search was to identify knowledge gaps concerning the potential uses of pharmacological fatigue countermeasures in aviation. This type of review is a necessary step in developing an operationally based, safe-to-fly pharmacological doctrine that extends mission performance without introducing unwanted side effects. The review was conducted with respect to seven potential pharmacological countermeasures to fatigue: dextroamphetamine, modafinil, caffeine, temazepam, zolpidem, zaleplon, and melatonin. Thirty-four operationally relevant terms and phrases, such as acceleration, memory, computational performance, and predisposition to heat injury, were used. The searches were conducted in ten different on-line, scientific and medical databases on literature published in or after 1980. Of the hundreds of returned citations, 117 were relevant and are categorized, and the obvious knowledge gaps discussed. Aggressive research is indicated for both non-pharmacological and pharmacological countermeasures to fatigue.

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Recommendations

Combat and other flight stresses increase adrenergic output, helping the crewmember overcome the fatigue. However, this seems to produce a significant "letdown" after the combat interaction. This real-world performance letdown needs to be documented objectively in a manner that will lead to the development of effective fatigue countermeasures.

We need to develop new performance metrics in flight simulation and validate them with actual performance in the air. This will help us predict more accurately the level of aircrew fatigue and performance degradation in flight, and allow us to improve the effectiveness of fatigue countermeasures that limit risks to aircrews.

The known sympathomimetic properties of stimulants such as dextroamphetamine suggest that acceleration tolerance should be improved due to central and peripheral hypertensive effects. No relevant data were found to address this issue.

Future re-reviews of the literature such as this one would benefit from neuropsychiatry and pharmacology input to assess potential drug interactions with, for example, quinolones and doxycycline.

The residual presence of a drug and its metabolic products in blood and tissue may continue to cause cognitive problems after one or more half-lives. Empiric investigations of cognition are required to detect these problems. These investigations must be designed with high statistical power.

Aircrew may be awakened for unexpected operations before reaching even one half life of sleep aid metabolism. Investigations of benzodiazepine reversal with flumazenil will be helpful in terms of clarifying the nature of that reversal process.

We need to determine the optimal combinations (timing and dose) of sleep and alertness aids. The extent of neurotransmitter depletion and/or enhancement is not known for such combinations. Similarly, the polypharmacological effects on cognition are unknown.

All of our military fatigue laboratories should collaborate to acquire data that may be used to improve the power and comprehensiveness of pharmacological fatigue countermeasure research and, ultimately, provide the service member additional safety and efficacy in the field.

## PREFACE

Thank you to the staff of the Brooks Air Force Base Aeromedical Library for the hours of assistance in ordering and processing the technical articles used for this review.

James C. Miller, Ph.D., CPE, Warfighter Fatigue Countermeasures R&D Program, Air Force Research Laboratory (AFRL/HEPM-WFC) served as the project manager for this effort. The project was carried out primarily by Maj (Dr.) Lee G. Saltzgaber under the auspices of the Residency in Aerospace Medicine, US Air Force School of Aerospace Medicine during the period 1 July 00 – 30 Jun 01.

# CRITICAL KNOWLEDGE GAPS CONCERNING PHARMACOLOGICAL FATIGUE COUNTERMEASURES FOR SUSTAINED AND CONTINUOUS AVIATION OPERATIONS

## INTRODUCTION

The purpose of this literature search was to identify knowledge gaps concerning the potential uses of pharmacological fatigue countermeasures in aviation. This type of review is a necessary step in developing an operationally based, safe-to-fly pharmacological doctrine that extends mission performance without introducing unwanted side effects.

Of those items that make up one's physiological state and therefore determine human performance, fatigue degrades mental sooner than physical performance (Evans, 1991; Krueger, 1991). The significant impact fatigue has made upon flying safety can be demonstrated by the 20-25% of aircraft accidents that have listed fatigue as a contributing factor (Lyman 1980; Hoey 1992). Numerous investigations document fatigue's role in reducing the effectiveness of one's judgment and decision-making process that can be transferred into operational strategy and tactics selection. Dawson (1997) found that just 18 hours of sustained wakefulness decreased mental performance by as much as 30%, and at 24 hours all subjects showed some cognitive and motor decrement. With partial sleep deprivation, alertness and performance decline more gradually. After several days of sleep debt, alertness and performance degrade to nearly the same levels seen following 1-2 days of total sleep deprivation, at which time the fully debilitating effects of sleep loss are taking place.

As sleep loss progresses, fatigue can threaten judgment and decision-making. Caldwell (1997) stated that "task-related details are missed and responses to task demands often do not occur and the aviator's ability to pay attention to flight instruments, radio communications, crew coordination, and navigational tasks is severely impaired by fatigue." The attribution of about 70% of aircraft accidents to human error (Feggetter, 1982) highlights the significant impact that fatigue can have upon all facets of flying. Fatigued pilots also make less frequent but larger control errors that appear earlier in the task while their poorest performances become progressively worse (Bartlett, 1942).

Several countries have used stimulants to reduce fatigue and increase performance since World War II. The United States Air Force has used stimulants irregularly since 1960 in a variety of conflicts (Vietnam War, 1986 Libyan Raid, and Operation Desert Storm). Stimulant use was terminated after the Gulf War and reestablished in 1996 for use by a single pilot aircraft during deployment greater than 8 hours or on missions less than 8 hours when the departure was during their normal sleep cycle. Most often, stimulant use was for transoceanic flight where the demands upon the pilot were limited. However, F-15C pilots did note significant fatigue when flying combat air patrol missions over Iraq. More recently, stimulant availability has been extended by Air Combat Command to long-duration bomber missions.

Whether it provides general activation (amphetamine, caffeine) or stimulates only the waking systems (modafinil) as Jouvet (1997) proposed, the alertness aid of choice should support

wakefulness, vigilance and performance without interfering with sleep induction or recovery sleep when aircrew have the opportunity to sleep.

Desynchronization of circadian rhythms due to deployment across numerous meridians significantly impacts one's ability to sleep and adapt to a new time zone. Krueger (1991) noted that psychomotor vigilance performance (sustained cognition, vigilance, and response time) after a six-hour transmeridian flight drops 8-10% during the first day and demonstrates even more degradation in the early morning (0230-0600). When these circadian lows coincide with critical phases of flight (take off, landing, air-to-air refueling (AAR,) low altitude, intercepts, and ordinance delivery), the effectiveness of the pilot can be significantly affected. A 509th B-2 bomber pilot from Whiteman AFB, Mo expressed concern about his unit's inability to take "go" pills their 20-36 hour missions during the Operation Allied Force's After Action Medical Review in Mar 2000. The fatigue that developed over these missions placed them at increased risk because the multiple AAR's before and after the adrenaline surge associated with the enemy threats while performing their combat missions occurred over a variety of circadian peaks and troughs. The lack of stimulant use program for multiple seat aircraft was identified as a top priority due to the prolonged attention, vigilance, and performance increase the physiological requirements on aircrew and increases their risk for mission failure. In light of this, scheduling should be done so that local flights at the deployed location should be aligned with the adjusting body clock so that they might equate to a less demanding evening sortie instead of a night sortie when fatigue in conjunction with a circadian low might play a more significant factor in their performance.

Sustained[1] and continuous[2] operations demand that safe-to-fly evaluations of a medication include those unique parameters found in military aviation. Environmental stressors of heat, cold, noise, and vibration impact aircrew vigilance and can affect performance during prolonged periods of sustained attention. Evolving enemy threats require consistent improvements in avionics, ordinance, and human weapons systems. Concurrently, these improvements require increasing pilot vigilance when performing low altitude ground attack during instrument meteorological conditions at night. Any decrements in visual (especially night and vision aided with night vision goggles) or auditory perception can significantly limit assimilation of necessary information to coordinate with friendly forces or detect and persecute enemy forces, equipment, or structures. Any vestibular malfunction would increase the risk for a loss of spatial situational awareness several fold. Any clouding or altering of consciousness would impair cognitive performance. Interactions with nuclear-biological-chemical (NBC) medications associated with ground testing procedures, gender differences, synergy of the combination of medications, and reversibility need to be addressed. Decrements in manual dexterity, strength, aerobic capacity, or heat or acceleration tolerance might require limiting mission parameters. Reduced time of useful consciousness or increased risk of decompression at altitude significantly increase an aircrew's opportunities for idiosyncratic reactions.
Acknowledging the increased demand and subsequent risk to mission and aircrew, the Air Force Medical Operations Agency (1999) evaluated its current operations and identified

[1] SUSOPS: Shifts greater than 12 hr where one works nonstop for as long as possible.
[2] CONOPS: Uninterrupted schedule employing workers on regular schedules (7-12 hrs) that relieve the other workers,

fifteen Human Weapons System (HWS) Deficiencies and Priorities to protect the aircrew and optimize operational capabilities. Four of the top six (Sustained Operations, Performance Sustainment and Protective Gear, Night Operations, and Simulators and Distributive Mission Training) can be affected by the use of alertness aids and sleep aid medications.

## METHODS

This literature review was conducted to determine the gaps in knowledge on operationally relevant variables with respect to seven potential pharmacological countermeasures to fatigue:

Alertness Aids
- Dextroamphetamine
- Modafinil
- Caffeine

Sleep Aids
- Temazepam
- Zolpidem
- Zaleplon
- Melatonin

These seven medications were all searched against the following, operationally relevant terms and phrases (presented here in alphabetical order), occurring in the title, abstract, and descriptor or key word fields:

| | | |
|---|---|---|
| Acceleration | Hypoxia | Sleep interference |
| Altitude | NBC | Strength |
| Amnesia or memory | Night vision goggles | Subjective fatigue |
| Ciprofloxicin | Noise | Tracking |
| Cognition or judgment | Predisposition to cold injury | Vestibular effects |
| Computational performance | Predisposition to heat injury | Vibration |
| Decompression | Psychomotor function | Vigilance |
| Doxycycline | Pyridostigmine | Vision |
| Exercise capacity | Reaction time | |
| G Force | Reversibility | |
| Gender specificity | Sleep architecture | |
| Hearing | Sleep inertia | |

Additionally, searches on the following terms and phrases were conducted to reveal pertinent topics and situations for and in which these medications were used:

Sustained operations
Continuous operations
Performance enhancement and degradation
Sleep enhancement and degradation
Fatigue
Military

The searches were conducted in the following databases:

Academic Search Elite  Military Library

| | |
|---|---|
| Academic Search Premier | MEDLINE |
| Business Source Elite | Comp MEDLINE w/ MeSH |
| GRATEFULMED | PUBMED |
| MasterFILE Premier | PsycINFO |

The year, 1980, was selected as the earliest search date to help limit the quantity of retrievals, with the understanding that it would preclude earlier, enlightening investigations of dextroamphetamine and caffeine. The review was limited to English language primary research papers, references from their bibliographies, and foreign language paper abstracts.

These search criteria and engines identified 462 articles from which 117 research and 38 background papers were selected. Evaluations of half-life, amnesic effects, and sedative-hypnotic properties have been well documented in pharmacodynamic literature and were excluded here. Investigations involving children less than 18, adults older than 60, or patients with mental or physical illness were excluded. Some investigations selected subjects based upon various criteria (e.g., quality of EEG) and were therefore excluded also because the general population of military pilots and aircrew are not selected in a similar manner.

Standard pharmacological evaluations of all medications address basic impacts upon human physiology, but are limited to experiences on the ground (ca. 1 gravity force, 747 mmHg air pressure, 21% oxygen,) and normal day wake-night sleep cycles. The operationally relevant investigations of alertness aids that were selected here investigated the alertness aid's effects upon 'fatigued' as opposed to 'rested' subjects, because the goal of a alertness aid is to restore and maintain vigilance, cognition, and performance. Alertness aid investigations were not selected if their goal was to enhance performance beyond baseline levels, because of the possibilities of long-term psychological and physical dependence. Hypnotic and sedative investigations were selected here if they addressed secondary effects or effects still present after awakening due to residual sedation. Most hypnotic-sedative investigations also included both diurnal and nocturnal administrations.

## RESULTS

The results of the literature search are presented in a series of tables, one table for each of the seven potential pharmacological countermeasures. Within each table, the studies are sorted into three categories: descriptive statistical assessments, inferential statistical assessments with sample size less than 30 and inferential statistical assessments with sample size greater than 30. Within each category, the number of citations listed in each cell indicates how many times a primary research article concluded that there was a "pro" (contributing to mission success) or "con" (detracting from mission success) effect. Each investigation usually had more than one finding so the total number of findings exceeds the number of articles. The relevant articles are listed by citation number in each cell.

## Alertness Aids

**Dextroamphetamine**

There were 21 relevant investigations returned for dextroamphetamine (Table 1). No citations were returned that fit the following search topics: circadian rhythm adaptation, visual perception, night vision goggles, auditory perception, psychomotor function,

TABLE 1. Results of literature search concerning dextroamphetamine for descriptive studies and inferential studies with sample sizes less than and greater than 30.

| | **Descriptive** | | Experimental < 30 | | **Experimental > 30** | |
|---|---|---|---|---|---|---|
| | Con | Pro | Con | Pro | Con | Pro |
| Vestibular effects | | | 1 | 2 | | |
| | | | *11 4* | *33,115* | | |
| Cognition / Judgment | | | | 3 | | 4 |
| | | | | *96,101,102* | | *3,75,76,81* |
| Vigilance | | | | 1 | | |
| | | | | *102* | | |
| Computational Performance | | | | | | 2 |
| | | | | | | *3,75* |
| Psychomotor function | | | | 5 | | |
| | | | | *21,22,23,26,27* | | |
| Sleep architecture / length | | | 1 | | 1 | |
| | | | *93* | | *2 0* | |
| Memory | | | | 1 | | |
| | | | | *101* | | |
| Interference with Sleep | | | 1 | | 1 | 1 |
| | | | *29* | | *2 0* | *76* |
| Reaction Time | | | | 1 | | 1 |
| | | | | *33* | | *81* |
| Subjective Fatigue | | 2 | | 6 | | 3 |
| | | *45,9 5* | | *21,22,23,26,38, 96* | | *75,76,81* |
| Totals | 0 | 2 | 3 | 19 | 2 | 11 |

Modafinil

There were 13 relevant investigations returned for modafinil (Table 2). No citations were returned that fit the following search topics: circadian rhythm adaptation, night vision goggles, auditory perception, exercise capacity, strength, g force, acceleration, hypoxia, altitude, decompression, vibration, noise, predisposition to heat injury, reversibility, NBC, pyridostigmine, ciprofloxicin, or doxycycline.

TABLE 2. Results of literature search concerning modafinil.

| | **Descriptive** | | **Experimental < 30** | | **Experimental > 30** | |
|---|---|---|---|---|---|---|
| | Con | Pro | Con | Pro | Con | Pro |
| Visual Perception | | | | 3 | | |
| | | | | *8,63,84* | | |
| Vestibular effects | | | | 1 | | |
| | | | | *84* | | |
| Cognition / Judgment | | | | 5 | | 2 |
| | | | | *4,8,24,61,63* | | *3,81* |
| Vigilance | | | | 3 | | |
| | | | | *61,84,103* | | |
| Computational Performance | | | | 4 | | 1 |
| | | | | *4,61,63,84* | | *3* |
| Psychomotor function | | | | 6 | | |
| | | | | *5,8,24,25,61,63* | | |
| Predisposition to Cold Injury | | | | 1 | | |
| | | | | 16 | | |
| Gender specificity | | | 1 | | | |
| | | | *113* | | | |
| Sleep architecture / length | | | | | | 1 |
| | | | | | | *20* |
| Memory | | | | 3 | | |
| | | | | *5,8,63* | | |
| Interference with Sleep | | | | 1 | | 1 |
| | | | | *93* | | *20* |
| Reaction Time | | | | 5 | | 1 |
| | | | | *4,5,8,24,84* | | *81* |
| Subjective Fatigue | | | | 4 | | 1 |
| | | | | *24,25,61,62* | | *81* |
| Totals | 0 | 0 | 1 | 36 | 0 | 7 |

Caffeine

There were 16 relevant investigations returned for caffeine (Table 3). No citations were returned that fit the following search topics: circadian rhythm adaptation, night vision goggles, auditory perception, vestibular effects, strength, g force, acceleration, hypoxia, altitude, decompression, vibration, noise, predisposition to heat or cold injury, gender specificity, reversibility, NBC, pyridostigmine, ciprofloxicin, doxycycline, sleep architecture / length, memory.

TABLE 3. Results of literature search concerning caffeine.

| | **Descriptive** | | **Experimental < 30** | | **Experimental > 30** | |
|---|---|---|---|---|---|---|
| | Con | Pro | Con | Pro | Con | Pro |
| Visual Perception | | | | 1 | | 1 |
| | | | | *92* | | *66* |
| Cognition / Judgment | | | | 2 | | 2 |
| | | | | *15,41* | | *66,73* |
| Vigilance | | | | 2 | | 3 |
| | | | | *15,92* | | *57,66,91* |
| Computational Performance | | | | 1 | | |
| | | | | *15* | | |
| Exercise capacity | | | | 1 | | |
| | | | | *10* | | |
| Psychomotor function | | 1 | | 2 | | 3 |
| | | *7* | | *53,85* | | *57,73,97* |
| Interference with Sleep | | | | 1 | | 2 |
| | | | | *15* | | *58,97* |
| Reaction Time | | | | 1 | | 3 |
| | | | | *92* | | *57,66,91* |
| Subjective Fatigue | | 1 | | 3 | | 5 |
| | | *7* | | *14,53,85* | | *57,73,79,91,97* |
| Totals | 0 | 2 | 0 | 14 | 0 | 19 |

## Sleep Aids

Temazepam

There were 29 relevant investigations returned for temazepam (Table 4). No citations were returned that fit the following search topics: night vision goggles, auditory perception, vestibular effects, g force, acceleration, hypoxia, decompression, vibration, noise, predisposition to heat or cold injury, reversibility, NBC, pyridostigmine, doxycycline, or sleep inertia.

TABLE 4. Results of literature search concerning temazepam.

| | **Descriptive** | | **Experimental < 31** | | **Experimental > 31** | |
|---|---|---|---|---|---|---|
| | Con | Pro | Con | Pro | Con | Pro |
| Circadian rhythm adaptation | | | 1 | | | |
| | | | *41* | | | |
| Visual Perception | | | | 5 | | |
| | | | | 31,42,48,50,67 | | |
| Cognition / Judgment | | | | 7 | | 1 |
| | | | | *42,51,64,87, 104,111,112* | | *82* |
| Vigilance | | | | 2 | | |
| | | | | *30,111* | | |
| Computational Performance | | | | 1 | | |
| | | | | *112* | | |
| Exercise capacity | | | 1 | 1 | | |
| | | | *59* | *31* | | |
| Psychomotor function | | | 1 | 5 | | |
| | | | *12* | *18,31,48,60,67* | | |
| Strength | | | | 1 | | |
| | | | | *48* | | |
| Altitude | | | | 2 | | |
| | | | | *44,90* | | |
| Gender specificity | | | 1 | 1 | | |
| | | | *40* | *99* | | |
| Ciprofloxicin | | | | 1 | | |
| | | | | *56* | | |
| Sleep architecture / length | | | 1 | 1 | | |
| | | | *88* | *46* | | |
| Amnesia / Memory | | | | 1 | | |
| | | | | *104* | | |
| Residual Effects | 2 | | 3 | 10 | | 2 |
| | *1,77* | | *11,30,50* | *18,42,48,51,64,67, 83,88,109,112* | | *17,82* |

| | | | | | | |
|---|---|---|---|---|---|---|
| Reaction Time | | | 3 | 4 | | |
| | | | *50,109,111* | *31,42,48,51* | | |
| Subjective Fatigue | | | | 1 | | 1 |
| | | | | *30,44* | | *17* |
| Totals | 0 | 2 | 11 | 43 | 0 | 4 |

Zolpidem

There were 33 relevant investigations returned for temazepam (Table 5). No citations were returned that fit the following search topics: night vision goggles, auditory perception, vestibular effects, strength, g force, acceleration, altitude, decompression, vibration, noise, predisposition to heat injury, predisposition to cold injury, NBC, pyridostigmine, ciprofloxicin, or doxycycline.

TABLE 5. Results of literature search concerning zolpidem.

| | **Descriptive** | | **Experimental < 30** | | **Experimental > 30** | |
|---|---|---|---|---|---|---|
| | Con | Pro | Con | Pro | Con | Pro |
| Circadian rhythm adaptation | | | 1 | | | |
| | | | *35* | | | |
| Visual Perception | | | | 1 | 1 | |
| | | | | *86* | *36* | |
| Cognition / Judgment | | | 1 | 3 | | 1 |
| | | | *106* | *8,28,47* | | *2* |
| Vigilance | | | | 1 | | |
| | | | | *39* | | |
| Computational Performance | | | | | | 1 |
| | | | | | | *2* |
| Exercise capacity | | | | 2 | | |
| | | | | *71,72* | | |
| Psychomotor function | | | | 5 | | |
| | | | | *8,32,39,47,98* | | |
| Hypoxia | | | 1 | | | |
| | | | *69* | | | |
| Gender specificity | | | | 2 | | |
| | | | | *49,94* | | |
| Reversibility | | 1 | 2 | 1 | | 1 |
| | | *65* | *68*,94** | *78* | | *110* |
| Sleep architecture / length | | | 1 | 5 | | |
| | | | *35* | *6,28,47,72,74* | | |
| Sleep inertia | | | | 1 | | |
| | | | | *28* | | |
| Amnesia / Memory | | | 5 | 4 | 2 | |
| | | | *39,43,54,89,106* | *9,32,47,70* | *36,52* | |
| Residual Effects | | | | 11 | 1 | |
| | | | | *9,13,19,28,39,47, 55,74,85,89,98* | *36* | |
| Reaction Time | | | | 4 | 2 | |
| | | | | *9,32,47,86* | *36,52* | |
| Subjective Fatigue | | | | 1 | | |
| | | | | *28* | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Totals | 0 | 1 | 11 | 41 | 6 | 3 |

Zaleplon

There were 5 relevant investigations returned for temazepam (Table 6). No citations were returned that fit the following search topics: circadian rhythm adaptation, night vision goggles, auditory perception, cognition / judgment, vigilance, computational performance, exercise capacity, strength, g force, acceleration, hypoxia, altitude, decompression, vibration, noise, predisposition to heat injury, predisposition to cold injury, gender specificity, reversibility, NBC, pyridostigmine, ciprofloxicin, doxycycline, sleep architecture / length, subjective fatigue.

TABLE 6. Results of literature search concerning zaleplon.

| | **Descriptive** | | **Experimental < 30** | | **Experimental > 30** | |
|---|---|---|---|---|---|---|
| | Con | Pro | Con | Pro | Con | Pro |
| Visual Perception | | | | | | 1 |
| | | | | | | *36* |
| Vestibular effects | | | | 1 | | |
| | | | | *108* | | |
| Psychomotor function | | | | 2 | | 2 |
| | | | | *106,108* | | *36,52* |
| Sleep inertia | | | | 1 | | |
| | | | | *108* | | |
| Amnesia / Memory | | | 2 | 1 | | 2 |
| | | | *106,108* | *43* | | *36,52* |
| Residual Effects | | | | 1 | | 1 |
| | | | | *108* | | *36* |
| Reaction Time | | | | | | 1 |
| | | | | | | *36* |
| Totals | 0 | 0 | 2 | 6 | 0 | 7 |

Melatonin

There were 9 relevant investigations returned for temazepam (Table 7). No citations were returned that fit the following search topics: visual perception, night vision goggles, auditory perception, vestibular effects, exercise capacity, strength, g force, acceleration, hypoxia, altitude, decompression, vibration, noise, predisposition to heat injury, predisposition to cold injury, gender specificity, reversibility, NBC, pyridostigmine, ciprofloxicin, doxycycline, sleep inertia, or reaction time.

TABLE 7. Results of literature search concerning melatonin.

| | **Descriptive** | | **Experimental < 30** | | **Experimental > 30** | |
|---|---|---|---|---|---|---|
| | Con | Pro | Con | Pro | Con | Pro |
| Circadian rhythm adaptation | | | 2 | 2 | 1 | |
| | | | *37,107* | *34,80* | *100* | |
| Cognition / Judgment | | | 1 | 2 | | |
| | | | *116* | *37,104* | | |
| Vigilance | | | | 1 | | |
| | | | | *34* | | |
| Computational Performance | | | | 1 | | |
| | | | | *117* | | |
| Psychomotor function | | | | 1 | | |
| | | | | *37* | | |
| Sleep architecture / length | | | | 1 | | |
| | | | | *117* | | |
| Amnesia / Memory | | | | 1 | | |
| | | | | *104* | | |
| Residual Effects | | | | 1 | | |
| | | | | *117* | | |
| Subjective Fatigue | | | 1 | 1 | | 1 |
| | | | *116* | *80* | | *105* |
| Totals | 0 | 0 | 4 | 11 | 1 | 1 |

## DISCUSSION

Due to the reduced size of our military forces, post-cold war global power projection has required that fewer people work more hours to maintain peace and stability. This has also necessitated a concurrent increase in trans-meridian deployments and the need for immediate operational capability upon employment. In turn, our personnel have been exposed to a greater likelihood of suffering from circadian rhythm disturbance, sleep loss, and fatigue. The terrorist attacks of 11 September 2001 and the subsequent military mobilization have made things much worse[3]. All weather, continuous day and night operations, long duration flights enabled by inflight refueling, low-level flying, and dependence upon advanced technology also act to introduce significant fatigue and sleep deficit.

The resulting fatigue decreases an individual's accuracy and timing, increases the likelihood that he or she will accept poor performance as being adequate, decreases the ability to integrate information, and increases the likelihood of channelized attention with a resultant loss of situational awareness (Caldwell, 1997). Subsequent, fatigue-induced mission failures, loss of valuable aerospace platforms, and fatal mishaps may significantly impair force strength. Thus, aggressive research is indicated for both non-pharmacological and pharmacological countermeasures to fatigue.

Thinking in terms of pharmacological countermeasures, we do not advocate a medicated force. First, Air Force personnel need to be physically and emotionally fit and optimally trained to deal with the stresses of today's contingency environment. Efforts should be made to maximize aircrew health and confidence in their training and skill. Second, non-pharmacological fatigue countermeasures should be employed. These include training and education, dedication by management and individual to practice sleep hygiene and chronohygiene, fatigue-relevant approaches to mission scheduling, and decision assistance for the identification and management of fatigue-induced, mission-specific operational risks. Finally, we may use pharmacological countermeasures to sustain performance or to return performance to non-fatigued states. We do not advocate using alertness aids to improve the performance of non-fatigued warfighters beyond baseline.

### Alertness Aids

Surprisingly, the dextroamphetamine review revealed no articles concerning strength, exercise capacity or acceleration tolerance, and few articles addressing dizziness, a known side effect of dextroamphetamine. This apparent research gap was probably caused by the relatively recent (1980) cut-off date for the search.

The general stresses of aviation plus weather conditions, maintenance and communication issues, and the threat of being killed by the enemy or a mishap increase the body's adrenergic output, helping the crewmember overcome the effects of fatigue sufficiently to carry out a nighttime or long-duration mission. However, the adrenaline surge associated with putting "bombs on target on time" in a real mission seems to produce a significant "letdown" after the combat interaction. This letdown may introduce more fatigue-related performance

[3] The number of operational consults performed by the Warfighter Fatigue Countermeasures R&D staff for Air Force units involved in deployments and homeland defense increased from one or two per month to several times that number.

degradation than the degradation introduced in a simulator mission. The real-world performance letdown needs to be documented objectively in a manner that will lead to the development of effective fatigue countermeasures.

Caldwell (2000) assessed the sensitivity of simulators compared with inflight testing and found that the added stresses associated with actual flight decreased dextroamphetamine's effectiveness in aiding aviator performance. Thus, we need to develop new performance metrics in simulation and validate them with actual performance in the air. This will help us predict more accurately the level of aircrew fatigue and performance degradation in flight, and allow us to improve the effectiveness of fatigue countermeasures that limit risks to aircrews.

Although direct references to or experiments on the effects of alertness aids on acceleration tolerance were not found, the known sympathomimetic properties of stimulants such as dextroamphetamine suggest that acceleration tolerance should be improved due to central and peripheral hypertensive effects. Obviously, one would like to know about this issue when deciding between the use, for example, of dextroamphetamine or modafinil (when approved) as an alertness aid for long-duration fighter missions that may require acceleration tolerance.

Sleep Aids

The temazepam search revealed few several investigations that addressed effects on vestibular function. This was surprising because dizziness is a major side effect of temazepam. Many of the 'con' investigations evaluated cognitive functions within two half lives of ingestion, a period within which one would expected to detect dizziness, if present.

Zolpidem has vertigo as one of its major reported side effects but no investigations evaluated this potentially dangerous side effect. There are both diplopia and vision abnormalities described in the pharmacological literature as zolpidem side effects and only two investigations were found that evaluated this side effect.

Concerning zaleplon, only one investigation on vestibular affects was found despite the fact that this is listed as one of the major side affects. Attention also needs to be directed at its potential for memory disturbance record.

Investigations of melatonin were more concerned with circadian resynchronization than its hypnotic capability. Thus, comparisons with the other sedative/hypnotics was difficult.

In general, sleep aids produce drowsiness and sedation, affect motor and mental performance, and may cause amnesia. Sleep aids are used to facilitate sleep at non-optimal times and in non-optimal places. They should help induce sleep rapidly without interfering with normal sleep architecture, allow users to awaken easily and/or respond to emergencies, and have no hangover or residual effects that may interfere with operations.

To some degree, insight into these issues may be gained by checking the half-life of a sleep aid. Few sleep-aid investigations of post-sleep performance have attempted to identify the

time needed to sufficiently clear the medication to define the minimal period between ingestion and mission planning. For temazepam, zolpidem, and zaleplon, differences in half-lives would predict fewer negative side or after effects with the latter two.

However, the residual presence of the drug and of its metabolic products in blood and tissue may continue to cause cognitive problems after one or more half-lives. Empiric investigations of cognition are required to detect these problems. These investigations must be designed with high statistical power, since type II statistical errors are of great concern here: that is, the investigation fails to detect cognitive impairment that actually exists. We base our acceptance of operational sleep aids, in part, on the basis of minimal post-sleep negative effects on cognition. Thus, we place ourselves in the position of trying to prove the negative. This is a specific weakness of the scientific method. This weakness may only be overcome through the use of designs of high statistical power and the replication of studies.

Aircrew may be awakened for unexpected operations before reaching even one half life of sleep aid metabolism. Meyler (2000) described mixed results for investigations of the reversal of sleep aid affects by Dexedrine. Investigations of benzodiazepine reversal with flumazenil will be helpful in terms of clarifying the nature of that reversal process.

Polypharmacy and drug interactions

We need to determine the optimal combinations (timing and dose) of sleep and alertness aids. The extent of neurotransmitter depletion and/or enhancement is not known for such combinations. Similary, the polypharmacological effects on cognition are unknown. Future re-reviews of the literature such as this one would benefit from neuropsychiatry and pharmacology input to help assess potential drug interactions. As an example, quinolones significantly decrease caffeine's clearance rate. Thus, anthrax prophylaxis may affect expected improvements of alertness due to caffeine intake. Similarly, we need to examine the interactive effects of doxycycline on aircrew performance while taking alertness and sleep aids, since almost all aircrew will be taking it for malaria prophylaxis in indicated geographic areas.

All of our military fatigue laboratories should collaborate to acquire data that may be used to improve the power and comprehensiveness of pharmacological fatigue countermeasure research and, ultimately, provide the service member additional safety and efficacy in the field.

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