AD_____

Award Number: DAMD17-00-2-0055

TITLE: A Fatigue Management System for Sustained Military Operations

PRINCIPAL INVESTIGATOR: William F. Storm, Ph.D.

CONTRACTING ORGANIZATION: NTI, Inc.
Fairborn, OH 45324

REPORT DATE: March 2008

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
31-03-2008	Final	1 SEP 2000 - 28 FEB 2008

4. TITLE AND SUBTITLE
A Fatigue Management System for Sustained Military Operations

5a. CONTRACT NUMBER

5b. GRANT NUMBER
DAMD17-00-2-0055

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
William F. Storm, Ph.D.

Email: william.storm@brooks.af.mil

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

NTI, Inc.
Fairborn, OH 45324

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This research program consisted of four tasks, three of them specific research experiments. The fourth major objective was to extend the model of a software-based scheduling tool that predicts cognitive performance based on sleep and circadian patterns. The three experiments systematically evaluated the use and the impact of selected hypnotics and alertness medications to enhance operator performance during sustained military operations. The results for the first experiment were published in the January 2007 issue of *Aviation, Space and Environmental Medicine*. The findings demonstrated significant decrements in cognitive performance when suddenly awakened while sleeping under the influence of zolpidem but not melatonin. Performance and polysomnography data from the second study evaluated the combined use of sleep aids (zolpidem or temazepam) and alertness aids (dextroamphetamine and melatonin) to extend performance and alertness during a simulated 120-hour bomber surge operation. Performance under the Placebo condition deteriorated significantly during the latter portions of each of three successive 24-hour missions but not under the four drug-combination conditions, which did not differ from each other throughout the missions. The third study demonstrated the potential efficacy of sublingual doses of flumazenil to reverse the soporific effects of zolpidem on performance in an operationally-relevant, sudden-awakening paradigm. Publishable reports are in preparation for the latter two studies.

15. SUBJECT TERMS
Fatigue model, cognitive performance, zolpidem, temazepam, melatonin, dextroamphetamine, modafinil, aircrew fatigue

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
U	U	U	UU	104	USAMRMC

TABLE OF CONTENTS

A FATIGUE MANAGEMENT SYSTEM FOR SUSTAINED MILITARY OPERATIONS (DAMD17-00-2-0055) FINAL REPORT 1 SEP 2001 – 28 FEB 2008

INTRODUCTION

Fatigue resulting from reduced sleep and disrupted circadian rhythms is well established to cause significant decrements in cognitive performance (Caldwell, 1997; Dinges and Kribbs, 1995). In the military aviation environment fatigue induced performance decrements during non-stop global deployments, bombing missions 40-50 hours in duration, and 8-10 hour combat air patrol sorties may result in outcomes ranging from severe crew discomfort, to mission degradation, to loss of crew and aircraft. Conservative aircrew fatigue countermeasures sometimes prove insufficient to counter the effects of the cumulative fatigue generated by extreme sustained and long-duration airborne operations. In these critical situations, the Air Force may employ the controlled, limited application of operationally tested pharmaceuticals to enhance aircrew sleep during crew rest (i.e., "no-go pills") and maintain alertness and performance during extended airborne missions (i.e., "go pills").

Three experiments were conducted to expand the knowledge base and, hence, develop the most effective and safe military application of these pharmaceutical agents in real-world military operations. A fourth task, completed and reported in previous annual reports, upgraded the software capabilities of the Fatigue Avoidance Scheduling Tool (FAST), which interfaces with the logic of the Sleep, Activity, Fatigue, and Task Effectiveness (SAFTE) model to permit predictive estimates of operator performance based on work and sleep schedules.

BODY

Task – Cognitive Performance Following Sudden Awakening while Sleeping Under the Influence of Zolpidem and Melatonin. (Study #2 in the original proposal)

Objective. The objective of this study was to determine the impact on cognitive performance when suddenly awakened while sleeping under the influence of the hypnotic zolpidem or the hormone melatonin.

Status. This task was completed with the publication of the research paper "Cognitive Performance Following Awakening From Daytime Sleep While Under the Influence of Zolpidem or Melatonin" in the peer-reviewed journal *Aviation, Space, and Environmental Medicine*, 2007, 78, 10-30 (Appendix II). Findings from this study were also reported in April 2004 at the USAMRMC Peer Reviewed Medical Research Program and in May 2004 at the Annual Scientific Meetings of the Aerospace Medical Association.

Task – Combined Use of Selected Hypnotics and Alertness Medications to Counteract Aircrew Fatigue Due to Disrupted Sleep During Sustained Operations. (Study #3 in the original proposal)

Objective. This study evaluated if there was a best combination of AF/SG approved hypnotic and alertness medications to, respectively, maximize the quality of pre-mission crew rest and counteract the impact of fatigue on aircrew performance during subsequent long-duration missions.

Status. This task has been completed. An incomplete draft of a USAF/AFRL Technical Report describing this ambitious effort is attached at Appendix III. This laboratory study was conducted against the background of a hypothetical one-week sustained airborne operation involving three simulated 24-hour missions separated by 16-hour crew-rest periods. The objective was to determine if there is a best combined use of USAF-approved hypnotic and alertness medications to, respectively, maximize the quality of pre-mission crew-rest and counteract the impact of fatigue on aircrew performance during subsequent long-duration missions. **Method:** The study evaluated and compared the overall counter-fatigue effectiveness of the repeated, cyclic use of the hypnotics temazepam and zolpidem when each was paired with the alertness agents dextroamphetamine or modafinil. During the simulated missions a battery of cognitive tests assessing problem solving, reasoning, memory, and simple reaction time were employed to assess the ability of the four drug-combinations to counteract the deteriorating effect of the fatigue generated by the combination of extended duty periods and associated circadian dysrthymia. Sleepiness and mood scales assessed affect. Sleep during the rest periods and maintenance-of-wakefulness-tests inserted into the missions was evaluated polysomnographically. **Results:** The findings overwhelmingly and consistently demonstrated cognitive performance and subjective affect to deteriorate under the placebo condition as a mission progressed in time, but to remain relatively stable or decrement little both within and across the three missions for each of the four drug-combination conditions. Statistically significant different main or interactive effects between the four drug-combinations were very rare and seemingly random. No consistent findings related to the drug conditions were statistically detected for any of the sleep metrics. **Conclusion:** The combined sequential use of sleep- and alertness-aid medications currently approved by the USAF for pre-mission crew-rest and long-duration missions significantly extended cognitive performance during a simulated surge. There were no statistical differences among the four drug-combinations in their efficacy to maintain cognitive performance. The effects of the drug-combinations on pre-mission sleep quantity and quality did not systematically differ from each other or the placebo condition.

Task – The Reversal of Zolpidem Intoxication by Sublingual Flumazenil. (Study #1 in the original proposal)

Objective. This study assessed the usefulness of sublingually administered flumazenil to reverse sleep aid intoxication for daytime sleep and improve performance on cognitive tests in a dose dependent manner in a rapid awakening paradigm.

Status. This task has been completed. A near-complete manuscript in USAF/AFRL Technical Report format describes the entire study at Appendix IV. In

military operational environments, fatigue induced performance decrements resulting from reduced sleep and disrupted daily rhythms may result in outcomes ranging from severe discomfort, to mission degradation, to loss of life. In the operational environment, sleep aids cannot be used to rest the warfighter because the warfighter may be called upon to act on short notice and the sleep aid might itself degrade performance resulting in the same poor outcome. However, if the sleepiness and cognitive degradation caused by the sleep aid could be reversed, the use of sleep aids could be expanded to include more operational environments. The objective of this study was to evaluate the ability of flumazenil, administered as a liquid sublingually, to quickly and safely counteract the sleep-inducing or drowsiness effect of zolpidem. Thirteen participants received 10 mg zolpidem or placebo, were instructed to sleep 90 minutes, were awakened and given either 1 mg flumazenil or placebo and tested. At the beginning of the second hour after awakening, participants were given a second sublingual, 1 mg does of flumazenil or placebo and tested over the next 5 hours. The repeated-measures, double-blind design showed flumazenil provided partial recovery from the soporific effects of zolpidem. Conclusions: 1.Sublingual flumazenil, administered immediately on awakening, was shown to reverse the cognitively degrading effects of zolpidem by 23%, restoring performance to 92.5% of placebo. 2. One to two hours after awakening, performance did not return to the level of the placebo after flumazenil administration, but rather joined the zolpidem-only decay function which continued to be approximately 20% degraded compared to placebo. 3. At five hours post awakening, performance remained degraded by 10-11% compared to placebo. 4. Consideration should be given to developing a new means of administering liquid flumazenil in a form that can be self-administered and quickly dissolved when placed under the tongue.

Task - Revisions and Upgrades to SAFTE/FAST

Objective. The objective of this task was to extend the capabilities and operational applicability of the Sleep, Activity, Fatigue, and Task Effectiveness (SAFTE) model and its associated scheduling tool, the Fatigue Avoidance Scheduling Tool (FAST™). Specifically, the task was to incorporate into the SAFTE model, and FAST™, algorithms for computing the shift of the human circadian rhythm when crossing time zones.

Status. This task was completed as reported in the third annual report delivered in 2005. The SAFTE model has been selected as the referent for further development of a DoD Warfighter and Fatigue model. The FAST™ software now predicts the degrading effects of jet lag when traveling east and west commensurate with the scientific literature. The model also predicts the amplitude and duration of the recovery once the sleeping pattern stabilizes. The FAST™ software is available to all government agencies without cost by downloading it from the NTI website, www.ntiinc.com.

The Air Force Research Laboratory has provided additional funding to develop a web-based product that has all of the functionality of FAST™. Although the AF effort SBIR received no funding from the Army BAA, DAMD17-00-2-0055 contract, we wanted to give a short description of how the tool has continued to advance building on the Army BAA funding.

The web-based tool provides support for various specialized users making data entry and reporting compatible with their normal tasks. The internet-based tool was initially called the Intelligent Scheduling Tool (IST) and has subsequently been called the Fatigue-Performance Assessment Tool (F-PAS). The tool provides support for regular, cyclic work-rest schedules, for irregular work-rest schedules, for pharmaceutical countermeasures, and for formal Operational Risk Management (ORM) of fatigue effects. Special interfaces have been created for shift work schedulers, mishap investigators, mission schedulers, pilots, and flight surgeons, providing pharmaceutical countermeasures. Each user group has been involved in the development of their interface through a Task-Centered System Design (TCSD). final delivery of the web-based tool will commence July 2008.

F-PAS Capabilities: Essentially F-PAS has all the capabilities of FAST™ in a web-based product. In addition, it requires user identification and a password to enter the website for required DoD security. The application allows multiple users to access the website simultaneously while preventing users from accessing each other's schedules. The special interfaces of F-PAS allow user data entry and displays to be integrated into their respective work environment and tasks. After entering the system and selecting an interface, the user begins data entry. Each interface has associated help that is context sensitive. While the mishap and shift work interfaces are unique, the mission interface will serve anyone working with an irregular schedule, like mission schedulers, pilots, ground commanders, squad leaders, and medical personnel. The mission interface is closest to the data entry approach used in FAST™. However, it uses a calendar input format similar to Microsoft™ Outlook™ for entry of sleep and work making it more familiar to novice users.

Once a user completes data entry, F-PAS processes the sleep and location changes with the SAFTE model (reservoir, circadian, and sleep inertia components) to produce various output displays and reports, some designed for the specific user groups. The most general output is a graph similar to FAST™. F-PAS has new reports that present reasoned analyses based on entered schedules. While the mishap and shift work reports are unique, the mission report is more general. All reports will present fatigue ratings for Operational Risk Management (ORM). These ratings may be used in conjunction with the criticality of the mission to determine if the mission should be initiated. Alternatively, fatigue countermeasures may be selected and the mission can be re-evaluated for fatigue risk.

Many features are common to all interfaces. Schedules may be saved on the server or on the user's computer. All data are encrypted for security. Reports, graphs, timelines, and schedules can be copied to the clipboard and pasted into word processing documents, spreadsheets, or slides similar to FAST™. They can also be printed or saved to files on the users' computer.

KEY RESEARCH ACCOMPLISHMENTS

Three complex, ambitious experiments were conducted in simulated operational environments. Each experiment evaluated the efficacy and best application of USAF and USA approved sleep- and alertness-aids as warfighter fatigue countermeasures. Precise and thorough protocols were prepared, reviewed, defended, and approved by both USA and USAF Institutional Review Boards. FDA INDs were submitted for review and approval as appropriate. Sophisticated experimental designs were applied to simulate long duration and surge military operations, requiring data collection over sessions lasting as long as 24 hours and around-the-clock across several successive days. Outcome measures included cognitive measures assessing decision making, memory, and problem solving; psychophysiological measures included sleep polysomnography, strength, and balance. Each experiment resulted in a publishable paper providing findings of interest to both the scientific and operational military communities.

The SAFTE Model (Sleep, Activity, Fatigue, and Task Effectiveness) and its associated scheduling software (Fatigue Avoidance Scheduling Tool) have been enhanced to predict transmeridian travel across times zones and to predict the cognitive performance of individuals undergoing shiftwork schedule changes.

The SAFTE Model was selected as the DoD Warfighter and Fatigue Model referent for future research and development.

FAST is now available at a website for all DoD agencies, and is being embedded into the Army MANPRINT system.

REPORTABLE OUTCOMES/PUBLICATIONS & ABSTRACTS

Publications.

Storm, W., Eddy, D., Welch, C., Hickey, P., Fischer, J., and Cardenas, B. Cognitive Performance Following Premature Awakening from Zolpidem or Melatonin Induced Daytime Sleep. *Aviation, Space, and Environmental Medicine,* 2007, 78, 10-20. (Appendix 1)

Hursh, S., Redmond, D., Johnson, M., Thorne, D., Belenkey, G., Balkin, T., Storm, W., Miller, J., and Eddy, D. Fatigue Models for Applied Research in Warfighting. *Aviation, Space, and Environmental Medicine,* 2004, 75, A44-A53.

Published Abstracts/Presentations at Scientific Meetings.

Storm, W., Eddy, D., Cardenas, R., Hickey, P., Ramsey, K., and Welch, C., Cognitive performance following sudden awakening while under the influence of zolpidem and melatonin, Abstract/oral presentation/poster presentation at the USAMRMC Peer

Reviewed Medical Research Program (PRMRP), San Juan, Puerto Rico; April 25-28, 2004.

Hursh, S., Eddy, D., and Charlton, M., Validation of the sleep, activity, fatigue, and task effectiveness model, Abstract/oral presentation at the Aerospace Medical Association Annual Scientific Meeting, Anchorage, AK; May 2-6, 2004.

Storm, W., Eddy, D., Cardenas, R., Hickey, P., Ramsey, K., and Welch, C., Cognitive performance following sudden awakening while under the influence of zolpidem and melatonin, Abstract/oral presentation at the Aerospace Medical Association Annual Scientific Meeting, Anchorage, AK; May 2-6, 2004.

Gibbons, J., Eddy, D., Storm, W., and Fischer, J. Reversal of Zolpidem Intoxication by Sublingual Flumazenil, Abstract/oral presentation accepted for presentation at Annual Meeting of the Aerospace Medical Association, Boston, MA; May 12-15, 2008.

Publications in Preparation.

Storm, W., Eddy, D., Welch, C, Fischer. J. Combined Use of Selected Hypnotic and Alerting Medications to Counteract Aircrew Fatigue Due to Disrupted Sleep During Sustained Operations. (Appendix III)

Eddy, D., Storm, W., Gibbons, J., Miller, J., French, J. Reversal of Zolpidem Intoxication By Sublingual Flumazenil. (Appendix IV)

PERSONNEL RECEIVING PAY

Barton, Emily
Bradford, Brenda
Campbell, Heather
Campbell, Linda
Cardenas, Beckie
Cardenas, Fernando
Charlton, Matita
Crabtree, Aaron
Crabtree, Mark
Doran, Beth
Eddy, Douglas
Eddy, Patricia
Hermosillo-Heart, Belinda
Hickey, Patrick
Jones, Margaret
McCrory, Amy
Mendez, Juan
Moise, Samuel
O'Donnell, Robert
Ramsey, Katy
Sanchez, Laura
Shaw, Robert
Smith, Lisa
Storm, William
Welch, Cory

CONCLUSIONS

Findings indicated that when operational personnel sleeping with the aid of zolpidem are prematurely awakened, it would be prudent to evaluate their general well-being and possible needed for assistance prior to their being permitted to depart crew-rest

or to perform tasks and duties. In contrast, there was no evidence of deteriorated well-being or need for assistance when awakened while sleeping under the influence of melatonin.

The combined sequential use of sleep- and alertness-aid medications currently approved by the USAF for pre-mission crew-rest and long-duration missions significantly extended cognitive performance during a simulated surge. There were no statistical differences among the four drug-combinations in their efficacy to maintain cognitive performance. The effects of the drug-combinations on pre-mission sleep quantity and quality did not systematically differ from each other or the placebo condition.

The potential efficacy of sublingual doses of flumazenil to reverse the soporific effects of zolpidem on performance were demonstrated in an operationally-relevant, sudden-awakening paradigm. Further research directed at improving the effectiveness of sublingual administration and refining the dosage could provide both military and civilian communities.

So what? Warfighter fatigue is a critical operational issue, contributing to depressed morale, significant performance deterioration, and, most importantly, risk and loss of life in military operations. The appropriate and knowledgeable use of carefully assessed fatigue-countermeasure pharmaceuticals during periods of increased opstempo provides the US Warfighter with another edge in the battle environment.

REFERENCES

Dinges, DF, and Kribbs, NB. Performance effects of fatigue. *Fatigue Symposium Proceedings, National Transportation Safety Board and NASA Ames Research Center*, Nov 1-2, 1995; 41-46.

Caldwell, JA. Fatigue in the aviation environment: An overview of the causes and effects as well as recommended countermeasures. *Aviation, Space, and Environmental Medicine*, 1997, 932-938.

APPENDIX I

Hursh, S., Redmond, D., Johnson, M., Thorne, D., Belenkey, G., Balkin, T., Storm, W., Miller, J., and Eddy, D. Fatigue Models for Applied Research in Warfighting. *Aviation, Space, and Environmental Medicine,* 2004, 75, A44-A53.

Fatigue Models for Applied Research in Warfighting

Steven R. Hursh, Daniel P. Redmond, Michael L. Johnson, David R. Thorne, Gregory Belenky, Thomas J. Balkin, William F. Storm, James C. Miller, and Douglas R. Eddy

Hursh SR, Redmond DP, Johnson ML, Thorne DR, Belenky G, Balkin TJ, Storm WF, Miller JC, Eddy DR. *Fatigue models for applied research in warfighting.* Aviat Space Environ Med 2004; 75(3, Suppl.):A44–53.

The U.S. Department of Defense (DOD) has long pursued applied research concerning fatigue in sustained and continuous military operations. In 1996, Hursh developed a simple homeostatic fatigue model and programmed the model into an actigraph to give a continuous indication of performance. Based on this initial work, the Army conducted a study of 1 wk of restricted sleep in 66 subjects with multiple measures of performance, termed the Sleep Dose-Response Study (SDR). This study provided numerical estimation of parameters for the Walter Reed Army Institute of Research Sleep Performance Model (SPM) and elucidated the relationships among several sleep-related performance measures (6). Concurrently, Hursh extended the original actigraph modeling structure and software expressions for use in other practical applications. The model became known as the Sleep, Activity, Fatigue, and Task Effectiveness (SAFTE) Model, and Hursh has applied it in the construction of a Fatigue Avoidance Scheduling Tool. This software is designed to help optimize the operational management of aviation ground and flight crews, but is not limited to that application. This paper describes the working fatigue model as it is being developed by the DOD laboratories, using the conceptual framework, vernacular, and notation of the SAFTE Model (16). At specific points where the SPM may differ from SAFTE, this is discussed. Extensions of the SAFTE Model to incorporate dynamic phase adjustment for both transmeridian relocation and shift work are described. The unexpected persistence of performance effects following chronic sleep restriction found in the SDR study necessitated some revisions of the SAFTE Model that are also described. The paper concludes with a discussion of several important modeling issues that remain to be addressed.

Keywords: sleep, fatigue, circadian rhythm, performance, model, cognitive throughput, sleep inertia, sleep deprivation.

THE U.S. DEPARTMENT OF DEFENSE (DOD) has long pursued applied research concerning fatigue in sustained and continuous military operations. Lead DOD laboratories are the Walter Reed Army Institute of Research (WRAIR) in Silver Spring, MD, the Naval Health Research Center (NHRC) in San Diego, CA, the Air Force Research Laboratory (AFRL) at Brooks City-Base, TX, and the U. S. Army Aviation Research Laboratory (USAARL) at Fort Rucker, AL. Research teams at these locations are responsible for investigating fatigue-related impairment of cognitive readiness, "for developing countermeasures to fatigue, and for providing guidance to the Services in the management of fatigue."

A three-process, quantitative model was initially conceived in the 1980s, jointly by WRAIR and Scientific Applications International Corp. (SAIC), in an attempt to estimate a relationship between crewmen's sleep and the delivery of artillery rounds on target (30). During the 1990s, WRAIR focused on the study of sleep per se as a determinant of cognitive performance, which contributed to refinements of the original model from data obtained from studies of total and partial sleep deprivation (7). WRAIR sponsored the development of an actigraph with an embedded sleep model, and Hursh at SAIC developed a simple homeostatic fatigue model and, working with Precision Control and Design, programmed the model into an actigraph to give a continuous indication of performance.

These efforts suggested the need for a large-scale study of partial sleep deprivation to fill a major knowledge gap between normal sleep and total sleep deprivation. A study was undertaken of 1 wk of restricted sleep in 66 subjects with multiple measures of performance, termed the Sleep Dose-Response Study (SDR). This study provided numerical estimation of parameters for the WRAIR Sleep Performance Model (SPM), and elucidated the relationships among several sleep-related performance measures (6). Concurrently, Hursh at SAIC extended the original actigraph modeling structure and software expressions for use in other practical applications.

Work sponsored by the Natick Research and Development Center focused attention on the development of the fatigue model for incorporation into the Integrated Unit Simulation System (IUSS), a simulation of solder performance under hypothetical combat scenarios (31). With support from the AFRL's Warfighter Fatigue Countermeasures (WFC) Program, Hursh further developed the Sleep, Activity, Fatigue, and Task Effectiveness (SAFTE) Model, and has applied it in the construction of a Fatigue Avoidance Scheduling Tool (FAST) under an AF SBIR awarded to NTI, Inc. (16). This software is designed to help optimize the operational management of aviation ground and flight crews, but is not limited to that application. Current laboratory collaborations between NHRC and AFRL, additional field data collection by both groups, and studies of sleep depri-

From the Science Applications International Corporation, Biomedical Modeling and Analysis Program, Joppa, MD (S. R. Hursh); the Walter Reed Army Institute of Research Division of Neuropsychiatry, Silver Spring, MD (D. P. Redmond, M. L. Johnson, D. R. Thorne, G. Belenky, T. J. Balkin); and the Air Force Research Laboratory, Brooks City-Base, TX (W. F. Storm, J. C. Miller).

Address reprint requests to: Steven R. Hursh, Ph.D., who is Program Area Manager, BioMedical Modeling & Analysis Program, SAIC, 626 Towne Center Drive, Suite 201, Joppa, MD 21085; hurshs@saic.com.

vation and pharmaceutical effects in the Army laboratories all promise to add quantitative input and validation for model development.

This combined progress led to a meeting among DOD principal investigators in January 2002 for the purpose of more closely coordinating their research and converging parallel efforts in modeling development. Given their common origin, the WRAIR SPM and AFRL/SAIC SAFTE Models do not differ greatly. Structural differences are minor. The key distinction between the two approaches is the temporal perspective of their application. The WRAIR SPM Model, with its roots in an actigraph-based monitoring technology, attempts to take prior, measured sleep history of individuals to estimate current cognitive capacity, or "readiness," of both the individual and the crew or group in which he/she operates. It may be used to provide feedback to the individual who may need sleep, to allow selection among candidate individuals or units for a particular operation, or to provide a weighting function for performance in higher order models of operational scenarios. On the other hand, SAFTE is applied to hypothetical or prospective work/sleep schedules in order to identify potential performance problems, and to optimize operational planning and management. Clearly these perspectives are complementary and overlap considerably and can share a common model of sleep and performance prediction. In addition, the SAFTE Model was elaborated with a fourth process that modulates the sleep reservoir capacity during chronic sleep restriction to account for findings from recent chronic sleep restriction studies showing slower than expected rebound of performance following recovery sleep. The SAFTE Model has also been enhanced to account for circadian shifts due to transmeridian crossings vs. shift work changes.

This paper describes the working model as it is being developed by the DOD laboratories, using the conceptual framework, vernacular, and notation of the SAFTE Model (16). At specific points where the WRAIR SPM may differ from SAFTE, this is discussed. This model is intended to be a tool for the operational components of the Services; that is, its framework is heuristic, and the research focus is toward application. In the background are a number of basic research efforts, supported by government, industrial, and academic enterprise, which will be cited by the authors but not discussed in the depth they deserve. Nonetheless, such efforts both add to the body of knowledge on which a valid, practical tool can be constructed, and impose important theoretical and practical constraints. In order to plan future studies leading to useful and accurate predictions, in DOD laboratories and elsewhere, basic issues must be considered, and are discussed critically in the context of the present model. Hopefully, this paper will help guide our laboratories in coordinating their research, and allow the reader to assess the status of our applied research as it progresses toward a transition to practical applications.

The conceptual architecture of the SAFTE Model is shown in **Fig. 1**. The core of this model is schematized as a sleep reservoir, which represents sleep-dependent

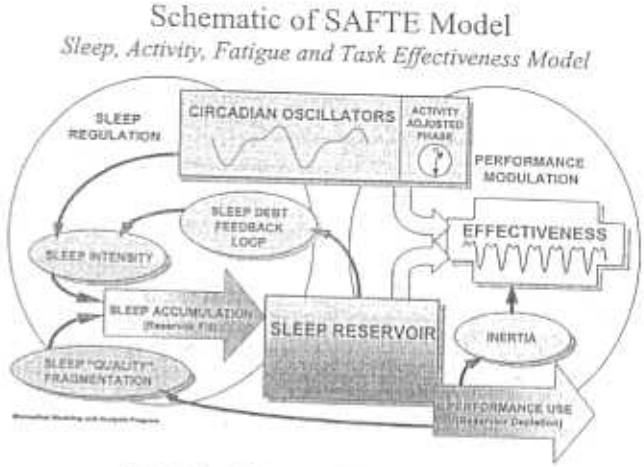

Fig. 1. Block diagram of the SAFTE Model.

processes that govern the capacity to perform cognitive work. Under fully rested, optimal conditions, a person has a finite, maximal capacity to perform, annotated as the reservoir capacity (Rc). While one is awake, the actual "contents" of this reservoir are depleted, and while asleep, they are replenished. Replenishment (sleep accumulation) is determined by sleep intensity and sleep quality. Sleep intensity is in turn governed by both the time-of-day (circadian process) and the current level of the reservoir (sleep debt). Sleep quality is modeled as its continuity, or conversely, fragmentation, in part determined by external, real-world demands, or requirements to perform. Performance effectiveness is the output of the modeled system. The level of effectiveness is simultaneously modulated by time-of-day (circadian) effects and the level of the sleep reservoir. Transient post-sleep decay of performance is modeled by the term inertia.

The foregoing terminology has been selected to provide operational users of the model an intuitive grasp of the processes involved. SAFTE is a three-process, quantitative model similar to that suggested by Folkard and Åkerstedt (18), Achermann and Borbély (1), Åkerstedt and Folkard (2), and Jewett and Kronauer (33). The modulation of reservoir volume essentially represents the homeostatic regulation of wakefulness, involving two subprocesses with respect to performance capacity (equivalent to their S process). The second process is the major influence of circadian rhythms (process C). The third process involves "sleep inertia" (process W). The following discussion will take up the individual components of the model in some detail.

METHODS

Process 1: The Homeostatic Process

Wakefulness – reservoir depletion: The performance use function is a mathematical formula describing the rate at which cognitive performance capacity declines during continuous wakefulness. SAFTE expresses this function in terms of an equation for a straight line, Eq. 1:

$$P = K \cdot t, \qquad \text{Eq. 1}$$

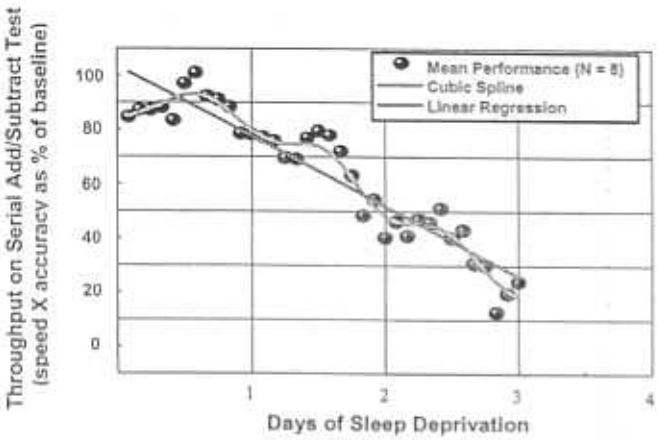

Fig. 2. Performance decrement on the Serial Addition/Subtraction Task across 72 h of sleep deprivation.

where P is performance use, or reservoir depletion over a period of time, t. The model pegs the reservoir capacity, Rc, at 2880 arbitrary units, and the default value for K, the slope of this line, is 0.5 units per minute. Thus, after 4 d (5760 min) of continuous sleep loss, the reservoir will be fully depleted.

The rationale for both linearity and the value for the decay slope (about 1% per hour awake) is derived from a straight-line fit of cognitive throughput data obtained during 72 h of total sleep deprivation. In that study, performance declined by approximately 25% for every 24 h of total sleep deprivation (46). The residual data from this treatment show a clear circadian rhythm (**Fig. 2**). The SAFTE Model with a linear performance use function combined with a two-frequency circadian process (see below) can fit the data of Fig. 2 with an R^2 of 0.89.

The performance use function is a linear approximation of what may be a more complex pattern of decay over time. There remain a number of unresolved issues concerning both its slope and its shape. For instance, data from the SDR study (66 subjects sleeping either 9, 7, 5, or 3 h per day for 7 d), yielded a straight-line slope of about 0.5% per hour using a simple reaction time task (PVT) (14) instead of an arithmetic task (6). Whether this twofold difference from the previous estimate is task-specific, or due to other factors (e.g., demographic) remains unclear. Furthermore, other modeling efforts have postulated curvilinear decay functions based on other data sets. Folkard and Åkerstedt (18) use an exponential expression for decreasing alertness (as opposed to performance). A linear approximation of their function over 24 h yields a slope of about 1.8% per hour. For both alertness and performance, Jewett (32,33) fits data to a sigmoidal function, reflecting both a delay in the onset of decay after awakening, and a slowing of decay rates after about 36 h of sleep deprivation. Jewett also suggests that the decay waveform may be influenced by both circadian phase at wake time and by prior sleep debt. Most researchers would probably agree with us that the variance of grouped data tends to increase with the duration, measured in days, of sleep deprivation experiments, which makes precise description of the waveform all the more difficult. For the time being, then, we continue to utilize the linear approximation.

Sleep accumulation – reservoir replenishment: The sleep/restoration function is a mathematical formula describing the rate at which restoration of cognitive performance capacity accrues during sleep. For SAFTE, additions to the reservoir (S) resulting from sleep over an interval of time, t, depend on the sleep intensity (SI, or rate of recuperation due to sleep) over that interval, shown in Eq. 2:

$$S = SI \cdot t \qquad \text{Eq. 2}$$

SI (units/minute) varies during the interval such that it is the weighted sum of 1) sleep propensity (SP), a function of time-of-day, and 2) the current reservoir deficit, or sleep debt (SD), in the reservoir (R_c-R_t) as it changes during the interval, multiplied by a feedback factor, f. This latter quantity is sometimes referred to as the sleep/wake cycle because it depends on the pattern of sleep and wakefulness. Thus, SI is given by the following sum, Eq. 3:

$$SI = SP + SD, \text{ where } SD = f \cdot (R_c - R_t) \qquad \text{Eq. 3}$$

SP incorporates a circadian process, c, and an amplitude factor, a_s (default = 0.55 units; see below), and f has a default value of 0.0026564 min. Rc is the reservoir capacity and R_t is the reservoir level at time t. SAFTE incorporates a maximum level of sleep intensity, set to 4.4 units/min. This limit permits an equilibrium state to be reached with as little as 3 $h \cdot d^{-1}$ of sleep, but not with less. Note, however, that with only 3 $h \cdot d^{-1}$ of sleep, performance is severely degraded until recovery sleep is obtained.

The proposition that sleep intensity is increased by sleep debt is a feature recognized by all the models recently offered. For the WRAIR SPM and the homeostatic model of Folkard and Åkerstedt (18), this is explicitly stated as an exponential "recharging" function. The rationale for this derives from observations that the rate at which recuperation occurs during sleep varies continually as a function of extant sleep debt. Recuperation at the beginning of the sleep period, when sleep debt is relatively high, occurs at a faster rate than at the end of the sleep period, when sleep debt is relatively low (28,38). Whether this is due to shifts of sleep architecture toward more restorative slow-wave sleep in the early hours has been discussed recently by Wesensten, Balkin, and Belenky (48). If expressed as a discrete function, as above, or exponentially, the results of the SPM and SAFTE converge for small intervals, ignoring the circadian process in the SAFTE Model. The value of f in SAFTE is the reciprocal of the time constant of recuperation in the exponential equation of the SPM, and is equivalent to about 375 min (based on a performance throughput measure). This value is derived from earlier studies in which 84 h of sleep deprivation were interrupted by daily 0.5-h naps (7). After the SDR study, the SPM was modified to a much slower rate of recuperation, with a time constant of about 1300 min (based on a reaction time measure). As with the value for waking decay, this large difference in recovery rate is not entirely understood. It is consistent with the observation that the 3- and 5-h sleep groups in the SDR did

not recover to baseline after three full nights of sleep, a slower rate of recovery than SAFTE would predict, suggesting a needed revision, described below.

The circadian component of SI, or Sleep Propensity (SP), essentially postulates that the restorative effect of sleep depends in part on the time-of-day at which the sleep occurs (10,36). In SAFTE, this is expressed by Eq. 4:

$$SP = -a_s \cdot c \qquad \text{Eq. 4}$$

in units per minute, where a_s is a weighting factor (default = 0.55 units), and c is the circadian rhythm of body temperature and arousal, which varies between +1 and −1 (see below). For a person taking a normal 8 h sleep from midnight to 08:00, sleep is most intense in the early morning at about 03:00. There is a mid-afternoon increase in sleep propensity at about 16:00 that coincides with the mid-afternoon dip in alertness and consistent with the observation of increases in sleep related traffic accidents (36). The rhythm of SP is taken to be 180° out of phase with alertness and performance; hence the resulting value is subtracted from the restoration rate due to sleep. Jewett and Kronauer (33) incorporate a similar term in their model that modulates the rate of recovery, arguing that the actual amount of sleep obtained (given equal amounts of time allowed for sleep) varies according to time of day, without implying that changes in sleep architecture (or quality) mediate changes in sleep intensity. By the same argument, the SPM omits altogether any correction for circadian effects on sleep quality or quantity, since the SPM is concerned with sleep as it is actually measured. This, again, is the key difference between SPM and SAFTE, and SAFTE thus has the advantage of being able to optimize both sleep amount and sleep timing for prospective work/rest schedules.

The final influence on sleep accumulation results from sleep fragmentation. This is expressed as a non-linear term that has the effect of delaying onset of sleep restoration (by setting SI = 0) at the end of any wake period. This is based on empirical evidence that the early minutes of sleep are generally Stage 1 (48). By screening out the first several minutes of sleep, the model enhances the effect of fragmented sleep and frequent awakenings, an effect by which such influences on cognitive performance capacity as age, environmental disruptions, divided work/rest schedules, and sleep pathology are expressed. At present, this delay is set at 5 min following each arousal or awakening, based on studies of simulated sleep apnea in which 12 awakenings per hour were equivalent to total sleep deprivation (9). However, it is likely that future research will lead to refinement of this function such that it will be modulated by extant sleep debt and/or time of day. Both SAFTE and SPM contain this factor, and it is closely related to the time-of-sleep discussion by Jewett and Kronauer (33), although not explicitly expressed in their model.

Process 2: Sleep Inertia

Sleep inertia can be described as the delay, after awakening from sleep, before expected levels of alertness and performance resume. The modeling of this transient phenomenon is based on studies of post-sleep performance (13) and of brain metabolism using positron emission tomography (PET) (5). Jewett and Kronauer (33) and Folkard and Åkerstedt (17) both invoke a short-lived exponential deviation from the homeostatic process. The SAFTE Model estimates this effect as an exponential discharge function that is invoked for 2 h after awakening from sleep, whose output is subtracted from the effectiveness output of the overall model according to Eq. 5:

$$I = -I_{max} \cdot e^{-0.04/SD}, \text{ for } t_s = 0 \text{ to } 120 \text{ min} \qquad \text{Eq. 5}$$

where I_{max} is the maximal inertia effect on awakening, set to 5%, and i is the inertia time constant, set to 0.04. Since the time constant is also related to the sleep intensity at time of awakening, SI, sleep inertia will last longer for awakenings that occur during deep sleep, such as early in the sleep period or during sleep periods of individuals carrying a large sleep debt.

Process 3: The Circadian Process

Performance while awake and the drive to sleep are both controlled, in part, by a circadian process (17,41). Studies of performance [e.g., reaction time (15)], alertness ratings (22,42), measures of the tendency to fall asleep [e.g., multiple sleep latency tests (11,40,45); see also Lavie (37)], and body temperature (22,42) indicated that the underlying circadian process is not a simple repeating sine wave. Performance and alertness reach a major peak in the early evening, about 20:00, and fall to a minimum at about 04:00. There is a secondary minimum in the early afternoon, about 14:00, and a secondary morning peak at about 10:00. Correlated with this pattern is a varying tendency to fall asleep that reaches a peak at about the same time performance and alertness reach their minima. The existence of both a major and a minor peak in performance and two corresponding minima at other times suggests that at least two oscillations are involved in the circadian process (47).

Both SAFTE and SPM estimate this circadian process with a function that is composed of the sum of two cosine waves, one with a period of 24 h and one with a period of 12 h. The two oscillations are out of phase, producing an asymmetrical wave form: a gradual rise during the day with a plateau in the afternoon and a rapid decline at night that closely parallels published studies of body temperature (22,24,42). The circadian rhythm of performance is not a simple mirror image of variations in body temperature (20,21). The asymmetrical circadian rhythm combines with a gradually depleting reservoir process resulting in a bimodal variation in cognitive effectiveness that closely parallels published patterns of performance and alertness, described above. The circadian process is represented by Eq. 6:

$$c_t = \cos(2\pi (T - p)/24) + \beta\cos(4\pi (T - p - p')/24) \qquad \text{Eq. 6}$$

where T is the time of day in hours, p is the time of the peak of the 24 h rhythm, p' is the relative time of the 12 h peak, and β is the relative amplitude of the 12 h

rhythm. Initially, in the SAFTE Model, p is set to 18:00 (6 pm), and is adjusted in a manner described below. The value for p' is 3 h, and β is 0.5. Parameters derived from analysis of SDR data are implemented in one version of the SPM. These phase values are somewhat later in the day, with a major peak at about 23:00 and an afternoon nadir at 17:00. Because the SDR study was not designed optimally for elucidation of circadian rhythms, having only four unequally spaced data points during each day, the consensus of our laboratories favors the values used in SAFTE, which better track the timing and amplitude of known circadian processes. Note also that since c is a compound of two cosine functions, the peak of the resulting waveform does not coincide with the peak of the 24-h component, p; with p equal to 18:00 and p' set to 3 h, the peak of the resulting compound is about 20:00.

Modification of the Circadian Process by Activity Patterns

When subjects move to another time zone or alter work pattern so that sleep and work occur at different times of day, the internal circadian oscillator that controls body temperature and alertness shifts to this new schedule. During the period of adjustment, subjects experience performance degradation, disrupted mood, and feelings of dysphoria, called circadian desynchronization or "jet lag" (24,29,35). The SAFTE Model mimics this process and automatically adjusts the phase of the circadian rhythm to coincide with the activity pattern of the subject. This feature is critical for the accurate prediction of the effects of moving to a new time zone or changing to a new and regular work pattern, such as changing from the day shift to the night shift. The model detects the average time of the awake period and maintains a running average "awake time." The peak of the circadian rhythm has a reliable relationship to the timing of the period of wakefulness. When one moves to a new work schedule or a new time zone, the change in average awake time (relative to a reference time zone) is detected and a new "target phase" is computed. For example, after moving from the central U.S. time zone to Germany, the awake time of the subject advances 6 h. This causes a gradual shift of 6 h in the circadian process of the model. In general, a phase advance (eastward time change) takes about 1.5 d per hour of shift (23–25,29,35,39,43). The model, therefore, adjusts to the new "target phase" gradually over the course of 9 d. During that time, the performance of the subject will show net degradation due to the desynchronization of the internal circadian process from the new rhythm of work and sleep. Likewise, westerly travel causes a phase delay in the circadian rhythm and takes less time for adjustment, about 1 day per hour of shift (23–25,29,35,39,43). Folkard et al. (19) similarly utilize time of awakening as the basis for phase adjustments, while Jewett and Kronauer (33) emphasize the synchronizing effect of light exposure in their model. It is acknowledged that light exposure may be a fundamental driver for phase adjustment, along with sleep, activity, and social cues; however, in practice, light exposure information is normally not available to the planner in advance of an operation. As an approximation, periods of awake activity are normally closely linked to times of exposure to light (either natural or artificial) so that the timing of awake activity coincides with the timing of light exposure and can serve as a reasonable basis for the estimation of phase changes. Limitations of this approximation may occur in situations of continuous low-level artificial light (e.g., aboard submarines or orbiting spacecraft) or when exposure to bright light is deliberately arranged to induce a phase shift (12,34).

Recently, the SAFTE Model has been incorporated into a planning tool called the Fatigue Avoidance Scheduling Tool (FAST), which also includes features to track changes in geographic location and calculated levels of sunlight. In this implementation, the model can detect the difference between transmeridian schedule shifts and shift-work changes at the same location. When a shift-work change is detected, a slower rate of phase adjustment is implemented to reflect the inhibitory effects of both light exposure and social cues. At its extreme, a shift-work induced change in circadian phase may take 2.6 times as long to complete as a comparable transmeridian shift in phase (21).

Combined Processes: Performance Effectiveness

The final output of the SAFTE Model consists of a summation of the homeostatic process (sleep reservoir balance) and the circadian process (performance rhythm), with transient adjustments for sleep inertia as required. In the WRAIR SPM, these terms are combined differently, by multiplying (modulating) the reservoir balance with the circadian process. The SAFTE Model is computed as a weighted, additive modulation of the level of performance, expressed as a percent of baseline. Thus, effectiveness at time t (E_t) is given by Eq. 7:

$$E_t = 100 \cdot (R_t/Rc) + C_t + I \qquad \text{Eq. 7}$$

where I is the transient inertia term; $100 \cdot (R_t/Rc)$ is the reservoir level, expressed as % of capacity; and C_t is computed from the circadian process (c) as follows:

$$C_t = c_t \cdot (a_1 + a_2(Rc - R_t)/Rc)$$

$$\text{where } a_1 = 7\% \text{ and } a_2 = 5\% \qquad \text{Eq. 8}$$

The computation of the circadian component (C_t, Eq. 8) includes a variable amplitude expression that effectively increases circadian modulation of effectiveness with increasing sleep debt (4).

Adaptation to Specific Task Effectiveness

The SAFTE Model can predict changes in cognitive capacity as measured by standard laboratory tests of cognitive performance. For example, the model can predict degradation of serial add-subtract throughput during 72 h of sleep deprivation [$R^2 = 0.89$, data from Thorne et al. (48)] as well as average cognitive throughput across a series of cognitive tests during 54 h of sleep deprivation [$R^2 = 0.98$, data from Angus and Heslegrave (3)]. A modified version of SAFTE (see below) with appropriate parameter settings can predict average cognitive throughput and average psychomotor vigilance (PVT) speed during restricted sleep duration

over 7 d [R^2 = 0.94, data from Balkin et al. (6)]. It is assumed that these cognitive tests measure changes in the fundamental capacity to perform a variety of tasks that rely, more or less, on the cognitive skills of discrimination, reaction time, mental processing, reasoning, and language comprehension and production. However, specific tasks, such as specific military tasks, vary in their reliance on these skills, and deficits in cognitive capacity may not produce identical reductions in the capacity to perform all military tasks. It is reasonable to assume, however, that the changes in military task performance would correlate with changes in the underlying cognitive capacity. In other words, if one were to plot changes in military task performance as a function of measured changes in cognitive capacity, there would be a monotonic relationship between the two variables. Therefore, if these two sets of data were available from a test population subjected to sleep deprivation, linear (or nonlinear) regression techniques could be applied to derive a transform function; this transform translates predicted cognitive changes into changes in military task performance. Based on this reasoning, the method for evaluating the effectiveness, discussed previously as the cognitive effectiveness, can be extended to predict variations in any task or component of a task (given appropriate test data) using the generalized task effectiveness (TE), Eq. 9 expression as follows:

$$TE = A\,(R_l/Rc) + B + C1\,[\cos(2\pi\,(T - P)/24) + C2[\cos(4\pi(T - P - p')/24)]] + I, \quad \text{Eq. 9}$$

where A = linear component slope, B = linear component intercept, $C1$ = circadian weighting factor, $C2$ = 12 h weighting factor, and p = acrophase of the task. The other factors in the equation (R_l/Rc and I) are as they would be predicted by the SAFTE Model for cognitive effectiveness.

Implications of Model Structure

Equilibrium states: If a subject is scheduled to take less than an optimal amount of sleep each night, for example, 4 h · d^{-1}, the reservoir initially loses more units during the awake period than are made up during the sleep period. This results in a sleep debt at the end of the sleep period that accumulates over days. However, since the rate of sleep accumulation increases with sleep debt, eventually, the rate of sleep accumulation increases such that 4 h of sleep equilibrates with the depletion of 20 h awake. At this point, the reservoir reaches an equilibrium state and no further debt is accumulated, although the initial deficit remains as long as the person remains on this schedule. By the 6th d of the restricted sleep schedule, cognitive performance oscillates about a stable level well below the baseline level achieved with 8 h of sleep. Minimum effectiveness is about 64% on the seventh day.

Progressive sleep debt under extreme schedules: The sleep homeostat is not infinitely elastic; there is a limit to the rate of sleep accumulation (sleep intensity), set in SAFTE at 4.4 units per minute. The effect of this is that any schedule that provides less than about 3 h of sleep per day will not reach an equilibrium state and performance capacity will gradually deplete to zero, although the rate of depletion slows over the first week of restriction as sleep intensity rises to its maximum level. Under a schedule of only 2 h of sleep per day, minimum performance declines to about 19% on the seventh day.

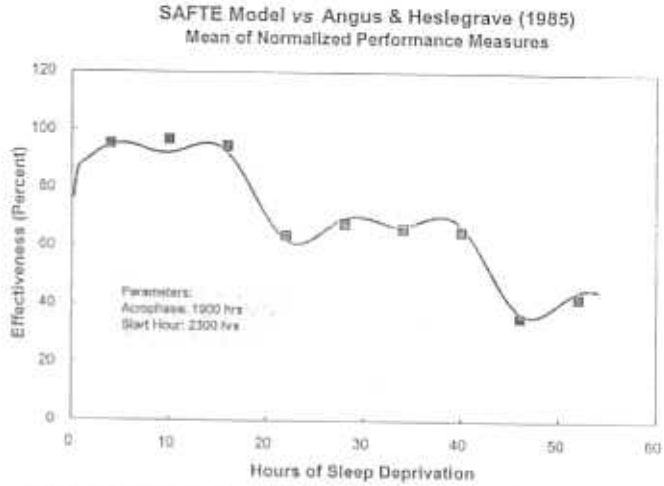

Fig. 3. SAFTE Model predictions for cognitive performance under total sleep deprivation (solid line) compared with mean normalized cognitive performance (filled squares) reported by Angus and Heslegrave (3).

Sleep timing: The SAFTE Model is sensitive to the time of day of the sleep period. The performance of an individual given 8 h of sleep per day starting at 12:00 (noon) each day reaches a peak of 100% at the start of each work period (20:00) but rapidly declines during the late night and early morning hours to a strong dip at about 05:00. Minimum predicted performance under this schedule is predicted to be as low as 66% compared with minimum performance under a normal sleep schedule of 86%. This alteration in pattern results from two factors. First, sleep intensity is initially less for sleep periods starting at noon. This results in a small accumulated debt that is quickly offset by the homeostatic sleep mechanism. The second, more persistent effect is the circadian oscillator of performance that reaches its minimum in the early morning hours. This pattern has important implications for performance under shift schedules that require daytime sleep. It is well documented that most mistakes on the night shift occur during the early morning hours and this is predicted by the model (8,26,27,44).

Retrospective validation: The predictions of the model for the effects of total sleep deprivation were compared with an independent set of data reported by Angus and Heslegrave (3). Their results were plotted against the predictions of the sleep model and are shown in Fig. 3. All parameters within the model were set to the default values with the acrophase (peak of the 24-h circadian rhythm) and start time as indicated in the legend. The SAFTE Model predictions for the actual data were exceptionally good (R^2 = 0.98).

Prospective validation: The results of the sleep dose response study provide an opportunity to conduct a prospective validation of the SAFTE Model against a range of sleep conditions between total sleep deprivation and normal amounts of sleep. Fig. 4 is a summary of the results of that study showing the average perfor-

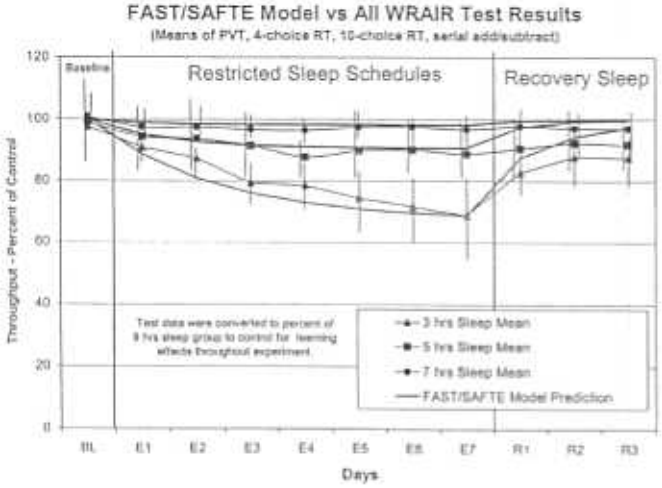

Fig. 4. Fit of the original SAFTE Model to the results of the sleep dose-response study conducted by the Walter Reed Army Institute of Research (6).

mance across all cognitive tasks as a percent of the performance of the group provided 9 h to sleep. This group was used for normalization to account for the clear learning effect that occurred with some of the tasks. The heavy lines through the points are the original SAFTE Model predictions. The model does a reasonably good job of predicting the average performance during the course of the 7 d of sleep restriction but does not predict the slow recovery seen during the 3 d of recovery sleep.

Virtually all models would have predicted full recovery of performance following 3 d of recovery sleep. The relatively permanent effect of chronic sleep restriction suggests that some aspect of sleep homeostasis undergoes a gradual change that is slow to recover. In an accompanying paper, researchers from the WRAIR propose a method to account for this effect. Within the context of the SAFTE Model, a simple gradual down-regulation of the sleep reservoir capacity (Rc) during chronic restriction can account for this change. A single equation modulates Rc during sleep, Eq 10:

$$Rc_{(t)} = Rc_{(t-1)} + t \cdot \{k_1 \cdot [1 - (SD_{(t-1)}/k_2)] + k_3 \cdot (2880 - Rc_{(t-1)})\}, \quad \text{Eq. 10}$$

where $SD_{(t-1)}$, is the sleep debt component of sleep intensity at time $t - 1$, $[f \cdot (Rc_{(t-1)} - R_{(t-1)})]$. Current sleep intensity, SI, is unchanged from Eq. 3 except that $Rc_{(t)}$ is allowed to adjust according to Eq. 10. As before, SP is the sleep propensity, the circadian component of sleep intensity. Parameter f is the amplitude of feedback in the original model and $R_{(t)}$ is the current reservoir balance. The exact value of f is adjusted to a slightly higher value (0.00312) when implementing Eq. 10 to ensure that a person getting 8 h of sleep per day is in balance. Based on the SDR study, the limit of SI is reduced to 3.4 units per minute. In addition, Eq. 10 is constrained so that when Rc is restored it may not exceed the full capacity of 2880, as represented in the original version of the model. No changes to Rc occur during awake periods. Good fits to data are achieved with constants about equal to the following:

$k_1 = 0.22$, down-regulation time constant

$k_2 = 0.5$, the reference level for SI regulation (note: normal sleep averages one SI unit per minute of sleep)

$k_3 = 0.0015$, recovery time constant.

Eq. 10 functions as follows: the first expression within brackets becomes negative when SD exceeds k_2 and down-regulates Rc according to the rate constant k_1; when SD is less than k_2, then the second expression within brackets tends to gradually restore Rc according to the rate constant k_3. Jointly, this expression tends to down-regulate Rc when sleep intensity is high ($> k_2$) and to restore Rc when sleep intensity is low ($< k_2$). During a normal 8-h period of sleep, Rc is down-regulated slightly and is restored by the end of the night. During prolonged periods of restricted sleep, Rc is down-regulated more than it is restored so that a gradual shift in the reservoir "set point" occurs. If we think of SD as a measure of "sleepiness," then this process tends to reduce sleepiness by reducing the difference between the current reservoir level and the reservoir capacity or "set point." During periods of restricted sleep, performance tends to be more severely degraded (compared with the original model) because the reservoir reaches equilibrium at a reduced set point. During recovery sleep, performance recovers more slowly (compared with the original model) because both the level of the reservoir and the reservoir capacity must be restored.

The heavy lines in **Fig. 5** are the predictions of the modified SAFTE Model optimized for average cognitive throughput and using the parameters listed above for Eq.10. This version of SAFTE makes identical predictions for total sleep deprivation, so the results in Fig. 3 are unchanged. The R^2 for this fit to the mean cognitive performance observed in the SDR study is 0.94.

Fig. 6 displays the average PVT speed from the same study shown in Fig. 5 (7). The lines in the figure indicate the predictions of the revised SAFTE Model optimized for average PVT speed $R^2 = 0.94$). Results are shown for the baseline, seven experimental days (E1-E7), and the three recovery days (R1-R3). Note that compared with

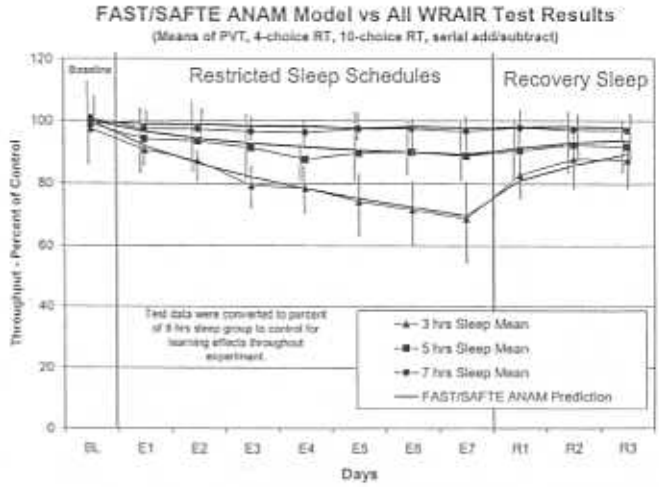

Fig. 5. Fit of the modified SAFTE Model to the average cognitive performance results of the sleep dose-response study based on actual sleep durations (6).

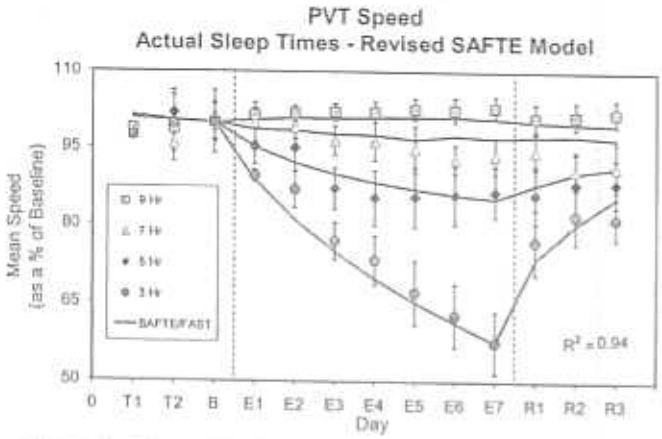

Fig. 6. Fit of the modified SAFTE Model to the PVT results of the sleep dose-response study based on actual sleep durations (6).

average cognitive throughput, PVT speeds tends to be more severely degraded and the parameters of the SAFTE Model reflect this difference in sensitivity of PVT speed compared with general cognitive throughput.

DISCUSSION: CRITICAL ISSUES

All models of sleep and performance have shortcomings, including the SAFTE Model. The importance of those limitations depends on the application. Two major limitations are that the model does not provide an estimate of group variance about the average performance prediction and it does not incorporate any individual difference parameters, such as age, morningness/eveningness, or sleep requirement for full performance. These individual characteristics may be relatively unimportant if the application of the model is for prediction of average group performance or for design of a generic schedule to be used by an entire work force. For these applications, ordinal predictions are sufficient to decide which of several alternative schedules is best or to decide if average performance at some future time is expected to be at an acceptable level. If the purpose is to judge a particular person's fitness for duty against some criterion level of performance or to predict the level of performance of a particular person some time in the future, then greater fidelity to these individual variables and some representation of the amount of predictive error would be valuable. In theory, some of these features could be added to the model based on the available literature. Other features, such as age effects and individual sleep requirements, would be difficult to incorporate without extensive additional research.

The performance of all models will also depend on the quality of the data used to establish the sleep history prior to the period of prediction. The WRAIR SPM model was designed explicitly to use actigraph records of sleep and wakefulness as the basis for prediction. The SAFTE Model as it is implemented in the schedule prediction tool, the Fatigue Avoidance Scheduling Tool (FAST) can take actigraph data as input to the prediction. Nevertheless, the results of the WRAIR SDR study showing slow recovery from restricted sleep, if replicated and confirmed, suggests that even a week of prior data may not be entirely adequate to account for the long-term effects of chronic sleep restriction. Indeed, these data suggest that most laboratory studies of sleep deprivation or sleep restriction may be flawed because few of them consider the possible contamination of the results by chronic sleep deprivation that might have preceded the laboratory measurements, especially in college students who have often served as the subjects in these experiments.

Military applications of sleep and performance models will require the incorporation of algorithms to predict the effects of pharmacological countermeasures, such as stimulants to extend performance or sedatives to enhance sleep. Some preliminary work has been done to model the effects of d-amphetamine and modafinil on performance in the SAFTE Model but the incorporation of these algorithms into a user tool is somewhat premature. Not only do stimulants temporarily improve performance in the face of sleep deprivation effects, they can also interfere with the ability to obtain restful sleep during the period of their arousal effects. Any complete model of the effects of stimulants must represent both the beneficial effects on cognitive performance and the temporary detrimental effects on sleep if attempted immediately after the drug administration. Similarly, any model that attempts to represent the beneficial effects of a sedative on sleep must also represent any detrimental cognitive effects that follow drug administration if performance, instead of sleep, is demanded of the subject.

Finally, all fatigue models presume some performance metric as the cardinal standard for prediction. Some models are explicitly designed to predict subjective alertness as measured by a rating instrument; others are designed to measure cognitive performance. For those designed to predict performance changes, some, like the WRAIR SPM, are optimized to predict reaction time performance on the psychomotor vigilance task (PVT), while others were designed to predict performance throughput (correct answers per minute) across a battery of cognitive tests. The SAFTE Model has two sets of parameters that can be used to predict either PVT speed or average cognitive throughput. Even if the PVT is used as the standard test, some researchers focus on speed and others focus on the occurrence of lapses, i.e., unusually long reaction times that may represent brief microsleeps that increase in frequency with duration of sleep deprivation. Fig. 7 shows that based on the SDR data, there is a linear relationship between lapse probability and the inverse of cognitive throughput or PVT speed. Hence, to properly test a cognitive throughput model, such as the SAFTE Model when using lapse data, an inverse transform of the prediction is necessary. Without such a transform, one finds an exponential relationship between cognitive throughput and lapse probability, and this nonlinearity, if not adjusted for, would cause an increase in prediction error with increases in amount of sleep deprivation. Unfortunately, an inverse transform was not applied to the cognitive throughput predictions for two of the scenar-

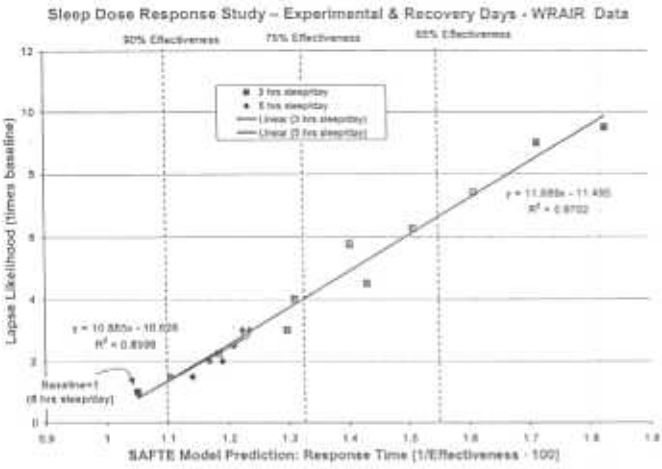

Fig. 7. Likelihood of lapses on the PVT is a linear function of the inverse of effectiveness predicted by the SAFTE Model optimized for PVT speed. These data are based on the results of the sleep dose-response study (6).

ios at the Seattle Fatigue and Performance Modeling Workshop in which the performance metric was PVT lapses, and this would naturally have inflated estimates of prediction error.

It may not be possible or desirable to adopt a universally accepted standard for performance measurement, but in the absence of a standard, great care must be taken when applying a model to a performance metric distinct from the one used to design the model. Ultimately, all models will be judged by their ability to make useful predictions of the performance of greatest interest to the user, which is most likely not going to be performance on a standard cognitive test, but rather performance of some job. The greatest challenge facing fatigue modeling is how to bridge this gap between laboratory metrics of performance and performance in the natural environment of work and war.

REFERENCES

1. Achermann P, Borbély A. Combining different models of sleep regulation. J Sleep Res 1992; 1:144–7.
2. Åkerstedt T, Folkard S. Validation of the S and C components of the three-process model of alertness regulation. Sleep 1995; 18:1–6.
3. Angus R, Heslegrave R. Effects of sleep loss on sustained cognitive performance during a command and control simulation. Behav Res Methods Instrum Comput 1985; 17:55–67.
4. Babkoff H, Mikulincer M, Caspy T, Sing HC. Selected problems of analysis and interpretation of the effects on sleep deprivation on temperature and performance rhythms. Ann NY Acad Sci 1992; 658:93–110.
5. Balkin TJ, Braun AR, Wesensten NJ, et al. The process of awakening: a PET study of regional brain activity patterns mediating the reestablishment of alertness and consciousness. Brain 2002; 125:2308–19.
6. Balkin T, Thorne D, Sing H, et al. Effects of sleep schedules on commercial driver performance. Washington, DC: U.S. Department of Transportation, Federal Motor Carrier Safety Administration; 2000; Report No.: DOT-MC-00–133.
7. Belenky G, Balkin T, Redmond D, et al. Sustaining performance during continuous operations: The U.S. Army's sleep management system. 20th Army Science Conference, 1996 Jun; 24–27 Norfolk:VA.
8. Bjerner B, Holm A, Swenson A. Diurnal variation of mental performance. A study of three-shift workers. Br J Ind Med 1955; 12:103–10.
9. Bonnet MH. Sleep fragmentation as the cause of daytime sleepiness and reduced performance. Wien Med Wochenschr 1997; 146(13–14):332–4.
10. Borbely A, Achermann P, Trachsel L, Tobler I. Sleep initiation and initial sleep intensity: interactions of homeostatic and circadian mechanisms. J Biol Rhythms 1989; 4:49–60.
11. Carskadon M, Dement W. Sleep tendency: an objective measure of sleep loss. Sleep Res 1977; 6:200.
12. Czeisler C, Kronauer R, Allan, J, et al. Bright light induction of strong (type 0) resetting of the human circadian pace-maker. Science 1989; 244:1328.
13. Dinges D, Orne M, Orne E. Sleep depth and other factors associated with performance upon abrupt awakening. Sleep Res 1985; 14:92.
14. Dinges DF, Powell JW. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. Behav Res Methods Instrum Comput 1985; 17:652–65.
15. Dinges D, Powell JW. Sleepiness impairs optimum response capability. Sleep Res 1989; 18:366.
16. Eddy DR, Hursh SR. Fatigue Avoidance Scheduling Tool (FAST). Brooks AFB, TX: Human Effectiveness Directorate, Biodynamics and Protection Division, Flight Motion Effects Branch; 2001; AFRL-HE-BR-TR-2001–0140, SBIR Phase I Final Report.
17. Folkard S, Åkerstedt T. A three process model of the regulation of alertness-sleepiness. In: Ogilvie R, Broughton R, eds. Sleep, arousal and performance problems and promises. A tribute to Bob Wilkinson. Boston: Birkhauser; 1992:11–26.
18. Folkard S, Åkerstedt T. Towards a model for the prediction of alertness and/or fatigue on different sleep/wake schedules. In: Oginski A, Pokorski J, Rutenfranz J, eds: Contemporary advances in shiftwork research. Krakow: Medical Academy; 1987:231–40.
19. Folkard S, Åkerstedt T, Macdonald I, et al. Beyond the three-process model of alertness: estimating phase, time on shift, and successive night effects. J Biol Rhythms 1999; 14:577–87.
20. Folkard S, Monk T. Shiftwork and performance. Hum Factors 1979; 21:483–92.
21. Folkard S, Monk T. Circadian performance rhythms. In: Folkard S, Monk T, eds. Hours of work: temporal factors in work schedules. New York: John Wiley and Sons; 1985; 37–52.
22. Froberg J. Twenty-four-hour patterns in human performance, subjective and physiological variables and differences between morning and evening active subjects. Biol Psychol 1977; 5:119–34.
23. Gander P, Kronauer R, Graeber R. Phase shifting two coupled circadian pacemakers: Implications for jet lag. Am J Physiol 1985; 249:704–19.
24. Graeber RC. Recent studies relative to the airlifting of military units across time zones. In: Scheving LE, Halberg F, eds. Chronobiology: principles and applications to shifts in schedules. Rockville, MD: Sijthoff and Noordhoff; 1980:353–70.
25. Gundel A, Wegmann H. Resynchronization of the circadian system following a 9-hr advance or a delay zeitgeber shift: real flights and simulations by a Van-der-Pol oscillator. Prog Clin Biol Res 1987; 227B:391–401.
26. Hamelin P. Lorry drivers times habits in work and their involvement in traffic accidents. Ergonomics 1987; 30:1323–33.
27. Harris W. Fatigue, circadian rhythm and truck accidents. In: Mackie R, ed. Vigilance. New York: Plenum Press 1977; 133–47.
28. Harrison Y, Horne JA. Long-term extension to sleep—are we really chronically sleep deprived? Psychophysiology 1996; 33: 22–30.
29. Haus E, Halberg F. The circadian time structure. In: Scheving LE, Halberg F, eds. Chronobiology: principles and applications to shifts in schedules. Rockville, MD: Sijthoff and Noordhoff; 1980:47–94.
30. Hursh SR, McNally R. Modeling human performance to predict unit effectiveness. In: Kamely D, Bannister K, Sasmor R, eds. Army science: the new frontiers, military and civilian applications. Saratoga, WY: Borg Biomedical Books; 1993:309–28.
31. Hursh SR. Modeling sleep and performance within the Integrated Unit Simulation System (IUSS). Final report for the United States Army Soldier Systems Command; Natick Research, Development and Engineering Center. Natick, MA: Science and

Technology Directorate; 1998;Technical Report: Natick/TR-98/026L.
32. Jewett M. Models of circadian and homeostatic regulation of human performance and alertness. [Dissertation]. Cambridge, MA: Harvard University; 1997.
33. Jewett M, Kronauer R. Interactive mathematical models of subjective alertness and cognitive throughput in humans. J Biol Rhythms 1999; 4:588–97.
34. Khalsa S, Jewett M, Klerman E, et al. Type 0 resetting of the human circadian pacemaker to consecutive bright light pulses against a background of very dim light. Sleep Res 1997; 26:722.
35. Klein K, Wegmann H. The effect of transmeridian and transequitorial air travel on psychological well-being and performance. In: Scheving LE, Halberg F, eds. Chronobiology: principles and applications to shifts in schedules. Rockville, MD: Sijthoff and Noordhoff; 1980:339–52.
36. Lavie P. The 24-hour sleep propensity function (SPF): Practical and theoretical implications. In: Monk T, ed. Sleep, sleepiness and performance. Chinchester, UK: Wiley 1991; 65–93.
37. Lavie P. To nap perchance to sleep–ultradian aspects of napping. In: Dinges D, Broughton R, eds. Sleep and alertness: chronobiological, behavioral, and medical aspects of napping. New York: Raven Press; 1989:99–120.
38. Lumley M, Roehrs T, Zorick F, et al. The alerting effects of naps in sleep-deprived subjects. Psychophysiology 1986; 23:403–8.
39. Minors D, Åkerstedt T, Waterhouse J. The adjustment of the circadian rhythm of body temperature to simulated time-zone transitions: a comparison of the effect of using raw versus unmasked data. Chronobiol Int 1994; 11:356–66.
40. Mitler M, Gujavarty S, Sampson G, Bowman, C. Multiple daytime nap approaches to evaluating the sleepy patient. Sleep 1982; 5:119–27.
41. Monk T. Circadian aspects of subjective sleepiness: a behavioral messenger? In: Monk T, ed. Sleep, sleepiness and performance. Chichester, UK: Wiley; 1991:39–63.
42. Monk T, Embry D. A field study of circadian rhythms in actual and interpolated task performance. In: Reinberg A, Vieux N, Andlauer P, eds. Night and shift work: biological and social aspects. Oxford: Pergamon Press; 1981:473–80.
43. Nicholson A, Stone B. Sleep and wakefulness handbook for flight medical officers. Neuilly-sur-Seine, France: NATO, Advisory Group for Aerospace Research & Development; 1982: 34–37; AGARDograph No. 270(E).
44. Ribak J, Ashkenzia I, Klepfish A, et al. Diurnal rhythmicity and air force flight accidents due to pilot error. Aviat Space Environ Med 1983; 54:1096–9.
45. Richardson D, Carskadron M, Flagg W, et al. Excessive daytime sleepiness in man: multiple sleep latency measurement in narcoleptic and control subjects. Electroencephalogr Clini Neurophysiol 1978; 45:621–7.
46. Thorne DR, Genser S, Sing H, Hegge F. Plumbing human performance limits during 72 hours of high task load. In: Proceedings of the 24th DRG seminar on the human as a limiting element in military systems. Toronto: Defence and Civil Institute of Environmental Medicine; 1983:17–40.
47. Wever R. Mathematical models of circadian one- and multi-oscillator systems. Lect Math Life Sci 1987; 19:205–65.
48. Wesensten NJ, Balkin TJ, Belenky G. Does sleep fragmentation impact recuperation? A review and reanalysis. J Sleep Res 1999; 8:237–46.

APPENDIX II

Storm, W., Eddy, D., Welch, C., Hickey, P., Fischer, J., and Cardenas, B. Cognitive Performance Following Premature Awakening from Zolpidem or Melatonin Induced Daytime Sleep. *Aviation, Space, and Environmental Medicine,* 2007, 78, 10-20.

Cognitive Performance Following Premature Awakening from Zolpidem or Melatonin Induced Daytime Sleep

WILLIAM F. STORM, DOUGLAS R. EDDY, CORY B. WELCH, PATRICK A. HICKEY, JOSEPH FISCHER, AND REBECCA CARDENAS

STORM WF, EDDY DR, WELCH CB, HICKEY PA, FISCHER J, CARDENAS R. *Cognitive performance following premature awakening from zolpidem or melatonin induced daytime sleep.* Aviat Space Environ Med 2007; 78:10–20.

Background: The hypnotic zolpidem and the hormone melatonin were evaluated and directly compared for their effects on performance when subjects sleeping under their influence were prematurely awakened from daytime sleep. ***Method:*** Non-sleep deprived volunteers (eight men and five women) received single oral doses of 5 or 10 mg melatonin (Mel-5; Mel-10), 10 or 20 mg zolpidem (Zol-10; Zol-20), or placebo immediately before retiring at 13:00. Performance testing and subjective evaluations occurred prior to dosing and following forced awakening at 15:00, 2 h after dosing. ***Results:*** Compared with placebo, on being awakened under Zol-20, significant performance decrements were prevalent on 9 of 10 cognitive tasks, including grammatical reasoning, mathematical processing, and word memory. Recovery required up to 6 h post-awakening for the more complex tasks. Loss of coordination and nausea were also present on awakening under Zol-20. On being awakened under Zol-10, significant but relatively less severe and shorter duration performance decrements occurred for 4 of the 10 tasks and recovered by 4 h post-awakening. Under Mel-5 or Mel-10, performance decrements seldom occurred and were considerably less severe, briefer, and less systematic than for zolpidem. ***Conclusion:*** Findings indicated that when operational personnel sleeping with the aid of either 10 or 20 mg zolpidem are prematurely awakened, it would be prudent to evaluate their general well-being and possible need for assistance prior to their being permitted to depart crew-rest or to perform tasks and duties. In contrast, we found little to no evidence of deteriorated well-being or need for assistance when awakened while sleeping under the influence of melatonin.

Keywords: reaction time, memory, problem solving, multiple tasking, postural sway, fatigue, sleepiness.

MILITARY REQUIREMENTS can involve sustained around-the-clock operations, long-duration missions, quick-turn forays and sortie surges, global deployments, and bare-base operational and living environments. During these and other demanding operations, combat and support personnel must often take advantage of rest opportunities at atypical times of the day, out of sync with the body's internal circadian clock, and under less than ideal environmental conditions, resulting in delayed, shortened, and restless sleep. The physical and psychological restoration acquired under these impoverished sleeping conditions is often insufficient for maintaining optimal or even adequate performance efficiency. In such cases a sleep-promoting medication may be prescribed to provide a more recuperative rest.

Zolpidem tartrate (Ambien®, Sanofi-Aventis, Bridgewater, NJ) is one of three hypnotic compounds approved by the USAF Surgeon General (25) for use to promote sleep in aircrews and special duty personnel that must acquire pre-mission crew rest under adverse and demanding operational situations (the two other USAF-approved sleep-aids are temazepam and zaleplon). Prior to reporting for airborne missions, USAF aircrews are required by regulation to receive 12 h of inviolate crew rest, during which they must be afforded the opportunity for at least 8 h of uninterrupted sleep. When approved for use by the unit commander and flight surgeon, the recommended therapeutic dose of 10 mg zolpidem may be taken no less than 6 h before reporting for the scheduled crew duty day and mission. Zolpidem's pharmacokinetic profile makes its designated application during the regulated 12-h aircrew rest periods effective and safe. Peak plasma concentrations are reached 1.0–1.5 h after ingestion and the elimination half-life is 2.0–2.5 h.

Decisions on the use of zolpidem to enhance the restorative value of sleep during crew rest must weigh the benefits and risks given the nature of the military operation, the condition of the personnel, the sleeping environment, and the likelihood that the sleep could be interrupted while under the influence of zolpidem. Studies seldom find residual effects following an uninterrupted night's sleep or an extended daytime sleep period with 10 or 20 mg zolpidem (3,16,17). However, emergency and contingency situations can arise during intense, sustained military operations like those de-

From NTI, Inc. (W. F. Storm, D. R. Eddy, C. B. Welch, P. A. Hickey, R. Cardenas) and General Dynamics-AIS (J. R. Fischer), Brooks City-Base, TX.

This manuscript was received for review in April 2006. It was accepted for publication in October 2006.

Address reprint requests to: Dr. William F. Storm, NTI, Inc., 2485 Gillingham Dr., Bldg. 170, Rm. 211, Brooks City-Base, TX 78235-5105; william.storm.ctr@brooks.af.mil.

scribed above that require sleeping personnel be awakened prior to completion of their allotted rest period. The sedation induced by zolpidem is the result of central nervous system depression and personnel may be ineffective until the soporific effects of the compound wear off. Cognitive performance has consistently been found to be impaired when zolpidem is present at peak or near-peak plasma levels during the immediate hours following ingestion (4,23,27). However, the use of 20 mg zolpidem in some operational situations continues to be an option of interest. Researchers at the Walter Reed Army Institute of Research have compared zolpidem dosages in a series of studies and concluded that 20 mg of zolpidem may be required to significantly improve daytime sleep in "non-sleep-conducive" environments in non-sleep-deprived healthy young adults (2,28). In addition researchers and flight surgeons at the Air Force Research Laboratory and the USAF School of Aerospace Medicine continue to receive inquiries regarding the potential use of 20 mg zolpidem in the field.

The naturally occurring hormone melatonin is another sleep-inducing compound that has received widespread public acceptance as a safe, non-prescriptive means to induce sleepiness with doses typically of 3–10 mg. It has a pharmacokinetic profile comparable to zolpidem. The mean peak plasma level for a daytime dose occurs about an hour after ingestion and the elimination half-life is about 2–3 h across a wide variety of doses. Unlike zolpidem and other hypnotic compounds melatonin does not promote sleep by central nervous system depression. As Caldwell (5) points out in her pragmatic review of aeromedical considerations in the use of melatonin, hypnotics like zolpidem force sleep to occur, whereas melatonin acts as a soporific, allowing sleep to occur. Melatonin has short-lived or no impact on cognitive performance and an almost complete absence of side-effects (5,18). However, the fact that melatonin is manufactured as an over-the-counter dietary supplement without Food and Drug Administration regulated safety trials, quality control standards, or dosage recommendations remains a critical concern and a primary factor in its not being considered for regulated use by U.S. military personnel. Nevertheless, melatonin remains an interesting and enticing alternative to hypnotics as a means of enhancing daytime sleep. Field experiments by researchers at the U.S. Army Aeromedical Research Laboratory and Defence Research and Development Canada-Toronto have demonstrated the potential operational utility of melatonin as a daytime sleep aid during actual rapid deployment and global airlift operations (6,20).

The current study was designed to evaluate and directly compare the magnitude and duration of the effects of the hypnotic zolpidem (10- and 20-mg doses) and the hormone melatonin (5- and 10-mg doses) on a broad range of cognitive and physical performance measures in an operationally relevant, sudden-awakening paradigm. Performance was assessed immediately following premature awakening from daytime sleep 2 h after ingestion of a single oral dose of zolpidem or melatonin administered on the assumption of an uninterrupted sleep period of about 7–9 h. Awakening was timed to occur when the zolpidem or melatonin would be at peak or near-peak plasma levels.

METHODS

Participants

There were 13 volunteer participants, 5 women and 8 men (mean age 28.0 yr, range 21–42 yr), who completed all 5 sessions of the study. A total of 16 volunteers initiated participation in the study, but midway through data collection 3 withdrew; one for illness unrelated to the study and two for personal reasons. Participants were medically examined (including blood chemistry and liver function) by a qualified medical practitioner knowledgeable with the objectives and requirements of the study. Volunteers were thoroughly briefed on the possible risks and discomforts associated with participation. Volunteers with evidence of any current significant illness, sleep abnormalities, use of tobacco, or excessive use of caffeine or alcohol were not allowed to participate. Women who were pregnant or attempting to become pregnant were excluded. Female participants were given a urine pregnancy test immediately prior to each experimental session. Participants gave written informed consent before participating and were paid for their participation. The research protocol was reviewed and approved in advance of subject recruitment by the Brooks City-Base Institutional Review Board and the U.S. Army Surgeon General Human Subjects Research Review Board.

Experimental Design

The study was conducted using a repeated measures design with two within-subject factors: five experimental sessions and nine testing blocks during each session. Each participant experienced five drug conditions, one each during each of the experimental sessions. The five conditions were single oral doses of 10 or 20 mg zolpidem (Zol-10 and Zol-20), 5 or 10 mg melatonin (Mel-5 and Mel-10), and placebo. Drug administration was randomized and double-blind. The experimental sessions were each 20 h in duration (11:00–07:00) and separated by at least 6 d. Participants were directed not to consume alcohol the evening before an experimental session and to obtain a normal night's sleep prior to each session. Subjects participated in the experimental sessions in groups of two to five. On each of 3 d prior to participating in their initial experimental session each subject received a 3-h training session with the amount of training on each performance task proportional to task complexity. Subjects were trained to asymptotic performance on each of the cognitive tasks.

Facility and Materials

The study was conducted in the Air Force Research Laboratory Fatigue Countermeasures Lab at Brooks City-Base, San Antonio, TX. During experimental sessions each participant was assigned to a private room equipped with a personal computer workstation for testing, a bed, and a private bath. Throughout the experimental sessions the participants were always under

the direct observation of research personnel or knowingly monitored from a central control station by closed circuit television, excluding of course the private baths. Lying down or napping were never permitted except for the scheduled 2-h sleep period integral to the study. While the objective of this study was not to evaluate the efficacy of zolpidem and melatonin, sleep was monitored and scored polysomnograpically (PSG) to document time slept during the 2-h sleep periods (21). Total sleep time was assessed using the Stellate Harmonie software (Stellate Systems, Inc., Montreal Quebec, Canada) with oversight and review by an experienced PSG scorer blind to the experimental conditions.

The zolpidem, melatonin, and placebo doses were acquired, prepared, coded, and randomly assigned by the Inpatient Pharmacy at USAF Wilford Hall Medical Center. One gram of melatonin powder, manufacturing lot number QM0686–1, with an assay purity of 96%, was obtained from Spectrum Laboratory Products, Inc. of New Brunswick, NJ. The melatonin was packaged using a standard compounding technique. A measured quantity of the melatonin powder was thoroughly mixed with a known amount of psyllium fiber. Portions of the resultant mixture were weighed to ensure that 5- or 10-mg doses of melatonin were measured and placed into unmarked gelatin capsules. Psyllium was also used as filler for the doses of zolpidem and placebo, which were also individually packed in the same identical gelatin capsules as the melatonin.

Tests and Measures

Automated neuropsychological assessment metrics (ANAM): Five cognitive performance assessment tasks from the PC-based ANAM battery (22) were applied in this study. The five tasks required a total of about 18 min for a well-practiced, alert subject to complete under baseline conditions. Response times and correct and incorrect responses were recorded and used to calculate the single outcome measure "throughput" (mean number correct responses per minute) for each of the ANAM tasks except simple reaction time. The advantage of throughput lies in the fact that its calculation is a function of both the accuracy and the speed of the subject's responses. The five ANAM tasks were performed in the following sequence during each testing block.

1. Code substitution – This task is a modification and expansion of the Digit Symbol Substitution Test (DSST) frequently used in studies assessing hypnotics and alertness aids. ANAM code substitution consists of three phases within each testing block: learning; immediate recall; and delayed recall. During the learning phase, which is similar to the traditional DSST, the assigned pairings of a unique symbol with each of the digits 1–9 are presented in a row across the top of the monitor screen. The subject learns the pairings as he/she refers to them to determine whether individual "test-pairs" presented sequentially at the bottom of the screen correctly match one of the assigned pairings. Symbol/digit pairings are randomly reassigned for each testing block. In this study the immediate recall phase was administered on completion of the learning phase, and the delayed recall phase occurred about 12 min later following completion of the four other ANAM tasks. During the immediate and delayed recall phases only test pairs were presented one at a time and the subject responded as to whether or not each displayed pair was correct or incorrect based on his/her recollection. The learning phase consisted of 72 test-pair presentations, immediate recall 36, and delayed recall 18.

2. Reaction time – Simple reaction time was evaluated by having subjects press a computer mouse key in response to a visual stimulus presented at a centrally fixed point on the computer screen. Mean reaction time to 20 stimuli (interstimulus interval of 650–1200 ms) presented during a less than 1-min trial was the outcome measure.

3. Mathematical processing – Each problem in this task included two mathematical operations (addition and/or subtraction) on sets of three single-digit numbers (e.g., 5 + 3 − 4 = ?). The subject was instructed to read and calculate from left to right and indicate whether the answer was greater than or less than '5' by pressing one of two specified response buttons on the mouse. Trials were 3 min in duration.

4. Grammatical reasoning – The subject determined as quickly as possible whether each of two simple summary statements (e.g., & follows * and # precedes *) correctly described the sequential relationships among three symbols (e.g., # & *). If one statement was true and one false, one response was correct; if both statements were true or both were false an alternative response was made. A trial consisted of 48 presentations.

5. Continuous processing – Subjects were directed to continuously monitor a randomized sequence of the numerals 0 through 9 presented one at a time in the center of the screen and to press the left mouse key if the numeral currently on the screen matched the numeral that immediately preceded it. If not a match the right mouse key was pressed. Trials were 3 min in duration. (This task is also referred to as 'running memory.')

Synthetic work task: "SynWin: A Synthetic Work Program for Windows" (11) is a PC-based four-component task that provides a generic work environment. A memory (Sternberg) task, an arithmetic task, a visual monitoring task, and an auditory monitoring task were presented simultaneously, each in one quadrant of the screen. The subject was required to remember and classify items on demand, perform a self-paced task, and monitor and react to both visual and auditory information. A composite score was the outcome measure for a 10-min trial.

Word memory task: The Williams Word Memory Task provided an assessment of short-term memory. During the immediate post-awakening testing block at 15:00, the subject listened to an auditory presentation of 15 recorded words. Each word was spoken, spelled, and then spoken again. The subject wrote down each word as it was presented. On completion of the presentation, the subject studied the list for 1 min. The written list was then collected and the subject was directed to immediately recall in 1 min as many of the words as possible by writing them on a fresh paper form. De-

layed recall of the same list occurred 4 h later during the third post-awakening testing block at 19:00. The number of words recalled from the list of 15 was the outcome measure for this task.

Psychomotor Vigilance Task (PVT): The PVT (Model PVT-192, CWE Inc., Ardmore, PA) is a portable, self-contained visual reaction time task requiring sustained attention and a simple, discrete push-button motor response to each signal, which was the onset of a elapsed-time digital clock. The clock appeared within a well-defined display window and was extinguished and reset to zero within a second after each response. Signals occurred randomly every 2–12 s. Trials were 10 min in duration and the outcome measure was mean reciprocal reaction time.

Postural sway: Postural or body sway was assessed using a force platform that measured changes in the body's center of pressure over time (Platform model OR6–5-1, AMTI, Watertown, MA). The apparatus resembled an oversized home bathroom scale, with an area of approximately 18 by 20 in and a height of 3 in. The subject was directed to stand as motionless as possible while 1 min of data was collected for both eyes open and eyes closed conditions at a sampling rate of 10 Hz. The amplitude, velocity, and frequency of change in the center of pressure reflected the participant's ability to maintain balance. An elliptical area of measurement that accounted for 95% of the variation in the center of changes in pressure provided the outcome measure.

Grip strength: Strength was measured as the highest value attained of two grip squeezes, separated by 1 min, on a Sammons-Preston Inc. JAMAR (Bolingbrook, IL) hydraulic hand dynamometer.

Sleepiness: The ANAM battery offered a sleepiness scale that, while a modification of the Stanford Sleepiness Scale (14), maintained the 7-point scale rating subjective sleepiness from "1-very alert, wide awake, and energetic" to "7-very sleepy and cannot stay awake much longer." The ANAM sleepiness scale was presented on the computer monitor as the first item of business at the start of each testing block.

Symptoms: Participants completed a 73-item paper and pencil symptom checklist at the end of each testing block, indicating the severity (none, some, moderately, or severely) they were experiencing for each symptom at that point in time.

Procedures

The standardized testing schedule for the experimental sessions is presented in **Table I**. Participants arrived at the laboratory about 09:30, allowing time for them to settle into their rooms, have a light lunch at least 1 h prior to dosing, and for the PSG electrodes to be applied prior to the first (baseline) testing block beginning at 11:00. Except for including the word memory task in the 15:00 and 19:00 blocks, all nine testing blocks within a session were identical, beginning at the top of an hour, and requiring about 90 min to complete. Drug doses were administered 2–3 min before 13:00, following which the participants were immediately shepherded to bed, the electrode leads attached to the ambulatory recorder, the room door closed, and the lights turned off. The subjects were awakened at 15:00 when blood levels of the experimental doses were anticipated to be at peak or near-peak plasma levels. The subjects were awakened by voice instruction over the intercom system and simultaneous turning on of the lights, followed immediately by research staff entering each room to disconnect and collect the ambulatory recorders and assist the participants as needed in getting the 15:00 testing block underway within 5 min of awakening. Participants were subsequently tested at 2-h intervals through the final ninth testing block beginning at 05:00. Vital signs (BP, heart rate, and oral temperature) were monitored once during each testing block. Participants were required to make arrangements to be chauffeured home from the laboratory on completion of each testing session.

TABLE I. EXPERIMENTAL SESSION TESTING SCHEDULE.

Start	End	Activity/Task
09:30	11:00	Arrival/prep/lunch
11:00	11:30	ANAM*
11:30	12:00	Synthetic work
12:00	12:15	Force platform; grip strength; vitals
12:15	12:30	PVT**; symptom survey
12:30	13:00	Break/no food
13:00	15:00	Drug; to bed
15:00	15:30	ANAM; word memory: memorization
15:30	16:00	Synthetic work; word memory: recall
16:00	16:15	Force platform; grip strength; vitals
16:15	16:30	PVT; symptom survey
16:30	17:00	Break/snack
17:00	17:30	ANAM
17:30	18:00	Synthetic work
18:00	18:15	Force platform; grip strength; vitals
18:15	18:30	PVT; symptom survey
18:30	19:00	Break/snack

*ANAM: Automated Neuropsychological Assessment Battery
** PVT: Psychomotor Vigilance Task
Subsequent testing blocks occurred at 19:00, 21:00, 23:00, 01:00, 03:00, and 05:00. All the testing blocks were identical with one exception—word memory: delayed recall for the list learned in the 15:00 session was tested during the 19:00 session.

Statistical Analyses

For each continuous, normally distributed outcome measure, a repeated measures two-factor analysis of variance (ANOVA) was performed to test for significant drug and time main effects and drug × time interactions. A Huyhn-Feldt adjustment was made to the degrees of freedom for tests that failed Mauchley's Test of Sphericity. To reduce excessive post hoc testing, a two-stage process was applied when significant drug or drug × time effects were detected. First, an individual ANOVA was performed at each time point to compare the five drug conditions. Only when this analysis indicated significance were Student's paired *t*-tests used to identify specific differences between the various drug conditions. For outcome measures where non-normality was suspected, non-parametric analyses were conducted also using a two-stage process: Friedman tests as an initial screen for significance followed by Wilcoxon signed-rank tests. Significance testing was performed at the 0.05 α level. For the tests of primary interest

(post hoc comparisons of the drug conditions), the final sample of 13 participants provided an 83% chance (power = 0.83) of detecting relatively large differences between two means (i.e., effect size = 0.85 = mean difference divided by the standard deviation of the difference) when testing at the two-tailed 0.05 α level.

RESULTS

Self-report sleep logs and actigraphy records indicated that the participants were rested when reporting for the testing sessions, averaging 8.2 h of sleep on the nights immediately preceding the experimental sessions (average hours slept ranged from 6.8–9.3 h). The 11:00 baseline values for each dependent measure were consistently stable across the five testing sessions, demonstrating that the subjects were trained to reliable asymptotic levels on the performance tasks and supporting procedures. Missing data occurred less than 2% of the time due to infrequent technical problems and occasional nausea related to the 20-mg zolpidem condition. To facilitate statistical analyses, estimates were made of missing data based on the average of corresponding percent changes in data available from other subjects. Three subjects when awakened at 15:00 under the influence of 20 mg zolpidem were too nauseated, try though they did, to successfully perform all of the cognitive tasks as scheduled for up to 4 h. To minimize the disruptive impact of the nausea and emesis caused by the 20-mg zolpidem condition in these and to a lesser extent other subjects, time scheduled for synthetic work task testing during the 15:00 and 17:00 testing blocks was sometimes sacrificed to assure the completion of other tasks and procedures. Nausea, if present, subsided considerably 4–6 h after being awakened and all 13 participants completed their 20-mg zolpidem session. All but 1 of the 13 subjects acquired some sleep under each of the treatments. Including this subject there were eight instances in which subjects were not asleep at 15:00; three under placebo, two under Mel-5, one under Mel-10, and two under Zol-10. In seven of these eight instances the subjects acquired less than 15 min of sleep in each 2-h sleep period Excluding these seven cases, the range for time slept during the 2-h sleep periods was 49.0–114.5 min (median = 93.0).

Code Substitution: Learning

A significant drug × time interaction was detected for throughput performance [$p = 0.002$, $F(10,117) = 3.0$, MSE = 201.0; **Fig. 1A**]. For the 15:00 test block, post hoc paired-comparison tests indicated performance was significantly poorer under Zol-20 than under each of the other conditions. At 17:00, performance under Zol-20 was poorer than under the placebo and the two melatonin conditions. Performance under Zol-10 was poorer than under the placebo.

Code Substitution: Immediate Recall

A significant drug × time interaction was detected for throughput [$p \leq 0.001$, $F(22,262) = 2.5$, MSE = 201.9; **Fig. 1B**]. At 15:00, performance was significantly poorer under Zol-20 than each of the other conditions. Performance under Mel-5 was poorer than under placebo. At 17:00, performance under Zol-20 and Zol-10 was poorer than under placebo and both of the melatonin conditions.

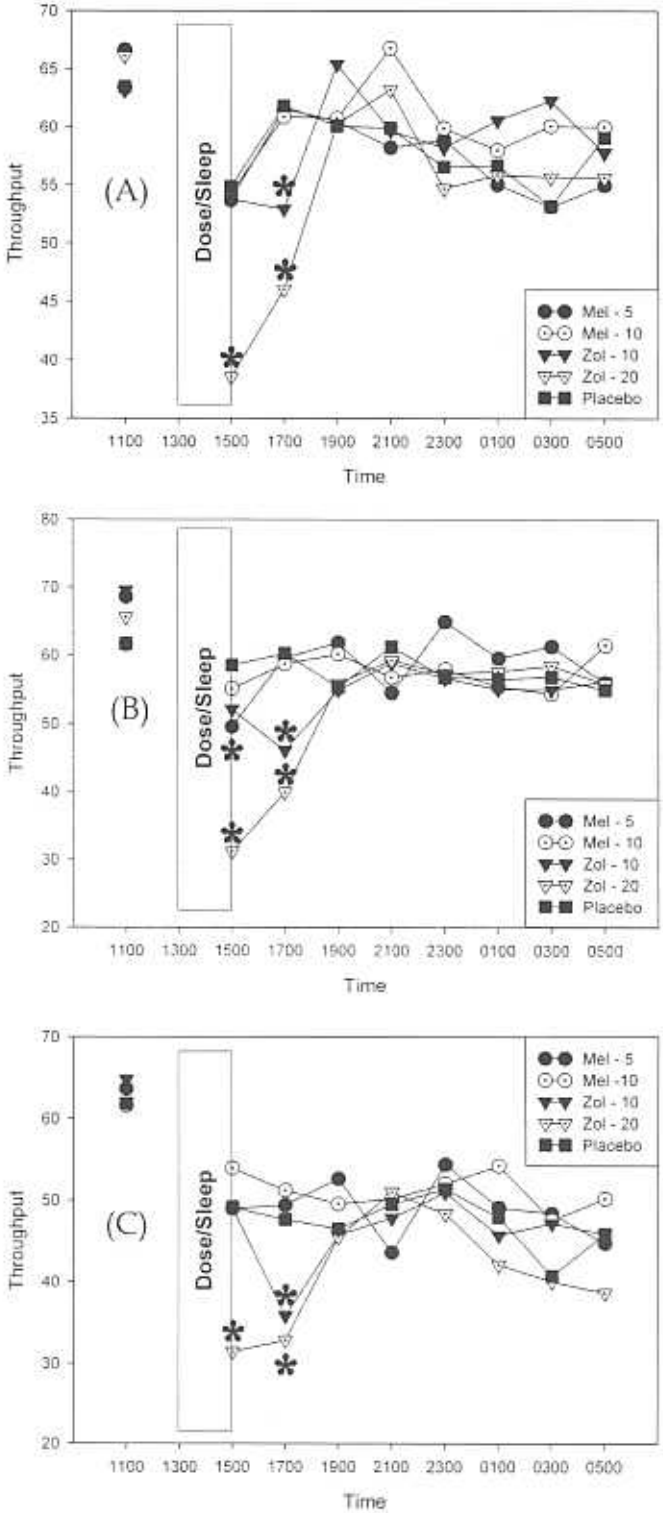

Fig. 1. Code substitution: A) learning; B) immediate recall; C) delayed recall. * Significantly ($p \leq 0.05$) different from placebo.

Code Substitution: Delayed Recall

A significant drug × time interaction was detected for throughput [$p = 0.024$, $F(10,122) = 2.2$, MSE =

304.2; **Fig. 1C**]. At 15:00 performance was significantly poorer under Zol-20 than under each of the other conditions. At 17:00, performance under Zol-20 and Zol-10 was poorer than under placebo and both of the melatonin conditions. A three-factor, repeated-measures ANOVA performed across the three code substitution phases (learning, immediate recall, and delayed recall) did not detect a significant drug × time × phase interaction, indicating immediate recall and delayed recall were not differentially affected by any of the drug conditions.

Math Processing

A significant drug × time interaction was detected for throughput [$p \leq 0.001$, $F(12,145) = 4.2$, $MSE = 46.9$; **Fig. 2**]. At 15:00, performance under Zol-20 was poorer than under of the other conditions. At 17:00, performance under Zol-20 was poorer than under each of the other conditions and performance under Zol-10 was poorer than under both of the melatonin conditions. At 19:00, performance under Zol-20 was poorer than under each of the other conditions.

Grammatical Reasoning

A significant drug effect was detected for throughput [$p = 0.024$, $F(2,23) = 4.5$, $MSE = 92.4$; **Fig. 3**]. At 15:00, performance under Zol-20 was poorer than under each of the other conditions. Performance under Mel-5 was poorer than under placebo. At 17:00, performance under Zol-20 was poorer than each of the other conditions. Performance under Zol-10 was poorer than that under both of the melatonin conditions. At 19:00, performance in the Zol-20 condition was poorer than under each of the other conditions.

Continuous Processing

A significant drug x time interaction was detected for throughput [$p \leq 0.001$, $F(8,94) = 4.0$, $MSE = 830.8$; **Fig. 4**]. At 15:00 and 17:00, performance under Zol-20 was poorer than under each of the other conditions. At 19:00, performance under Zol-20 was poorer than under placebo and both of the melatonin conditions.

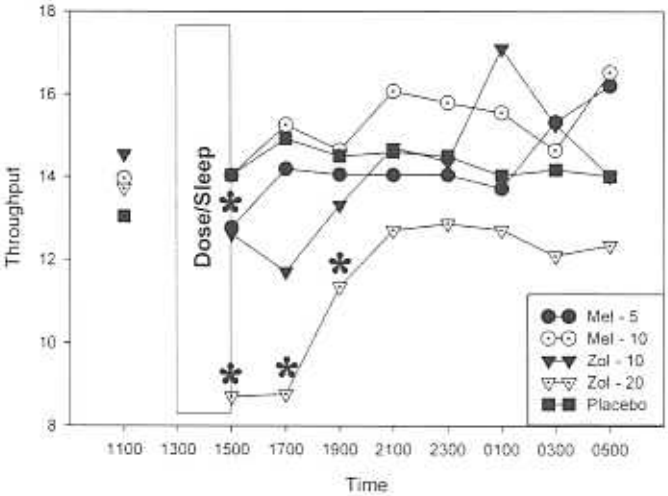

Fig. 3. Grammatical reasoning. * Significantly ($p \leq 0.05$) different from placebo.

Simple Reaction Time

No statistically significant drug or drug × time effects were detected for simple reaction time performance, although notable increases in mean reaction time occurred at 15:00 and 17:00 for the Zol-20 condition (**Fig. 5**).

Synthetic Work

Loss of data due to nausea associated with the Zol-20 condition along with technical problems with this task resulted in complete data being available from only 6 of the 13 participants. Analyses of the composite score variable for these six subjects revealed a significant drug × time interaction [$p = 0.021$, $F(9,43) = 2.5$, $MSE = 3596586.1$; **Fig. 6**]. At 15:00, performance under Zol-20 was poorer than that for placebo and the two melatonin conditions.

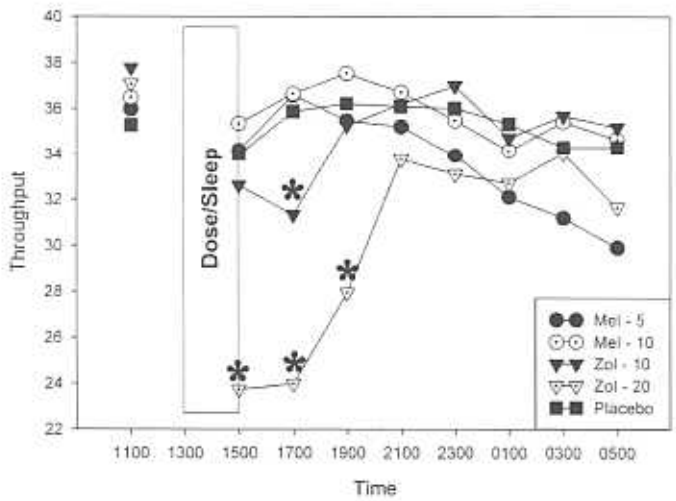

Fig. 2. Math processing. * Significantly ($p \leq 0.05$) different from placebo.

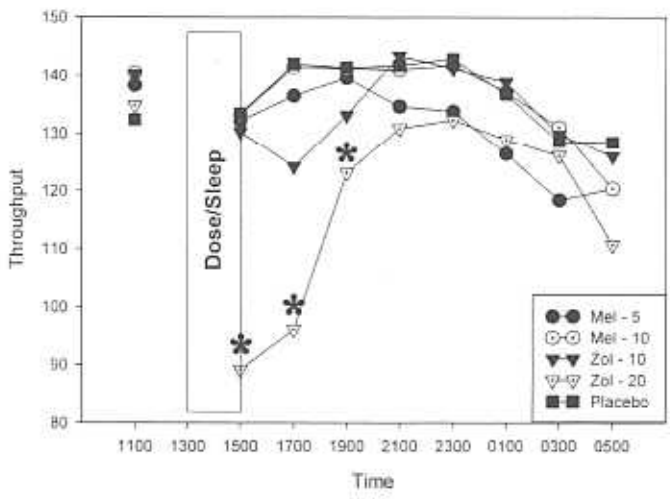

Fig. 4. Continuous processing. * Significantly ($p \leq 0.05$) different from placebo.

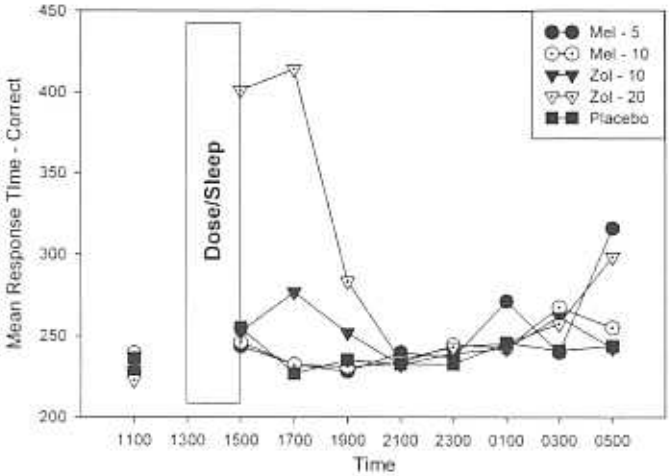

Fig. 5. Simple reaction time. * Significantly ($p \leq 0.05$) different from placebo.

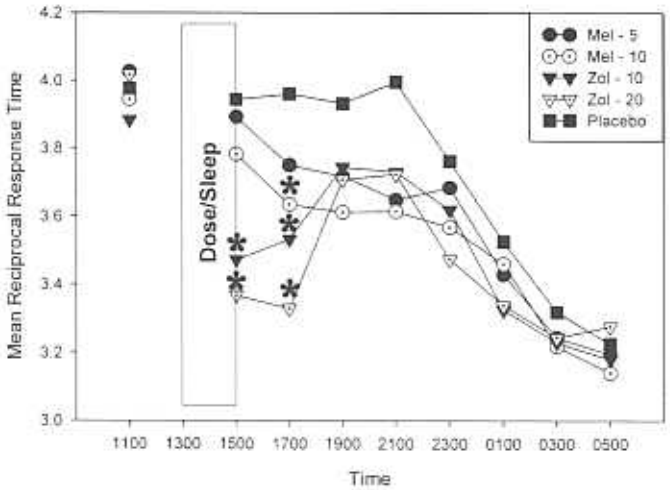

Fig. 7. Psychomotor vigilance task. * Significantly ($p \leq 0.05$) different from placebo.

Psychomotor Vigilance Task

The drug × time interaction for mean reciprocal reaction time was marginally significant [$p = 0.056$, $F(10,121) = 1.87$, MSE = 0.526; **Fig. 7**]. At 15:00, performance under Zol-20 and Zol-10 was poorer than that under placebo. At 17:00, performance under Zol-20, Zol-10, and Mel-10 was poorer than under placebo.

Postural Sway: Eyes Open

The statistical results and summary data for the eyes-open and eyes-closed conditions were very similar and, therefore, only findings for the eyes-open condition are presented graphically (**Fig. 8**). Significant drug × time interactions occurred for both the eyes-open [$p = 0.018$, $F(8,97)$, MSE = 25.4] and the eyes-closed [$p \leq 0.001$, $F(4,50) = 5.2$, MSE = 78.4] conditions. At both 15:00 and 17:00, for both eyes open and eyes closed, body sway was greater for the Zol-20 and the Zol-10 conditions than for placebo and both of the melatonin conditions.

Grip Strength

A significant drug × time interaction [$p = 0.004$, $F(17,205) = 2.3$, MSE = 15.9; **Fig. 9**] was found for maximum grip strength. At 15:00, performance under Zol-20 was poorer than under placebo and Mel-10. At 17:00, performance under Zol-20 was poorer than under placebo, Zol-10, and Mel-10. Performance under Mel-5 was poorer than under placebo.

Sleepiness Ratings

Friedman tests detected significant differences among the drug conditions at 15:00 [$\chi^2(4) = 16.76$, $p = 0.002$], 17:00 [$\chi^2(4) = 17.01$, $p = 0.002$], and 01:00 [$\chi^2(4) = 10.40$, $p = 0.034$] (**Fig. 10**). At 15:00, paired comparisons found ratings under Zol-20 to be higher (i.e., sleepier) than those for placebo, Mel-5, and Zol-10. At 17:00, ratings under Zol-20 were higher than those for placebo, Mel-5, and Mel-10, and ratings under Zol-10 were higher than those for placebo and Mel-5. At 01:00, ratings under Zol-20 were higher than those for Mel-5.

Word Memory

Number of words recalled on the word memory test was significantly poorer under Zol-20 than under pla-

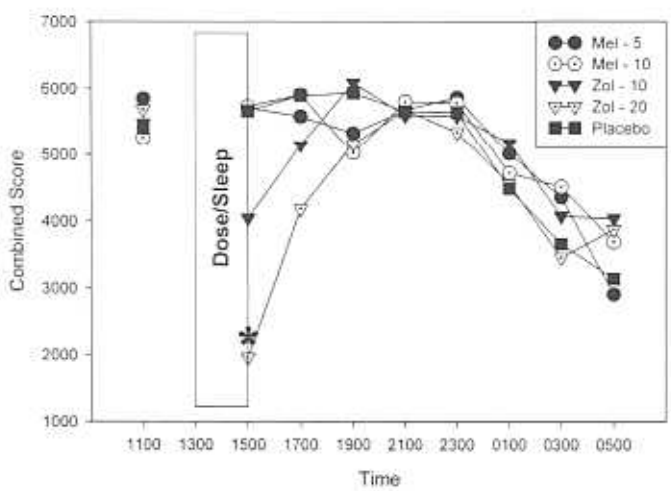

Fig. 6. Synthetic work. * Significantly ($p \leq 0.05$) different from placebo.

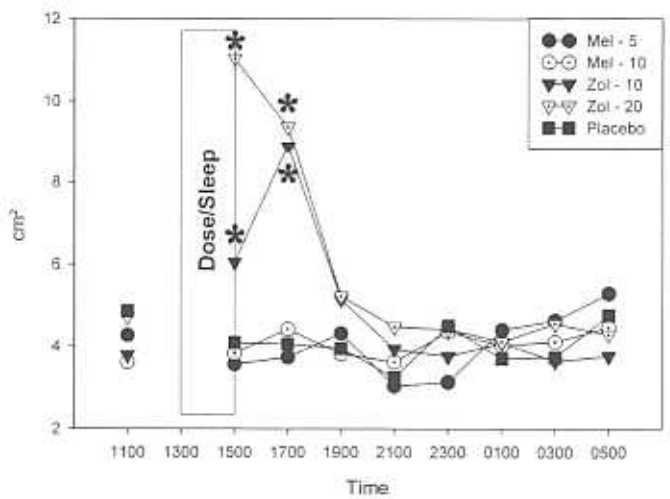

Fig. 8. Postural sway: eyes open. * Significantly ($p \leq 0.05$) different from placebo.

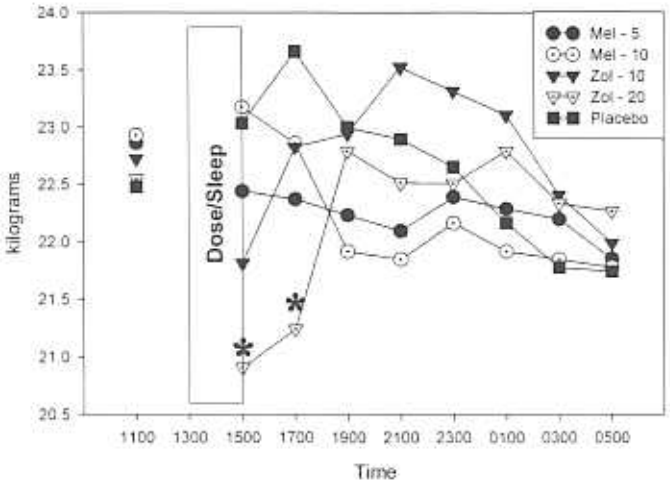

Fig. 9. Grip strength. * Significantly ($p \leq 0.05$) different from placebo.

cebo for both immediate recall at 15:00 [χ^2 (4) = 18.93; $p \leq 0.001$] and delayed recall at 19:00 [χ^2 (4) = 19.25; $p \leq 0.001$]. Word-recall performance was very similar for the other three drug treatment conditions, none of which differed from performance under placebo at immediate or delayed recall. The mean number of words recalled from the 15-item word lists under each condition at immediate recall and delayed recall were, respectively, placebo: 8.3, 7.6; Mel-5: 8.4, 7.2; Mel-10: 8.2, 7.6; Zol-10: 7.2, 6.5; and Zol-20: 2.8, 2.2.

Symptoms

Responses to the 73-item symptom checklist were evaluated for the initial 8 h following drug ingestion at 13:00 (i.e., at 15:00, 17:00, 19:00, and 21:00), the interval during which the plasma levels were assumed to go from maximal to minimal or near-zero. Within this time span statistical comparisons were performed only on symptoms for which 20% or more of the subjects experienced, under at least one of the five conditions, an increase in severity compared with baseline at 11:00. The percentages of subjects reporting increased severity for each of the 16 symptoms meeting the 20% criterion are listed in **Table II**. Friedman tests followed by Wilcoxon signed-rank tests were performed on the original severity-ratings for each of these 16 symptoms, comparing each treatment condition to placebo within each time block. Significant increases in severity occurred for 8 of the 16 symptoms under Zol-10 and Zol-20 at either or both 15:00 and 17:00 (Table II). At 19:00 "difficulty staying awake" under Zol-10 was the only symptom with increased severity. At 21:00 there were no significant findings under either dose of zolpidem. Statistically significant increases in severity did not occur at any time for either of the melatonin doses. Although the percentages presented in Table II were not uniquely involved in the calculation of the Wilcoxon tests (the tests also took into account the magnitude of the differences), they are highly related to the test outcomes and provide more descriptive information than the means of the signed ranks.

DISCUSSION

The most prominent finding was the consistent and orderly performance impairment that occurred while under the influence of Zol-20, not only when compared with placebo, but also to the Zol-10, Mel-5, and Mel-10 treatments. Performance impairment under Zol-20 was relatively severe immediately following awakening at 15:00 when plasma levels were estimated to be considerably elevated, followed by gradual, systematic recovery over the subsequent 4–6 h (19:00–21:00) as plasma levels subsided. Of the nine cognitive outcome measures that were tested at 2-h intervals, eight demonstrated significant impairment under Zol-20 immediately following awakening at 2 h post-dose (15:00), seven of those eight measures at 4 h post-dose (17:00), and three of those seven at 6 h post-dose (19:00). Notable increases in ANAM simple reaction time at 2 and 4 h post-dose under Zol-20 were not statistically different from placebo. The three tasks requiring more than 6 h (i.e., beyond 19:00) post-ingestion for performance to return to normal levels under Zol-20 were the more complex cognitive tasks assessing math processing, grammatical reasoning, and continuous processing.

Compared with the substantial and pervasive disruptive impact of Zol-20, performance impairments were not as frequent, systematic, or severe when the subjects were awakened under the influence of Zol-10 and Mel-5 or Mel-10. Performance under Zol-10 was impaired on only one (PVT) of the nine cognitive tasks on being awakened at 2 h post-dose, but impaired on four of the tasks at 4 h post-dose (PVT and the three code substitution tasks). Paradoxically, performances on the three demanding cognitive tasks that were impaired for more than 6 h post-dose under Zol-20 were not at any time, including testing at 15:00 immediately after awakening, impaired by Zol-10. Three disjointed instances of cognitive performance impairment occurred following awakening under the influence of Mel-5 or Mel-10. Code substitution: immediate recall and grammatical reasoning were both impaired at 2 h post-dose for Mel-5, and PVT performance was impaired at 4 h post-dose for Mel-10. Significant differences in cognitive per-

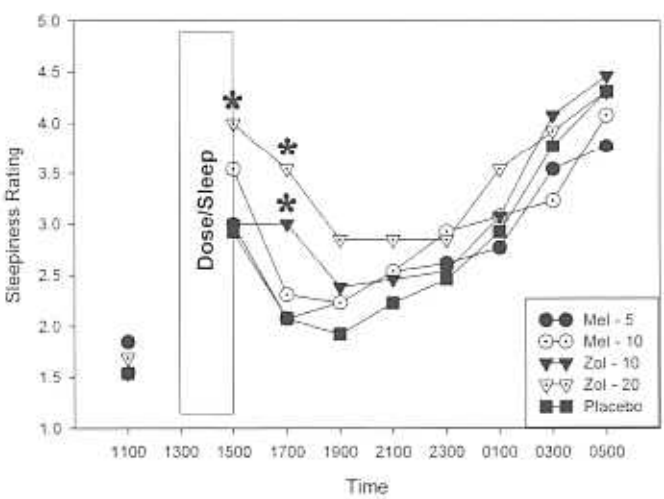

Fig. 10. Sleepiness ratings. * Significantly ($p \leq 0.05$) different from placebo.

TABLE II. PERCENT OF SUBJECTS REPORTING INCREASED SYMPTOM SEVERITY RELATIVE TO BASELINE RATING.

	15:00					17:00				
Symptom	Placebo	Mel-5	Mel-10	Zol-10	Zol-20	Placebo	Mel-5	Mel-10	Zol-10	Zol-20
Blurred vision	0	0	0	23	15	0	0	0	8	8
Chills	8	0	8	0	15	0	0	0	0	25
Loss of coordination	0	0	0	23	39*	0	0	0	15	23
Difficulty concentrating	8	8	0	15	46*	8	8	0	8	8
Dizzy	0	0	0	31*	15	0	0	0	31*	8
Drowsy	0	8	23	31*	31*	8	15	15	31	31
Drugged feeling	31	15	15	46	69*	15	8	8	46	39
Dry mouth	8	8	0	15	23	8	8	0	8	23
Fatigue	0	0	8	15	39	8	8	8	25	31
Difficulty focusing	8	15	8	39	46	15	8	8	31	39
Headache	15	15	0	15	31	8	15	0	23	15
Light-headed	15	15	8	62*	69*	0	8	0	23	31*
Loss of balance	0	0	0	31*	62*	0	0	0	23	46*
Nausea	8	8	0	0	23	0	8	0	0	23
Difficulty staying awake	0	15	8	31*	39*	0	31	0	46*	31*
Stomach cramps	0	0	0	0	8	0	0	0	0	23

* Significantly ($p \leq 0.05$) different from placebo.

formance did not occur at or beyond 8 h post-dose (21:00–05:00) for any of the treatments when compared with placebo or to each other.

The findings in the present study on the daytime effects of zolpidem replicate and extend the results reported in previous studies. Greenblatt et al. (12) and Rush and Griffiths (23) independently evaluated daytime dosing with 10 and 20 mg zolpidem and reported orderly dose- and time-related performance impairments similar to those reported here. Wesensten et al. (27,28) found daytime administration of 15 mg zolpidem (but not 5 or 10 mg) to slow response time and impair memory on being awakened 1.5 h but not 6.0 h post-ingestion. Berlin et al. (4) reported impairment during the daytime on several psychomotor and memory tasks 1.5 h post-ingestion of 10 mg zolpidem but not 4, 6, or 8 h after administration.

Results of studies evaluating the impact of zolpidem on performance when administered during the nighttime and tested on morning awakening (26) are also relevant to the present findings. Danjou et al. (7) and Hindmarch et al. (13) both found 10 mg zolpidem to cause significant impairment on several cognitive tasks when administered 5 or fewer hours before awakening. Troy et al. (24) reported both 10 and 20 mg doses of zolpidem caused psychomotor impairment when awakened 1.25 h post-ingestion with the impact greater for 20 than 10 mg. Performance impairment persisted 8.25 h post-ingestion for 20 but not 10 mg zolpidem. In independent studies Bensimon et al. (3) administered 20 mg zolpidem and Nicholson and Pascoe (16) 10, 20, or 30 mg zolpidem at bedtime. Neither found cognitive performance effects on awakening after 9 h of uninterrupted nighttime sleep.

The few instances in the present study of performance impairment related to daytime melatonin administration are also consistent with previously reported findings that melatonin seldom impairs performance, and then only shortly and briefly, after dosing. In a series of three studies that progressively evaluated smaller and smaller daytime doses of melatonin ranging from 240 mg to 0.1 mg (8,9,15), significant decrements relative to placebo occurred infrequently and within 1 or 2 h post-ingestion. Another series of laboratory and field studies evaluating the potential operational utility of melatonin as a daytime sleep aid has been reported by the researchers at Defence Research and Development Canada (18,19,20). Compared with placebo, time-released 6 mg melatonin was not associated with performance impairment on any of a number of cognitive tests immediately through 7 h post-ingestion, whereas significant impairments occurred for 10 mg zaleplon, 7.5 mg zopiclone, and 15 mg temazepam.

Continuous processing, code substitution, and word memory each involved a memory component. Working memory was impaired by 20 mg zolpidem for 6 h post-dosing as evaluated by the attention-demanding continuous processing task. While acquisition of material was impeded by the presence of 20 mg zolpidem during the learning phases of the code substitution and word memory tasks, delayed recall performance of the material that was learned was not differentially impacted by the drug treatment conditions on either of the tasks, indicating anterograde amnesia did not occur. Performance on the word memory test under 20 mg zolpidem for both immediate recall at 15:00 and delayed recall 4 h later at 19:00 was significantly poorer than that for placebo. The very poor word-recall performance at 15:00 when under the influence of 20 mg zolpidem was likely due in part to the subjects' inability to concentrate on learning the word lists because of the presence of symptoms like dizziness and nausea. Greenblatt et al. (12) also found daytime doses of 20 but not 10 mg zolpidem to impair initial learning on a word memory test administered 1.5 h after dosage, but unlike our findings they reported both 10 and 20 mg zolpidem to impair delayed recall. Berlin et al. (4) found 10 mg zolpidem to impair memory 1.5 h after ingestion. Rush and Griffiths (23) reported 5, 10, and 20 mg zolpidem per 70 kg to impair in a dose-dependent manner delayed recall and recognition of pictures studied 4 h earlier at 1 h post-dosing. Wesensten et al. (27) demonstrated anterograde memory impairment to occur for

material acquired when under the influence of 15 but not 5 or 10 mg zolpidem. As for the impact of daytime doses of melatonin on memory, Lieberman et al. (15) found a 240-mg dose of melatonin administered hourly in three 80-mg doses to not affect immediate recall or delayed recognition.

Previously we have found assessment of postural sway (10,29) to be a sensitive indicator of the general effects of fatigue and centrally acting compounds, and that was also the case in the present study for 10 and 20 mg zolpidem. The increase in postural sway through 4 h post-ingestion while plasma levels of zolpidem were estimated to be elevated aligned with the cognitive performance impairment and the relatively high incidence of dizziness, loss of balance, and lightheadedness reported and witnessed during that interval of time. Berlin et al. (4) found zolpidem 10 mg to significantly increase postural sway under both eyes-open and eyes-closed conditions at 1.5 h after morning administration but not later at 4–8 h post-ingestion. In contrast Allain et al. (1) reported 10 mg zolpidem ingested in the late evening did not significantly affect postural sway during repeated nighttime testing from 0.5–10 h post-administration. We also found 20 mg zolpidem but not 10 mg zolpidem or either dose of melatonin to reduce grip strength up through 4 h post-ingestion (a significant difference in grip strength between placebo and 5 mg melatonin at 17:00 appeared to be the result of a spurious elevation in performance under placebo rather than a decrement related to melatonin). These impairments of general coordination and physical strength suggest personnel may not be capable of caring for or protecting themselves and performing critical physical tasks, even if well practiced, when under the influence of peak and near-peak plasma levels of 10 or 20 mg zolpidem.

The occurrence of relatively higher self-ratings of sleepiness compared with placebo when awakened under the influence of 10 and 20 mg zolpidem also closely aligned in time with the incidences of significant impairments in performance for these treatments. None of the other drug treatment conditions differed from placebo at any time after being awakened, although visual inspection of Fig. 10 suggests the sleepiness ratings for all five conditions were elevated to some degree at 15:00 by sleep inertia. From 17:00–19:00 the sleepiness ratings generally receded toward normal afternoon levels with the placebo condition leading the way. The ratings "regrouped" into a single cluster around 21:00–23:00 when any drug effects would have dissipated and normal circadian influences were taking over as feelings of sleepiness again increased through the late evening, nighttime, and early morning hours.

Some of the symptoms identified in Table II as having increased in severity on being awakened while under the influence of 10 or 20 mg zolpidem complement the increase in sleepiness ratings reported at that time. Soporific symptoms such as fatigue, drowsiness, and difficulty staying awake are acceptable and even desirable when an individual is expecting to sleep. However, these symptoms in combination with others from the checklist such as difficulty focusing, loss of balance, and nausea, in addition to volunteered reports of feeling drunk or stoned and experiencing hallucinations would likely create an unacceptable and unsafe situation in an operational setting where alertness and decisiveness may be critical following an unexpected awakening.

Conclusion

This study evaluated and directly compared the impact of the hypnotic zolpidem and the hormone melatonin on cognitive performance when individuals are prematurely awakened from daytime sleep 2 h after ingestion of a dose that would be administered on the assumption of an uninterrupted sleep period of about 7–9 h. The findings for the recommended therapeutic dose of 10 mg zolpidem confirm that a minimum interval of 6 h is required from the time of ingestion before cognitive capabilities are fully recovered. The pronounced and wide-ranging performance decrements under 20 mg zolpidem were accompanied by impairments in balance and strength and, in some cases, debilitating nausea and emesis. These findings strongly support and reinforce previous findings that if and when a 20-mg dose of zolpidem is employed to promote sleep, a minimum duration of 8 and perhaps as long as 10 h is required to ensure full recovery. When personnel sleeping with the aid of either 10 or 20 mg zolpidem are prematurely awakened, it would be prudent to evaluate their general well-being and possible need for assistance prior to their being permitted to depart crew-rest or to perform tasks and duties. In contrast, cognitive performance decrements related to 5 or 10 mg melatonin seldom occurred, and then without the severity, duration, and consistency seen under zolpidem. Side effects and symptoms related to melatonin seldom differed from placebo. Melatonin is worthy of additional evaluation and consideration as a sleep-aid alternative to hypnotics for promoting daytime sleep, particularly when uninterrupted sleep cannot be assured.

ACKNOWLEDGMENTS

This research was sponsored, solely funded, and approved by the U.S. Army Medical Research and Materiel Command under Contract Award No. DAMD17–00–2-0055 to NTI, Inc. No financial or other relationships existed that might be perceived as leading to a conflict of interest. The study was conducted using Air Force Research Laboratory facilities at Brooks City-Base, TX, under the Cooperative Research and Development Agreement 01–225-HE-01 between NTI, Inc., and the Biosciences and Protection Division (AFRL/HEP). Outstanding technical assistance was provided by Emily Barton, Juan Mendez, Katy Ramsey, Matita Charlton, and Amy McCrory. Mr. Luis Vega, RPSGT, supervised the polysomnography procedures. We thank Maj Stephen Carlisle, USAF, and CMSgt Oakley Morrison, (USAF ret), Wilford Hall Medical Center, for preparation and management of the drugs, and MSgt Bethane Prior, USAF, 311 Air Base Group/LGB, for acquiring the zolpidem. The views expressed in this paper are those of the authors and do not reflect an official position of the Department of the Air Force, Department of the Army, Department of Defense, or the U.S. Government.

REFERENCES

1. Allain H, Patat A, Lieury A, et al. Comparative study of the effects of zopiclone (7.5 mg), zolpidem, flunitrazepam and a placebo on nocturnal cognitive performance in healthy sub-

jects, in relation to pharmacokinetics. Eur Psychiatry 1995; 10(3, Suppl.):129–35.
2. Balkin TJ, O'Donnell VM, Wesensten N, et al. Comparison of the daytime sleep and performance effects of zolpidem versus triazolam. Psychopharmacology 1992; 107:83–8.
3. Bensimon G, Foret J, Warot D, et al. Daytime wakefulness following a bedtime oral dose of zolpidem 20 mg, flunitrazepam 2 mg and placebo. Br J Clin Pharmacol 1990; 30:463–9.
4. Berlin I, Warot D, Hergueta TP, et al. Comparison of the effects of zolpidem and triazolam on memory functions, psychomotor performances, and postural sway in healthy subjects. J Clin Psychopharmacol 1993; 13:100–6.
5. Caldwell JL. The use of melatonin: an information paper. Aviat Space Environ Med 2000; 71:238–44.
6. Comperatore CA, Lieberman HR, Kirby AW, et al. Melatonin efficacy in aviation missions requiring rapid deployment and night operations. Aviat Space Environ Med 1996; 67:520–4.
7. Danjou P, Paty I, Fruncillo R, et al. A comparison of the residual effects of zaleplon and zolpidem following administration 5 to 2 h before awakening. Br J Clin Pharmacol 1999; 48:367–74.
8. Dollins AB, Lynch HJ, Wurtman RJ, et al. Effect of pharmacological daytime doses of melatonin on human mood and performance. Psychopharmacology 1993; 112:490–6.
9. Dollins AB, Zhdanova IV, Wurtman RJ, et al. Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance. P Natl Acad Sci USA 1994; 91:1824–8.
10. Eddy D, Storm W, French J, et al. An assessment of modafinil for vestibular and aviation-related effects. Brooks City-Base, TX: Human Effectiveness Directorate, Biosciences Protection Division, Warfighter Fatigue Countermeasures Branch; 2005. AFRL-HE-BR-TR-2005–0129.
11. Elsmore T. SYNWORK1: a PC-based tool for assessment of performance in a simulated work environment. Behav Res Methods Instrum Comput 2003; 26:421–6.
12. Greenblatt DJ, Harmatz JS, von Moltke LL, et al. Comparative kinetics and dynamics of zaleplon, zolpidem, and placebo. Clin Pharmacol Ther 1998; 64:553–61.
13. Hindmarch I, Patat A, Stanley N, et al. Residual effects of zaleplon and zolpidem following middle of the night administration five hours to one hour before awakening. Hum Psychopharm Clin 2001; 16:159–67.
14. Hoddes E, Zarcone VP, Smythe H, et al. Quantification of sleepiness: a new approach. Psychophysiology 1973; 10:431–6.
15. Lieberman HR, Waldhauser F, Garfield G, et al. Effects of melatonin on human mood and performance. Brain Res 1984; 323:201–7.
16. Nicholson AN, Pascoe PA. Hypnotic activity of an imidazopyridine (zolpidem). Br J Clin Pharmacol 1986; 21:205–11.
17. Nicholson AN, Pascoe PA. Hypnotic activity of zolpidem: nighttime and daytime studies in young and middle-aged adults. In: Sauvanet JP, Langer SZ, Morselli PL, eds. Imidazopyridines in sleep disorders. New York: Raven Press; 1988:231–40.
18. Paul MA, Brown G, Buguet A, et al. Melatonin and zopiclone as pharmacologic aids to facilitate crew rest. Aviat Space Environ Med 2001; 72:974–84.
19. Paul MA, Gray G, Kenny G, Pigeau RA. Impact of melatonin, zaleplon, zopiclone, and temazepam on psychomotor performance. Aviat Space Environ Med 2003; 74:1263–70.
20. Paul MA, Gray G, Sardana TM, Pigeau RA. Melatonin and zopiclone as facilitators of early circadian sleep in operational air transport crews. Aviat Space Environ Med 2004; 75:439–43.
21. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Washington, DC: Public Health Service, U.S. Government Printing Office; 1968.
22. Reeves D, Winter K, Kane R, et al. ANAM 2001 user's manual: clinical & research modules. Special report NCRF-SR-2001–1. San Diego, CA: National Cognitive Recovery Foundation; 2001.
23. Rush CR, Griffiths RR. Zolpidem, triazolam, and temazepam: behavioral and subject-rated effects in normal volunteers. J Clin Psychopharmacol 1996; 16:146–57.
24. Troy SM, Lucki I, Unruh MA, et al. Comparison of the effects of zaleplon, zolpidem, and triazolam on memory, learning, and psychomotor performance. J Clin Psychopharmacol 2000; 20: 328–37.
25. USAF/AFMOA/CC. Memorandum: revised duty limitations for the ground testing and operational use of temazepam, zolpidem and zaleplon in aviators and special duty personnel. Oct 25, 2001; Retrieved March 21, 2005, from http://www.hep.afrl.af.mil/HEPF/Policy/nogo.pdf.
26. Unden M, Schechter BR. Next day effects after nighttime treatment with zolpidem: a review. Eur Psychiatry 1996; 11(1, Suppl.):21S–30S.
27. Wesensten NJ, Balkin TJ, Belenky GL. Effects of daytime administration of zolpidem versus triazolam on memory. Eur J Clin Pharmacol 1995; 48:115–22.
28. Wesensten NJ, Balkin TJ, Belenky GL. Effects of daytime administration of zolpidem and triazolam on performance. Aviat Space Environ Med 1996; 67:115–20.
29. Whitmore JN, Fischer JR, Barton EC, Storm WF. Performance following a sudden awakening from daytime nap induced by zaleplon. Aviat Space Environ Med 2004; 75:29–36.

APPENDIX III

Storm, W., Eddy, D., Welch, C, and Fischer, J. Combined Use of Selected Hypnotic and Alerting Medications to Counteract Aircrew Fatigue Due to Disrupted Sleep During Sustained Operations. *(in final preparation)*

Combined Use of Selected Hypnotic and Alerting Medications to Counteract Aircrew Fatigue Due to Disrupted Sleep During Sustained Operations

Storm WF, Eddy DR, Welch CB, Fischer JR

ABSTRACT

Background: This laboratory study was conducted against the background of a hypothetical one-week sustained airborne operation involving three simulated 24-hour missions separated by 16-hour crew-rest periods. The objective was to determine if there is a best combined use of USAF-approved hypnotic and alertness medications to, respectively, maximize the quality of pre-mission crew-rest and counteract the impact of fatigue on aircrew performance during subsequent long-duration missions. **Method:** The study evaluated and compared the overall counter-fatigue effectiveness of the repeated, cyclic use of the hypnotics temazepam and zolpidem when each was paired with the alertness agents dextroamphetamine or modafinil. During the simulated missions a battery of cognitive tests assessing problem solving, reasoning, memory, and simple reaction time were employed to assess the ability of the four drug-combinations to counteract the deteriorating effect of the fatigue generated by the combination of extended duty periods and associated circadian dysrthymia. Sleepiness and mood scales assessed affect. Sleep during the rest periods and maintenance-of-wakefulness-tests inserted into the missions was evaluated polysomnographically. **Results:** The findings overwhelmingly and consistently demonstrated cognitive performance and subjective affect to deteriorate under the placebo condition as a mission progressed in time, but to remain relatively stable or decrement little both within and across the three missions for each of the four drug-combination conditions. Statistically significant different main or interactive effects between the four drug-combinations were very rare and seemingly random. No consistent findings related to the drug conditions were statistically detected for any of the sleep metrics. **Conclusion:** The combined sequential use of sleep- and alertness-aid medications currently approved by the USAF for pre-mission crew-rest and long-duration missions significantly extended cognitive performance during a simulated surge. There were no statistical differences among the four drug-combinations in their efficacy to maintain cognitive performance. The effects of the drug-combinations on pre-mission sleep quantity and quality did not systematically differ from each other or the placebo condition.

Combined Use of Selected Hypnotic and Alerting Medications to Counteract Aircrew Fatigue Due to Disrupted Sleep During Sustained Operations

Storm WF, Eddy DR, Welch CB, Fischer JR

OBJECTIVE

Determine if there is a best combined use of USAF- approved hypnotic and alertness medications to, respectively, maximize the quality of pre-mission crew-rest and counteract the impact of fatigue on aircrew performance during subsequent long-duration missions.

INTRODUCTION

Fatigue resulting from reduced sleep and disrupted circadian rhythms is well established to cause significant decrements in cognitive performance (Caldwell, 1997; Dinges and Kribbs, 1995). In the military aviation environment fatigue induced performance decrements during long range global deployments, bombing missions 20-50 hours in duration, and 8-10 hour combat air patrol sorties may result in outcomes ranging from severe crew discomfort to mission degradation to loss of crew and aircraft. Conservative aircrew fatigue countermeasures sometimes prove insufficient to counter the effects of the cumulative fatigue generated by extreme sustained and long-duration airborne operations. In these critical situations, the Air Force may employ the controlled, limited application of operationally tested pharmaceuticals to enhance aircrew sleep during pre-mission crew rest and to maintain alertness and performance during extended airborne missions.

Three hypnotic drugs (temazepam, zolpidem, and zaleplon) and two alertness enhancing drugs (dextroamphetamine and modafinil) are currently approved for controlled use by Air Force aircrews under well-defined training and combat conditions that require extended wakefulness during extreme, sustained mission durations and intense, continuous surge operations. In aircrew parlance the hypnotics are referred to as "no-go pills" and the alertness aids as "go pills." Operationally, no-go and go pills may be used in tandem to counteract the fatigue and circadian dysrhythmia associated with sustained and continuous operational requirements - a single no-go dose to maximize pre-mission sleep to be as rested as possible for the upcoming long duration mission during which go pills may be taken periodically to maintain alertness and performance.

Zolpidem (Ambien®, 10mg) is a hypnotic drug approved by the Air Force (AFI 48-123 and ACC/SG policy letter 27 Sep 1999) for use by aircrew as a sleep aid during pre-mission crew rest. The Air Force directs that 10 mg zolpidem must be taken at a minimum of six hours prior to reporting for duty to assure clearance and no hangover effects. Operational use of zolpidem is restricted to a maximum of 7 consecutive days and no more than 20 days in a 60-day period (AFMOA/CC policy letter, 25 Oct 2001). Zolpidem is approved by the Food and Drug Administration (FDA) for short-term treatment of insomnia. The recommended adult dose is 10 mg. Zolpidem is a strong sedative with minor

anxiolytic, myorelaxant, and anticonvulsant properties, and has been shown to be effective in inducing and maintaining sleep in adults with various sleep pathologies. Studies further document that zolpidem produces no rebound or withdrawal effects and study subjects have experienced good daytime alertness after 20 mg doses given at night. Although infrequent, the most common side effects of zolpidem are dizziness, drowsiness, nausea, and diarrhea. Peak plasma concentrations are reached 0.5 to 1.0 hours after ingestion. The elimination half-life averages about 2.5 hours.

Temazepam (Restoril®, 15 mg and 30 mg), a benzodiazepine compound, is another hypnotic approved by the Air Force (AFI 48-123 and ACC/SG policy letter 27 Sep 1999) for use by aircrew as a sleep aid during pre-mission crew rest. The Air Force directs that a dose not to exceed 30 mg temazepam must be taken at a minimum of 12 hours prior to reporting for duty to assure clearance and absence of hangover effects. As with zolpidem, operational use of temazepam is restricted to a maximum of 7 consecutive days and no more than 20 days in a 60-day period (AFMOA/CC policy letter, 25 Oct 2001). Temazepam is approved by the FDA for short-term treatment of insomnia, providing symptomatic relief of difficulty in falling asleep, frequent nocturnal awakenings, and early morning awakenings. Although infrequent, the most common side effects are dizziness, drowsiness, nausea, and diarrhea. It has an elimination half-life of 8 hours and peak plasma concentration at 1.5 hours.

Dextroamphetamine (Dexedrine®, 5mg and 10mg) is approved by the Air Force (AFI 48-123) for use as an alertness enhancer in both single-pilot fighter and dual-pilot bomber long-duration missions. The specific applications and requirements for the operational use of dextroamphetamine are presented in USAF/XO message 200958Z Feb 01. Dextroamphetamine is FDA approved for the treatment of excessive daytime sleepiness (narcolepsy) and attention deficit disorder. The usual therapeutic dose is 5-60 mg/day in divided doses. Occasional side effects are rapid heart rate, elevated blood pressure, euphoria, dizziness, headache, diarrhea, and dry mouth. Existing data indicate that 10 mg doses of dextroamphetamine provide operationally relevant resistance to the effects of sleep deprivation in aviation contexts. Air Force guidance recommends 4-6 hours between successive doses of 10 mg dextroamphetamine, and a limit of 60 mg per 24-hour period. Retrospective studies on the use of dextroamphetamine in combat operations consistently report extended alertness in fatigued aircrews conducting long-duration missions, with no adverse side effects or a need to continue the drug after typical wake/sleep schedules were reinstated (Cornum, Cornum, and Storm, 1995; Emonson and Vanderbeek, 1993; Senechal, 1988). The elimination half-life of dextroamphetamine is 12 hours. Peak plasma concentrations occur at about 3 hours.

Modafinil (Provigil®, 100 mg and 200 mg) is a member of a class of drugs called Eugregorics. Eugregorics mimic the alerting effects of amphetamines by producing high quality wakefulness in sleep deprived subjects, while lacking the negative side effects sometimes associated with amphetamines (modafinil is a schedule IV controlled substance; dextroamphetamine is a schedule II substance). Cephalon (1998) received FDA approval to market modafinil for the management of excessive daytime sleepiness associated with narcolepsy, and recently for treatment of shift-worker sleep deficit. Modafinil has also been approved by ACC/SG for use by aircrew in some AF operations (2 Dec 03 Memorandum – Modafinil and Management of Aircrew Fatigue). Initially, the normal dose for AF operational use is 200 mg orally every eight hours as needed, not to exceed 400 mg in 24

consecutive hours. Preliminary reports from the field have suggested that for 24-hour and longer periods requiring continuous wakefulness, 600 mg per 24 hours should be considered as an option. It has been consistently demonstrated in several studies that 100 mg, 200 mg and 300 mg of modafinil administered either in single doses or in split doses at four- or eight-hour intervals significantly enhances cognitive performance over periods requiring extend alertness (Bensimon, Benoit, Lacomblez, Weiller, Warot, Weil, and Puech, 1991; Lagarde and Batejat, 1995; Batéjat and Lagarde, 1999; Baranski, Cian, Esquivie, Pigeau, and Raphel, 1998; Stivalet, Esquivie, and Barraud (1998). Unlike amphetamines, 100-300mg/day modafinil produces a long lasting waking effect with minimal concern for behavioral modification, addictive attributes, adverse symptoms, or sleep rebound effects (Lagarde, Batéjat, Van Beers, Sarafian and Pradella, 1995; Lin, Hou, Rambert, and Jouvet, 1997; Morehouse, Broughton, Fleming, George, and Hill, 1997; Warot, Corruble, Payan, Weil, Puech, 1993). Doses of 400-800 mg/day have sometimes generated reports of headache, elevated pulse rate and blood pressure, dizziness, and sleep rebound (Caldwell, Caldwell, Smythe, and Hall, 2000; Batéjat and Lagade, 1999; Lagarde and Batejat, 1995; Buguet, Montemayeur, Pigeau, and Naitoh, 1995). Modafinil has a half-life of 9-14 hours with peak blood concentrations 2-4 hours after absorption, making it a prime candidate for operational applications (Wong, Gorman, McCormick, and Grebow, 1997).

Under current concepts-of-operation a pilot or aircrew may be required to perform a sequence of back-to back long duration missions (each 20-50 hours) with minimal crew rest (16-24 hours) between missions. The sequential use of go and no-go medications may be an advisable option to counteract acute and cumulative fatigue during such an operation. Laboratory experiments and field trails have evaluated and compared the effects among either no-go or a go agents, but not the impact of using both as they may be applied to counteract fatigue during a sustained high-tempo operation. The B-1B exercise Operation Iron Thunder in which the 7th Bomb Wing flew 114 sorties over three consecutive days emphasized the need to evaluate the combined use of go and no-go medications during surge operations. The study reported here evaluated and compared the overall counter-fatigue effectiveness of the repeated, cyclic use of the hypnotics temazepam and zolpidem when each was paired with the alertness agents dextroamphetamine or modafinil. This laboratory study was conducted against the background of a hypothetical one-week sustained airborne operation involving three simulated 24-hour missions separated by 16-hour crew-rest periods.

METHODS

Participants

Fifty qualified volunteer subjects, 19 women and 31 men (18-45 years of age) were screened and selected to participate in the study. Volunteers were thoroughly briefed on the possible risks and discomforts associated with participation and medically examined (including blood chemistry and liver function) by a qualified medical practitioner knowledgeable with the objectives and requirements of the study. Volunteers with evidence of any current significant illness, sleep abnormalities, use of tobacco, excessive use of caffeine or alcohol, or being excessively over- or underweight were not selected to participate. The medical examiner reviewed a list of drugs known to interact

with those being evaluated in the study and, therefore, not to be used during the 60 days prior to participation. Qualified participants were required to have lived on a typical diurnal daily schedule (awake during the day and sleeping at night as opposed to working on a night or rotating shift schedule) for the 30 days preceding the start of the study. Women who were pregnant or attempting to become pregnant were excluded. Female participants were administered a urine pregnancy test immediately prior to each experimental session. Participants gave written informed consent before participating and were paid for their participation. The research protocol was reviewed and approved in advance of subject recruitment by the Brooks City-Base Institutional Review Board (#F-BR-2003-0048-H), the United States Air Force Surgeon General Research Oversight Committee, and the United States Army Surgeon General Human Subjects Research Review Board (HSRRB #A-9637.2). The FDA issued IND 70,181 in support of the research protocol.

Facility and Materials

This study was conducted at the Air Force Research Laboratory (AFRL/RHPG) Fatigue Countermeasures Lab (FCL) located at Brooks City-Base, Texas. The FCL is a unique laboratory and habitat/isolation facility specifically designed for scientific study of the impact of wake/sleep schedules and circadian factors on human performance and physiology. During the experimental sessions each participant was assigned to a private room equipped with a computer and desk for testing, a bed, an easy chair, and a private bath. Throughout the experimental sessions the participants were always under the direct observation of research personnel or knowingly monitored from a central control station by closed circuit television, excluding of course the private baths. Infra-red capability allowed monitoring of the subjects while sleeping in the darkened rooms. The FCL is equipped with a small kitchen facility comprised of refrigeration, microwave ovens, and a dining area. Meals, snacks, and beverages were catered to the FCL daily during the simulated sustained operations.

Controlled drugs were managed in accordance with AFRL/RHP OI 44-102, "Research Drug Control." Facilities within AFRL/RHPG and the FCL comply with Drug Enforcement Agency and U.S. Air Force requirements for the storage and maintenance of Schedule II-V pharmaceuticals. One of the investigators (DRE) for this study was registered with the Drug Enforcement Agency and the Texas Department of Public Safety and certified to dispense for study Schedule II-V drugs. Drug and placebo packaging and blinding were performed by the pharmacy staff at Wilford Hall Medical Center (WHMC) prior to the beginning of the study. The tablets or capsules were packed in standard size gelatin capsules using psyllium as filler. The capsules were red in color for the hypnotics and green for the alerting agents. Adhering to the experimental design described in the protocol, the WHMC pharmacy also coded and randomly assigned the doses by participant number and maintained a duplicate record of the assignments.

Experimental Design

This study employed a repeated measures design with one between-subjects factor (5 drug conditions) and two within-subjects factors (3 simulated missions and 13 testing

blocks within each mission). The five drug conditions (4 Drug-Combination conditions and a Placebo condition) are described in Table I. Ten subjects were assigned to each of the five drug conditions. A group of five subjects were tested in each experimental session, with each of the five drug conditions randomly assigned to one of the five subjects in each group. Aside from the investigators knowing that each drug-condition was represented in each group of five subjects, double-blind procedures were employed.

Table I

Five Conditions of Hypnotic, Alertness, and Placebo Agents

	12-Hour Crew Rest (single dose)	24-Hour Mission (repeated doses)
Condition 1	zolpidem-10 mg	dextroamphetamine-30 mg (5mg dose every 4 hours)
Condition 2	temazepam-30 mg	dextroamphetamine-30 mg (5mg dose every 4 hours)
Condition 3	zolpidem-10 mg	modafinil-600mg (100 mg dose every 4 hours)
Condition 4	temazepam-30 mg	modafinil-600mg (100 mg dose every 4 hours)
Condition 5	placebo	placebo (every 4 hours)

Procedures

During selection and training the participants were given considerable orientation on the study objectives and the relevance of the schedule to real-world operations. The importance of maintaining standardized procedures and performing the cognitive tasks as rapidly and accurately as possible were emphasized. On each of three days prior to participating in their assigned experimental session each subject received a three-hour training session with the amount of training on each performance task proportional to task complexity. Subjects were trained to asymptotic performance on each of the cognitive tasks and became proficient on the procedures for transitioning efficiently from one task or procedure to the next. Subjects participated in the experiment within 2-3 days of completing the nine hours of training.

The experimental sessions were each composed of a 16-hour baseline phase, a 120-hour simulated operational phase, and a 20-hour recovery phase (Table II). An experimental session began with a group of five participants reporting to the FCL at 2000 (Day 0) for the baseline phase which consisted of a baseline sleep-adaptation period from 2200-0600 and baseline testing the following morning (Day 1) from 0800-1100. The simulated operational phase began an hour later at 1200. The operational phase consisted of three 24-hour "missions," each preceded by a 16-hour "pre-mission crew rest period" [(16+24)×3= 120 hrs]. The first and last two hours of each of the 16-hour crew-rest periods served as transition intervals between being "on duty" and being "in crew-rest." The mid-twelve hours of each crew-rest period were designated as inviolate rest periods during which the subjects could sleep as desired without interruption. Testing blocks occurred at the start of each of the 24-hour missions and at two-hour intervals thereafter, generating 13 testing blocks per mission (Table II). Testing blocks were approximately 15 or 50 minutes in duration, being short for those that assessed only a selected battery of cognitive functions and longer for those that also included other cognitive, physiological,

==========

Table II
Wake/Sleep and Testing Schedule for 120-Hour Simulated Sustained Operation

Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
	0000/Slp	0000/Slp	0000 A,B X	0000 A,B X	0000/Slp	0000 A,B X
	0100/Slp	0100/Slp	0100	0100	0100/Slp	0100
	0200/Slp	*0200* Mm	0200 A,V,W	0200 A,V,W	0200/Slp	0200 A,V,W
	0300/Slp	*0300*	0300	0300	0300/Slp	0300
	0400/Slp	0400 A,B X	*0400* A,B	0400 A,B X	0400/Slp	0400 A,B X
	0500/Slp	0500	*0500*	0500	0500/Slp	0500
	0600	0600 A,Mr	0600/Slp Z	0600 A	0600/Slp	0600 A
	0700	0700	0700/Slp	0700	0700/Slp	0700
	0800 A,B	0800 A,B X	0800/Slp	0800 A,B X	0800/Slp	0800 A,B X
	0900	0900	0900/Slp	0900	0900/Slp	0900
	1000 A,V	1000 A,V,W	1000/Slp	1000 A,V,W	*1000* Mm	1000 A,V,W
	1100	1100	1100/Slp	1100	*1100*	1100
	1200 A,B	1200 A,B X	1200/Slp	1200 A,B X	1200 A,B X	*1200* A,B
	1300	1300	1300/Slp	1300	1300	*ad libitum sleep thru 0600 next morning*
	1400/Slp Z	1400 A	1400/Slp	1400 A	1400 A, Mr	
	1500/Slp	1500	1500/Slp	1500	1500	
	1600/Slp	1600 A,B X	1600/Slp	1600 A,B X	1600 A,B X	
	1700/Slp	1700	1700/Slp	1700	1700	
Report to FCL	1800/Slp	1800 A,V,W	*1800* Mm	1800 A,V,W	1800 A,V,W	
	1900/Slp	1900	*1900*	1900	1900	
2000	2000/Slp	2000 A,B X	2000 A,B X	*2000* A,B	2000 A,B X	
2100	2100/Slp	2100	2100	*2100*	2100	
2200/Slp	2200/Slp	2200 A	2200 A,Mr	2200/Slp Z	2200 A	
2300/Slp	2300/Slp	2300	2300	2300/Slp	2300	

Slp=sleep allowed
Z= no-go pill dose
X= go pill dose

A
Sleepiness Rating
Code Substitution
Reaction Time
Cont Processing
Math Processing
Gramm Reasoning
(vital signs)

B
Synthetic Work
Postural Sway
POMS

V
Vigilance (PVT)

W
Main. Wakefulness

Mm
Memory-memorize

Mr
Memory-recall

==========

and subjective factors. The 20-hour recovery phase began immediately on completion of the third mission at 1200 (Day 6), with the subjects being allowed to individually schedule their activities and sleep within the FCL as desired until 0600 the following morning (Day 7) when they performed a final testing block at 0800 and departed the FCL. Sleep acquired during the crew-rest periods and the recovery phase was evaluated polysomnographically.

The 16-hour-off/24-hour-on duty schedule was purposefully selected for two reasons as a realistic back-drop for simulation of the temporal aspects of an airborne operational surge. First, AFI11-2U-2V3 Physiological/Crew Rest Procedures (1 March 2000) stipulates a minimum of 12 hours inviolate crew-rest is required allowing for a minimum of 8 hours of uninterrupted sleep/rest prior to reporting for a mission. Second, the repeating 40-hour cycle would generate circadian disruption as the participants progressed through the three missions, compounding the fatigue resulting from the 24-hour duty periods. Although this schedule confounded elapsed time-on-duty with time-of-day, circadian disruption is frequently a contributing factor in generating aircrew fatigue and, therefore, was integrated into the design of the study.

At the start of each of the three 12-hour inviolate rest periods each participant was administered a single oral dose of their assigned sleep-aid (10 mg zolpidem; or 30 mg temazepam; or placebo). Immediately on taking their sleep-aid, subjects were required to go to bed with lights out and attempt to sleep. If still awake an hour after retiring, subjects were free to engage in other activities in or out of bed as long as other subjects were not disturbed. This procedure met the AF requirement that temazepam be administered no later than 12 hours before reporting for a mission and standardized the dosage time be it temazepam, zolpidem, or placebo. Participants were encouraged to acquire as much sleep as possible during the crew rest periods, but allowed to engage in other activities within the FCL (reading, television, very mild exercise, snacks, socializing with other awake subjects) if they could not sleep. Each participant was administered their assigned alertness-aid dose (5 mg dextroamphetamine; or 100 mg modafinil; or placebo) every four hours (six doses/mission) beginning at the start of each 24-hour mission.

During the experimental sessions the participants were allowed to consume only food and drinks provided by the study to control for the confounding effects of substances like caffeine and foods known to interfere with the action of some of the pharmaceuticals being evaluated (i.e., grapefruit juice and green tea have been reported inhibit the metabolism of zolpidem). Nutritious hot meals were provided during the transition periods at the start and the end of each crew-rest period. Selected snacks, light meals, and drinks were available throughout the simulated missions and crew-rest periods. Lying down or sleeping were never permitted except during the scheduled crew-rest periods integral to the study. The participants were allowed personal time in their assigned rooms and social time with other participants in a common day room or the dining area during lulls between testing blocks within missions, during the crew-rest periods between missions, and during recovery.

Tests and Measures

Automated Neuropsychological Assessment Metrics (ANAM). Five cognitive performance assessment tasks from the PC-based ANAM battery were applied in this study (Reeves, Winter, Kane, Elsmore, Bleiberg, 2001).). The five tasks required a total of about 18 minutes for a well-practiced, alert subject to complete under baseline conditions. The dependent measures of accuracy, mean reaction time for correct responses, and throughput (the number of correct responses per minute) are generated for each of the ANAM Code Substitution Tasks, Mathematical Processing, Grammatical Reasoning, and Continuous Processing. Only reaction time measures are available for the ANAM Simple Reaction Time Task. The five ANAM tasks were performed in the following sequence during each testing block. 1) *Code Substitution* – This task is a modification and expansion of the Digit Symbol Substitution Test (DSST) frequently used in studies assessing hypnotics and alertness-aids. ANAM Code Substitution consists of three phases within each testing block; Learning, Immediate Recall, and Delayed Recall. During the Learning phase, which is similar to the traditional DSST, the assigned pairings of a unique symbol with each of the digits 1-9 are presented in a row across the top of the monitor screen. The subject learns the pairings as he/she refers to them to determine whether individual "test-pairs" presented sequentially at the bottom of the screen correctly match one of the assigned pairings. Symbol/digit pairings are randomly reassigned for each testing block. In this study the Immediate Recall phase was administered on completion of the Learning phase, and the Delayed Recall phase occurred about 12 minutes later following completion of the four other ANAM tasks. During the Immediate and Delayed Recall phases only test-pairs are presented one-at-a-time and the subject responds as to whether or not each displayed pair is correct or incorrect based on his/her recollection. The Learning phase consisted of 72 test-pair presentations, Immediate Recall 36, and Delayed Recall 18. 2) *Reaction Time* – Simple Reaction Time - pressing a computer mouse key in response to a visual stimulus presented at a centrally fixed point on the computer screen – was evaluated. Mean reaction time to 20 stimuli (inter-stimulus interval of 650-1200 msec) presented during a less than one-minute trial was the outcome measure. 3) *Mathematical Processing* – Each problem in this task includes two mathematical operations (addition and/or subtraction) on sets of three single-digit numbers (e.g., 5+3–4=?). The subject is instructed to read and calculate from left to right and indicate whether the answer is greater-than or less-than '5' by pressing one of two specified response buttons on the mouse. Trials were three minutes in duration. 4) *Grammatical Reasoning* – The subject determines as quickly as possible whether each of two simple summary statements (e.g., *& follows** and *# proceeds**) correctly describe the sequential relationships among three symbols (e.g. *# &**). If one statement is true and one false, one response is correct; if both statements are true or both are false an alternative response is made. A trial consisted of 48 presentations. 5) *Continuous Processing* – Subjects are directed to continuously monitor a randomized sequence of the numerals 0 through 9 presented one at a time, one per second, in the center of the screen. Subjects press the left mouse key if the numeral currently on the screen matches the numeral that immediately preceded it and the right mouse key if there is not a match. Trials were three minutes in duration. The ANAM

battery was completed at the start of each mission and every subsequent test block thereafter (test blocks 1 through 13).

Synthetic Work Task. "SynWin: A Synthetic Work Program for Windows" (Elsmore, 1996) is a PC-based four-component task that provides a generic work environment. A memory (Sternberg) task, an arithmetic task, a visual monitoring task, and an auditory monitoring task are presented simultaneously, each in one quadrant of the screen. The subject is required to remember and classify items on demand, perform a self-paced task, and monitor and react to both visual and auditory information. A composite score was the outcome measure for a 10-minute trial. This task was performed at the start of each mission and at four-hour intervals thereafter (every other test block), generating seven evenly distributed test blocks per mission.

Word Memory Task. The Williams Word Memory Task provided an assessment of short-tem memory. At the end of the 12-hour inviolate rest-period that preceded each mission the subject listened to the auditory presentation of 15 recorded words. Each word was spoken, spelled, and then spoken again. The subject wrote down each word as it was presented. On completion of the presentation, the subject studied his/her list for one minute. The written list was then collected and the subject was directed to immediately recall in one minute as many of the words as possible by writing them on a fresh paper form. Delayed recall of the same list occurred four hours later at the completion of the second test block of each mission. A new list was used for each of the three missions. The number of words recalled from each list of 15 was the outcome measure for this task.

Psychomotor Vigilance Task (PVT). The PVT (Model PVT-192, CWE Inc., Ardmore, PA) is a portable, self-contained visual reaction time task requiring sustained attention and a simple, discrete push-button motor response to each signal - the onset of an elapsed-time digital clock. The clock appears within a well-defined display window and is extinguished and reset to zero within a second after each response. Signals occur randomly every 2-12 seconds. Trials were 10 minutes in duration and the outcome measure was mean reciprocal reaction time (MMRT). The PVT was performed three times during each mission, in each case immediately on completion of the Maintenance of Wakefulness Test (described below) during test blocks 4, 8, and 12.

Postural Sway. Postural or body sway was assessed using a force platform that measures changes in the body's center of pressure over time (Platform model OR6-5-1, AMTI, Watertown, MA). The apparatus resembles an oversized home bathroom scale, approximately 18 by 20 inches in area and 3 inches in height. The subject was directed to stand as motionless as possible while one minute of data was collected for both eyes open and eyes closed conditions at a sampling rate of 10 Hz. The amplitude, velocity, and frequency of change in the center of pressure reflect the participant's ability to maintain balance. An elliptical area of measurement that accounts for 95% of the variation in the center of changes in pressure provides the outcome measure.

Polysomnography (PSG). Sleep during the crew-rest periods was monitored with ambulatory electro-physiological equipment. Electroencephalogram (EEG) signals were acquired from the C3-A2 and the O1-A1 scalp leads of the International 10-20 system using a Stellate Notta ambulatory recorder system (Stellate Systems, Inc., Montreal Quebec, Canada). Electromyogram (EMG) and electrooculogram (EOG) signals were also recorded. In total, 14 skin surface electrodes were applied (6 scalp, 2

mastoid, 2 outer canthi, 2 chin, and 2 ground). Sleep onset latency (three consecutive 30-second epochs of stage 2 sleep), total sleep time, and total time spent in each of the five classic stages of sleep were polysomnographically determined using the Stellate Harmonie software (Stellate Systems, Inc.) with oversight and review by an experienced PSG scorer blind to the experimental conditions (Rechtschaffen and Kales, 1968)).

Maintenance of Wakefulness Test (MWT). Participants were evaluated on the MWT three times during each mission at test blocks 4, 8, and 12 (respectively, at 6, 14, and 22 hours into each mission). The subjects were comfortably reclined in the easy chair within each of their assigned rooms with the lights very dimly lit. They were instructed to remain awake with eyes open for 20 minutes without resorting to extraordinary means (e.g., slapping the face or singing). EEG was recorded during the test from the same sites used during sleep. If sleep was polysomnographically determined to occur the time of sleep onset was recorded.

Sleepiness. The ANAM battery offers a sleepiness scale that, while a modification of the Stanford Sleepiness Scale (14), maintains the original seven-point scale rating subjective sleepiness from "*1-very alert, wide awake, and energetic*" to "*7-very sleepy and cannot stay awake much longer*." The ANAM sleepiness scale was presented on the computer monitor as the first item of business at the start of each of the 13 testing blocks.

Symptoms. Participants completed a 73-item paper and pencil Symptom Checklist at the start of each mission and thereafter every four hours indicating the severity (*none, some, moderately, or severely*) they were experiencing for each symptom at that point in time. Subjects completed the checklist at the start of each mission and every four hours thereafter.

Affect. Subjective evaluations of mood were acquired using the Profile of Mood States (McNair, Lorr, and Droppleman, 1971). The POMS consists of a listing of 65 adjectives that are each rated on a five-point scale. A standardized "state" measure is generated for each of six categories; anger, confusion, depression, fatigue, tension, and vigor. A POMS survey was completed at the start of each mission and at subsequent eight-hour intervals during each mission (test blocks 1, 5, 9, and 13).

Statistical Analyses

To determine the appropriate sample size for this study, a power analysis was based on the post-hoc oaired-comparisons to insure that there would be sufficient power to identify specific differences among the five drug conditions. Based on procedures defined by Cohen (1988), when testing at the 0.05 alpha level a sample of 10 subjects per group will provided a 78% chance (power) of detecting a large effect (i.e., an effect in which the standard deviation (sd) of the group means is 0.5 the magnitude of the within-group sd). If the means were even more dispersed (for instance, with an sd that is 0.6 times the magnitude of the within-group sd), the chance of detection increased to 92%.

The means of the performance measures and subjective ratings for each subject's data collected during the three testing blocks conducted on Day 1 at 0800, 1000, and 1200 just prior to the start of the initial pre-mission rest period served as Baseline reference values to which all subsequent data were arithmetically referenced to develop "change-scores." These changes-scores maintained the absolute units of measurement from which they were

derived. (i.e., the derived scores are not percent change scores). This procedure offered some adjustment for any initial differences among the groups of subjects assigned to each of the five drug-combination conditions, and common reference points for each group at the start of each of the three missions.

Independent within-mission-analyses were conducted on the data for each of the three missions, thereby avoiding the complexity of time-on-duty being confounded with time-of-day across the three missions. For each normally distributed outcome variable, a repeated measures analysis of variance (ANOVA) with one between-subjects factor (drug conditions) and one within-subjects factors (testing blocks within mission) was separately conducted for each of the three missions. A Huyhn-Feldt adjustment was made to the degrees of freedom for tests that failed Mauchley's Test of Sphericity. To reduce excessive post hoc testing, a two-stage process was applied when either significant Drug or Drug X Block (D x B) effects were detected. One-way ANOVAs were conducted for each testing session within that mission. Sessions indicating a significant Drug effect ($p \leq .05$) were then subjected to Student-Newman-Keuls analyses to identify specific differences ($p \leq .05$) between Drug conditions. For discrete outcome variables, or those that were not normally distributed, non-parametric Kruskal-Wallace H-tests, with follow-up Wilcoxon signed rank tests, when appropriate, were performed at each time point.

It was acknowledged prior to data collection that conducting only independent ANOVAs on the data generated within each of the three missions limited the ability to describe overall differences between missions, information which would be of considerable interest and value to operational planners and schedulers. Thus, while violating some assumptions and not the foundation of the findings, between-mission ANOVAs comparing data across the three missions were also conducted to allow these comparisons. These analyses are considered to be of secondary importance to the objectives of the study and supplement the primary, in-depth ANOVAs individually performed on each of the three missions.

For each polysomnography variable, a repeated measures ANOVA with one between-subjects factor (drug conditions) and one within-subject factor (missions) tested for drug condition differences. Appropriate post-hoc comparisons (as described in the previous paragraph) were performed when dictated by the ANOVA results. Non-parametric procedures were employed for those outcome measures that are not normally distributed.

RESULTS

Data Loss and Adjustments

Data were successfully collected from 43 of the 50 trained participants. One female withdrew from the study just prior to her experimental session. In addition, the data collected from four of the participants assigned to the placebo condition and two assigned to the temazepam/modafinil condition were excluded from statistical analyses for the following reasons. Two of the placebo subjects were severely stressed by the surge schedule and were able to complete the entire study only by being allowed to occasionally nap during the missions. One of these two, a male, complained of a headache throughout the study (he subsequently admitted to having a history of migraines) and the other, a

female, was driven to tears and mild hysteria by her need for sleep during the missions. The vital signs for the other two excluded placebo subjects, both males, indicated one to have a mild fever (accompanied by nausea and chills) during the first half of the data collection period, and the other to have significantly elevated blood pressure from the start of the first mission throughout the data collection period. In all four of these cases appropriate over-the-counter medications were administered as directed by the Medical Monitor. The two subjects, both males, assigned to the temazepam/modafinil condition whose data were excluded from analyses each became very nauseous during data collection, the first after receiving his sixth modafinil dose at start of the 11th test block (0000) towards the end of the first mission, and the second after receiving his third modafinil dose at the start of the 5th test block (0400) about one-third of the way into the second mission. Both subjects were too ill to properly complete their upcoming performance testing block and were allowed to rest in bed, feeling much improved following 3-4 hours. The Medical Monitor and Principal Investigator determined it best to cease administration of both the temazepam and modafinil doses to these two subjects for the duration of the study. After deleting the data for the six excluded subjects missing data occurred less than 2% of the time for the outcome measures submitted to statistical analyses,[1] usually due to technical problems. To facilitate statistical analyses estimates were made of missing data based on the average of corresponding percent changes in data available from other subjects in the same condition.

During data collection it was often observed, and later verified during inspection of raw reaction time data for each ANAM cognitive task, that some subjects were unable to maintain their concentration on a task (especially during the last 2-3 testing blocks within a mission) and were simply gaming the situation by responding randomly and as rapidly as possible, thereby corrupting both their reaction time and throughput data which, in many instances given this behavior, falsely indicated maintenance or even improvement in performance although it was actually deteriorating. Accuracy, however, was appropriately sensitive to this strategy, with the correctness of a response decrementing to chance levels. Accuracy of performance was therefore selected as the only reliable dependent measure for the six ANAM tasks for which it was available.

The separate within-mission ANOVAs conducted on each of the three missions revealed that although several Drug and/or Drug X Block effects did not attain or exceed the traditional level of statistical significance ($p \leq .05$) for some of the outcome measures, these effects did frequently approach significance ($p \leq .10$). Given the primary objective of this study was directed at providing information and guidance on the maximal effective application of selected medications to unique military operations, it was decided that the consistent trends indicated by the near-statistically-significant findings in the initial overall within-mission ANOVAs were worthy of inclusion in the ad hoc one-way ANOVAs and subsequent legitimate Student-Newman Keuls paired-tests. Thus, a posteriori for the within-mission ANOVAs, overall Drug and/or Drug X Block effects attaining near-significance at alpha level of $p \leq .10$ were submitted to the subsequent two-stage analyses, for which statistical significance was maintained at $p \leq .05$.

---

[1] Statistical analyses were not performed on the Synthetic Work Task data or the Postural Sway data. Synthetic Work was omitted due to significant performance improvement (i.e., learning) as the study progressed, and Postural Sway due to incomplete and unreliable data resulting from undetected technical problems.

Between-Mission ANOVA Findings.

A statistically significant three-way interaction of Drug x Mission x Block was not detected for any of the performance or subjective outcome measures evaluated during the missions. Statistically significant Mission x Block effects occurred for all but one of the ANAM tasks, and for PVT performance, the sleepiness ratings, and fatigue, vigor, and confusion on the Mood Scale II survey ($p < .02$ in each case, but for Code Substitution – Learning for which $p = .10$). Significant Drug x Block effects occurred for the three Code Substitution tasks, Continuous Processing, and Grammatical Reasoning. The Mission x Block interactions consistently reflected deteriorating performance, alertness, and mood across missions, with greater and sometimes earlier deterioration within missions (i.e., across blocks) as the missions progressed. The significant Drug x Block interactions consistently demonstrated performance to generally deteriorate within a mission from the early to the later blocks for the Placebo condition, but to remain relatively stable both within and across the three missions for each of the four Drug-Combination conditions. Representative examples of these performance and subjective findings are presented in Figures 1-3 for the Drug x Mission interaction and Figures 4-6 for the Drug x Block interaction. As for sleep acquired during the three pre-mission crew-rest periods, Drug x Mission interactions did not approach statistical significance ($p \geq .20$ in all cases) for any of the sleep metrics. Statistically significant overall Between-Mission effects ($p \leq .04$ in all cases) were detected for each of the sleep metrics except Time-in-Stage -1.

The within-mission ANOVAs discussed in the following section present greater in-depth evaluation of the data with the inclusion of post hoc paired-comparison tests.

Within-Mission ANOVA and Follow-on Post Hoc Findings.

Tables III – XIII present summaries of the mean data and statistical results for the within-mission ANOVAS and subsequent pot hoc tests conducted on each of the three missions for each of the outcome measures. In each table significant paired-comparison differences are identified for each test block within each of the missions. The reader may wish to refer to each of the referenced tables for the statistical data while reviewing the following summary statements describing each of the significant findings.

Code Substitution Task – Learning (Table III).

Mission 1: A near-significant Drug effect and a significant Drug x Block effect were detected. Accuracy of performance was better under each of the Drug-Combination conditions than under the Placebo condition during Test Blocks 12 and 13.

Mission 2: A near-significant Drug effect occurred. Performance was better under each of the Drug-Combination conditions than under the Placebo condition during Test Blocks 8 and 12; and better under Zol-Dex and Tem-Mod conditions than under Placebo during Block 11.

Mission 3: A near-significant Drug effect occurred. Performance was better under Tem-Mod than Zol-Mod during Block 3.

Code Substitution Task – Immediate Recall (Table IV).

Mission 1: A significant Drug effect was detected. Performance was better under Zol-Dex than Placebo during Test Block 3; performance was better under Zol-Dex, Zol-Mod, and Tem-Mod than under Placebo during Block 8; and performance was better under Zol-Dex

Table III.

ANAM Code Substitution Task: Learning - Accuracy Performance

Within-Mission ANOVA and Post Hoc Analyses Results for Change-from-Baseline Means[1]

Mission 1													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	4:00	6:00	8:00	10:00	12:00	14:00	16:00	18:00	20:00	22:00	0:00	2:00	4:00
Placebo	*0.12*	*-1.74*	*-1.51*	*-0.58*	*-0.58*	*-0.58*	*0.12*	*-1.27*	*-0.12*	*-0.81*	*-1.51*	*-4.05*	*-8.31*
Zol-Dex	*-0.31*	*0.93*	*1.85*	*0.46*	*0.77*	*0.93*	*1.39*	*1.23*	*1,70*	*2.62*	*1.39*	*0.93*	*0.77*
Zol-Mod	*-0.63*	*0.2*	*-0.49*	*-1.04*	*-1.32*	*-1.18*	*-0.62*	*-0.35*	*-0.9*	*-0.07*	*-0.07*	*0.76*	*-0.07*
Tem-Dex	*-0.14*	*0.69*	*-0.83*	*0.42*	*-0.14*	*-0.97*	*-0.42*	*-0.83*	*0.42*	*0.97*	*-0.14*	*0.55*	*1.67*
Tem-Mod	*-0.26*	*0.61*	*-1.13*	*0.44*	*-0.61*	*0.78*	*1.48*	*-0.96*	*1.3*	*0.95*	*0.78*	*-0.78*	*1.13*
Mission 2													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	20:00	22:00	0:00	2:00	4:00	6:00	8:00	10:00	12:00	14:00	16:00	18:00	20:00
Placebo	*-1.74*	*-0.35*	*-3.59*	*-1.97*	*-2.43*	*-4.05*	*-3.36*	*-5.21*	*-2.66*	*-2.89*	*-3.59*	*-4.51*	*-4.79*
Zol-Dex	*-0.46*	*0.6*	*0.46*	*1.08*	*-0.46*	*0.31*	*-0.77*	*-0.31*	*-0.31*	*0.15*	*1.23*	*-0.01*	*0*
Zol-Mod	*0.21*	*-2.72*	*-1.88*	*-0.9*	*-3.54*	*-2.99*	*-2.98*	*-0.76*	*-3.08*	*-3.26*	*-1.46*	*-1.18*	*0.35*
Tem-Dex	*1.39*	*0.28*	*0.28*	*0*	*0.42*	*-2.88*	*-0.14*	*0.69*	*0.41*	*1.11*	*-0.28*	*0.69*	*-1.53*
Tem-Mod	*-0.78*	*-0.78*	*-0.61*	*0.43*	*-0.43*	*-1.32*	*-0.78*	*-0.43*	*-0.78*	*1.65*	*0.61*	*-0.62*	*0.09*
Mission 3													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	12:00	14:00	16:00	18:00	20:00	22:00	0:00	2:00	4:00	6:00	8:00	10:00	12:00
Placebo	*-2.2*	*-4.05*	*-1.74*	*-3.82*	*-3.37*	*-3.36*	*-3.12*	*-5.21*	*-5.44*	*-2.9*	*-3.12*	*-7.79*	*-8.14*
Zol-Dex	*0.77*	*-0.93*	*-1.39*	*-0.46*	*-1.72*	*-0.93*	*0.46*	*-0.63*	*-0.64*	*-1.7*	*-3.13*	*-2.08*	*-3.88*
Zol-Mod	*-0.21*	*-1.04*	*-2.85*	*-2.71*	*-2.01*	*-1.73*	*-2.29*	*-2.29*	*-3.68*	*-2.5*	*-3.99*	*-1.19*	*-2.44*
Tem-Dex	*0.28*	*0.28*	*-0.56*	*-0.14*	*-1.25*	*0.14*	*0*	*-0.88*	*1.25*	*-0.84*	*0.83*	*-0.69*	*-0.56*
Tem-Mod	*-0.26*	*0.09*	*0.96*	*-0.26*	*-0.27*	*-1.47*	*-0.78*	*0.43*	*-0.44*	*-1.13*	*-0.1*	*-0.47*	*0.26*

Within-Mission ANOVA Results

Mission 1

Drug: F(4,38) = 2.231; MSE = 39.94 **p = .084**

Block: F(10,375) = 1.60, MSE = 6.86 **p = .105**

D x B: F(39,375) = 2.13; MSE = 6.86 **p < .001**

Mission 2

Drug: F(4,38) = 2.34; MSE = 78.83 **p = .073**

Block; F(9,342) = 1.51; MSE = 13.54 p = .142

D x B: F(36,342) = 1.04; MSE = 13.54 p = .413

Mission 3

Drug: F(4,38) = 2.08; MSE = 114.11 **p = .103**

Block: F(8,287 = 2.10; MSE = 19.53 **p = .039**

D x B: F(52,492) = 1.29; MSE = 19.53 p = .483

[1] Mean Baseline Scores: Placebo = 98.49; Zol-Dex = 96.45; Zol-Mod = 97.57; Tem-Dex =96.81 ; Tem-Mod = 96.27

X.XX Post hoc Student-Newman-Keuls detected performance to be significantly ($p \leq .05$) better than under the Placebo condition.

X.XX Post hoc Student-Newman-Keuls detected performance to be significantly ($p \leq .05$) better under Tem-Mod than Zol-Mod.

Table IV.

ANAM Code Substitution Task: Immediate Recall - Accuracy Performance

Within-Mission ANOVA and Post Hoc Analyses Results for Change-from-Baseline Means[1]

Mission 1													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	4:00	6:00	8:00	10:00	12:00	14:00	16:00	18:00	20:00	22:00	0:00	2:00	4:00
Placebo	*-1.39*	*-6.95*	*-3.24*	*-2.32*	*-3.24*	*-0.47*	*-1.39*	*-6.02*	*-1.39*	*-4.17*	*-4.17*	*-1.39*	*-5.1*
Zol-Dex	*2.16*	*4.01*	*5.25*	*3.39*	*0.93*	*4.01*	*2.78*	*5.25*	*4.01*	*4.63*	*4.63*	*5.25*	*3.39*
Zol-Mod	*0.28*	*-0.83*	*0.83*	*-0.28*	*3.61*	*1.94*	*1.39*	*2.5*	*2.5*	*1.94*	*-0.28*	*3.06*	*0.73*
Tem-Dex	*-1.67*	*-4.45*	*-4.44*	*-1.67*	*-1.67*	*1.11*	*-0.56*	*-1.11*	*-4.44*	*0*	*-7.22*	*-4.45*	*-0.56*
Tem-Mod	*3.12*	*-2.43*	*1.04*	*0.35*	*3.82*	*5.91*	*-0.35*	*4.52*	*4.52*	*3.13*	*2.43*	*-0.35*	*3.82*
Mission 2													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	20:00	22:00	0:00	2:00	4:00	6:00	8:00	10:00	12:00	14:00	16:00	18:00	20:00
Placebo	*-3.24*	*-4.17*	*-4.17*	*2.32*	*-3.24*	*-1.39*	*-10.65*	*-11.58*	*-0.46*	*-5.09*	*-2.32*	*-10.65*	*-6.02*
Zol-Dex	*2.78*	*3.39*	*5.25*	*0.31*	*5.86*	*0.93*	*3.4*	*1.54*	*6.48*	*4.01*	*2.78*	*0.93*	*6.48*
Zol-Mod	*3.61*	*0.83*	*0.83*	*3.61*	*-1.95*	*4.16*	*-0.28*	*1.39*	*2.5*	*1.94*	*1.39*	*-0.84*	*-1.39*
Tem-Dex	*0*	*-3.33*	*-1.11*	*-2.78*	*-1.67*	*-1.67*	*-2.22*	*0*	*-1.67*	*1.11*	*0*	*-1.11*	*-0.56*
Tem-Mod	*0.35*	*2.43*	*3.13*	*3.82*	*1.74*	*3.82*	*0.35*	*1.04*	*4,51*	*1.04*	*4.52*	*4.52*	*2.43*
Mission 3													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	12:00	14:00	16:00	18:00	20:00	22:00	0:00	2:00	4:00	6:00	8:00	10:00	12:00
Placebo	*0.46*	*0.46*	*-0.46*	*0.46*	*-3.24*	*-1.39*	*-3.24*	*0.46*	*-5.09*	*-8.8*	*-3.24*	*-7.87*	*-20.83*
Zol-Dex	*-2.16*	*3.4*	*4.63*	*5.25*	*-0.93*	*2.78*	*4.01*	*4.63*	*2.16*	*1.54*	*0.31*	*2.15*	*4.01*
Zol-Mod	*3.06*	*3.06*	*-1.39*	*-0.28*	*-0.83*	*0.28*	*-1.95*	*0.83*	*1.94*	*-0.84*	*0.83*	*0.83*	*-0.28*
Tem-Dex	*2.78*	*-1.67*	*1.67*	*-1.67*	*-1.67*	*-2.22*	*-8.63*	*-4.44*	*-1.67*	*-6.11*	*-5.55*	*-4.12*	*-7.78*
Tem-Mod	*-0.35*	*1.04*	*-2.43*	*0.35*	*1.04*	*-1.04*	*4.52*	*5.91*	*1.74*	*1.04*	*3.13*	*3.13*	*3.13*

Within-Mission ANOVA Results

Mission 1

Drug: F(4,38) = 5.06, MSE = 176.64 **p = .002**
Block: F(13,478) = 1.51; MSE = 31.95 p = .114
D x B: F(50,478) = 1.00; MSE = 31.95 p = .475

Mission 2

Drug: F(4,38) = 3.81; MSE = 240.27 **p = .011**
Block: F(11,410) = 1.71; MSE = 42.26 **p = .070**
D x B: F(43,410) = 1.28; MSE = 42.26 p = .116

Mission 3

Drug: F(4,38) = 1.83; MSE = 441.29 p = .144
Block: F(8,307) = 1.95; MSE = 84.98 **p = .052**
D x B: F(32,307) = 1.63; MSE = 84.98 **p = .019**

[1] Mean Baseline Scores: Placebo = 96.76; Zol-Dex = 92.90; Zol-Mod =94.72 ; Tem-Dex = 96.11; Tem-Mod = 94.10

X.XX Post hoc Student-Newman-Keuls detected performance to be significantly ($p \leq .05$) better than under the Placebo condition.

X.XX Post hoc Student-Newman-Keuls detected performance to be significantly ($p \leq .05$) better under Zol-Dex than Tem-Dex.

Table V.
ANAM Code Substitution Task: Delayed Recall - Accuracy Performance
Within-Mission ANOVA and Post Hoc Analyses Results for Change-from-Baseline Means[1]

Mission 1													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	4:00	6:00	8:00	10:00	12:00	14:00	16:00	18:00	20:00	22:00	0:00	2:00	4:00
Placebo	*-0.93*	*-7.87*	*-7.41*	*-6.48*	*-2.78*	*-1.39*	*-1.39*	*-6.95*	*-4.63*	*-1.39*	*-5.55*	*-12.03*	*-19.91*
Zol-Dex	*5.86*	*-2.16*	*0.93*	*1.85*	*-2.47*	*0*	*.5.86*	*0.31*	*-0.93*	*-0.62*	*0.93*	*4.42*	*1.24*
Zol-Mod	*-0.97*	*0.14*	*-2.93*	*0.42*	*-0.14*	*-1.81*	*-3.19*	*-2.64*	*-2.08*	*2.89*	*-11.15*	*-3.2*	*-2.36*
Tem-Dex	*-4.72*	*-6.11*	*-3.06*	*-6.66*	*-0.83*	*-0.83*	*0.28*	*0.56*	*-2.22*	*1.39*	*-4.45*	*-7.22*	*-3.61*
Tem-Mod	*4.69*	*-1.91*	*-0.87*	*-3.99*	*1.91*	*-0.17*	*-0.17*	*-3.3*	*-0.17*	*1.21*	*-1.56*	*-0.87*	*1.56*
Mission 2													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	20:00	22:00	0:00	2:00	4:00	6:00	8:00	10:00	12:00	14:00	16:00	18:00	20:00
Placebo	*6.48*	*-1.39*	*-7.87*	*-5.56*	*-6.48*	*-7.34*	*-15.28*	*-18.52*	*-13.43*	*-6.02*	*-14.81*	*-13.42*	*-13.43*
Zol-Dex	*6.17*	*3.7*	*-3.09*	*-1.23*	*-0.31*	*-0.31*	*-6.48*	*-8.95*	*-1.23*	*0.31*	*-1.24*	*-0.31*	*2.16*
Zol-Mod	*3.19*	*-2.92*	*-4.03*	*-1.81*	*-7.08*	*-3.64*	*-7.64*	*-3.75*	*-1.81*	*-5.69*	*-9.03*	*-3.75*	*-5.69*
Tem-Dex	*2.78*	*-0.83*	*-3.33*	*-7.22*	*-6.11*	*-10.52*	*0.55*	*0.28*	*-5.83*	*0.83*	*0.55*	*-2.22*	*1.11*
Tem-Mod	*-1.21*	*1.56*	*-2.6*	*0.17*	*-5.38*	*-3.64*	*-0.87*	*-5.38*	*3.3*	*-0.52*	*-1.91*	*-0.17*	*-3.3*
Mission 3													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	12:00	14:00	16:00	18:00	20:00	22:00	0:00	2:00	4:00	6:00	8:00	10:00	12:00
Placebo	*2.32*	*-2.78*	*-4.17*	*-2.78*	*-7.87*	*-6.02*	*-8.79*	*-6.02*	*-5.55*	*-9.26*	*-20.37*	*-12.44*	*-20.4*
Zol-Dex	*3.4*	*1.54*	*0*	*4.01*	*-2.16*	*0.31*	*1.85*	*4.01*	*-1.23*	*-2.78*	*-5.56*	*-5.25*	*3.09*
Zol-Mod	*0.42*	*-2.36*	*-4.58*	*-6.53*	*-8.19*	*-10.49*	*-5.14*	*-4.03*	*-3.85*	*-9.03*	*-7.08*	*-3.52*	*-4.38*
Tem-Dex	*7.78*	*-1.67*	*-5*	*-2.02*	*-3.89*	*-8.94*	*-13.47*	*-6.94*	*0.25*	*-6.11*	*-7.5*	*-9.87*	*-2.78*
Tem-Mod	*-0.52*	*-0.17*	*0.18*	*-3.99*	*1.91*	*-6.08*	*0.87*	*4.34*	*-0.52*	*-6.77*	*-10.24*	*-3.99*	*2.95*

Within-Mission ANOVA Results

Mission 1

Drug: F(4,38) = 2.23; MSE = 40.00; **p = .084**
Block: F(10,375) = 1.60; MSE = 6.86; p = .105
D x B: F(40, 375) = 2.13; MSE = 6.86 **p < .001**

Mission 2

Drug: F(4,38) = 2.34; MSE = 78.83 **p = .073**
Block: F(9,342) = 1.51, MSE = 13.54 p = .142
D x B: F(36,342) = 1.04; MSE = 13.53 p = .413

Mission 3

Drug: F(4,38) = 2.08; MSE = 114.11 **p = .103**
Block: F(8,287) = 2.10; MSE = 19.53 **p = .039**
D x B: F(30,287) = 0.992; MSE = 19.53 p = .483

[1] Mean Baseline Scores: Placebo = 89.81; Zol-Dex = 87.65; Zol-Mod = 91.53; Tem-Dex = 86.67; Tem-Mod = 90.10

X.XX Post hoc Student-Newman-Keuls detected performance to be significantly ($p \leq .05$) better than under the Placebo condition.

and Tem-Mod than Placebo during Sessions 13. Performance was better under Zol-Dex than under Tem-Dex during Block 11.
Mission 2: A significant Drug effect occurred. Performance under each of the Drug-Combination conditions was better than that under Placebo during Blocks 8 and 10.
Mission 3: A significant Drug x Block effect occurred. Performance under each of the Drug-Combination conditions was better than that under Placebo during Block 13.

Code Substitution Task – Delayed Recall (Table V).

Mission 1: A near-significant Drug effect and a significant Drug x Block effect occurred. Performance under Zol-Dex was better than that under Placebo during Block 12; performance was better under each of the Drug-Combination conditions than under Placebo during Block 13.
Mission 2: A near-significant Drug effect was detected. Performance was better under Zol-Mod, Tem-Dex, and Tem-Mod than under Placebo during Block 3; performance was better under Tem-Dex than Placebo during Block 11; and performance was better under Zol-Dex and Tem-Dex than under Placebo during Block 13.
Mission 3: A near-significant Drug effect was detected. Performance was better under each of the Drug-Combination conditions than under Placebo during Block 13.

Continuous Processing Task (Table VI).

Mission 1: A significant Drug x Block interaction was detected. Post hoc tests revealed performance under each of the Combined Drug conditions to be superior to that under Placebo during Test Block 13.
Mission 2: A significant Drug x Block interaction was detected. Performance under each of the Combined Drug conditions was superior to that under Placebo during Test Blocks 8, 11, 12, and 13. Performance was better under both Zol-Mod and Tem-Mod than Placebo during Blocks 9 and 10.
Mission 3: A significant Drug x Block interaction was detected. Performance was better under Zol-Mod than Placebo during Test Block 8. During Block 10 performance was better under Zol-Dex, Zol-Mod, and Tem-Mod than Placebo. Performance was better under each of the four Drug Combination conditions that under Placebo during Blocks 12 and 13.

Simple Reaction Time Task (Table VII).

There were no statistically significant ANOVA effects for the main effect of Drug or for the Drug x Block interaction during any of the missions for this task, thus post hoc testing was not conducted.

Mathematical Processing Task (Table VIII).

Mission 1: A near-significant Drug x Block effect occurred. Post hoc testing indicated performance under each of the Combined Drug conditions to better than that under the Placebo condition during Block 13.
Mission 3: A near-significant Drug x Block effect occurred. Performance under each of the Combined Drug conditions was better than that under the Placebo condition during Block 12.

Grammatical Reasoning Task (Table IX).

Mission 1: A near-significant Drug x Block effect was detected. Post hoc testing indicated performance to be significantly better under Tem-Mod than Zol-Dex during Block 6.
Mission 2: A near-significant Drug x Block effect was detected. Performance under the Zol-Med, Tem-Dex, and Tem-Mod conditions were superior to that under the Placebo condition during Block 11.

Table VI.
ANAM Continuous Processing Task - Accuracy Performance
Within-Mission ANOVA and Post Hoc Analyses Results for Change-from-Baseline Means[1]

Mission 1													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	4:00	6:00	8:00	10:00	12:00	14:00	16:00	18:00	20:00	22:00	0:00	2:00	4:00
Placebo	*1.18*	*-0.01*	*0.31*	*-1.97*	*-0.26*	*0.03*	*-0.24*	*-1.1*	*-0.36*	*-0.26*	*-1.54*	*-3.03*	*-4.9*
Zol-Dex	*0.11*	*-0.67*	*0.86*	*-0.51*	*0.27*	*0.43*	*0.3*	*0.31*	*0.86*	*0.55*	*0.87*	*0.97*	*0.1*
Zol-Mod	*1.04*	*1.3*	*1.25*	*1.79*	*1.29*	*1.7*	*1.61*	*1.68*	*1.92*	*1.68*	*1.67*	*1.09*	*1.36*
Tem-Dex	*0.66*	*0.51*	*-0.28*	*-0.11*	*-0.37*	*-0.14*	*-0.12*	*-0.03*	*0.92*	*1.56*	*0.08*	*-0.03*	*0.44*
Tem-Mod	*0.04*	*-0.23*	*-0.79*	*-2.55*	*1.66*	*0.71*	*0.8*	*0.85*	*1.73*	*0.83*	*1.26*	*1.58*	*1.27*
Mission 2													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	20:00	22:00	0:00	2:00	4:00	6:00	8:00	10:00	12:00	14:00	16:00	18:00	20:00
Placebo	*-1.3*	*0.33*	*-0.24*	*-0.22*	*-2.46*	*-3.71*	*-4.52*	*-7.51*	*-2.83*	*-2.96*	*-4.41*	*-7.07*	*-4.09*
Zol-Dex	*0.67*	*0.08*	*-0.99*	*-0.46*	*0.07*	*0.08*	*-0.16*	*-1.85*	*-0.51*	*-0.22*	*0.69*	*0.49*	*0.17*
Zol-Mod	*1.74*	*2.05*	*1.41*	*1.38*	*0.92*	*2.02*	*0.7*	*1.01*	*1.76*	*2.04*	*1.3*	*1.54*	*1.94*
Tem-Dex	*0.31*	*-0.06*	*-0.9*	*-0.46*	*0.8*	*-0.36*	*-0.97*	*-0.03*	*-0.66*	*-0.21*	*0.32*	*-0.09*	*0.25*
Tem-Mod	*1.68*	*1.13*	*-0.2*	*0.46*	*-0.02*	*-2.37*	*-1.61*	*0.2*	*1.15*	*1.69*	*1.53*	*2.05*	*1.49*
Mission 3													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	12:00	14:00	16:00	18:00	20:00	22:00	0:00	2:00	4:00	6:00	8:00	10:00	12:00
Placebo	*-0.18*	*-0.03*	*-0.59*	*-1.35*	*0.37*	*-1.71*	*-1.74*	*-2.43*	*-3.23*	*-7.91*	*-7.06*	*-11.05*	*-10.92*
Zol-Dex	*0.26*	*0.15*	*1.42*	*1.16*	*0.08*	*-0.15*	*0.72*	*0.79*	*0.5*	*-1.11*	*-2.66*	*-1.69*	*0.02*
Zol-Mod	*1.49*	*1.29*	*1,58*	*2.11*	*0.75*	*1.72*	*0.54*	*1.88*	*0.92*	*1.39*	*0.14*	*-0.66*	*1.68*	*-0.46*
Tem-Dex	*0.26*	*-0.14*	*-0.3*	*0.51*	*0.3*	*0.57*	*0.75*	*-0.28*	*-0.25*	*-3.97*	*-3.74*	*-4.16*	*-0.46*
Tem-Mod	*0.58*	*0.68*	*1.53*	*1.5*	*0.78*	*-0.31*	*1.16*	*0.69*	*-3.45*	*-0.76*	*-2.71*	*-3.84*	*0.14*

Within-Mission ANOVA Results

Mission 1

Drug: F(4,38) = 1.90; MSE = 36.59 p = .131
Block: F(9,339) = 2.08; MSE = 5.81 **p = .031**
D x B: F(36,339) = 1.63; MSE = 5.81 **p = .016**

Mission 2

Drug: F(4,38) = 5.56; MSE = 46.67 **p = .001**
Block: F(8,301) = 2,65; MSE = 11.13 **p = .008**
D x B: F(32,301) = 1.77; MSE = 11.13 **p = .008**

Mission 3

Drug: F(4,38) = 4.41; MSE = 62.15 **p = .005**
Block: F(6,223) = 9.24; MSE = 26.56 **p < .001**
D x B: F(23,2230) = 1.68; MSE = 26.56 **p = .030**

[1] Mean Baseline Scores: Placebo = 97.17; Zol-Dex = 96.37; Zol-Mod = 95.47; Tem-Dex = 96.70; Tem-Mod = 96.84

X.XX Post hoc Student-Newman-Keuls detected performance to be significantly ($p \leq .05$) better than under the Placebo condition.

and Tem-Mod than Placebo during Sessions 13. Performance was better under Zol-Dex than under Tem-Dex during Block 11.
Mission 2: A significant Drug effect occurred. Performance under each of the Drug-Combination conditions was better than that under Placebo during Blocks 8 and 10.
Mission 3: A significant Drug x Block effect occurred. Performance under each of the Drug-Combination conditions was better than that under Placebo during Block 13.

Code Substitution Task – Delayed Recall (Table V).

Mission 1: A near-significant Drug effect and a significant Drug x Block effect occurred. Performance under Zol-Dex was better than that under Placebo during Block 12; performance was better under each of the Drug-Combination conditions than under Placebo during Block 13.
Mission 2: A near-significant Drug effect was detected. Performance was better under Zol-Mod, Tem-Dex, and Tem-Mod than under Placebo during Block 3; performance was better under Tem-Dex than Placebo during Block 11; and performance was better under Zol-Dex and Tem-Dex than under Placebo during Block 13.
Mission 3: A near-significant Drug effect was detected. Performance was better under each of the Drug-Combination conditions than under Placebo during Block 13.

Continuous Processing Task (Table VI).

Mission 1: A significant Drug x Block interaction was detected. Post hoc tests revealed performance under each of the Combined Drug conditions to be superior to that under Placebo during Test Block 13.
Mission 2: A significant Drug x Block interaction was detected. Performance under each of the Combined Drug conditions was superior to that under Placebo during Test Blocks 8, 11, 12, and 13. Performance was better under both Zol-Mod and Tem-Mod than Placebo during Blocks 9 and 10.
Mission 3: A significant Drug x Block interaction was detected. Performance was better under Zol-Mod than Placebo during Test Block 8. During Block 10 performance was better under Zol-Dex, Zol-Mod, and Tem-Mod than Placebo. Performance was better under each of the four Drug Combination conditions that under Placebo during Blocks 12 and 13.

Simple Reaction Time Task (Table VII).

There were no statistically significant ANOVA effects for the main effect of Drug or for the Drug x Block interaction during any of the missions for this task, thus post hoc testing was not conducted.

Mathematical Processing Task (Table VIII).

Mission 1: A near-significant Drug x Block effect occurred. Post hoc testing indicated performance under each of the Combined Drug conditions to better than that under the Placebo condition during Block 13.
Mission 3: A near-significant Drug x Block effect occurred. Performance under each of the Combined Drug conditions was better than that under the Placebo condition during Block 12.

Grammatical Reasoning Task (Table IX).

Mission 1: A near-significant Drug x Block effect was detected. Post hoc testing indicated performance to be significantly better under Tem-Mod than Zol-Dex during Block 6.
Mission 2: A near-significant Drug x Block effect was detected. Performance under the Zol-Med, Tem-Dex, and Tem-Mod conditions were superior to that under the Placebo condition during Block 11.

Table VII.
ANAM Simple Reaction Time Task - Mean Reaction Time for Correct Responses
Within-Mission ANOVA# and Post Hoc Analyses Results for Change-from-Baseline Means[1]

Mission 1													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	4:00	6:00	8:00	10:00	12:00	14:00	16:00	18:00	20:00	22:00	0:00	2:00	4:00
Placebo	*3.99*	*0.05*	*8.45*	*6*	*6*	*15.85*	*3.79*	*16.88*	*14.21*	*11.57*	*11.68*	*9.2*	*24.48*
Zol-Dex	*4.02*	*24.1*	*-1.9*	*-6.03*	*4.01*	*-9.39*	*-4.67*	*-8.41*	*0.15*	*13.6*	*1.29*	*-6.78*	*4.63*
Zol-Mod	*9.96*	*3.97*	*-7.71*	*-1.37*	*-6.65*	*-7.39*	*-9.75*	*-12.48*	*-10.83*	*-3.92*	*-7.18*	*6.06*	*2.74*
Tem-Dex	*17.76*	*-12.38*	*-5.35*	*4.43*	*-6.3*	*-7.76*	*-8.44*	*-10.69*	*-4.63*	*4.51*	*-3.75*	*44.4*	*1.41*
Tem-Mod	*12.6*	*24.04*	15.01	*8.03*	*-4.43*	*5.49*	*1.08*	*-6*	*5.96*	*1.16*	*7.78*	*16.81*	*15.14*
Mission 2													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	20:00	22:00	0:00	2:00	4:00	6:00	8:00	10:00	12:00	14:00	16:00	18:00	20:00
Placebo	*1.31*	*1.97*	*-7.42*	*2.02*	*34.34*	*19.25*	*17.27*	*28.95*	*19.28*	*26.74*	*6.01*	*5*	*2.81*
Zol-Dex	*6.33*	*-0.46*	*-2.55*	*-6.44*	*-5.28*	*12.28*	*-0.96*	*5.77*	*0.47*	*-3.61*	*-1.34*	*-3.72*	*-4.66*
Zol-Mod	*-10.42*	*4.48*	*-5.15*	*5.72*	*8.26*	*3.97*	*14.69*	*12.5*	*7.66*	*5.74*	*10.66*	*-0.92*	*4.69*
Tem-Dex	*-12.15*	*2.41*	*-8.99*	*-11.03*	*15.25*	*10.32*	*-3.55*	*3.7*	*1.1*	*1.94*	*8.4*	*-7.87*	*4.38*
Tem-Mod	*8.86*	*6.53*	*-7.33*	*1.49*	*-9.74*	*1.53*	*14.88*	*6.2*	*8.51*	*14.55*	*10.21*	*2.96*	*11.91*
Mission 3													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	12:00	14:00	16:00	18:00	20:00	22:00	0:00	2:00	4:00	6:00	8:00	10:00	12:00
Placebo	*1.64*	*1.47*	*12.5*	*-0.04*	*-2.65*	*3.79*	*-4.58*	*7.12*	*22.51*	*27.01*	*21.56*	*42.32*	*39.62*
Zol-Dex	*5.42*	*4.87*	*-4.65*	*-18.36*	*-8.97*	*-9.83*	*-8.95*	*-8.11*	*-1.91*	*-3.43*	*13.02*	*-4.74*	*-8.5*
Zol-Mod	*-7.11*	*1.79*	*-7.62*	*-2.05*	*-12.43*	*-10.38*	*-10.08*	*14.42*	*-1.61*	*14.02*	*9.18*	*7.62*	*0.1*
Tem-Dex	*-18.87*	*0.85*	*-0.05*	*-9.97*	*-5.68*	*2.11*	*-0.93*	*33.68*	*13.1*	*31.55*	*3.68*	*-1.35*	*-13*
Tem-Mod	*3.64*	*5.53*	*1.07*	*-12.21*	*0.27*	*13.57*	*-7.72*	*16.11*	*11.1*	*2.3*	*12.89*	*18.25*	*19.67*

Within-Mission ANOVA Results

Mission 1

Drug: F(4,38) = 1.23; MSE = 2399.59 p = .316
Block: F(6,225) = 1.70; MSE = 1576.66 p = .122
D x B: F(24,225) = 0.96; MSE = 1575.66 p = .522

Mission 2

Drug: F(4,38) = 0.61; MSE = 2174.86 p = .661
Block: F(13,494) = 2.67; MSE = 449.75 **p = .001**
D x B: F(52,494) = 0.94; MSE = 449.75 p = .589

Mission 3

Drug: F(4,38) = 0.65; MSE = 6017.12 p = .629
Block: F(7,256) = 2.79; MSE = 1840.52 **p = .009**
D x B: F(27,256) = 10.84; MSE = 11840.52 p = .697

[1] Mean Baseline Scores: Placebo = 219.76; Zol-Dex =228.76 ; Zol-Mod = 218.40; Tem-Dex = 223.25 ; Tem-Mod = 214.60

There were no significant main ANOVA effects for Drug or Drug x Block, thus post hoc analyses were not appropriate.

Table VIII.
ANAM Mathematical Processing Task - Accuracy Performance
Within-Mission ANOVA and Post Hoc Analyses Results for Change-from-Baseline Means[1]

Mission 1													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	4:00	6:00	8:00	10:00	12:00	14:00	16:00	18:00	20:00	22:00	0:00	2:00	4:00
Placebo	*-1.24*	*-0.2*	*-0.86*	*-0.65*	*0.63*	*-1.25*	*-0.19*	*-0.14*	*1.74*	*-1.53*	*1.01*	*-0.34*	*-6.72*
Zol-Dex	*-0.54*	*-0.83*	*-1.15*	*-1.51*	*-0.41*	*1.44*	*1.03*	*1.07*	*1.25*	*1.55*	*-0.79*	*1.07*	*2.16*
Zol-Mod	*1.3*	*-0.06*	*1.47*	*0.88*	*-1.51*	*1.02*	*-0.15*	*0.91*	*0.98*	*1.7*	*1.39*	*1.13*	*1.94*
Tem-Dex	*0.87*	*-0.52*	*-1.06*	*0.79*	*0.31*	*1.49*	*-0.71*	*1.28*	*-0.1*	*1.52*	*1.69*	*1.39*	*0.27*
Tem-Mod	*1.91*	*-0.31*	*-0.66*	*-0.07*	*1.39*	*0.59*	*1.59*	*0.5*	*0.38*	*0.12*	*0.32*	*-0.8*	*-1.2*
Mission 2													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	20:00	22:00	0:00	2:00	4:00	6:00	8:00	10:00	12:00	14:00	16:00	18:00	20:00
Placebo	*-0.85*	*0.16*	*-0.91*	*-2.6*	*-1.43*	*-3.33*	*-3.54*	*-4.31*	*-0.72*	*-1.66*	*-1.26*	*-4.96*	*-5.45*
Zol-Dex	*-0.52*	*0.97*	*0.87*	*1.29*	*0.12*	*0.59*	*0.09*	*1.61*	*1.56*	*1.45*	*0.87*	*1.09*	*1.55*
Zol-Mod	*0.67*	*1.04*	*0.9*	*-0.07*	*0.14*	*0.82*	*0*	*-0.48*	*0.05*	*-0.61*	*1.4*	*0.08*	*0.57*
Tem-Dex	*1.31*	*2.72*	*0.34*	*1.07*	*1.71*	*0.12*	*1.73*	*-0.01*	*-0.29*	*0.66*	*0.81*	*2.47*	*0.87*
Tem-Mod	*-0.88*	*-1.16*	*1.01*	*-0.53*	*-1.56*	*-0.17*	*-2.06*	*-0.91*	*0.44*	*1.39*	*0.75*	*-0.03*	*-0.66*
Mission 3													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	12:00	14:00	16:00	18:00	20:00	22:00	0:00	2:00	4:00	6:00	8:00	10:00	12:00
Placebo	*-0.16*	*-2.22*	*-4.6*	*1.64*	*-0.47*	*-0.95*	*-2.3*	*-3.25*	*-2.12*	*-1.15*	*-3.25*	*-5.96*	*-3.28*
Zol-Dex	*1.3*	*0.08*	*1.93*	*2.75*	*1.11*	*1.75*	*0.9*	*0.04*	*-0.73*	*-0.14*	*-0.5*	*-0.15*	*2.3*
Zol-Mod	*0.11*	*0.36*	*-0.16*	*-0.06*	*-0.37*	*1.28*	*0.3*	*1.76*	*1.9*	*-1.2*	*-1.4*	*2.3*	*1.34*
Tem-Dex	*3.28*	*1.46*	*0.63*	*2.62*	*1.16*	*0.39*	*2.09*	*1.33*	*2.04*	*-0.95*	*1.66*	*1.81*	*1.59*
Tem-Mod	*-0.2*	*0.48*	*1.66*	*0.7*	*0.92*	*1.53*	*1.28*	*0.49*	*1.65*	*0.73*	*-1.05*	*-0.16*	*1.33*

Within-Mission ANOVA Results

Mission 1

Drug: F(438) = 0.41; MSE = 75.09	p = .802
Block: F(12,438) = 1.12; MSE = 10.59	p = .344
D x B: F(46,438) = 1.30; MSE = 10.58	**p = .098**

Mission 2

Drug: F(4,38) = 1.33; MSE = 120.55	p = .276
Block: F(12,448) = 1.04; MSE = 10.06	p = .415
D x B: F(47,448) = 0.44; MSE = 10.06	p = .440

Mission 3

Drug: F(4,38) + 1.35; MSE = 118.28	p = .268
Block: F(11,426) = 1.90; MSE = 10.39	**p = .036**
D x B: F(45,426) = 1.36; MSE = 10.39	**p = .066**

[1] Mean Baseline Scores: Placebo = 95.89 ; Zol-Dex = 94.96; Zol-Mod = 94.77; Tem-Dex = 94.20; Tem-Mod = 95.14

X.XX Post hoc Student-Newman-Keuls detected performance to be significantly ($p \leq .05$) better than under the Placebo condition.

Table IX.
ANAM Grammatical Reasoning Task - Accuracy Performance
Within-Mission ANOVA and Post Hoc Analyses Results for Change-from-Baseline Means[1]

Mission 1													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	4:00	6:00	8:00	10:00	12:00	14:00	16:00	18:00	20:00	22:00	0:00	2:00	4:00
Placebo	*1.57*	*1.22*	*0.52*	*-2.26*	*0.52*	*-0.52*	*-0.52*	*-1.21*	*-1.91*	*-2.95*	*-4.34*	*-4.69*	*-9.55*
Zol-Dex	*-1.16*	*-1.16*	*1.62*	*0.23*	*-0.93*	*-3.94*	*-0.46*	*1.85*	*1.16*	*-0.23*	*-2.78*	*-0.69*	*0.46*
Zol-Mod	*0.13*	*-0.11*	*-0.31*	*0.52*	*-0.73*	*0.31*	*0.73*	*0.31*	*0.73*	*-0.23*	*0.94*	*-1.15*	*-2.24*
Tem-Dex	*0.52*	*-1.35*	*0.1*	*-1.98*	*-2.19*	*-1.56*	*0.1*	*0.73*	*0.1*	*-0.94*	*-4.48*	*-2.6*	*1.98*
Tem-Mod	*2.21*	*3.52*	*2.21*	*0.39*	*4.82*	*2.21*	*2.73*	*1.95*	*2.73*	*0.65*	*1.17*	*1.95*	*-0.91*
Mission 2													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	20:00	22:00	0:00	2:00	4:00	6:00	8:00	10:00	12:00	14:00	16:00	18:00	20:00
Placebo	*-3.65*	*-2.95*	*-3.3*	*-2.95*	*-2.6*	*-3.64*	*-8.86*	*-8.85*	*-2.61*	*-5.73*	*-9.2*	*-5.4*	*-7.16*
Zol-Dex	*-1.62*	*-1.62*	*-0.23*	*-2.78*	*-3.01*	*-2.78*	*-5.65*	*-6.02*	*-4.86*	*-4.4*	*-3.24*	*-1.16*	*0*
Zol-Mod	*-0.33*	*-0.52*	*0.1*	*0.73*	*-0.11*	*1.77*	*-0.73*	*-0.12*	*0.52*	*-0.1*	*0.11*	*-2.4*	*1.15*
Tem-Dex	*-0.1*	*-0.11*	*-1.35*	*-2.6*	*-0.73*	*-3.23*	*-1.98*	*-2.19*	*0.52*	*0.73*	*0.31*	*-0.73*	*-5.31*
Tem-Mod	*-0.91*	*-0.13*	*2.21*	*-2.21*	*-1.17*	*0.13*	*-0.96*	*1.17*	*2.99*	*1.69*	*1.43*	*2.47*	*2.47*
Mission 3													
Test Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	12:00	14:00	16:00	18:00	20:00	22:00	0:00	2:00	4:00	6:00	8:00	10:00	12:00
Placebo	*-5.03*	*-1.21*	*-3.3*	*-1.91*	*-3.3*	*-0.87*	*-0.87*	*-0.17*	*-3.64*	*-4.34*	*-9.25*	*-8.13*	*-2.73*
Zol-Dex	*-1.39*	*-1.62*	*2.31*	*-2.78*	*-2.84*	*0.69*	*-1.85*	*-0.46*	*0*	*-4.86*	*-3.93*	*-3.01*	*-0.46*
Zol-Mod	*0.1*	*0.1*	*-0.73*	*-0.94*	*-0.52*	*-1.98*	*-1.15*	*1.15*	*0.31*	*-0.52*	*-3.44*	*-1.77*	*-3.02*
Tem-Dex	*-1.77*	*-1.77*	*-1.98*	*-1.79*	*-0.52*	*-1.98*	*-0.1*	*-3.85*	*-0.53*	*-6.15*	*-4.06*	*-3.23*	*-1.8*
Tem-Mod	*1.17*	*2.73*	*1,43*	*0.13*	*0.65*	*-0.13*	*0.13*	*1.95*	*-2.84*	*0.39*	*-4.3*	*1.17*	*1.43*

Within-Mission ANOVA Results

Mission 1

Drug: F(4,38) = 0.97: MSE = 180.88 p = .422
Block: F(8,320) = 2.49; MSE = 25.59 **p = .011**
D x B: F(34,320) = 1.42, MSE = 25.59 **p = .067**

Mission 2

Drug: F(4,38) = 1.22; MSE = 393.91; p = .320
Block: F(10,378) = 1.90; MSE = 26.62 **p = .044**
D x B: F(40,378) = 1.40; MSE = 26.62 **p = .069**

Mission 3

Drug: F(4,38) = 0.48; MSE = 363.25 p = .751
Block: F(10,362) = 3.55; MSE = 29.65 **p < .001**
D x B: F(38,362) = 0.97: MSE = 29.65 p = .525

[1] Mean Baseline Scores: Placebo = 95.66; Zol-Dex = 93.06; Zol-Mod = 95.31; Tem-Dex = 96.15; Tem-Mod = 93.13

X.XX Post hoc Student-Newman-Keuls detected performance to be significantly ($p \leq .05$) better than under the Placebo condition.

X.XX Post hoc Student-Newman-Keuls detected performance to be significantly ($p \leq .05$) better under Tem-Mod than Zol-Dex.

Psychomotor Vigilance Task - PVT (Table X).

Mission 1: A significant Drug x Block effect was detected for mean reciprocal reaction time. Performance under Zol-Dex was better than that under Placebo during Block 4. Performance under Zol-Dex, Tem-Dex, and Tem-Mod was better than that under Placebo during Block 8.

Mission 3: A near significant Drug x Block effect occurred during Mission 3. Performance was better under the Tem-Mod condition than the Placebo condition during Block 12 testing.

Williams Word Memory Test.

The number of words recalled decreased from an overall mean of 11.55 words at Immediate Recall to a mean of 7.08 words four hours later at Delayed Recall ( ). There were no significant Drug or Drug x Test Block interactions or differences among the three missions.

Sleepiness Ratings (Table XI).

Mission 1: Significant Drug and Drug x Block effects were detected. Early in the mission sleepiness ratings under Tem-Dex were lower that under Placebo during Block 3, and were lower than that under Placebo for each of the four Drug Combination conditions during Block 4. Ratings were lower than under Placebo for all of the Drug Combination conditions during Blocks 12 and 13.

Mission 2: A significant Drug x Block effect was detected. Ratings were lower under Tem-Dex than under Placebo during Blocks 7 and Block 10. Ratings were lower for each of the four Drug Conditions than for Placebo during Block 12. Ratings under the Zol-Dem condition were lower than that under Placebo during Block 13.

Mission 3: Near significant effects occurred for Drug and Drug x Block. Sleepiness ratings were lower under each of the Drug Combination conditions than the Placebo condition during Block 12. Ratings under Tem-Dex were lower than those for Placebo during Block 13.

Profile of Mood States - POMS (Tables XII and XIII).

Mood data were not available for the last Testing Block of Missions 1 and 2. Overall decreasing vigor and increasing fatigue as each mission progressed were the only consistent findings for the mood data. Statistically significant findings occurred at the same single point in time –Test Block 9 during Mission 1 – for both fatigue and vigor. A near significant Drug x Block effect was accompanied by fatigue scores being lower under the Zol-Dex than Placebo (Table XII). A significant Drug x Block interaction for vigor detected scores for all four Drug Combination conditions being higher than that those for Placebo (Table XIII).

Sleep: Pre-Mission Crew-Rest Periods (Table XIV).

Statistically significant differences among the five drug conditions were seldom detected and then, for the most part were a rather disconnected array occurring only during the crew-rest period preceding Mission 2 as summarized in Table XIV.

Table X.
Psychomotor Vigilance Task (PVT) - Mean Reciprocal Reaction Time
Within-Mission ANOVA and Post Hoc Analyses Results for Change-from-Baseline Means[1]

Mission 1			
Test Block	4	8	12
	10:00	18:00	2:00
Placebo	*-0.27*	*-0.33*	*-0.41*
Zol-Dex	*0.26*	*0.22*	*-0.08*
Zol-Mod	*-0.14*	*-0.07*	*-0.26*
Tem-Dex	*0.15*	*0.18*	*-0.07*
Tem-Mod	*0*	*0.29*	*0.02*

Mission 2			
Test Block	4	8	12
	2:00	10:00	18:00
Placebo	-0.14	-0.61	-0.28
Zol-Dex	*0.08*	*-0.25*	*-0.17*
Zol-Mod	*-0.17*	*-0.28*	*-0.44*
Tem-Dex	*0.02*	*-0.23*	*-0.01*
Tem-Mod	*0.21*	*-0.08*	*0.13*

Mission 3			
Test Block	4	8	12
	18:00	2:00	10:00
Placebo	*0.04*	*-0.36*	*-0.7*
Zol-Dex	*0.17*	*0.04*	*-0.4*
Zol-Mod	*-0.18*	*-0.36*	*-0.52*
Tem-Dex	*0.17*	*-0.07*	*-0.53*
Tem-Mod	*0.3*	*0.29*	*0.04*

Within-Mission ANOVA Results

Mission 1

Drug: F(4,35) = 2.90; MSE = 0.22	**p = .036**
Block: F(3,94) = 6.40; MSE = 0.06	**p = .001**
D x B: F(10,94) = 2.06; MSE = 0.06	**p = .032**

Mission 2

Drug: F(4,35) = 1.50; MSE = 0.31	p = .223
Block: F(3,105) = 9.85; MSE = 0.07	**p < .001**
D x B: F(12,105) = 1.44; MSE = 0.07	p = .162

Mission 3

Drug: F(4,35) = 2.41; MSE = 0.36	**p = .067**
Block: F(3,105) = 21.32; MSE = 0.09	**p < .001**
D x B: F(12,105) = 1.79; MSE = 0.09	**p = .060**

[1] Mean Baseline Scores: Placebo = 4.19; Zol-Dex = 3.89; Zol-Mod = 3.97; Tem-Dex = 4.09; Tem-Mod = 4.18

X.XX Post hoc Student-Newman-Keuls detected performance to be significantly ($p \leq .05$) better than under the Placebo condition.

Table XI.
ANAM Sleepiness Ratings
Within-Mission ANOVA and Post Hoc Analyses Results for Change-from-Baseline Means[1]

Mission 1													
Time Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	4:00	6:00	8:00	10:00	12:00	14:00	16:00	18:00	20:00	22:00	0:00	2:00	4:00
Placebo	*0.25*	*0.42*	*0.58*	*0.75*	*1.08*	*0.58*	*0.75*	*0.75*	*1.42*	*1.25*	*1.58*	*2.92*	*3.58*
Zol-Dex	*-0.11*	*-0.56*	*-0.67*	*-0.89*	*..78*	*-0.11*	*0.11*	*0*	*0.22*	*0.33*	*0.44*	*0.11*	*0.44*
Zol-Mod	*0.5*	*0.1*	*0.3*	*-0.4*	*-0.2*	*0.2*	*-0.25*	*0.5*	*-0.1*	*0.4*	*0.8*	*1.4*	*1.9*
Tem-Dex	*-0.4*	*-0.4*	*-0.9*	*-0.8*	*-0.6*	*-0.7*	*-0.4*	*-0.3*	*0.1*	*0*	*0.7*	*1.1*	*1.1*
Tem-Mod	*0.25*	*-0.38*	*-0.5*	*-0.25*	*-0.13*	*-0.38*	*-0.25*	*0.13*	*-0.13*	*0.5*	*0.38*	*0.88*	*1.25*

Mission 2													
Time Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	20:00	22:00	0:00	2:00	4:00	6:00	8:00	10:00	12:00	14:00	16:00	18:00	20:00
Placebo	*-0.25*	*-0.42*	*0.08*	*0.08*	*0.75*	*1.08*	*2.25*	*2.08*	*1.75*	*2.08*	*2.42*	*2.08*	*1.92*
Zol-Dex	*-0.56*	*-0.22*	*-0.11*	*-0.22*	*0.33*	*0.22*	*0.67*	*0.67*	*0.89*	*0.44*	*0.33*	*0.67*	*-0.11*
Zol-Mod	*0.5*	*0.3*	*0.1*	*0.6*	*1*	*1*	*0.8*	*0.9*	*0.5*	*0.6*	*0.8*	*1.3*	*1*
Tem-Dex	*-0.4*	*-0.5*	*-0.4*	*-0.4*	*0.1*	*0.4*	*0.3*	*0.6*	*0.9*	*0.1*	*0.1*	*0.4*	*0.8*
Tem-Mod	*0.25*	*0.25*	*-0.13*	*-0.25*	*1.25*	*1.38*	*1.88*	*1.13*	*1.13*	*1.13*	*0.75*	*1.38*	*1.38*

Mission 3													
Time Block	1	2	3	4	5	6	7	8	9	10	11	12	13
	12:00	14:00	16:00	18:00	20:00	22:00	0:00	2:00	4:00	6:00	8:00	10:00	12:00
Placebo	*-0.08*	*0.25*	*0.08*	*-0.25*	*0.08*	*0.42*	*0.58*	*0.92*	*1.75*	*2.25*	*3.08*	*4.08*	*3.75*
Zol-Dex	*-0.33*	*-0.44*	*-0.89*	*-0.78*	*-0.44*	*-0.22*	*-0.22*	*0.11*	*0.56*	*1.44*	*2.11*	*1.67*	*1.89*
Zol-Mod	*-0.5*	*-0.2*	*0*	*-0.1*	*0*	*0.3*	*0.4*	*0.6*	*1.6*	*1.4*	*2*	*1.6*	*2*
Tem-Dex	*-0.6*	*-0.8*	*-0.7*	*-0.8*	*-0.6*	*-0.6*	*-0.2*	*0.1*	*0.9*	*1.2*	*1.4*	*1.4*	*1.4*
Tem-Mod	*0.38*	*0.25*	*-0.25*	*-0.38*	*-0.25*	*0.38*	*0.88*	*0.88*	*1.25*	*1.38*	*1.75*	*1.88*	*2.13*

[1] Mean Baseline Scores: Placebo = 1.92; Zol-Dex = 2.56; Zol-Mod = 1.80; Tem-Dex =2.20 ; Tem-Mod = 1.75

Within-Mission ANOVA Results

Mission 1

Drug: F(4,38) = 3.00; MSE = 8.74	**p = .030**
Block: F(9,324) = 20.72; MSE = 1.05	**p < .001**
D x B: F(34,324) = 1.58; MSE = 1.05	**p = .025**

Mission 2

Drug: F(4,38) = 2.02; MSE =9.51	p = .112
Block: F(9,357) = 14.93; MSE = 1.09	**p < .001**
D x B: F(38,357) = 1.66, MSE = 1.09;	**p = .011**

Mission 3

Drug: F(4,38) = 2.30; MSE = 7.69	**p = .077**
Block: F(8,304) = 56.30; MSE = 1.22	**p < .001**
D x B: F(32,304) = 1.35; MSE = 1.22	**p = .107**

X.XX Post hoc Student-Newman-Keuls detected sleepiness to be significantly ($p \leq .05$) less than under the Placebo condition.

Table XII.
Profile of Mood States: Fatigue Scores
Within-Mission ANOVA and Post Hoc Analyses Results for Change-from-Baseline Means[1]

Mission 1				
Test Block	1	5	9	13
	4:00	12:00	20:00	4:00
Placebo	*-0.33*	*1.67*	*4.5*	*
Zol-Dex	*-5.17*	*-5.06*	*-4.83*	*
Zol-Mod	*-1.1*	*-3.5*	*-9*	*
Tem-Dex	*-1*	*-2.1*	*-1.1*	*
Tem-Mod	*0.38*	*-3.5*	*-2.25*	*
Mission 2				
Test Block	1	5	9	13
	20:00	4:00	12:00	20:00
Placebo	*-2*	*5.17*	*6*	*
Zol-Dex	*-4.72*	*-2.72*	*0.06*	*
Zol-Mod	*0.3*	*3.4*	*1.7*	*
Tem-Dex	*-2.5*	*1*	*2.9*	*
Tem-Mod	*1.13*	*7.88*	*5.5*	*
Mission 3				
Test Block	1	5	9	13
	12:00	20:00	4:00	12:00
Placebo	*-1.17*	*-2.17*	*5.67*	*13.83*
Zol-Dex	*-5.39*	*-4.28*	*1.28*	*2.28*
Zol-Mod	*-2*	*-2.2*	*2.7*	*7.7*
Tem-Dex	*-2.2*	*-3*	*3.8*	*6.5*
Tem-Mod	*0*	*-2.13*	*7*	*11.88*

Within-Mission ANOVA Results

Mission 1

Drug: F(4,38) = 2.00; MSE = 50.77	p = .115
Block: F(3,114) = 3.00, MSE = 12.42	**p = .034**
D x B: F(12,114) = 1.69; MSE = 12.42	**p = .078**

Mission 2

Drug: F(4,38) = 1.64; MSE = 87.65	p = .185
Block; F(3,114) = 8.12; MSE = 27.60	**p < .001**
D x B: F(12,114) = 1.11; MSE = 27.60	p = .363

Mission 3

Drug: F(4,38) = 1.60; MSE = 91.43	p = .205
Block: F(3,125) = 31.69; MSE = 35.21	**p < .001**
D x B: F(13,125) = 0.89; MSE =35.21	p = .571

[1] Mean Baseline Scores: Placebo = 39.00; Zol-Dex = 41.50; Zol-Mod = 37.80; Tem-Dex = 37.70; Tem-Mod = 37.63

X.XX Post hoc Student-Newman-Keuls detected scores to be significantly ($p \leq .05$) lower than under the Placebo condition.

* missing data

Table XIII.
Profile of Mood States: Vigor Scores
Within-Mission ANOVA and Post Hoc Analyses Results for Change-from-Baseline Means[1]

Mission 1				
Test Block	1	5	9	13
	4:00	12:00	20:00	4:00
Placebo	*-2.5*	*-7.83*	*-15.83*	*
Zol-Dex	*0.22*	*0.33*	*-2.33*	*
Zol-Mod	*-5.65*	*-3.95*	*-5.75*	*
Tem-Dex	*-1.1*	*2.6*	*-2.33*	*
Tem-Mod	*-5.75*	*2.75*	*1*	*
Mission 2				
Test Block	1	5	9	13
	20:00	4:00	12:00	20:00
Placebo	*1.67*	*-11*	*-11.67*	*
Zol-Dex	*-4.67*	*-7.78*	*-8.78*	*
Zol-Mod	*-10.05*	*-10.05*	*-12.05*	*
Tem-Dex	*0.1*	*-8.6*	*-6.5*	*
Tem-Mod	*-12.25*	*-16*	*-10.38*	*
Mission 3				
Test Block	1	5	9	13
	12:00	20:00	4:00	12:00
Placebo	*-5.5*	*2.67*	*-13.83*	*-16.33*
Zol-Dex	*-5.11*	*-5.89*	*-13.11*	*-13.11*
Zol-Mod	*-4.15*	*-7.35*	*-14.55*	*-17.35*
Tem-Dex	*1.2*	*1.7*	*-7.1*	*-9.4*
Tem-Mod	*-8.63*	*-9.13*	*-17.38*	*-19*

Within-Mission-ANOVA Results

Mission 1

Drug: F(4,38) = 2.52; MSE = 96.57	**p = .057**
Block: F(3,114) = 4.32, MSE = 124.28	**p = .006**
D x B: F(12,114) = 2.22; MSE = 124.28	**p = .015**

Mission 2

Drug: F(4,38) = 1.23; MSE = 174.05	p = .314
Block; F(3,114) = 20.83 MSE = 151.58	**p < .001**
D x B: F(12,114) = 1.44; MSE = 151.58	p = .157

Mission 3

Drug: F(4,38) = 1.94; MSE = 212.80	p = .124
Block: F(4,152) = 36.83; MSE = 191.22	**p < .001**
D x B: F(16,152) = 0.1.08; MSE =191.22	p = .378

[1] Mean Baseline Scores: Placebo = 49.83; Zol-Dex = 45.67; Zol-Mod = 48.75; Tem-Dex = 47.30; Tem-Mod = 51.50

X.XX Post hoc Student-Newman-Keuls detected scores to be significantly ($p \leq .05$) higher than under the Placebo condition.

* missing data

Table XIV
Mean Time (min.) Spent in Sleep States During Pre-Mission and Recovery Crew Rest Periods

	Crew Rest Period Preceding Mission 1						
	*Slp Lat	TST	Stg 1	Stg 2	Stg 3	Stg 4	REM
Placebo	8.5	447	32.4	204	35.8	88.9	84.8
Zol-Dex	13.3	522	38.5	281	30.1	87.6	73.1
Zol-Mod	7.5	509	34.9	266	32.1	90.5	80.9
Tem-Dex	13	487	29.3	264	27.1	77.6	89.1
Tem-Mod	64.3	450	42.5	234	20	73.1	79.4
	Crew Rest Period Preceding Mission 2						
	Slp Lat	**TST**	**Stg 1**	**Stg 2**	**Stg 3**	**Stg 4**	**REM**
Placebo	3.9	520	62.6[C]	208	29.4	107.3	111.9[D]
Zol-Dex	8.6	460	40.9[B]	222	26.7	127.4	33.8[D E]
Zol-Mod	9.6	385[A]	28.4[C]	157	21.2	114.8	63.9[D]
Tem-Dex	7.4	449	15.4[BC]	240	23.3	106.6	63.1[D]
Tem-Mod	12.2	487	36.4	230	19.8	125	67.5[D]
	Crew Rest Period Preceding Mission 3						
	Slp Lat	**TST**	**Stg 1**	**Stg 2**	**Stg 3**	**Stg 4**	**REM**
Placebo	15.3	638	24.6	332	41.3	87.4	152.5
Zol-Dex	16.1	596	33.4	318	27.6	119.4	97
Zol-Mod	14.1	612	25.1	292	33.7	127.4	133.1
Tem-Dex	15.2	617	32	332	25.3	9:36	106.7
Tem-Mod	15.4	632	79	263	32.6	117	121.6
	Recovery Period Following Mission 3						
	Slp Lat	**TST**	**Stg 1**	**Stg 2**	**Stg 3**	**Stg 4**	**REM**
Placebo	6.7	514	32.8	255	31.8	96.4	97.7
Zol-Dex	7.8	567	41.4	314	34	128.7	130.1
Zol-Mod	7.7	400	20.6	179	25.3	131.3	108
Tem-Dex	6.8	535	35.6	271	30.2	116.4	81.3
Tem-Mod	8.4	477	50.4	185	24.6	109.4	105.5

[A] TST was near-significantly (p = .052) less for Zol-Mod than Placebo.

[B] Zol-Dex had significantly (p ≤ .05) more Stg 1 sleep than did Tem-Dex.

[C] Zol-Mod and Tem-Mod had significantly (p ≤ .05) less REM sleep than Placebo.

[D] All four Drug-Combination conditions had significantly (p ≤ .05) less REM sleep than Placebo.

[E] Zol-Dex had significantly (p ≤ .05) less REM sleep than each of the other four conditions.

*Slp Lat: Mean Sleep Latency
TST: Mean Total Sleep Time
Stg 1: Mean Total Time in Stage 1 Sleep
Stg 2: Mean Total Time in Stage 2 Sleep
Stg 3: Mean Total Time in Stage 3 Sleep
Stg 4: Mean Total Time in Stage 4 Sleep
REM: Mean Total Time in Rapid Eye Movement Sleep

DISCUSSION *(not yet completed)*

The findings consistently demonstrated cognitive performance and subjective affect to deteriorate under the placebo condition as the simulated surge progressed in time within and across the three missions, but to remain relatively stable or deteriorate little both within and across the three missions for each of the four drug-combination conditions. Statistically significant differences in the outcome measures between the five drug conditions were overwhelmingly dominated by differences between the placebo condition and each of the other four dug-combination conditions. Statistically significant main or interaction effects between the four drug-combination conditions were very rare and seemingly random. No consistent findings related to the drug conditions were statistically detected for any of the sleep metrics.

CONCLUSION

The combined sequential use of sleep- and alertness-aid medications currently approved by the USAF for pre-mission crew-rest and long-duration missions significantly extended cognitive performance during a simulated surge. There were no statistical differences among the four drug-combinations in their efficacy to maintain cognitive performance. The effects of the drug-combinations on pre-mission sleep quantity and quality did not systematically differ from each other or the placebo condition.

ACKNOWLEDGEMENTS.

This research was sponsored, solely funded, and approved by the U.S. Army Medical Research and Materiel Command under Contract Award No. DAMD17-00-2-0055 to NTI, Inc. No financial or other relationships existed that might be perceived as leading to a conflict of interest. The study was conducted using Air Force Research Laboratory facilities at Brooks City-Base, TX, under the Cooperative Research and Development Agreement 01-225-HE-01 between NTI, Inc, and the Biosciences and Protection Division (AFRL/RHP). Outstanding technical assistance was provided by Juan Mendez, Amy McCrory, Matita Charlton, and Heather Campbell. We thank the Wilford Hall Medical Center, for preparation and management of the drugs. The views expressed in this paper are those of the authors and do not reflect an official position of the Department of the Air Force, Department of the Army, Department of Defense, or the U.S. Government.

REFERENCES.

Baranski, J., Cian, C., Esquivie, D., Pigeau, R., & Raphel, C. (1998). Modafinil during 64 Hr of sleep deprivation: Dose-related effects on fatigue, alertness, and cognitive performance. *Military Psychology*, 10(3), 173-193.

Batéjat, D., & Lagarde D. (1999). Naps and modafinil as countermeasures for the effects of sleep deprivation on cognitive performance. *Aviation, Space, and Environmental Medicine*, 70(5), 493-498.

Bensimon, G., Benoit, D., Lacomblez, L., Weiller, E., Warot, D., Weil, J.S., and Peuch, A.J. (1991). Antagonism by modafinil of the psychomotor and cognitive impairment induced by sleep- deprivation in 12 healthy volunteers. *European Psychiatry*, 6(2), 93-97.

Buguet, A., Montemayeur, A., Pigeau, R., & Naitoh, P. (1995). Modafinil, d-amphetamine and placebo during 64 hours of sustained mental work. II. Effects on two nights of recovery sleep. *Journal of Sleep Research*, 4, 229-241.

Caldwell, J.A., Caldwell J.L., Smythe, N., and Hall K. (2000). A double-blind, placebo-controlled investigation of the efficacy of modafinil for sustaining the alertness and performance of aviators: a helicopter simulator study. *Psychopharmacology*, 150, 272-282.

Caldwell, J. (1997). Fatigue in the aviation environment: An overview of the causes and effects a well as recommended countermeasures. *Aviation, Space, and Environmental Medicine,* 68: 932-938.

Cephalon, Inc. (1998). *Provigil Prescribing Information Sheet*. West Chester, PA.

Cohen, J. *Statistical power analysis for the Behavior Sciences*. Lawrence Erlbaum Assoc, 2nd Ed., Hillsdale, N.J.

Dinges, D.F. and Kribbs, N. B. Performance effects of fatigue. *Fatigue Symposium Proceedings, National Transportation Safety Board and NASA Ames Research Center*, Nov 1-2 1995; 41-46.

Cornum, K., Cornum, R., and Storm, W. (1995). Use of psychostimulants in extended flight operations: A Desert Shield experience. In Advisory Group for Aerospace Research and Development (AGARD) Conference Proceedings 579, 37: 1-4, *Neurological Limitations of Aircraft Operations: Human Performance Implications*, Koln, Germany.

Elsmore, T.F. (1994). SYNWORK1: a PC-based tool for assessment of performance in a simulated work environment. *Behavior Research Methods, Instruments, & Computers*, 26, 421-426.

Emonson, D.L. and Vanderbeek, R.D. (1993). The use of dextroamphetamine in support of tactical air operations during Operation Desert Shield/Storm. *Aviation, Space, and Environmental Medicine*, 64(5):421.

HQ ACC/SG Memorandum, 27 Sep 1999: Operational Use of No-Go Pills.

Lagarde, D., & Batejat, D. (1995). Disrupted sleep-wake rhythm and performance advantages of modafinil. *Military Psychology*, 7(3), 165-191.

Lagarde, D., Batéjat, D., Van Beers P., Sarafian D., & Pradella, S. (1995). Interest of modafinil, a new psychostimulant, during a sixty-hour sleep deprivation experiment. *Fundamentals of Clinical Pharmacology*, 9, 271-279.

Lin, J., Hou, Y., Rambert, F., & Jouvet, M. (1997). Awakening profiles of modafinil in sleep-deprived cats and its induction of brain c-fos expression pattern distinct from that caused by amphetamine or methylphenidate. *Sleep Research*, 26:23.

NcNair, D.M., Lorr, M.L., and Droppleman, L.F. (1971). Edits Manual: Profile of Mood States, Educational and Industrial Testing Service, San Diego, CA

Morehouse, R., Broughton, R.J., Fleming, J., George, C.F.P., & Hill, J. (1997). Favourable side effect profile of modafinil. *Sleep Research*, 26, 120.

Rechtschaffen, A. and Kales, A. (1968) A manual of standardized terminology, techniques, and scoring sytsem for sleep stages of human subjects. Washington, DC: Public Health Service, U.S. Government Printing Office.

Reeves, D., Winter, K., Kane, R., Elsmore, T., and Bleiberg, J. (2001). ANAM 2001 User's Manual: Clinical and Research Modules, National Cognitive Recovery Foundation, Special Report NCRF-SR-2001-1.

Senechal, P.H. (1988). Flight surgeon support of combat operations at RAF Upper Heyford. *Aviation, Space, and Environmental Medicine*, 59:776-777.

Stivalet, P., Esquivie, D., & Barraud, P. (1998). Effects of modafinil on attentional processing during 60 hours of sleep deprivation. *Human Psychopharmacology Clinical and Experimental*, 13(7), 501-507.

Warot, D., Curruble, E., Payan, Weil, J.S., and Peuch, A.J. (1993). Subjective effects of modafinil, a new central adrenergic stimulant in healthy volunteers: A comparison with amphetamine, caffeine, and placebo. *European Psychiatry*, 8:201-208.

Wong, Y., Gorman, S., McCormick, G., & Grebow, P. (1997). Single-dose pharmacokinetics of modafinil and Methylphenidate given alone and in combination to healthy male volunteers. *Sleep Research*, 26, 133.

APPENDIX IV

Eddy, D., Storm, W., Gibbons, J., Miller, J., and French, J. Reversal of Zolpidem Intoxication By Sublingual Flumazenil. *(in final preparation)*

DRAFT

Reversal of Zolpidem Intoxication By Sublingual Flumazenil

Prepared by
NTI, Incorporated

Douglas R. Eddy, Ph.D.
(503) 427-0535
douglas.eddy@comcast.net

William F. Storm, Ph.D.

Lt Col John A. Gibbons, D.O.
James C. Miller, Ph.D.
AFRL/RHPF

and

Jon French, Ph.D.
Embry Riddle University

Contract DAMD17-00-2-0055

for

Air Force Research Laboratory
Human Effectiveness Directorate
Biosciences and Protection Division
Bioperformance Branch
Scott Chaiken, Ph.D.
AFRL/RHPG
Brooks City-Base TX 78235-5104
(210) 536-1277

March 31, 2008

DRAFT

NOTICE

Using Government drawings, specifications, or other data included in this document for any purpose other than Government procurement does not in any way obligate the U.S. Government. The fact that the Government formulated or supplied the drawings, specifications, or other data does not license the holder or any other person or corporation; or convey any rights or permission to manufacture, use, or sell any patented invention that may relate to them.

Federal Government agencies and their contractors registered with Defense Technical Information Center should direct requests for copies of this report to:

Defense Technical Information Center
8725 John J. Kingman Rd., STE 0944, Ft Belvoir VA 22060-6218

CONTRACT DATA RIGHTS LEGEND

Contract Number**: DAMD17-00-2-0055**
Contractor Name**: NTI, Incorporated**

The Government's rights to use, modify, reproduce, release, perform, display, or disclose any technical data or computer software contained in this report are unrestricted

DISCLAIMER
This Technical Report is published as received and has not been edited by the Air Force Research Laboratory, Human Effectiveness Directorate.

AFRL-HE-BR-TR-2007-XXXX

THIS TECHNICAL REPORT HAS BEEN REVIEWED AND IS ACCEPTED UNDER THE PROVISIONS OF THE ???? PROGRAM

F. WESLEY BAUMGARDNER, Ph.D.
Deputy, Biosciences and Protection Division

This report is published in the interest of scientific and technical information exchange and its publication does not constitute the Government's approval or disapproval of its ideas or findings.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
30-03-2008	Interim	5-1-2002 to 7-1-2007

4. TITLE AND SUBTITLE
Reversal of Zolpidem Intoxication By Sublingual Flumazenil

5a. CONTRACT NUMBER
DAMD17-00-2-0055

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Douglas R. Eddy, William F. Storm, John A. Gibbons, James C. Miller, & Jon French

5d. PROJECT NUMBER

5e. TASK NUMBER
1

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

NTI, Inc.
1 ½ South Central Ave
Fairborn, OH 45324

AFRL/RHPG
2485 Gillingham Dr, Bldg 170
Brooks City-Base, Texas 78235

8. PERFORMING ORGANIZATION REPORT

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

13. SUPPLEMENTARY NOTES

14. ABSTRACT
In military operational environments, fatigue induced performance decrements resulting from reduced sleep and disrupted daily rhythms may result in outcomes ranging from severe discomfort, to mission degradation, to loss of life. In the operational environment, sleep aids cannot be used to rest the warfighter because the warfighter may be called upon to act on short notice and the sleep aid might itself degrade performance resulting in the same poor outcome. However, if the sleepiness and cognitive degradation caused by the sleep aid could be reversed, the use of sleep aids could be expanded to include more operational environments. The objective of this study was to evaluate the ability of flumazenil, administered as a liquid sublingually, to quickly and safely counteract the sleep-inducing or drowsiness effect of zolpidem. Thirteen participants received 10 mg zolpidem or placebo, were instructed to sleep 90 minutes, were awakened and given either 1 mg flamazenil or placebo and tested. At the beginning of the second hour after awakening, participants were given a second sublingual, 1 mg does of flumazenil or placebo and tested over the next 5 hours. The repeated-measures, double-blind design showed flumazenil provided partial recovery from the soporific effects of zolpidem. Conclusions: 1.Sublingual flumazenil, administered immediately on awakening, was shown to reverse the cognitively degrading effects of zolpidem by 23%, restoring performance to 92.5% of placebo. 2. One to two hours after awakening, performance did not return to the level of the placebo after flumazenil administration, but rather joined the zolpidem-only decay function which continued to be approximately 20% degraded compared to placebo. 3. At five hours post awakening, performance remained degraded by 10-11% compared to placebo. 4. Consideration should be given to developing a new means of administering liquid flumazenil in a form that can be self-administered and quickly dissolved when placed under the tongue.

15. SUBJECT TERMS
Flumazenil, Zolpidem, Sublingual administration, Fatigue management, Cognitive performance, Sleep

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
UNCLASSIFIED					Dr. Scott Chaiken
a. REPORT **UNCLASSIFIED**	**b. ABSTRACT** **UNCLASSIFIED**	**c. THIS PAGE** **UNCLASSIFIED**	**UNCLAS**	37	**19b. TELEPHONE NUMBER** *(include area code)* 210-536-3596

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

PREFACE

The contract technical monitor for this work was Dr. James C. Miller and the program managers were Lt Andrea Pinchak and Lt Andrew Workman both of the Biosciences and Protection Division. The work was performed as job order number S020P909.

This research was sponsored, solely funded, and approved by the U.S. Army Medical Research and Materiel Command under Contract Award No. DAMD17-00-2-0055 to NTI, Inc. No financial or other relationships existed that might be perceived as leading to a conflict of interest. The study was conducted using Air Force Research Laboratory facilities at Brooks City-Base, TX, under the Cooperative Research and Development Agreement 01-225-HE-01 between NTI, Inc, and the Biosciences and Protection Division (AFRL/HEP). Outstanding technical assistance was provided by Cory Welch, Amy McCrory, Juan Mendez, and Heather Campbell. We thank Real Arrendondo, Wilford Hall Medical Center, for preparation and management of the drugs and Mr. Joe Fischer, General Dynamics, for drug randomization and statistical analysis. The views expressed in this paper are those of the authors and do not reflect the official position of the Department of the Air Force, Department of the Army, Department of Defense, or the U.S. Government.

TABLE OF CONTENTS

FIGURES

TABLES

INTRODUCTION

Fatigue resulting from reduced sleep and disrupted circadian rhythms (daily sleep/wake cycles) is well established to cause significant decrements in cognitive or mental performance. In military operational environments, fatigue induced performance decrements resulting from reduced sleep and disrupted daily rhythms may result in outcomes ranging from severe discomfort, to mission degradation, to loss of life. Commonly used fatigue countermeasures such as improved sleeping conditions and more frequent rest breaks are sometimes insufficient or are not available options to counter the effects of the cumulative fatigue caused by disrupted and lost sleep during extreme sustained and long-duration military operations. In these critical situations, military commanders and physicians may jointly approve the controlled and limited operational application of sleep-aid medications to promote and enhance sleep during opportunities for rest and recovery under less than ideal sleeping conditions. These sleep medications have been previously approved by the Food and Drug Administration (FDA) for routine use to induce and maintain sleep in adults with various sleep disorders. The considerable advantages of using selected sleep-aid drugs to enhance sleep and subsequent performance in military personnel participating in sustained operations has been well documented in a number of recent conflicts, including Operation Desert Storm and Operation Iraqi Freedom (Cornum, Cornum, & Storm, 1995; Emonson & Vanderbeek, 1995). However, because the very reason for using these drugs is that they promote drowsiness and sleep, personnel administered a sleep-aid to enhance rest may not be able to remain alert and perform effectively if awakened while under the drug's influence. Thus, for military operations, it would be very useful to have available, when needed, another drug that could be readily self-administered to counteract the sleepiness effects of a recently administered sleep-aid drug.

Zolpidem tartrate (Ambien®, Sanofi-Aventis) is one of three hypnotic compounds approved by the USAF Surgeon General for use to promote sleep in aircrews and special duty personnel that must acquire pre-mission crew rest under adverse and demanding operational situations (the two other USAF approved sleep-aids are temazepam and zaleplon). Prior to reporting for airborne missions USAF aircrews are required by regulation to receive 12 hours of inviolate crew rest during which they must be afforded the opportunity for at least eight hours of uninterrupted sleep. When approved for use by the unit commander and flight surgeon the recommended therapeutic dose of 10 mg zolpidem may be taken no less than six hours before reporting for the scheduled crew duty day and mission. Zolpidem's pharmacokinetic profile makes its designated application during the regulated 12-hour aircrew rest periods effective and safe. Peak plasma concentrations are reached 1.0-1.5 hours after ingestion and the elimination half-life is 2.0-2.5 hours.

Decisions on the use of zolpidem to enhance the restorative value of sleep during crew-rest must weigh the benefits and risks given the nature of the military operation, the condition of the personnel, the sleeping environment, and the likelihood that the sleep could be interrupted while under the influence of zolpidem. Studies seldom find residual effects following an uninterrupted night's sleep or extended daytime sleep with 10 or 20 mg zolpidem (Caldwell, Prazinko, Rowe, et al., 2003; Eddy, Barton, Cardenas, et al., 2006). However, emergency and contingency situations can arise during intense, sustained military operations that require sleeping personnel be awakened prior to completion of their allotted sleep period. The sedation induced by zolpidem is the result of central nervous system depression and personnel may be ineffective until the soporific effects of the compound wear off (Storm, Eddy, Welch, et al.,

2007). Cognitive performance and alertness have consistently been found to be impaired when zolpidem is present at peak or near-peak plasma levels during the immediate hours following ingestion. Thus, for military operations, it would be very useful to have available, when needed, an agent that could be readily self-administered to counteract the sedation effects of a recently administered sleep-aid drug.

Flumazenil (Romazicon®) is an imidazobenzodiazepine derivative approved by the Food and Drug Administration (FDA) to be given intravenously in clinical settings. It antagonizes the actions of benzodiazepines on the central nervous system by competitively inhibiting activity at the benzodiazepine recognition site on the GABA/benzodiazepine receptor complex. Flumazenil is a weak partial agonist in some animal models of activity, but has little or no agonist activity in man. Flumazenil does not antagonize the central nervous system effects of drugs affecting GABA-ergic neurons by means other than the benzodiazepine receptor (including ethanol, barbiturates, or general anesthetics) and does not reverse the effects of opioids (Romazicon® package insert). Flumazenil does not appear to change zolpidem plasma concentrations, suggesting a pharmacodynamic interaction (Patat, Naef, van Gessel, et al., 1994). The manufacturer, Roche, notes, "The pharmacokinetics of benzodiazepines is unaltered in the presence of flumazenil."

When administered immediately after surgeries flumazenil shortens the time required for recovery from the sedative effects of surgical anesthetics. It also reverses the effects of overdoses of sleep-aid drugs including zolpidem. Flumazenil has been used to antagonize sedation, impairment of recall, psychomotor impairment, and ventilatory depression produced by overdoses of benzodiazepines. Wesensten, Balkin, Davis, et al., (1995) administered 20 mg zolpidem or 0.5 mg triazolam immediately followed by 90 minutes of daytime sleep. Intravenous flumazenil administered immediately on awakening prevented impairment by either drug, although sedation effects returned six hours after zolpidem administration.

Currently the only effective method of administering flumazenil is through intravenous administration. Obviously, intravenous administration of flumazenil under the conditions of an operational emergency or sudden call-to-duty is militarily impractical. The present study evaluated the efficacy of sublingual doses of flumazenil to counteract the soporific effects of zolpidem on cognitive performance in an operationally-relevant, sudden-awakening paradigm.

Flumazenil Elimination

Metabolism. Flumazenil, an imidazobenzodiazepine, has an elimination half-life of 54 minutes (range 41 – 79), and is primarily metabolized by the liver to two inactive metabolites that are excreted in the urine. It is primarily hydrolyzed by a liver carboxylesterase to flumazenil acid and N-dealkylated to N-demethylated flumazenil, probably by the cytochrome P-450 system, as are other benzodiazepine compounds (Kleingeist, Böcker, Geisslinger & Brugger, 1998). This remains to be determined.

Competition with benzodiazepines. Binding of benzodiazepines to the gamma-aminobutyric acid receptor occurs at the ω_1 and ω_2 subunits. Flumazenil does not discriminate between the subunits and has a dissociation coefficient of 0.60 ng/L (Lowenstein, Rosenstein, Caputti & Cardinali, 1984). Flumazenil is approximately 50% bound to serum protein (Romazicon® package insert). Zolpidem, an imidazopyridine, is highly selective for the ω_1 subunit, and has a similar dissociation coefficient of 1.5 – 2.1 ng/L (Munakata, Jin, Akaike, & Nielsen, 1998). Several studies have examined the pharmacokinetic interaction of flumazenil

with hypnotic agents. One small study found that 1mg of intravenous flumazenil prolonged the elimination half-life of 0.1 – 0.2 mg/kg of midazolam, a short-acting imidazobenzodiazepine (Bonfiglio, Fisher-Katz, Saltis, et al., 1996). A second study found that a smaller dose, 0.005 mg/kg, of intravenous flumazenil reversed cognitive impairment, due to 0.025 mg/kg of midazolam, on the Digit Symbol Substitution Test, without significantly altering midazolam pharmacokinetics (Rogers, Morrison, Nafziger, et al., 2002). Another study found that while effective for reversing zolpidem-induced sedation and psychomotor impairment, 0.04 mg/kg of intravenous flumazenil had no effect on zolpidem pharmacokinetics (Patat, et al., 1994). This study was unusual in that zolpidem was administered intravenously, rather than orally, and found a mean serum elimination half-life of 1.2 hours for zolpidem versus 2.4 hours after oral dosing. Similarly, a previous study showed 1 mg of intravenous flumazenil to ameliorate immediate and delayed memory impairment due to 20 mg of zolpidem or 0.5 mg of triazolam (Wesensten, et al., 1995).

It is possible that competition for elimination via the liver exists for flumazenil and hypnotic agents, such as zolpidem, but this is only seen when the quantities of both drugs are sufficient to saturate the liver CYP 3A4 enzyme binding. The zolpidem displaced from ω_1 and CYP 3A4 sites could remain in the serum or bind to another, unknown receptor.

Flumazenil formulation and administration

Intravenous solution administered sublingually. Currently, the only FDA approved formulation of flumazenil is a solution for intravenous administration, 1-mg per 10-ml. The time and logistical requirements for intravenous administration preclude this route of administration for military operational use. Flumazenil has been administered via other routes in research and clinical trials. Flumazenil pharmacokinetics was compared for oral administration (30-mg) versus intravenous administration (2-mg) in healthy young and elderly persons (Roncari, Timm, Zumbrunnen, et al., 1993). Bioavailability was found to be about 25%. Orally administered flumazenil reduced diastolic blood pressure. Side effects described were dizziness, mild confusion, and circulatory insufficiency. Though these were considered mild, they are not compatible with military operations, particularly the aerospace environment. Nasal administration has been used to reverse sedation in pediatric anesthesia (Scheepers, Montgomery, Kinahan, et al., 2000). Submucosal administration was compared to intravenous administration in dogs (Oliver, Sweatman, Unkel, et al., 2000). One study compared flumazenil administration (0.2-mg, then another 0.3-mg 30 seconds later) for the reversal of benzodiazepine-induced respiratory depression in dogs via intravenous (IV), sublingual (SL), intramuscular (IM), and rectal (PR) routes (Heniff, Morre, Trout, et al., 1997). The rapidity of reversal (in seconds) was: IV 120 ± 24.5, SL 262 ± 94.5, IM 310 ± 133.7, and PR 342 ± 84.4. The mean difference in time between IV and SL administration, 142 seconds, is far less than the time to establish intravenous access for administering flumazenil. This makes the SL route attractive for military operational use.

Goal of Study

The goal of the present study was to demonstrate the feasibility of delivering flumazenil by the sublingual route in humans and to determine its effects on cognitive performance, physiological performance, and side effects. It was understood that our method would not ensure

100% bioavailability. With the success of this feasibility study, it was hoped that it would stimulate the formulation and testing of a field ready product. Such a product might find use in military operations as a safe way to rest fatigued warfighters without diminishing their fighting capacity.

METHODS

Participants

Five women and eight men (mean age 28.8 years, range 20-42 years) completed the study. Volunteers were thoroughly briefed on the possible risks and discomforts associated with participation and medically examined (including blood chemistry and liver function) by a qualified medical practitioner with knowledgeable of the objectives and requirements of the study. Volunteers with evidence of any current significant illness, sleep abnormalities, use of tobacco, excessive use of caffeine or alcohol, or being excessively over- or underweight were not allowed to participate. The medical examination assured that participants were not currently using drugs that might interact with those being evaluated in the study. Women who were pregnant or attempting to become pregnant were excluded. Female participants were administered a urine pregnancy test immediately prior to each experimental session. The research protocol and Informed Consent Document (ICD) were reviewed and approved by the Brooks City-Base Institutional Review Board (IRB) in advance of participant recruitment. Participants gave written informed consent before participating and were paid for their participation. Review by the FDA determined that an Investigational New Drug (IND) application was not required for the protocol.

Preparation of sublingual Flumazenil

Flumazenil is insoluble in water but mostly soluble in acidic solutions. The intravenous formulation is adjusted to a pH of 4 (approximately the acidity of ascorbic acid). It has a slightly bitter and salty taste. Lemon extract was used to mask this taste by adding 1 ml of McCormick's Pure Lemon Extract (alcohol 84%, water and oil of lemon) to each 10 ml of flumazenil solution. Theoretically, this was adequate to maintain a pH of ≤ 4; the actual pH of the end solution was not assayed. The flumazenil placebo was formulated substituting distilled water for the flumazenil solution. To facilitate sublingual administration, five aliquots of approximately 2.2 ml each (1 mg of flumazenil) were drawn into syringes. This allowed a comfortable volume of solution beneath the tongue. Drug and placebo packaging with freshly made solutions and blinding were performed by the pharmacy staff at Wilford Hall Medical Center (WHMC) the morning of each experimental session.

Facility and Materials

This study was conducted at the Air Force Research Laboratory Biosciences and Protection Division (AFRL/HEP), Fatigue Countermeasures Lab (FCL) located at Brooks City-Base, Texas. During the experimental sessions each participant was assigned to a private room equipped with a computer and desk for testing, a bed, an easy chair, and a private bath.

Throughout the experimental sessions the participants were always under the direct observation of research personnel or knowingly monitored from a central control station by closed circuit television, excluding of course the private baths. Infra-red capability allowed monitoring of the participants while sleeping in the darkened rooms. An intercom system allowed the participants to contact the investigators at any time.

Controlled drugs were managed in accordance with AFRL/HEP Operating Instruction 44-102, "Research Drug Control." Facilities within AFRL/HEP and the FCL comply with Drug Enforcement Agency (DEA) and USAF requirements for the storage and maintenance of FDA Schedule II-V pharmaceuticals. One of the investigators (DRE) was registered with the DEA and the Texas Department of Public Safety and certified to dispense for study Schedule II-V drugs. Zolpidem 10 and 20 mg tablets were obtained from the WHMC pharmacy's normal stock and packed in standard size gelatin capsules using psyllium as filler. The placebo sleep aid consisted of the gelatin capsule filled with psyllium. Flumazenil was acquired from Roche in 10 ml multiple-use vials containing 0.1 mg/ml flumazenil.

The FDA recommends that flumazenil be administered as a distributed series of small injections for the reversal of the sedative effects of benzodiazepines administered for conscious sedation. The recommended initial dose of flumazenil is 0.2 mg (2 ml) administered intravenously over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, a further dose of 0.2 mg (2 ml) can be injected and repeated at 60-second intervals where necessary to a maximum total dose of 1 mg (10 ml). In the event of re-sedation, repeated doses may be administered at 20-minute intervals as needed. For repeat treatments no more than 1 mg, given as 0.2 mg/min, should be administered at any one time, and no more than 3 mg should be given in any one hour. Considering the FDA guidance, sublingual doses of flumazenil for this study were administered using small, blunt syringes filled with 2.2 ml of solution, flumazenil or placebo. A 1 mg dose of flumazenil or placebo consisted of administering five syringes at one-minute intervals.

Experimental Design

This study employed a double-blind, repeated-measures design. Four combinations of sleep-aid/sleep-aid-countermeasure treatments were evaluated (Table 1): passive control (zolpidem-placebo/2, flumazenil-placebo, P/P); zolpidem active control (10 mg zolpidem/2, flumazenil-placebo, Z10/P); experimental condition 1 (10 mg zolpidem/2, 1 mg flumazenil, Z10/F); experimental condition 2 (20 mg zolpidem/2, 1 mg flumazenil, Z20/F). A zolpidem-placebo/flumazenil condition was not included since it has been demonstrated that flumazenil has no intrinsic alerting effects on performance when administered alone (Wesensten, et al., 1996). A 20 mg zolpidem/flumazenil-placebo condition was not included since the effects would only be worse than under the Z10/P condition.

Table 1. Treatment Conditions for Flumazenil Study

		Countermeasure	
Sleep Aid		**Placebo**	**2, 1 mg doses flumazenil**
Placebo		Passive Control	-
10 mg zolpidem		Active Control	Experimental Condition 1
20 mg zolpidem		-	Experimental Condition 2

Four groups, each comprised of 2-4 participants, were randomly assigned to different 4x4 Latin squares, with each participant exposed to a different treatment during each of his/her four experimental sessions. The first (n=4) and second (n=4) groups completed their four experimental sessions during the same four consecutive weeks, one session per week. The third (n=3) and fourth (n=2) groups were subsequently tested on a similar four-week schedule. At the point of the first and second groups having completed data collection for their first two experimental sessions, the medical monitor determined that the Z20/F condition had, in four of four cases, resulted in considerable nausea and emesis on or soon after awakening and for up to five hours post-awakening, with there being no apparent relief from flumazenil. The medical monitor, the investigators, and the IRB considered it inappropriate and unnecessary to continue the Z20/F condition in the study. Unbeknown to the participants, but with expeditious review and approval of the IRB so as not to delay the testing schedule, the Z20/F condition was replaced for the remainder of the study by a second administration of the placebo/placebo (P/P) condition. This modification maintained the experimental design and testing milieu and allowed data collection to be completed for the Z10/F, Z10/P, and P/P conditions. The first and second groups were informed of the modification following completion of their fourth experimental session. Prior to initiating data collection for the third and fourth groups the IRB approved a modified protocol and ICD incorporating the deletion of the Z20/F condition to which the participants gave updated written informed consent. The limited and incomplete data collected under the Z20/F condition were not included in the statistical analyses.

Tests and Measures

Automated Neuropsychological Assessment Metrics (ANAM): Four cognitive performance assessment tasks from the PC-based ANAM battery were applied in this study. The four tasks required a total of about 14 minutes for a well-practiced, alert participant to complete under baseline conditions. Response times and correct and incorrect responses were recorded. The four ANAM tasks were performed in the following sequence during each testing block. 1) *Reaction Time* – Simple Reaction Time – pressing a computer mouse key in response to a visual stimulus presented at a centrally fixed point on the computer screen – was evaluated. Mean reaction time to 20 stimuli (inter-stimulus interval of 650-1200 msec) presented during a less than one-minute trial was the outcome measure. 2) *Mathematical Processing* – Each problem in this task includes two mathematical operations (addition and/or subtraction) on sets of three single-digit numbers (e.g., 5+3–4=?). The participant is instructed to read and calculate from left to right and indicate whether the answer is greater-than or less-than '5' by pressing one of two specified response buttons on the mouse. Trials were about three minutes in duration. 3) *Grammatical Reasoning* – The participant determines as quickly as possible whether each of two simple summary statements (e.g., *& follows** and *# precedes**) correctly describe the sequential relationships among three symbols (e.g., *# &**). If one statement is true and one false, one response is correct; if both statements are true or both are false an alternative response is made. A trial consisted of 48 presentations. 4) *Continuous Processing* – Participants are directed to continuously monitor a randomized sequence of the numerals 0 through 9 presented one at a time in the center of the screen and to press the left mouse key if the numeral currently on the screen matches the numeral that immediately preceded it. If not a match, they are to press the right mouse key. Trials were about minutes in duration. (This task is also referred to as Running Memory.)

Word Memory Task: The Williams Word Memory Task provided an assessment of short-tem memory. During the first post-awakening testing block at 1500, the participant listened to the auditory presentation of 15 recorded words. Each word was spoken, spelled, and then spoken again. The participant wrote down each word as it was presented. On completion of the presentation, the participant studied the list for one minute. The written list was then collected and the participant was directed to immediately recall in one minute as many of the words as possible by writing them on a fresh paper form. Delayed recall of the same list occurred two hours later during the third post-awakening testing block at 1700. The number of words recalled from the list of 15 was the outcome measure for this task.

Psychomotor Vigilance Task (PVT): The PVT (Model PVT-192, CWE Inc., Ardmore, PA) is a portable, self-contained visual reaction time task requiring sustained attention and a simple, discrete push-button motor response to each signal - the onset of an elapsed-time digital clock. The clock appears within a well-defined display window and is extinguished and reset to zero within a second after each response. Signals occurred randomly every 2-12 seconds. Trials were 10 minutes in duration and the outcome measure was mean reaction time and mean reciprocal reaction time.

Postural Sway: Postural or body sway was assessed using a force platform that measures changes in the body's center of pressure over time (Platform model OR6-5-1, AMTI, Watertown, MA). The apparatus resembles an oversized home bathroom scale, approximately 18 by 20 inches in area and 3 inches in height. The participant was directed to stand as motionless as possible while one minute of data was collected for both eyes open and eyes closed conditions at a sampling rate of 10 Hz. The amplitude, velocity, and frequency of change in the center of pressure reflect the participant's ability to maintain balance. An elliptical area of measurement that accounts for 95% of the variation in the center of changes in pressure provides the outcome measure.

Comment [DRE1]: Was this 2 minutes?

Grip Strength: Strength was measured as the highest value attained of two grip squeezes, separated by one minute, on a Sammons-Preston Inc. JAMAR (Bolingbrook, IL) hydraulic hand dynamometer.

Sleepiness: The ANAM battery offers a sleepiness scale that, while a modification of the Stanford Sleepiness Scale (Hoddes, Zarcone, Smythe, et al., 1973), maintains the seven-point scale rating subjective sleepiness from "*1-very alert, wide awake, and energetic*" to "*7-very sleepy and cannot stay awake much longer*." The ANAM sleepiness scale was presented on the computer monitor as the first item of business at the start of each testing block.

Symptoms: Participants completed a 73-item paper and pencil Symptom Checklist at the end of each testing block, indicating the severity (*none, some, moderately, or severely*) they were experiencing each symptom at that point in time

Affect: Subjective evaluations of mood were acquired using the Mood Scale II, available through ANAM. It consists of a listing of 36 adjectives that are each rated on a three-point scale. A standardized "state" measure is generated for each of six categories; anger, happiness, anxiety, depression, activity, and fatigue. It was completed every four hours during each mission.

Activity Log: Each participant was provided with a formatted log to manually record his/her wake and sleep times daily throughout training, mission, and recovery.

Procedures

During selection and training the participants were given considerable orientation on the study objectives and the relevance of the experimental manipulations to real-world operations. The importance of maintaining standardized procedures and performing the cognitive tasks as rapidly and accurately as possible was emphasized. Prior to their initial experimental session participants were trained to asymptotic performance on each of the cognitive tasks and became proficient on the procedures for transitioning efficiently from one task or procedure to the next. Coaching and practice were also provided on self-administration of solutions using the blunt needle syringes until each participant was comfortable with the sublingual procedure. Using water for training, participants were taught to empty a syringe into their buccal cavity in 10-15 seconds and to hold the fluid in their mouth for 45-50 seconds as timed by an attending research observer. At the end of the timed interval, the participant was directed to swallow the remnant fluid and immediately self-administer the next of the five syringes to simulate the administration of a complete single dose.

The testing schedule for the experimental sessions is presented in Table 2 starting with Test Session 1. The participants were directed to sleep from about 10:00 pm to 7:00 am the night before scheduled experimental sessions, and to not consume alcoholic beverages the evening prior to or the day of a session. Experimental sessions began at 1200 and were completed at 2100. Participants were allowed time to settle into their rooms and have a light lunch prior to the baseline testing block at 1230. During each session the participants completed one test block before and six blocks after a 1.5-hour sleep period. Each test block was about 50 minutes in duration, with the balance of the hour serving as a brief rest-break. Except for including the Williams Word Memory Task in the 1500 and 1700 blocks, all seven testing blocks were identical. The sleep aid was administered at 1330, participants were encouraged to sleep and the lights were extinguished.

Table 2. Test Session 1 – Experimental Treatment

Day	Time	Procedure
Day 1	1130-1200	Arrive FCL; Attach instruments; Collect logs/actigraphs
	1200-1230	*Light lunch/break*
	1230-1300	ANAM, PVT, Surveys
	1300-1315	FP/GS/Vitals*
	1315-1330	*Break*
	1330-1500	*Sleep Aid Dose*/Sleep (lights out)
	1500-1530	*Countermeasure* Dose/ANAM+WMm, Surveys
	1530-1555	PVT, FP/GS/Vitals*
	1555-1600	Break
	1600-1630	*Countermeasure* Dose/ANAM, Surveys
	1630-1655	PVT, FP/GS/Vitals*
	1655-1700	Break
	1700-1720	ANAM, surveys
	1720-1745	PVT, FP/GS/Vitals*
	1745-1800	*Break/Snack*/Detach instruments
	1800-1820	ANAM, Surveys
	1820-1845	PVT, FP/GS/Vitals*
	1845-1900	*Break*
	1900-1930	ANAM+WMr, Surveys
	1930-1955	PVT, FP/GS/Vitals*
	1955-2000	Break
	2000-2020	ANAM, Surveys
	2020-2045	PVT, FP/GS/Vitals*
	2045-2100	Hand out logs/actigraphs; release

(*FP:Force Platform; GP:Grip Strength; Vitals: BP, HR, temperature).

Session 2	Same as Session 1 (with Training omitted) – Dose 2
Session 3	Same as Session 1 (with Training omitted) – Dose 3
Session 4	Same as Session 1 (with Training omitted) – Dose 4

The drug doses were always ingested under the close observation and attendance of an investigator or senior technician. Sleep-aid capsules (zolpidem or placebo) were orally ingested within 2-3 minutes of 1330, following which the participants were immediately shepherded to bed, the room door closed, and the lights turned off. Participants were instructed to remain in bed for the 1.5-hour duration even if they could not fall or remain asleep. The participants were awakened at 1500 by voice instruction over the intercom system and simultaneously lights were illuminated, followed immediately by research staff entering each room to assist the participants in the administration of the flumazenil treatment. The FDA-approved, distributed-dose-schedule for administering zolpidem intravenously as a countermeasure to the sedative effects of the zolpidem was employed. Two, 1 mg sublingual doses of flumazenil were administered one hour apart to counteract the sedative effects of the zolpidem ingested 1.5 hours prior to the first countermeasure dose. On being awakened, the participants were assisted as required to a comfortable sitting position in bed. They then self-administered sublingually, at one-minute intervals, the five syringes (0.2 ml each) comprising the total 1 mg countermeasure dose. The participants then walked the few steps to their computer station and performed the 1500 test block. A second 1 mg dose was ingested one hour later at 1600 just before the 1600 test block using the same method of administration. In this case the participant self-administered the five syringes sublingually while sitting at his/her computer testing station.

Comment [DRE2]: monitor?

Vital signs (blood pressure, heart rate, and oral temperature) were monitored once during each testing block. Water and selected non-caffeinated drinks were available throughout the experimental sessions. Lying down or sleeping were never permitted except during the scheduled sleep period integral to the study. Participants were required to make arrangements to be chauffeured home from the laboratory on completion of each testing session. Once home, participants were directed to acquire at least six hours of sleep prior to operating machinery, driving, or performing similar tasks that may involve hazards.

Statistical Analyses

For each continuous, normally distributed, outcome measure, a repeated-measures analysis of variance with two within-subject factors: drug condition (the three drug combinations) and time (baseline and six post-awakening data collection periods) was performed to test for significant treatment main effects and/or treatment by trial interaction. When significant drug effects were detected, post-hoc simple effects tests (Winer, 1971, p. 174) were used to compare the treatment conditions at each trial, separately. For discrete outcome measures, and measures where non-normality was suspected, non-parametric procedures (Friedman's test and Wilcoxon signed-rank test) were performed to compare the treatment conditions at each trial, separately. The Statistical Package for the Social Sciences (SPSS Version 15) was used for the computations.

We wanted to evaluate and report only operationally significant flumazenil-reversals of sleep aid intoxication, compared to the flumazenil placebo (Active Control), as being significant. Thus the effect size was set at 1 standard deviation unit (sdu). To insure sufficient power for identifying specific differences, we based our power analysis on the post-hoc simple effects tests. When testing at the 0.05 alpha level a sample of 16 participants would provide a 96% chance (power) of detecting a difference of 1 sdu when comparing any two treatment conditions at a given time point. Since the desired flumazenil-reversal performance should not be different than

performance in the Passive Control condition, the power should be the same with the identical assumptions.

RESULTS

Measures of accuracy, mean reaction time and their product, throughput, were available for the grammatical reasoning, mathematical processing, and continuous processing tasks. Mean reaction time and mean reciprocal reaction time were analyzed for the PVT in addition to mean reaction time for the simple 20-item reaction time task. For these measures, the P/P condition did not significantly differ from the baseline condition at anytime. The within-subject analysis of variance statistic was applied to difference from baseline measures for all continuous, normally distributed, outcome measures. Analysis procedures for other dependent measures are described separately.

Comment [DRE3]: I didn't see the analysis for this statement.

Cognitive Performance

Grammatical Reasoning

An analysis accuracy measures, there were no significant differences among the three conditions. Table 3 shows differences between the means for each drug condition and its baseline along with the standard deviation. The variability of the Z10/P condition appears to have prevented the 10% decrease in accuracy from reaching statistical significance (pair wise comparison, $t_{(11)} = 1.623$, $p = 0.133$). For mean reaction time shown in Table 4, the drug by time interaction was significant allowing pair wise comparisons of the drug conditions at each test time ($F(4, 46) = 3.066$, $p = 0.024$ using Huynh-Feldt correction). The Z10/P to baseline change significantly differed from the P/P condition at 1500, 1600, and 1700 hours ($p < 0.05$). The difference approached significance at the 1900 testing session ($p = 0.053$) showing the degrading effects of this drug on reaction time. Similarly, the Z10/F to baseline change differed significantly from P/P at the 1600, 1700, and 1800 testing sessions ($p < 0.05$). The 1500 testing session approached significance ($p = 0.062$). However, the Z10/P and Z10/F were almost different at 1500 and 1600 ($p = 0.067$ and 0.051, respectively). Figure 1 shows that reaction time for Z10/F was intermediate between P/P and Z10/P for the first few hours after awakening.

Table 3. Change from Baseline in Each Drug Condition for Grammatical Reasoning Accuracy (SD)

Time of Day	Placebo	Zolpidem-Only	Zolpidem + Flumazenil
Baseline	96.18 (2.64)	96.01 (3.71)	97.74 (3.01)
1500	0.18 (4.12)	-10.24 (20.19)	-0.52 (3.78)
1600	0.70 (4.47)	-0.91 (6.51)	-1.93 (4.04)
1700	0.35 (4.34)	-5.76 (14.81)	-1.74 (5.88)
1800	-1.91 (8.54)	-2.60 (15.79)	-2.43 (5.17)
1900	-2.08 (8.62)	-3.42 (18.73)	-1.91 (6.73)
2000	-0.52 (6.83)	-2.79 (11.46)	-1.56 (4.87)

Table 4. Change from Baseline in Each Drug Condition for Grammatical Reasoning Mean Reaction Time (SD)

Time of Day	Placebo	Zolpidem-Only	Zolpidem + Flumazenil
Baseline	4102 (899)	4251 (1053)	4192 (820)
1500	105 (299)	2129 (1970)*	736 (1107)
1600	79 (460)	1455 (1400)*	884 (1000)*
1700	-259 (293)	1399 (1619)*	1048 (1557)*
1800	-87 (605)	802 (1671)	976 (1102)*
1900	-58 (478)	493 (591)	655 (1149)
2000	18 (580)	310 (475)	393 (920)
* $p \leq 0.05$			

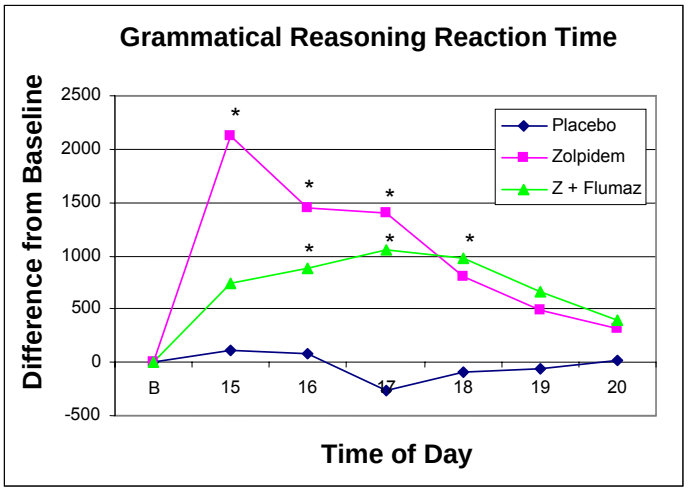

Figure 1. Grammatical reasoning reaction time as affected by the three drug conditions: placebo, zolpidem, and zolpidem with flumazenil.

The drug by time interaction for grammatical reasoning throughput was significant ($F(4, 53) = 2.682$, $p = .032$ using Huynh-Feldt correction) allowing pair wise comparisons of the drug conditions at each test time. Differences from baseline are shown in Table 5. In pair wise comparisons, the Z10/P change from baseline differed significantly from the P/P condition at 1500, 1600, 1700, and 1800 hours ($p < 0.05$), while the Z10/F differed significantly at the 1600 and 1700 testing sessions only ($p < 0.05$). Z10/F approached significance at the 1800 testing session ($p = .069$). Figure 1 shows the degrading effects of zolpidem on grammatical reasoning throughput with significant recovery from flumazenil only during the first hour with little recovery thereafter. The Z10/P and Z10/F conditions did not differ from each other at any time point.

Table 5. Change from Baseline in Each Drug Condition for Grammatical Reasoning Throughput (SD)

Time of Day	Placebo	Zolpidem-Only	Zolpidem + Flumazenil
Baseline	14.59 (3.40)	14.30 (3.68)	14.55 (3.19)
1500	-0.01 (1.76)	-4.69 (4.78)*	-1.64 (3.02)
1600	0.11 (2.05)	-2.81 (3.49)*	-2.40 (2.33)*
1700	1.27 (1.62)	-3.64 (4.39)*	-2.89 (4.36)*
1800	0.46 (3.79)	-2.07 (3.78)*	-3.06 (3.47)
1900	0.18 (2.17)	-1.47 (2.60)	-1.88 (3.89)
2000	0.17 (1.87)	-1.20 (1.97)	-1.47 (3.15)
* $p \leq 0.05$			

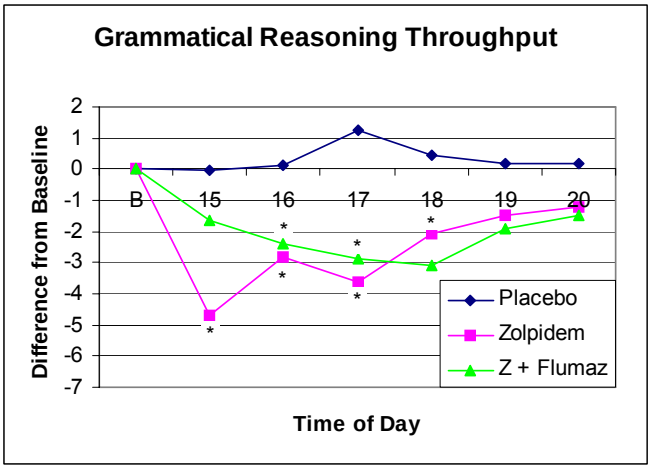

Figure 2. Grammatical reasoning throughput as affected by the three drug conditions: placebo, zolpidem, and zolpidem with flumazenil.

Mathematical Processing

Mathematical processing accuracy did not significantly change from baseline versus P/P for either Z10/P or Z10/F as shown in Table 6. The difference from baseline scores for mean reaction time, showed significant effects for drug and time ($p < 0.05$), but not for the drug by time interaction ($F(12, 120) = 1.47$, $p = 0.144$). Significant difference scores were found for Z10/P and for Z10/F when compared to P/P at 1600, 1700, and 1800 hour testing sessions ($p < 0.05$) and at 2000 hours for Z10/F ($p = 0.012$) as shown in Table 7. Figure 3 shows similar performance effects to grammatical reasoning. The lack of significance at 1500 hours ($p = .069$) was likely due to the joint effect of an increased RT in the P/P condition, Figure 3, and high variability in the Z10/P condition, Table 7.

Table 6. Change from Baseline in Each Drug Condition for Mathematical Processing Accuracy (SD)

Time of Day	Placebo	Zolpidem-Only	Zolpidem + Flumazenil
Baseline	96.47 (2.42)	98.48 (1.53)	97.21 (2.44)
1500	-1.02 (3.53)	-8.79 (9.50)	-2.29 (5.74)
1600	-0.07 (2.95)	-2.86 (8.05)	-1.40 (3.52)
1700	-0.16 (3.06)	-7.75 (22.24)	-2.24 (7.99)
1800	0.05 (2.93)	-8.46 (20.92)	-0.15 (3.59)
1900	-2.27 (6.27)	-6.38 (19.80)	-0.54 (3.91)
2000	-3.48 (6.26)	-4.33 (11.69)	-1.04 (7.53)

Table 7. Change from Baseline in Each Drug Condition for Mathematical Processing Mean Reaction Time (SD)

Time of Day	Placebo	Zolpidem-Only	Zolpidem + Flumazenil
Baseline	1566 (584)	1558 (545)	1520 (455)
1500	114 (234)	490 (649)	235 (340)
1600	40 (241)	331 (370)*	266 (278)*
1700	3 (171)	362 (332)*	360 (360)*
1800	16 (225)	317 (281)*	333 (343)*
1900	30 (253)	161 (265)	252 (318)
2000	-67 (182)	177 (367)	262 (313)*
* $p \leq 0.05$			

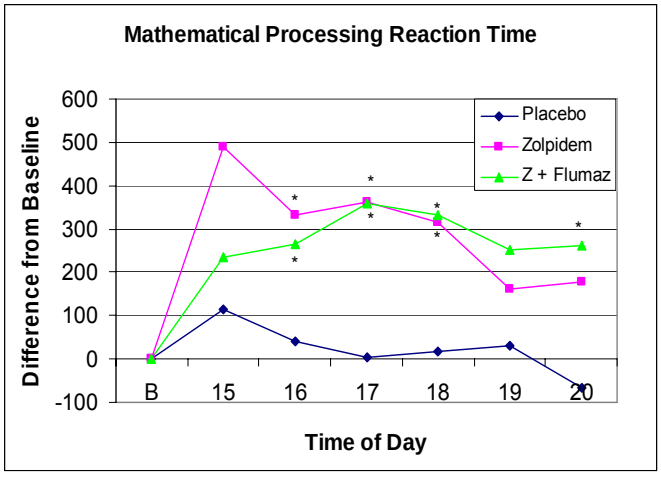

Figure 3. Mathematical processing reaction time as affected by the three drug conditions: placebo, zolpidem, and zolpidem with flumazenil.

For mathematical processing throughput, the ANOVA resulted in significant effects for drug and time ($p < 0.05$), but again not for drug by time ($F(4, 37) = 1.608$, $p = 0.196$) using Huynh-Feldt correction. Differences from baseline are shown in Table 8. The Z10/P and Z10/F change from baseline differed significantly from the P/P condition at 1500 through 1800 hours, and for Z10/F at 2000 hours ($p < 0.05$). At 1900 hours there was a trend for Z10/F ($p = 0.051$) and at 2000 hours a trend for Z10/P ($p = 0.059$). Similar to reaction time and grammatical reasoning throughput, Figure 4 shows that flumazenil appears to only protect performance during the first hour of administration. One hour after flumazenil administration, performance is no better under Z10/F than Z10/P.

Table 8. Change from Baseline in Each Drug Condition for Mathematical Processing Throughput (SD)

Time of Day	Placebo	Zolpidem-Only	Zolpidem + Flumazenil
Baseline	40.29 (11.21)	41.62 (12.23)	41.09 (11.30)
1500	-0.80 (5.29)	-9.61 (10.99)*	-3.83 (5.79)
1600	0.91 (6.04)	-6.24 (7.56)*	-5.08 (4.28)*
1700	1.17 (4.05)	-7.28 (6.24)*	-6.17 (7.21)*
1800	2.09 (4.54)	-8.07 (8.09)*	-6.00 (6.91)*
1900	0.74 (6.45)	-5.47 (8.10)	-4.86 (4.91)
2000	2.01 (5.01)	-4.22 (8.16)	-4.29 (6.90)*
* $p \leq 0.05$			

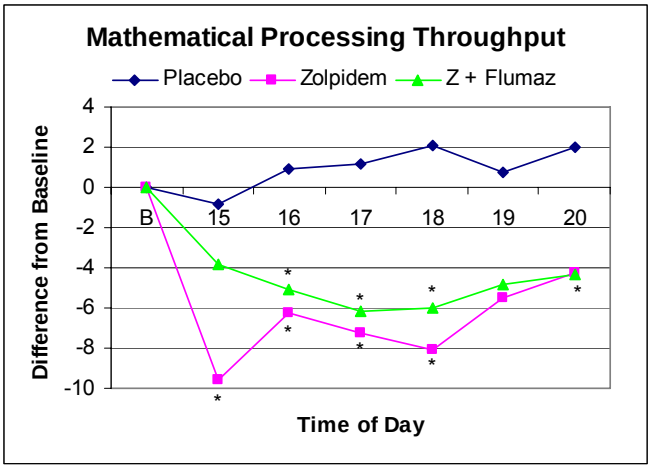

Figure 4. Mathematical processing throughput as affected by the three drug conditions: placebo, zolpidem, and zolpidem with flumazenil.

Continuous Processing

Continuous processing task accuracy did not significantly change from baseline for drug, time, or the drug by time interaction ($p > 0.05$). The difference from baseline scores for mean reaction time, showed significant effects for drug and time ($p < 0.05$), but not for the drug by time interaction ($F(3, 38) = 1.39$, $p = 0.259$, Huynh-Feldt corrected). As shown in Table 10, significant difference scores were found for Z10/P and Z10/F when compared to P/P at 1500 and 1800 hours ($p < 0.05$) and a trend was seen at 1600 hours for Z10/P ($p = 0.054$). Figure 5 shows the degrading performance effects of zolpidem at 1500 and 1600 hours compared to P/P with reaction time in the Z10/F condition situated between them. The Z10/P and Z10/F effects at 1800 appear to be due to the improved performance of the P/P condition.

Table 9. Change from Baseline in Each Drug Condition for Continuous Processing Task Accuracy (SD)

Time of Day	Placebo	Zolpidem-Only	Zolpidem + Flumazenil
Baseline	98.70 (1.37)	97.89 (1.68)	97.43 (1.37)
1500	-1.52 (1.69)	-8.87 (13.60)	-2.13 (5.51)
1600	-1.19 (2.32)	-4.98 (9.93)	-1.86 (3.67)
1700	-0.98 (1.63)	-9.82 (15.09)	-4.07 (5.18)
1800	-1.93 (3.08)	-7.24 (16.17)	-1.95 (3.69)
1900	-1.89 (3.34)	-8.68 (20.47)	-1.28 (1.77)
2000	-1.53 (3.02)	-4.43 (10.38)	-0.36 (2.55)

Table 10. Change from Baseline in Each Drug Condition for Continuous Processing Task Mean Reaction Time (SD)

Time of Day	Placebo	Zolpidem-Only	Zolpidem + Flumazenil
Baseline	416.6 (65.6)	431.2 (102.8)	430.1 (96.4)
1500	-2.3 (39.1)	74.2 (113.8)*	21.8 (25.0)*
1600	-10.3 (28.8)	33.6 (71.0)	18.7 (32.9)
1700	-2.1 (30.7)	38.9 (78.0)	34.5 (77.7)
1800	-15.5 (43.9)	25.7 (43.9)*	33.0 (74.4)*
1900	-0.4 (64.7)	12.4 (42.4)	6.4 (64.0)
2000	-13.3 (48.0)	8.0 (54.7)	3.7 (56.5)
* $p \leq 0.05$			

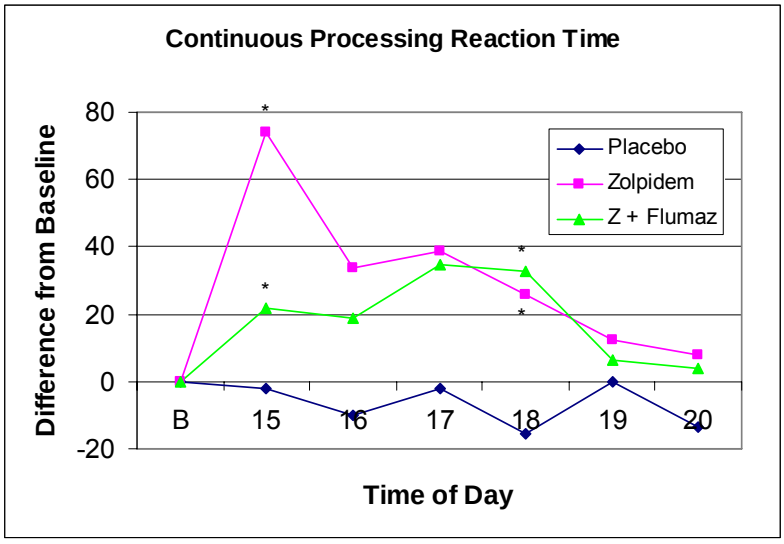

Figure 5. Continuous processing reaction time as affected by the three drug conditions: placebo, zolpidem, and zolpidem with flumazenil.

For continuous processing throughput, the ANOVA resulted in significant effects for drug and time ($p < 0.05$), but again not for the interaction ($F(3, 32) = 1.378$, $p = 0.267$) using Huynh-Feldt correction. Differences from baseline at each hour are shown in Table 11. The Z10/P condition was significantly different from the P/P condition at every hour and it was also significantly different from Z10/F at the 1500 hour ($p < 0.05$). Although the statistical results appear to be very clear that the Z10/P condition is degrading performance while the Z10/F is no different than P/P, Figure 6 shows the Z10/F condition to be intermediate between the two (except at 1500), similar to other cognitive performance dependent measures.

Table 11. Change from Baseline in Each Drug Condition for Continuous Processing Task Throughput (SD)

Time of Day	Placebo	Zolpidem-Only	Zolpidem + Flumazenil
Baseline	145.11 (19.49)	141.72 (27.06)	140.50 (23.78)
1500	-1.81 (10.35)	-30.28 (34.23)*	-7.15 (11.34)
1600	1.78 (7.79)	-15.17 (26.24)*	-5.55 (12.50)
1700	-1.26 (8.58)	-25.44 (26.20)*	-16.04 (26.61)
1800	1.96 (13.41)	-16.16 (23.65)*	-12.38 (25.19)
1900	-1.18 (19.20)	-15.89 (26.88)*	-5.98 (19.57)
2000	2.15 (14.73)	-10.92 (19.08)*	-2.26 (18.12)
* $p \leq 0.05$			

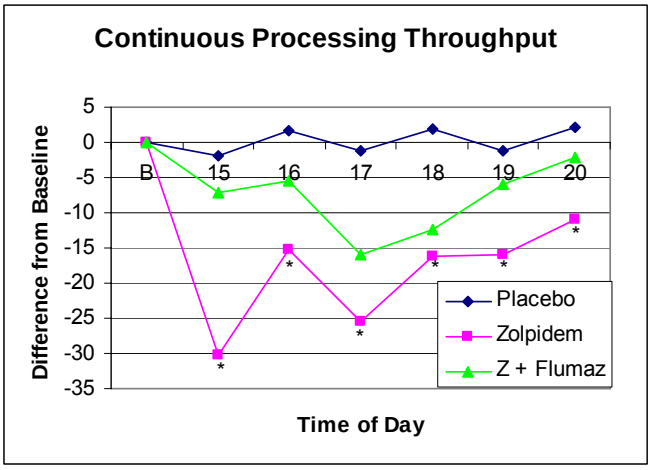

Figure 6. Continuous processing throughput as affected by the three drug conditions: placebo, zolpidem, and zolpidem with flumazenil.

Psychomotor Vigilance Task (PVT) and Simple Reaction Time

The PVT change from baseline measures, mean reaction time and mean reciprocal reaction time, were not significantly different for drug, time, or their interaction with α set at 0.05. The mean values for difference from baseline and their standard deviations are shown in Tables 12 and 13. With no significant main effects or interaction, paired comparisons at each hour of testing were not pursued.

Table 12. Change from Baseline in Each Drug Condition for PVT Mean Reaction Time (SD)

Time of Day	Placebo	Zolpidem-Only	Zolpidem + Flumazenil
Baseline	265.0 (37.8)	288.3 (86.8)	280.6 (72.4)
1500	-12.9 (29.7)	281.5 (599.6)	84.7 (175.2)
1600	2.4 (34.1)	253.7 (657.1)	137.9 (334.1)
1700	-4.0 (37.2)	495.5 (1042.3)	27.6 (62.2)
1800	13.7 (62.7)	618.1 (1420.2)	47.9 (74.5)
1900	74.7 (211.4)	416.6 (906.2)	8.0 (78.8)
2000	23.4 (95.8)	295.4 (870.9)	1.9 (58.2)

Table 13. Change from Baseline in Each Drug Condition for PVT Mean Reciprocal Reaction Time (SD)

Time of Day	Placbo	Zolpidem-Only	Zolpidem + Flumazenil
Baseline	4.037 (0.541)	3.859 (0.589)	3.929 (0.476)
1500	0.102 (0.293)	-0.243 (0.599)	-0.304 (0.685)
1600	-0.076 (0.331)	-0.446 (0.677)	-0.437 (0.379)
1700	-0.026 (0.413)	-0.559 (0.657)	-0217 (0.486)
1800	-0.126 (0.589)	-0.509 (0.616)	-0.271 (0.481)
1900	-0.291 (0.633)	-0.508 (0.487)	-0.130 (0.480)
2000	-0.153 (0.563)	-0.261 (0.517)	-0.057 (0.444)

The simple reaction time changes from baseline were not significantly different among the Z10/P, Z10/F, and placebo conditions. The simple reaction time did not show any significant difference in mean reaction time differences from baseline for any testing session as shown in Table 14.

Table 14. Change from Baseline in Each Drug Condition for Simple Reaction Time (SD)

Time of Day	Placbo	Zolpidem-Only	Zolpidem + Flumazenil
Baseline	213.41 (45.84)	206.62 (24.83)	213.04 (26.21)
1500	6.03 (24.62)	27.16 (38.83)	9.53 (20.27)
1600	-9.10 (24.55)	16.35 (29.89)	8.24 (27.14)
1700	-0.70 (22.51)	42.51 (90.82)	4.51 (27.34)
1800	-5.50 (28.13)	61.34 (145.43)	12.81 (31.68)
1900	1.53 (32.71)	29.30 (88.63)	5.38 (28.62)
2000	-4.64 (29.53)	4.50 (22.22)	-9.25 (28.87)

Memory

The Williams Word memory test was administered after the first awakening from sleep (1500) and again at 1700. For the number of words correctly recalled, a repeated-measures analysis of variance with two within-subject factors: drug condition (the three drug combinations) and time (1500 and 1700) was performed to test for significant treatment main effects and/or treatment by trial interaction. When significant drug effects were detected, post-hoc simple effects tests (Winer, 1971, p. 174) were used to compare the treatment conditions at each trial time, separately. The ANOVA resulted in significant effects for time ($F(1, 11) = 44.759$, $p = 0.001$ using Huynh-Feldt correction), but not for drug ($F(1, 15) = 2.904$, $p = 0.100$ using Huynh-Feldt correction), or the interaction ($F(2, 32) = 1.900$, $p = 0.173$). The number of correctly recalled words at each hour are shown in Table 15. The Z10/P condition was significantly different from the P/P condition at 1500 ($p = 0.021$). No other pair wise comparisons were found to be significant, $\alpha = 0.05$. Figure 7 shows the mean number of recalled items at each time for each drug condition.

Table 15. Mean Words Recalled by Drug Condition (SD)

Time of Day	Placebo	Zolpidem-Only	Zolpidem + Flumazenil
1500	12.08 (1.68)	8.75 (4.16)*	10.92 (3.55)
1700	8.17 (3.10)	6.42 (4.08)	8.75 (3.62)
* $p \leq 0.05$			

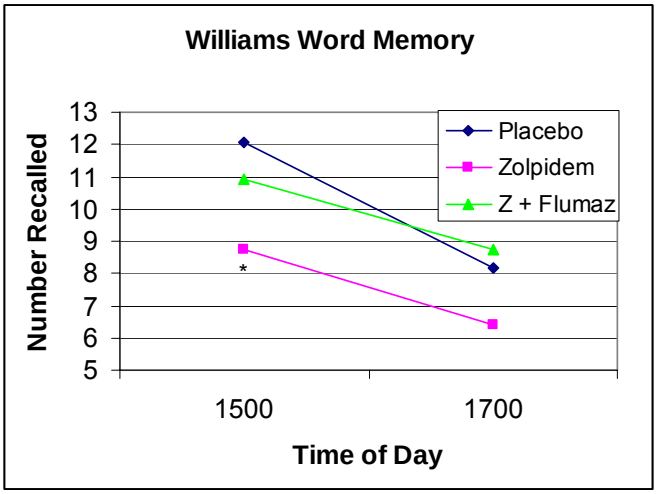

Figure 7. Williams Word Memory, number correct as affected by the three drug conditions: placebo, zolpidem, and zolpidem with flumazenil.

Physiological Performance

Two measures of physiological state were used to assess the vestibular system and physical strength. Both postural sway and grip strength are interval measures and were subjected to the same statistical analysis as the cognitive performance measures. The within-subject analysis of variance statistic was applied to difference from baseline measures for all measures.

Postural Sway

Postural sway is measured by an elliptical area of measurement that accounts for 95% of the variation in the center of changes in pressure, A95. The mean values for difference from baseline and their standard deviations are shown in Tables 16 and 17. The A95 change from baseline measure for eyes open and eyes closed was not significantly different for drug, time, or their interaction with α set at 0.05. Because of equipment malfunctions the data for only 10 participants were analyzable for eyes open and only 9 participants for eyes closed. Similarly, the postural sway data for the 1500 test time was not included in the analysis because large portions

were missing. With no significant main effects or interaction, paired comparisons at each hour of testing were not pursued.

Table 16. Change from Baseline in Each Drug Condition for Eyes Open, Postural Sway (SD).

Time of Day	Placbo	Zolpidem-Only	Zolpidem + Flumazenil
Baseline	2.07 (1.40)	3.22 (4.68)	1.94 (0.86)
1600	-0.22 (0.96)	0.09 (5.62)	3.04 (5.64)
1700	0.33 (1.00)	0.61 (4.60)	2.38 (1.99)
1800	0.11 (1.09)	-0.14 (4.79)	2.51 (2.20)
1900	0.95 (2.61)	-0.45 (4.54)	1.25 (2.46)
2000	-0.09 (1.29)	-0.94 (4.96)	1.50 (2.07)

Table 17. Change from Baseline in Each Drug Condition for Eyes Closed, Postural Sway (SD).

Time of Day	Placbo	Zolpidem-Only	Zolpidem + Flumazenil
Baseline	3.30 (3.19)	2.74 (1.69)	2.65 (1.41)
1600	0.40 (2.67)	3.21 (6.21)	3.63 (7.55)
1700	-0.10 (3.01)	1.86 (3.50)	4.01 (6.80)
1800	0.25 (3.27)	1.02 (1.78)	4.18 (8.46)
1900	1.78 (3.55)	-0.28 (1.23)	0.59 (1.57)
2000	0.46 (4.57)	0.28 (2.06)	1.14 (2.76)

Grip Strength

Physical strength was measured with a hydraulic hand dynamometer. None of the variables individually (drug or time) or in combination (drug by time interaction, ($F(4, 35) = 1.621$, $p = 0.192$)) had an effect on grip strength. However the values at 1500 presented the same pattern as other variables with the Z10/F falling between the P/P and the Z10/P conditions.

Subjective Report

Sleepiness

The Stanford Sleepiness Scale (SSS) ratings provided numerical ratings of subjective sleepiness. These were analyzed with ANOVA using the same procedures as with the cognitive test data at alpha = 0.05. The difference from baseline scores showed significant effects for time ($p < 0.05$) and for the drug by time interaction ($F(12, 72) = 2.22$, $p = 0.019$). As shown in Table 18, significant differences were found with pair wise comparisons for Z10/P ($t(6) = -3.29$, $p = 0.017$) and Z10/F ($t(6) = 2.83$, $p = 0.030$) when compared to P/P at 1600 and 2000 hours ($p < 0.05$). Figure 8 shows the degrading performance effects of zolpidem at 1600 hours compared to

P/P with the Z10/F condition showing less sleepiness toward the end of the evening. Further, Z10/P and Z10/F differed at 1600 ($t(6) = 2.65$, $p = 0.038$) with Z10/F in close proximity to P/P. The high sleepiness rating in the P/P condition at 2000 is somewhat explained by one participant giving a high rating compared to the rest of the participants; Table 18 shows the standard deviation the highest for any condition. Interestingly, the SSS showed a significant elevation from baseline at 1500 under P/P reflecting sleep inertia ($t(6) = 3.29$, $p = 0.017$). Similarly, the Z10/P condition showed differences from baseline at 1500 and 1600 ($p < 0.05$).

Table 18. Change from Baseline in Each Drug Condition for the Stanford Sleepiness Scale (SD).

Time of Day	Placebo	Zolpidem-Only	Zolpidem + Flumazenil
Baseline	1.57 (0.54)	1.71 (0.49)	2.14 (0.90)
1500	0.86 (0.69)	1.57 (1.13)	0.57 (0.98)
1600	0.29 (0.95)	1.14 (1.22)*	0.14 (1.07)
1700	0.43 (1.13)	0.86 (1.07)	0.29 (1.25)
1800	0.57 (.98)	0.86 (1.07)	0.43 (1.13)
1900	0.71 (1.25)	0.71 (0.95)	0.29 (0.76)
2000	1.14 (1.46)	0.14 (0.69)	0.00 (0.82)*
* $p \leq 0.05$, $n = 7$.			

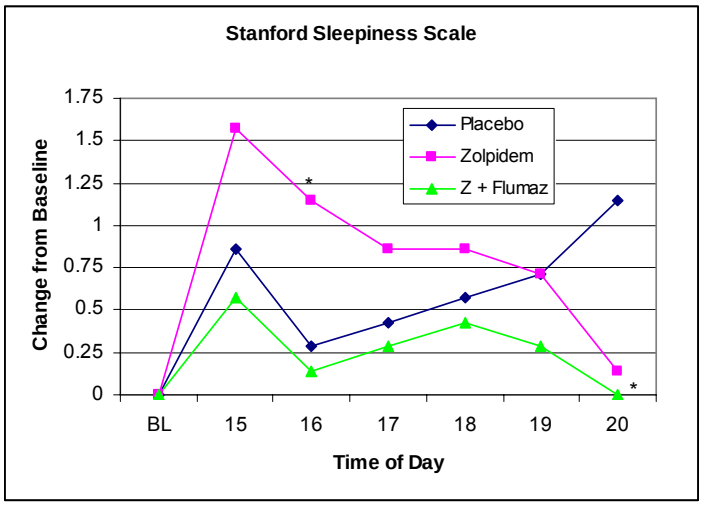

Figure 8. Stanford Sleepiness Scale as affected by the three drug conditions: placebo, zolpidem, and zolpidem with flumazenil.

Symptoms

Participants completed a 73-item paper and pencil Symptom Checklist at the end of each testing block, indicating the severity (none, some, moderately, or severely) they were experiencing for each symptom at that point in time. Only symptoms showing an increase from baseline were examined for drug effects with the Wilcoxon Signed Rank test. Further, only those symptoms for which at least 25% of the participants (i.e., at least 3 participants) exhibited an increased severity under at least one of the conditions are shown in Table 19. The tabled value is the percentage of participants showing an increase from baseline for the symptom at the time of testing. Bolded values represent conditions that are significantly different from the P/P condition ($p < 0.05$).

From the analysis, a significant number of participants presented symptoms of Trouble Staying Awake, "Drugged" Feeling, Light headed, and Difficulty Concentrating. Participants experienced these symptoms between one and three hours after zolpidem administration (1500-1700) and six of the eight symptoms were under the Z10/P condition. For the Z10/F condition, the "Drugged" Feeling and Light Headed symptoms were significant at 1500 and 1700, respectively.

Table 19. Symptoms Showing Increased Severity by Time and Drug Condition.

Symptom	Condition	1500	1600	1700	1800	1900	2000
Trouble Staying Awake	Placebo	0.0	0.0	0.0	8.3	16.7	8.3
	Zolpidem Only	27.3	18.2	**36.4**	30.0	36.4	18.2
	Z + Flumazenil	8.3	16.7	25.0	25.0	25.0	16.7
"Drugged" Feeling	Placebo	0.0	0.0	0.0	0.0	0.0	0.0
	Zolpidem Only	36.4	**45.5**	**54.5**	20.0	18.2	9.1
	Z + Flumazenil	**33.3**	41.7	33.3	33.3	8.3	16.7
Light headed	Placebo	8.3	0.0	0.0	0.0	0.0	0.0
	Zolpidem Only	27.3	**36.4**	27.3	20.0	18.2	9.1
	Z + Flumazenil	25.0	25.0	**41.7**	16.7	0.0	0.0
Loss of Balance	Placebo	0.0	0.0	0.0	0.0	0.0	0.0
	Zolpidem Only	9.1	9.1	27.3	20.0	9.1	9.1
	Z + Flumazenil	16.7	25.0	8.3	8.3	0.0	0.0
Fatigue	Placebo	8.3	8.3	8.3	8.3	16.7	25.0
	Zolpidem Only	18.2	18.2	18.2	30.0	18.2	9.1
	Z + Flumazenil	8.3	8.3	16.7	8.3	8.3	8.3
Drowsiness	Placebo	8.3	0.0	8.3	8.3	25.0	16.7
	Zolpidem Only	36.4	27.3	45.5	20.0	36.4	27.3
	Z + Flumazenil	16.7	8.3	16.7	25.0	8.3	8.3
Headache	Placebo	16.7	16.7	8.3	8.3	8.3	8.3
	Zolpidem Only	9.1	18.2	18.2	10.0	9.1	18.2
	Z + Flumazenil	16.7	25.0	8.3	16.7	8.3	8.3
Difficulty Focusing	Placebo	0.0	8.3	0.0	0.0	0.0	0.0
	Zolpidem Only	36.4	18.2	36.4	30.0	27.3	18.2
	Z + Flumazenil	8.3	25.0	8.3	0.0	8.3	0.0
Nausea	Placebo	0.0	16.7	0.0	0.0	0.0	0.0
	Zolpidem Only	18.2	27.3	27.3	20.0	9.1	9.1
	Z + Flumazenil	16.7	25.0	16.7	25.0	8.3	8.3
Difficulty Concentrating	Placebo	0.0	0.0	0.0	0.0	0.0	0.0
	Zolpidem Only	**27.3**	27.3	**45.5**	30.0	18.2	18.2
	Z + Flumazenil	16.7	8.3	16.7	0.0	0.0	0.0
Stomach Awareness	Placebo	16.7	25.0	0.0	8.3	0.0	0.0
	Zolpidem Only	9.1	9.1	9.1	10.0	9.1	9.1
	Z + Flumazenil	8.3	16.7	8.3	8.3	8.3	8.3
Vivid Dreams	Placebo	0.0	0.0	0.0	0.0	0.0	0.0
	Zolpidem Only	9.1	0.0	0.0	0.0	0.0	0.0
	Z + Flumazenil	25.0	8.3	0.0	0.0	0.0	0.0

Note: Bold values were significant, $p \leq 0.05$, using the Wilcoxon Signed Rank test.

Examining the subjective symptoms reported by participants and collapsing across the various sample times, we can see what symptoms were associated with each of the drug conditions. Table 20 shows the percentage of participants reporting symptoms at a level higher

than baseline regardless of the time. Bolded values represent significantly increased symptom severity compared with the P/P condition ($p < 0.05$).

Table 20. Percentage of Participants Reporting Symptoms Within Each Drug Condition at Any Time.

Symptom	Placebo	Zolpidem Only	Zolpidem plus Flumazenil
Trouble Staying Awake	16.7	**54.5**	25.0
Visual Illusions	0.0	9.1	25.0
"Drugged" Feeling	0.0	**63.6**	**83.3**
Light headed	8.3	**45.5**	**50.0**
Difficulty Staying Awake	8.3	36.4	25.0
Loss of Balance	0.0	27.3	**50.0**
Loss of Coordination	0.0	27.3	25.0
Fatigue	25.0	45.5	33.3
Drowsiness	25.0	63.6	41.7
Headache	16.7	36.4	25.0
Eye Strain	8.3	27.3	25.0
Difficulty Focusing	8.3	**54.5**	41.7
Nausea	16.7	27.3	33.3
Difficulty Concentrating	0.0	**54.5**	**41.7**

Note: Bold values were significant, $p \leq 0.05$, using the Wilcoxon Signed Rank test.

Table 20 shows that participants experienced many symptoms under the Z10/P and Z10/F conditions, five and four respectively. Whereas participants under the Z10/P condition appeared to experience the "Drugged" Feeling more frequently than the Z10/F condition, when only the number of participants are considered the percentage for Z10/F condition is 83.3 percent (10 out of 12). Similarly for Loss of Balance, half the participants experienced an increase in this symptom at some time whereas no single time was significant. The Z10/P condition showed a similar effect for Difficulty Focusing including 54.5 percent of the participants. Again for Difficult Concentrating the Z10/F condition increased this symptom to a significant 41.7 percent. Somewhat surprisingly participants did not identify either Fatigue or Drowsiness as increasing under any of the conditions. However, since 25 percent of participants indicated at baseline that they were experiencing these as symptoms setting a high mark to overcome with only a four point scale.

Subjective evaluations of mood were acquired using the ANAM Mood Scale II. Unfortunately, these data were lost during a move from one building to another.

DISCUSSION

The overall results of this investigation demonstrate that the sublingual administration of flumazenil can partially nullify the soporific effects of zolpidem. These findings confirm those of Wesensten et al. (1995) and others who found impairment reversed by intravenous

administration of flumazenil, but that the sedation effects returned six hours after the original zolpidem administration. While the debilitating effects of zolpidem were shown on cognitive performance, memory, sleepiness, and side effects, flumazenil only reversed these effects for one to two hours. While these effects can not be seen clearly in the reaction time measure of the three cognitive tests, Figure 9 shows this effect for the throughput measure. It shows the number of significant differences with P/P at each time. Although accuracy frequently does not show significant effects because of its limited range, the Z10/P condition showed 8-10 percent degradation relative to P/P while the Z10/F conditions showed 2-3 percent degradation. The throughput measure shows the restorative effect of flumazenil because it includes accuracy and reaction time. Performance under flumazenil typically fell between zolpidem and P/P for the first hour or two and then often joined the zolpidem performance curve as performance returned to that of the P/P condition with the metabolism of the zolpidem. The treatment conditions had similar effects on the limited Williams Word Memory test. Participants in the flumazenil condition recalled nearly as many words as the P/P condition while recall was down approximately three words in the zolopidem-only condition.

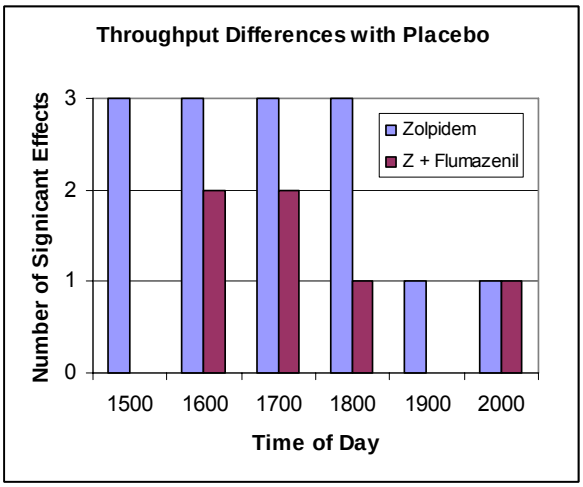

Figure 9. This figure summarizes the results of the three cognitive tests by showing the number of significant differences with placebo at each time.

While the physiological measures were not different from P/P, the subjective measures of sleepiness and symptoms showed significant effects for Z10/P. Interestingly, the Stanford Sleepiness Scale showed that flumazenil nearly completely nullified the sleepiness effects of zolpidem for the entire data collection session. However, the high baseline level of sleepiness for the zolpidem plus flumazenil condition contributed to this effect by reducing the differences for the subsequent time samples. The symptom results also present a picture of flumazenil only partially nullifying the effects of zolpedim. Significant numbers of participants under zolpidem indicated they had trouble staying awake, felt "drugged," felt light headed, and had difficulty concentrating from one and three hours after zolpidem administration. Flumazenil helped to

eliminate most of these symptoms, but still left most participants experiencing some of these symptoms at some time during the data collection period.

One other way of understanding at these data is to look at the restorative value of flumazenil on the percentage of degradation induced by zolpidem. Using the throughput measures for each of the three cognitive tests, the sample mean for each time and drug condition was divided by the conditions baseline. Then each proportion was divided by the P/P value for each time and multiplied by 100. The percentages for each test were used to compute a mean for Z10/P and Z10/F at each time. Figure 10 shows a plot of these values, average percent change from P/P. From this chart it can be seen that zolpidem degrades performance about 25%, 90 minutes after administration. After flumazenil administration, these data show that performance is restored to 92%, a significant 17% improvement. An hour later after the second administration of flumazenil, performance drops another 5% providing only a 4% improvement over Z10/P. In the next hour, performance in the flumazenil condition drops another 6% to 82%, providing only a 5% improvement over zolpidem. Thereafter, zolpidem is slowly metabolized allowing performance to recover. However, even at 2000, performance remains 10-11% degraded compared to P/P. In the Williams Word Memory test, similar percentages were found at 1500, but at 1700 flumazenil appeared to completely restore memory to the same level as P/P. The Z10/P condition was restored to 90% of the P/P condition at 1700.

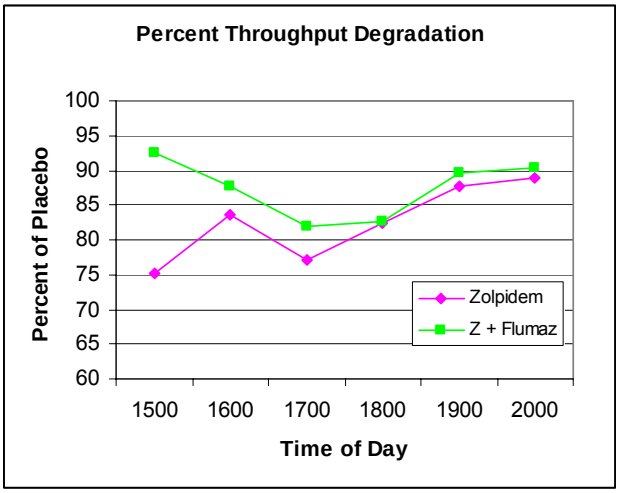

Figure 10. Percent degradation from placebo across throughput measures for three cognitive tests.

Flumazenil Elimination

Metabolism. Flumazenil, an imidazobenzodiazepine, has an elimination half-life of 54 minutes (range 41 – 79), and is primarily metabolized by the liver to two inactive metabolites that are excreted in the urine. It is primarily hydrolyzed by a liver carboxylesterase to flumazenil

acid and N-dealkylated to N-demethylated flumazenil, probably by the cytochrome P-450 system, as are other benzodiazepine compounds. This remains to be determined.

Competition with benzodiazepines. Binding of benzodiazepines to the gamma-aminobutyric acid receptor occurs at the ω_1 and ω_2 subunits. Flumazenil does not discriminate between the subunits and has a dissociation coefficient of 0.60 ng/L. Flumazenil is approximately 50% bound to serum protein. Zolpidem, an imidazopyridine, is highly selective for the ω_1 subunit, and has a similar dissociation coefficient of 1.5 – 2.1 ng/L. Several studies have examined the pharmacokinetic interaction of flumazenil with hypnotic agents. One small study found that 1mg of intravenous flumazenil prolonged the elimination half-life of 0.1 – 0.2 mg/kg of midazolam, a short-acting imidazobenzodiazepine. A second study found that a smaller dose, 0.005 mg/kg, of intravenous flumazenil reversed cognitive impairment, due to 0.025 mg/kg of midazolam, on the Digit Symbol Substitution Test, without significantly altering midazolam pharmacokinetics. Another study found that while effective for reversing zolpidem-induced sedation and psychomotor impairment, 0.04 mg/kg of intravenous flumazenil had no effect on zolpidem pharmacokinetics. This study was unusual in that zolpidem was administered intravenously, rather than orally, and found a mean serum elimination half-life of 1.2 hours for zolpidem versus 2.4 hours after oral dosing. Similarly, a previous study showed 1 mg of intravenous flumazenil to ameliorate immediate and delayed memory impairment due to 20 mg of zolpidem or 0.5 mg of triazolam.

It is possible that competition for elimination via the liver exists for flumazenil and hypnotic agents, such as zolpidem, but this is only seen when the quantities of both drugs are sufficient to saturate the liver CYP 3A4 enzyme binding. The zolpidem displaced from ω_1 and CYP 3A4 sites could remain in the serum or bind to another, unknown receptor.

Zolpidem Side Effects

A fourth arm of this study, administering 20 mg of zolpidem, then two doses of sublingual flumazenil, was discontinued after three of the exposed four participants experienced vomiting, two with projectile vomiting. The fourth participant experienced only nausea. This incidence of nausea and vomiting is higher than seen in a previous study using 20 mg of zolpidem without flumazenil administration. Conversation with the lead author of the study that showed flumazenil to reverse memory impairment (reference 12) due to zolpidem revealed their incidence of nausea and vomiting to be around 60 % with 20 mg of zolpidem. Though 20 mg of zolpidem is greater than the FDA approved doses of 5 and 10 mg, clinical trials with 20 mg doses report an incidence of approximately 2% for nausea. There is a possibility that interaction between high doses of flumazenil and zolpidem results in nausea and vomiting.

Flumazenil and Other Hypnotics

Currently, temazepam, zolpidem, and zaleplon are the only hypnotic agents approved for use by USAF aircrew. A PubMed search did not find any studies on using flumazenil to reverse sedation due to temazepam. Publications were found related to studies administering flumazenil to precipitate withdrawal symptoms with zaleplon use but not specifically to reverse sedation. Zopiclone is a non-benzodiazepine hypnotic that offers some benefits compared to the currently USAF approved hypnotic medications. It has a half life similar to temazepam, making it suitable for use to reduce fatigue due to circadian rhythm disruption. Also like temazepam, it binds to

both ω_1 and ω_2 subunits. Unlike temazepam, it maintains a normal proportion of slow-wave sleep during an eight hour sleep period. It has been well studied for 25 years and is available in Europe and Canada. The s-enantimer, eszopiclone, recently became available in the United States under the brand name Lunesta. Zopiclone does not bind directly to the ω_1 and ω_2 subunits but to a related, allosteric site. An in vitro experiment demonstrated this when a single dose of flumazenil fully reversed all zopiclone influence at the GABA receptor. This was not true for zolpidem, triazolam, and flunitrazepam. The combination of eszopiclone and sublingual flumazenil suggests the possibility of inducing normal sleep architecture of any desired duration up to eight hours and awaken quickly after flumazenil administration without risk of resedation.

CONCLUSIONS

Under the conditions of this experiment, the data and analysis provide the following conclusions.

1. Sublingual flumazenil, administered immediately on awakening, was shown to reverse the cognitively degrading effects of zolpidem by 23%, restoring performance to 92.5% of P/P.
2. After a second administration of flumazenil one hour post awakening, beneficial effects were minor.
3. One to two hours after awakening, performance did not return to the level of the P/P after flumazenil administration, but rather joined the Z10/P decay function which continued to be approximately 20% degraded compared to P/P.
4. At five hours post awakening, performance remained degraded by 10-11% compared to P/P.

The improvement in the throughput measure for three cognitive performance tests demonstrates that further research using more sophisticated formulations should be continued. Other sublingual formulations such as eszopiclone are likely to have greater bioavailability and provide more complete restoration of performance over a longer period of time.

REFERENCES

Bonfiglio MF, Fisher-Katz LE, Saltis LM, Traeger SM, Martin BR, Nackes NA, Perkins TA (1996). A pilot pharmacokinetic-pharmacodynamic study of benzodiazepine antagonism by flumazenil and aminophylline. *Pharmacotherapy*, *16(6)*, 1166-1172.

Caldwell JL, Prazinko BF, Rowe T, et al. (2003). Improving daytime sleep with temazepam as a countermeasure for shift lag. *Aviat Space Environ Med*, *74*, 153– 63.

Cornum K, Cornum R, & Storm WF (1995). Use of psychostimulants in extended flight operations: A Desert Shield experience. In *Advisory Group for Aerospace Research and Development (AGARD) Conference Proceedings 579*, *37,* 1-4. Neurological Limitations of Aircraft Operations: Human Performance Implications, Neuilleysur-Seine, France: NATO Advisory Group for Aerospace Research and Development; 1995 October.

Eddy DR, Barton E, Cardenas R, French J, Gibbons JA, Hickey PA, Miller JC, Ramsey CS, Storm WF (2006). *Daytime sleep aids and nighttime cognitive performance*. (AFRL

Technical Report No. AFRL-HE-BR-TR-2006-0039). Brooks City-Base, TX: Human Effectiveness Directorate, Biosciences and Protection Division, Warfighter Fatigue Countermeasures Branch.

Emonson DL, & Vanderbeek RD (1995, March). The use of amphetamines in U.S. Air Force tactical operations during Desert Shield and Storm. *Aviation, Space, and Environmental Medicine*, *66(3)*, 260-263.

Heniff MS, Moore GP, Trout A, Cordell WH, & Nelson DR (1997). Comparison of routes of flumazenil administration to reverse midazolam-induced respiratory depression in a canine model. *Academic Emergency Medicine*, *4*, 1115-1118.

Hoddes E, Zarcone V, Smythe H, Phillips R, & Dement WC (1973). Quantification of sleepiness: a new approach. *Psychophysiology*, *10(4)*, 431-436.

Kleingeist B, Böcker R, Geisslinger G, & Brugger R (1998). Isolation and pharmacological characterization of microsomal human liver flumazenil carboxylesterase. *J Pharm Pharmaceut Sci*., *1(1)*, 38-46.

Lowenstein PR, Rosenstein R, Caputti E, & Cardinali DP (1984). Benzodiazepine binding sites in human pineal gland. *Eur J Pharmacol*., *106(2)*, 399-403.

Munakata M, Jin YH, Akaike N, & Nielsen M (1998). Temperature-dependent effect of zolpidem on the GABAA receptor-mediated response at recombinant human GABAA receptor subtypes. *Brain Res*., *807*, 199-202.

Oliver FM, Sweatman TW, Unkel JH, Kahn MA, Randolph MM, Arheart KL, & Mandrell TD (2000). Comparative pharmacokinetics of submucosal vs. intravenous flumazenil (Romazicon) in an animal model. *Pediatr Dent*, *22(6)*, 489-93.

Patat A, Naef MM, van Gessel E, Forster A, Dubruc C, & Rosenzweig P (1994). Flumazenil antagonizes the central effects of zolpidem, an imidazopyridine hypnotic. *Clin Pharmacol Ther*, *56(4)*, 430-6.

Rogers JF, Morrison AL, Nafziger AN, Jones CL, Rocci ML, & Bertino JS (2002). Flumazenil reduces midazolam-induced cognitive impairment without altering pharmacokinetics. *Clin Pharmacol Ther*., *72(6)*, 711-7.

Romazicon package insert (2007), Roche Laboratories.

Roncari G, Timm U, Zumbrunnen R, et al. (1993). Flumazenil kinetics in the elderly. *Eur J Clin Pharmacol*, *45,* 585-587.

Scheepers LD, Montgomery CJ, Kinahan AM, Dunn GS, Bourne RA, & McCormack JP (2000). Plasma concentrations of flumazenil following intranasal administration in children. *Canadian Journal of Anesthesia*, *47*, 120-124.

Storm WF, Eddy DR, Welch CB, Hickey PA, Fischer J, Cardenas R (2007). Cognitive performance following premature awakening from Zolpidem or Melatonin induced daytime sleep. *Aviat Space Environ Med*, *78*, 10-20.

Wesensten NJ, Balkin TJ, Davis HQ, Belenky GL (1995). Reversal of triazolam- and zolpidem-induced memory impairment by flumazenil. *Psychopharmacology* (Berl), *121*(2), 242-9.

Winer BJ (1971). *Statistical principles in experimental design*. Second Edition, McGraw-Hill Book Company, New York, NY.