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14. ABSTRACT Coordination of strategies for transitioning psychoactive pharmacological compounds from basic laboratory research to the field environment has been an ongoing effort among military laboratories. Several workshops have been held specifically to address the operationally relevant issues and other military and scientific challenges as they relate to the enhancement and sustainability of cognitive performance. In this preface, we tie together recommendations of the Pharmacological Strategies Focus Team for one such Workshop, review current literature, and discuss findings reported at recent professional meetings. The papers presented within this pharmacology section are discussed. These section papers are organized into three areas of operational relevance—the first assesses the effectiveness of a treatment given for migraines, a condition with known detrimental effects on productivity and readiness; the second discusses ethical considerations surrounding the use of pharmaceutical countermeasures for fatigue in the operational environment; and the third discusses a case report highlighting the aeromedical considerations regarding selective serotonin reuptake inhibitors (SSRIs) and aviator flight performance, particularly as assessed with neuropsychological testing. The papers and commentaries in this section encourage us to consider the complex variables effecting the decisions to administer pharmacological agents, as the impact of their use is weighed against the cognitive performance effects they may have in the operational environment.					
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Considerations of Pharmacology on Fitness for Duty in the Operational Environment

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Coordination of strategies for transitioning psychoactive pharmacological compounds from basic laboratory research to the field environment has been an ongoing effort among military laboratories. Several workshops have been held specifically to address the operationally relevant issues and other military and scientific challenges as they relate to the enhancement and sustainability of cognitive performance. In this preface, we tie together recommendations of the Pharmacological Strategies Focus Team for one such Workshop, review current literature, and discuss findings reported at recent professional meetings. The papers presented within this pharmacology section are discussed. These section papers are organized into three areas of operational relevance—the first assesses the effectiveness of a treatment given for migraines, a condition with known detrimental effects on productivity and readiness; the second discusses ethical considerations surrounding the use of pharmaceutical countermeasures for fatigue in the operational environment; and the third discusses a case report highlighting the aeromedical considerations regarding selective serotonin reuptake inhibitors (SSRIs) and aviator flight performance, particularly as assessed with neuropsychological testing. The papers and commentaries in this section encourage us to consider the complex variables effecting the decisions to administer pharmacological agents, as the impact of their use is weighed against the cognitive performance effects they may have in the operational environment.

Keywords: fatigue countermeasures, pharmacology countermeasures, cognitive performance, psychotropic, military operations, pharmaceuticals.

WITHIN THE LABORATORIES supported by the U.S. Army Medical Research and Materiel Command (USAMRMC), the Defense Advanced Research Projects Agency (DARPA), and the Air Force Research Laboratory (AFRL), there is continued emphasis on standardizing assessment strategies and maximizing coordination for transitioning psychoactive pharmacological compounds from basic laboratory research to the field environment.

Pharmacology Focus Team Discussions

At a U.S. Army Medical Research and Materiel Command (USAMRMC)-sponsored workshop “Cognitive Performance: Force Multiplication through Human-in-the-loop Augmentation” (Las Vegas, NV, July, 2005), a group of invited participants met to discuss and plan future operationally relevant research strategies for investigating psychoactive pharmaceuticals, including fatigue countermeasures. The goals of this group were broadly described as follows: to examine the impact of pharmaceutical agents (e.g., stimulant and hypnotic countermeasures, as well as analgesics and psychoac-

tive compounds such as antidepressants) on performance decrements associated with cognitive workload, fatigue, and sleep deprivation, and to recommend plans to replicate and validate these laboratory findings in the operational environment.

One focal point of this cognitive performance workshop group was a discussion of the selective serotonin reuptake inhibitors (SSRIs) with the purpose of determining the direction of future research and of developing military guidance for their use in operational settings. Specifically, the Pharmacological Strategies Focus Team finalized details for a proposal to evaluate the effects of SSRIs on cognition and flight performance, and to prepare recommendations to convey back to the U.S. Army Aeromedical Activity (USAAMA; the tertiary central aeromedical review authority for all Army aircrew members worldwide).

As background for this discussion, and as described in detail by Doan et al. (11), “the issue of importance for the operational community, with regard to both clinical and fatigue countermeasures usage of psychoactive agents, should not be whether an individual warrior is on a psychotropic medication, or which medication, but rather whether the psychotropic medication impairs or does not impair the cognitive and operationally relevant performance of the warfighter. That is, does the treatment itself alter some aspect of operational performance, assuming circumstances in which the medical condition is either well controlled or in itself does not impair performance?”

Of particular interest to the focus team was one of the Aeromedical Policy Letters (APL), regarding the regulation that aviators using the selective serotonin or

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norepinephrine reuptake inhibitor (SSRI/SNRI) medications were disqualified to fly. One of the most common reasons for prescribing SSRIs is for the treatment of depression. The initial rationale for disqualifying individuals who were taking antidepressant medications from aviation activities was the known side effects of fatigue and drowsiness, which are clearly incompatible with flying duties. However, the newer psychotropic medications are proving to be efficacious while showing minimal side effects. SSRIs are used for a variety of reasons, including some "off-label" conditions (for example, as a prophylaxis for tension headaches in otherwise healthy individuals) which are not reasons for grounding the pilots. However, as they are considered psychotropic medications, this grounding action was applied regardless of the diagnosis or without having the flight surgeon determine the aviator's ability to perform flight duties.

This information was taken into consideration to support the possibility of a waiver/exception to policy for certain uses of these medications. Specifically, the newly appointed AAMA Chief, LTC Stephen Bernstein, was in the process of seeking recommendations and feedback for an SSRI/SNRI APL revision at the time of the workshop. After reviewing and discussing this APL draft, the group established communication with the AAMA Chief via teleconference to provide direct feedback and discuss the development of a plan of action regarding this policy letter.

The consensus from our meeting was that what was needed was a clear indication of the prevalence of SSRI use among aviators and a relevant study of the performance effects of SSRI's within their operational environment; i.e., using a flight simulator. One specific action called for conducting a survey of all (active duty and deployed) Army aviators using the Army Knowledge Online (AKO) portal to ask individuals to anonymously respond to questions regarding Post Traumatic Stress Disorder (PTSD) and depression. The intent was to gather data to determine the prevalence of SSRI and SNRI use among these operators. A suggestion was made to offer amnesty to aviators who stepped forward with the admission of legal drug use by perhaps grounding them for 1 mo while they served in an instructor or trainer role.

A second action called for compiling a file of "read-ahead" documents of the SSRI policies and research findings from other countries such as Australia, Britain, and Canada, with the intent to distribute these documents to identified interested personnel from the U.S. Army, Air Force, Navy, and the Federal Aviation Administration (FAA). By enlisting the help of these key personnel, it was thought that it might be possible to develop a long-term goal of establishing one unified policy for SSRI use among aviators in the operational environment across both the military and civilian sectors.

As an extended long-term goal for the military, and as similarly discussed by Doan et al. (11), it was proposed to engage these same key points of contact in discussions that would attempt to establish a broader unified Armed Forces Psychoactive Agent Evaluation

System that was integrated across services and that included multiple operators in addition to aviators (e.g., Special Operations, Ground Forces, and Command and Control). Such a system would allow for a user-focused approach to standardizing the laboratory testing and decision-making process for approving the use of new and existing psychoactive agents being considered for application in the operational environment.

Studies would be required to show clear relevance to the operational environment, and perhaps follow the two-tiered approach described at an earlier DARPA-sponsored workshop (September 2004). Such an approach would involve, first, that healthy volunteers be studied under laboratory conditions which would best emulate the stressors experienced in operational environments, and second, military or operationally-matched volunteers be studied in simulated or field environments under stressful conditions to evaluate performance on military tasks in the operational community. The key would be to follow the model established with the SSRI procedures previously developed.

Ideally, the Psychoactive Agent Evaluation System would consist of a performance-based evaluation that would be tailored to the individual and the job rather than to the specific drug, similar to the current procedures where a flight surgeon decides whether a pilot can tolerate dextroamphetamine as determined by ground-based testing. Further, as part of this evaluation effort, it also would be necessary to establish guidelines for the use of such a system in the operational environment. These guidelines would include: 1) identifying the mechanism(s) for obtaining feedback from the field should problems arise with the applied drug (i.e., determine a follow-up timeline and a point of contact); and 2) identifying a plan to communicate the recommendations for this evaluation system (in the form of white papers, pamphlets, literature, etc.) and a way to implement it.

Since the time of the workshop, a revised policy was released, effective January 2006. Pursuant to following the conditions of this revised policy, a waiver is now in effect that may return applicable aviators to flight as early as 4-5 mo after they presented for care. The revised APL also acknowledges that the lack of flight performance data will soon be rectified by a study proposed by the U.S. Army Aeromedical Research Laboratory (USAARL). Although there have been numerous clinical studies performed showing a lack of impairment with regard to SSRI's effects on cognitive performance, there appear to be no flight performance data. The USAARL group proposed to validate the supposed lack of decrements in flight performance by studying participants currently undergoing medication therapy. As Russo suggested in a recent Aerospace Medical Association presentation, "Measuring performance is a more valid basis for determining fitness for flight duties than evaluating the list of potential aviation incompatible events associated with a specific treatment" (29).

Operationally Relevant Research Status

One of the most challenging aspects of the operational environment is the handling of sleep as a logistical resource. Numerous studies have documented the

effects of pharmacological agents on cognitive performance, most notably as they relate to sleep. The pharmaceuticals typically are either given to optimize sleep in non-sleep-conducive environments or to maintain and/or enhance wakefulness when sleep is not an option. Recent articles have reviewed the current literature and are mentioned briefly below. Of particular interest here are the reviews that highlight the findings relevant to the U.S. military. We also present a brief overview of some recent unpublished findings that indicate the direction in which the field is headed.

In the case of using hypnotics to optimize sleep, a number of options are available for military personnel, particularly in aviation. The U.S. Navy, Army, and Air Force all approve the use of temazepam, zaleplon, and zolpidem under conditions where personnel are having difficulty sleeping due to circadian disruption and/or predeployment schedules that interfere with adequate sleep. The U.S. Army also authorizes triazolam. Each of these medications has specific grounding times, depending on the medication and the branch of service, and all use is under the supervision of the unit flight surgeon. Which medication is chosen depends on the flight surgeon and the user, taking into account the reason the hypnotic is needed. While many reviews of various hypnotics have been published, a recent publication reviews the specific hypnotics approved for use in U.S. military aviation settings and provides a lengthy description of each (6). Other hypnotics have been introduced in the market over the past few years, but are currently not approved for use in military aviation. For example, in July 2005, ramelteon was approved by the U.S. Food and Drug Administration (FDA). This hypnotic has an elimination half-life of 1.4 h and has been shown in clinical trials to decrease sleep latency in clinical populations (21) as well as in a sample of normal sleepers who were sleeping in a novel environment (28), a situation that is common to military personnel. While this medication is not currently approved for use in military settings, future studies could be conducted to determine its potential use for these unusual applications.

In the case of wake-promoting agents used to sustain alertness and performance in sleep-deprived individuals, only a few options are available to military personnel. For the U.S. Army, only caffeine and dextroamphetamine are approved for use, and dextroamphetamine use is approved only under very specific circumstances. For the U.S. Air Force, dextroamphetamine is approved for some aviation personnel, with modafinil approved recently for select fighter and bomber crews. As with the hypnotics, flight surgeon oversight is required for the use of any of the controlled substances (dextroamphetamine and modafinil). Many articles have been published which review the pros and cons of these stimulants as well as others, however, controversy over which stimulants are best still remains. For example, a review by the stimulant task force of the American Academy of Sleep Medicine indicates that caffeine is the stimulant of choice (3), however, an earlier review of stimulants for use in military settings indicated that other stimulants may be needed to provide the neces-

sary alertness boosts for military aviation needs (6). A review of modafinil (33) suggests that flight surgeons assess the pros and cons of each wake-promoting medication before deciding which stimulant to prescribe to overcome performance and alertness impairments due to sleep deprivation. As with hypnotics, new stimulants have come on the market over the past few years that have not been evaluated in a military setting and, therefore, should be evaluated for specific use of the military. For example, a new formulation of modafinil, armodafinil, is currently being evaluated for approval by the FDA (10). Slow-release caffeine is another option for sleep-deprived individuals (1). Finally, the controversy of the effectiveness of caffeine in long-time and habituated users continues (13).

Important Considerations and Future Directions

An important area for study regarding approved and potential hypnotics and stimulants for military use is their ability to not only specifically maintain alertness, either by promoting wakefulness indirectly through adequate sleep (hypnotics) or directly maintaining wakefulness (stimulants), but also to sustain simple and complex cognitive performance. Critical to nighttime and continuous/sustained military operations is the ability of these pharmacologic agents to augment mental abilities that support both lower-order and higher-order cognition resulting in performance outcomes of optimal response accuracy and speed of information processing. Lower-order cognition includes mental functions associated with simple tasks such as attention, psychomotor vigilance (stimulus reaction time), and recognition. Higher-order cognition includes mainstream mental functions associated with complex tasks such as short-term or working memory, long-term memory storage and retrieval, and addition/subtraction. The highest-order abilities related to executive function comprise language/communication, planning, reasoning, situational awareness, judgment, and decision making.

In general, there is a lack of studies conducted to determine the effects of hypnotics on both sleep and subsequent next-day higher-order executive function cognitive performance to determine either the benefits of drug-induced obtained sleep or potential detrimental hang-over effects. Only relatively recently have tasks that go beyond the lower-order and mainstream higher-order cognitive functions been studied in paradigms involving nighttime and sleep deprivation conditions and stimulant countermeasures to determine efficacy or possible detrimental effects. These studies have specifically targeted performance on executive function-neuropsychological type tasks with a few in fully published reports; several of the results are in preliminary publications. Some studies report single drug evaluations (vs. placebo) while others have involved multidrug comparisons.

In single drug trials, one study (32) demonstrated the attenuating effects of modafinil on some executive functions (i.e., verbal fluency, flexibility, originality and verbal response inhibition) during a simulated nightshift paradigm. In a preliminary report of three consecutive nights without sleep (17), better performance was ob-

served with chronic administration of caffeine vs. placebo on a long-term strategic planning task. A study of total sleep deprivation (12) showed that caffeine ameliorated deficits in random number generation task performance, but only a simple aspect of it (i.e., decreased responses) and not more complex aspects (i.e., rule violations and increased stereotypy of responding or perseverance). Lastly, in a preliminary report of a novel cognitive enhancement agent, a high dose of the short half-lived ampakine CX717 administered at approximately 16 h awake was noted to improve attention and information processing shortly after administration and into the early morning, up to 4 h post-dose (4).

Examples of improved executive function during sleep loss in multidrug comparison trials are also becoming evident. One such study (34) found performance on a few tests of executive function to be improved, such as learning on the Wisconsin Card Sort Test with caffeine, modafinil, and dextroamphetamine, and on the Biber cognitive estimation task with caffeine and modafinil. However, over 2 d of sleep deprivation occurred before the drug was administered (at 64 h awake), indicating that the doses may not have been sufficient to restore other aspects of executive performance. Another study of total sleep deprivation (19), found the executive function of visual humor appreciation was enhanced with an acute dose of modafinil, and to some extent, with dextroamphetamine, but not with caffeine. In a preliminary report from this same study (16), significant improvements were again found for modafinil and dextroamphetamine, and not caffeine, on a test of working memory and immediate planning, while long-term strategic planning was unaffected. Another preliminary report from the study (14) noted that during sleep deprivation all three psychostimulants improved the ability to identify subtle emotional differences on a task consisting of complex emotional face perception. A preliminary account of a 42-h simulated military operation also reported performance maintenance with slow-release caffeine and modafinil administered at midnight (midway through the 18-h work period), on a dual task and a task of working memory and verbal interference suppression throughout the 18-h work period (2).

It is important to note that numerous studies thus far indicate that while stimulants are effective for attenuating decreases in alertness and simple task performance such as vigilance, there are limited data on executive function effects, with no one wake-promoting substance appearing as yet to ameliorate the variety of higher-order cognitive deficits resulting from inadequate sleep. This lends further support to the idea that pharmacologic compounds may need to be considered on the basis of the specific military group or mission scenario. Additional research is therefore required to understand the differential benefits of these agents—which ones perhaps provide the most executive function benefit—given in either acute larger doses or smaller chronic doses, during total sleep deprivation and sub-optimal chronic partial sleep deprivation situations. The evaluation of lower-dose drug cocktails where wake-promoting substances might be combined

to enhance more aspects of executive function relative to their potential interactions on safety and side effects remains to be investigated.

In addition, pharmacologic countermeasure studies should include measures of subjective mood and alertness, as well as post-study questions pertaining to drug experiences such as the ability to detect the drug physiologically, as these issues may affect operator (particularly pilot) confidence levels. This would be the case where one stimulant may be more suitable than another (depending on the mission and recovery sleep requirements), but the confidence level for the drug is low for purely subjective reasons. For example, if the trial use of the pharmaceuticals by the operator occurs in the rested state, where differential peripheral nervous system or mood effects may be more noticeable or pronounced, the implication is that the operator may experience less confidence in the drug that is less noticeably felt. Also, there may be other differential effects of the drugs in terms of subjective mood and energy levels. In a preliminary report of 61 h of total sleep deprivation (26), differential effects were found in subjective mood, with dextroamphetamine increasing ratings of energetic and happy; modafinil increasing ratings of energetic; and caffeine increasing ratings of energetic, but also ratings of afraid, confused, and tense.

Graduation from laboratory-based studies to platform simulator (e.g., 7,8) and simulation-based [e.g., Battlélabs as noted in the preface on Operational Processes and Cognitive Mapping (9)] studies followed by platform/operational exercise confirmation studies are also needed, such as the study by Caldwell and Caldwell (5) in the actual helicopter environment with dextroamphetamine, and a planned study with modafinil (Russo M. Personal communication; August 22, 2006). However, in actual platform and operational exercise studies, some components of executive function such as planning, communication, situational awareness, judgment, and decision making should also be incorporated and measured in addition to assessing the operator's ability to remain awake and run the equipment and/or interact with monitors and consoles. Other studies may also be needed that evaluate individual differences on simple and complex task performance in response to inadequate sleep and sleep loss, particularly where drugs may have differential effects as suggested by recent preliminary reports on stress management capacity, introversion-extroversion, and male-female sex differences in response to caffeine and/or dextroamphetamine during sleep deprivation (18,23,24). These types of studies would help improve our understanding of using sleepiness countermeasures at the individual level.

Section Papers

In this Pharmacological Strategy section, the papers presented address three areas of operational relevance: the first assesses the effectiveness of a treatment given for migraines, a condition with known detrimental effects on productivity and readiness; the second discusses ethical considerations surrounding the use of pharmaceutical countermeasures for fatigue in the op-

erational environment; and the third discusses a case report highlighting the aeromedical considerations regarding selective serotonin reuptake inhibitors (SSRIs) and aviator flight performance, particularly as assessed with neuropsychological testing. The following information will be covered in the papers presented in this section:

1. *"Botulinum Toxin Type-A in the Prevention of Migraine: A Double-Blind Controlled Trial."* In a clinical research study that addresses the detrimental effect that migraine headaches may have on productivity and troop readiness, Vo et al. (31) administered botulinum neurotoxin type-A (BTX-A) to volunteers with known occurrences of migraines. Although this study reported negative findings with BTX-A in the reduction of the frequency of migraine headaches, their additional findings suggest a potential protective effect of botox against the severity of this type of headache, a factor self-reported to be of the most importance as a quality of life issue. The authors discuss a very timely topic since this frequent medical complaint has recently surfaced in the popular press regarding the higher rate of migraines reported by soldiers in Iraq relative to the general population. This highlights the critical nature of such studies as Vo et al. have undertaken to help determine effective treatment paradigms for conditions that otherwise are debilitating to the individual, and are a potentially disqualifying factor for specific duties.

2. *"Recommendations for the Ethical Use of Pharmacologic Fatigue Countermeasures in the U.S. Military. An Engagement in the Battle Over the Use of Cognitive Enhancement Technologies in War."* Russo (30), in a thought-provoking position paper on bioethics, discusses the need for ethical considerations when deciding to employ the various pharmacological options. He proposes the term "cogniceuticals" for those agents used specifically to alter mentation in operational conditions, and provides guidelines for ethical consideration when the operational environment calls for fatigue countermeasures. Russo presents this discussion at a time when the use of psychoactive enhancements in the military is on the rise, while there is little in the way of doctrine being written to guide their use. Noting that military operations increasingly encompass multiple nations, this paper discusses the use of psychoactive pharmaceuticals within a coalition framework and includes a discussion of the circumstances that call for the use of psychoactive agents. Guidelines are provided as an attempt to aid leaders in making ethically acceptable decisions in the use of these agents. This guidance is presented as a compilation of four criteria, including the notion that the use of a given medication is: voluntary, safe, used for stated purposes, and that non-pharmacological alternatives have been exhausted.

In response to Russo's paper on bioethics (30), four invited commentaries from internationally respected physicians and scientists reflect alternative views:

a) Hilary F. Jaeger, M.D. (15), the Surgeon General, Canadian Forces, presents the first commentary. She notes that the Canadian Forces have not yet codified any guidance on this topic. Although Russo is congratulated for his efforts to discuss this topic while recog-

nizing national differences in policies, and for providing preliminary guidelines for the soldier in the field, Jaeger cautions that the reality of human decision making during the risks of combat may counterbalance the benefits of the "cogniceutical" agents. Overall, General Jaeger's commentary supports a conservative use of "cogniceuticals," perhaps with caffeine serving as a benchmark for acceptability and as the most ethical for use in the operational environment when needed.

b) Marten Meijer, Ph.D. (22), Commander, Royal Netherlands Navy, presents the second commentary. Dr. Meijer is the NATO Human Factors and Medicine Panel Executive and presents a human performance perspective on manned weapons systems as an alternative non-pharmacologic method of supporting cognition. Quality of life in manned weapons systems is discussed as it contributes to operational performance and is provided as a criterion for the ethical use of "cogniceuticals." Recommendations are made to enlarge the evidence base of the subjective and objective effects of "cogniceuticals" on military performance, especially as it relates to vigilance performance and decision making, and to estimate their effects on the performance of manned weapons systems as well as on the quality of life in manned weapon systems. This position emphasizes the need for optimal rest and recuperative conditions within the operational environment.

c) Jan Nybo Nielsen, Ph.D. (25), Major, Danish Armed Forces, presents the third commentary. The Danish military has only recently (i.e., within the past 15 yr) taken a position on the use of pharmacological measures to counter fatigue during military operations. Theirs is a conservative position consisting of a strict adherence to non-pharmacological measures; for example, practicing good sleep hygiene as part of proper mission planning. When deemed necessary by the operational environment or circumstances, caffeine tablets are the only pharmacological countermeasure used. Under Danish law, amphetamines have been approved only for the clinical use of treating narcolepsy and modafinil use is still under consideration.

d) Erich Roedig, M.D. (27), Surgeon General, German Air Force, presents the fourth and final commentary. The position of the German military is clearly stated that only caffeine may be used for sustainment in an operational environment and is used under the close supervision of medical officers. Similar to the Danish point of view, more emphasis is placed on non-pharmacological measures to counter the effects of fatigue.

3. *"Premenstrual Dysphoric Disorder: Treatment with Sertraline, Neuropsychological Effects, and Flight Status."* Kratz et al. (20), in a more traditional case study report, describe a classic example of disqualification of an individual for flight duty based on perceived cognitive impairment for a condition being treated by a psychoactive agent. Premenstrual Dysphoric Disorder (PMDD) is typically associated with affective symptoms that are commonly treated with selective serotonin reuptake inhibitors (SSRIs). Such a medication, sertraline, was the treatment given to the aviator diagnosed with this disorder in this present case report. Kratz et al. discuss the aeromedical issues associated

with PMDD, the specific treatment with the SSRI, and the aeromedical issues associated with those compounds, and neuropsychological testing in general (and in this case, with and without the administration of sertraline) as an assessment tool for determining cognitive functioning as it relates to flight status.

The papers and commentaries in this section encourage us to consider the complex variables affecting the decisions to administer pharmacological agents, as the impact of their use is weighed against the cognitive performance effects they may have in the operational environment.

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