(8)

SMART PILL CHAPTER

I. Human intellectual function covers a very broad scope of different activities. This chapter's discussion will be limited to reaction time, concentration and vigilance, and overall intellectual function.

II. Important degradation factors are those which are dealt with in other chapters: sleep loss, physical fatigue, and fear. Drugs which combat the deficits of these factors are discussed elsewhere, so this chapter will look particularly at time on task and infomation overload as degradation factors. Note that these factors interact strongly with sleep loss, physical fatigue, and fear.

III. CONCENTRATION/VIGILANCE

a. AMPHETAMINE AND OTHER STIMULANTS: Demonstrated to improve vigilance/concentration in normals under baseline and degradation conditions. Tradeoff is perseveration, fixation, stereotypy.

Note relevance of other problems as listed in introduction.

b. Other drugs

IV. OVERALL INTELLECTUAL FUNCTION

a. Is this meaningful/realistic?

b. NOOTROPICS:

c. Drugs which increase cerebral blood flow/energy metabolism:

TRH, hydergine, etc.

c. HERBALS: Ginseng/Eleutherococcus

V. REACTION TIME

a. note simple vs. complex trade off as in atropine

b. note false alarm trade off

c. drugs:

RESEARCH PROTOCOL

PROJECT TITLE

Pharmacologic Optimization of Alertness in Continuous and Sustained Operations (Phase I)

IDENTIFYING WORDS

Continuous operations, pharmacologic adjuncts, sleep, alertness, cognitive performance

PRINCIPAL INVESTIGATOR

Paul A. Newhouse, M.D., MAJ, MC, Research Psychiatrist
Continuous Operations Research Branch, Dept. of Behavioral Biology, WRAIR

CO-PRINCIPAL INVESTIGATORS

Stephen C. Vance, M.D., MAJ, MC
Gregory L. Belenky, M.D., COL, MC

ASSOCIATE INVESTIGATORS

Maria L. Thomas, M.A.
David R. Thorne, Ph.D
Helen C. Sing, M.S.

LOCATION OF STUDY

Department of Behavioral Biology, WRAIR
Forest Glen, Bldg. 189

ESTIMATED DURATION OF STUDY

2 years (December 1986 through December 1988)

NUMBER AND KIND OF SUBJECTS NEEDED

	Number	Sex	Age Range
Normal Volunteers:	160	M/F	21-65

OTHER REQUIREMENTS

All subjects selected for this study will be screened for significant cardiovascular, autonomic, renal, hepatic, endocrine, or psychiatric disease and will be excluded if the dysfunction is significant. Pregnant females will be excluded. Informed consent will be obtained from each subject following a verbal explanation which will be given in terms suited to each subject (Appendix H). The rights of all subjects to withdraw from the study or refuse any individual procedure will be respected.

PRECIS

To evaluate the role that pharmacologic adjuncts may have in improving the performance of the soldier in continuous and sustained operations, we propose to screen and test the effects of selected groups of candidate drugs on tests of alertness and performance. Following initial selection procedures, promising compounds will be examined with more detailed laboratory testing of their cognitive, performance, and alerting effects, with the goal of moving to actual field trials of candidate agents. The goal of these studies is not simply to identify promising drugs but to examine in a more sophisticated way the variables that may affect drug responses, such as dose, pharmacokinetics, absorption, route and time of administration in relation to task, as well as a number of intrinsic human variables that may affect responses such as preexisting emotional conditions, level of fatigue and stress, etc. By examining candidate compounds in this manner, we will be able to assess the feasibility and potential of pharmacologic adjuncts to sustain performance and provide precise direction to later field trials of candidate agents identified from this study. Further, this study will expand on knowledge of the cognitive and behavioral effects of these drugs.

GENERAL INTRODUCTION TO THE PROJECT

Technological developments in the second half of the 20th century now permit combat operations to be conducted in a far different manner than heretofore possible. Dramatic improvements in mobility allow rapid deployment and movement of forces across great distances with greatly increased speed. Sophisticated fighting vehicles and weaponry allow operations to continue in spite of inclement weather. Technological advances also now permit essentially around-the-clock combat without need to cease operations due to nightfall. Doctrinal changes have followed technological advances and current military thinking on both sides expects major conflicts to be conducted in a continuous manner with no pauses. The lethality and potentialities of modern weaponry and transport mandate that the battle be conducted on this basis to maximize the effectiveness of these technological advances.

The modern integrated battlefield will place unprecedented pressure and stress on the soldier. He will be asked to perform increasingly complex and demanding tasks in an environment that could not be more ill suited for the performance of these tasks. The technological sophistication of modern weaponry can be its "Achilles' Heel." Without a competent, alert soldier to evaluate, make decisions, and operate complex weaponry, the weapons may well become ineffective, or still worse, dangerous to friendly troops. Although the ability of machines to function continuously has been repeatedly assessed and improved, little attention has been paid to the operator of that machinery. The nature of the modern battlefield will tend to rapidly degrade the performance of every soldier.

Command and control may suffer most of all. It has been shown (1) that continuous operations degrade evaluation and decision making more rapidly and severely than overtrained, more reflexive task performance. Appropriate coordination, communication, command, and control are more important than weaponry in deciding the outcome of battle, and it is these that will be degraded first by continuous and sustained operations.

Advancements in weaponry, transport, and communication have not been matched by advances in the abilities of men to function in the environment that these advancements create. The problem of how humans are to conduct a continuous war has not been solved. The first and most logical place to look for progress has been in doctrine, and this has been done by sleep studies, performance assessments, etc. These have led to recommendations for sleep discipline, hierarchies of rest within units, and training recommendations. These, while necessary, may not be sufficient, especially during actual combat operations when these recommendations may be difficult to implement. Gaining critical improvements in sustained performance may require other approaches.

Short of permanent biological alteration of the human's need for sleep and rest, temporary modification of these needs appears to be the most practical approach. Modification of apparently fixed biological systems or requirements is not unprecedented in medicine. The development of effective analgesia and anesthesia is an example of temporary system-wide blockade. Metabolic modifications for short-term periods of decreased food and/or water intake demonstrate a limited but real flexibility on the part of the organism to respond to environmental change. There is no inherent reason to believe that the neuraxis is completely unable to modify some of its requirements, especially with adjunctive assistance. Several neuro- or psychopathological conditions demonstrate the range of neuraxis function and its modifications. In the disorder of narcolepsy, the individual's system for promoting wakefulness and alertness is impaired with consequent hypersomnolence. Drugs that increase central catecholamine functioning improve this disorder (2,3). In mania, a different dysregulation appears to dramatically decrease the need for sleep; such individuals may sleep little, if at all. Drugs that decrease central catecholamine functioning can successfully control these symptoms (4,5). It is clear that there can be wide variability in the need for sleep, and that the ability of the human to remain awake is subject to neurochemical and neuropharmacological modification. Pharmacologic intervention would seem the most promising approach to neurochemical modification of the need for sleep and perhaps of the performance decrements that accompany fatigue and long-term wakefulness.

Possible beneficial effects from pharmacologic interventions in the fatigued individual may include:

a. extended wakefulness
b. sustained alertness
c. sustained performance of complex tasks
d. decreased sleep requirement
e. increased self confidence
f. restoration of motivation, initiative, and decision making capabilities
g. improved vigilance and frequency monitoring
h. better filtering of distracting stimuli and improved focusing of attention
i. maintenance of speed and efficiency
j. decreased anxiety
k. improved mood and/or affect
l. improved physical endurance.

It must be recognized that the effects of any drug on cognitive and behavioral functioning are state dependent, and to some extent, trait dependent. For example, the effects of stimulant or sedative drugs are intimately tied to the arousal state of the individual, and what may improve performance under one arousal state may not improve and may even impair performance under another state. In animal and human studies, compounds that improve learning and/or performance do so most consistently in those individuals whose baseline performance is poor. This finding provides direction for the appropriate place for pharmacologic intervention. It is unlikely that pharmacologic interventions can improve baseline performance in normal humans, especially under ideal conditions. There are no candidate agents that realistically offer this possibility. However, there is the real possibility, based on prior studies, that drugs may offer a way to temporarily compensate for deteriorations in performance secondary to fatigue and maintain performance at or near baseline levels for longer periods of time.

Several research studies have been conducted in both the field and laboratory to assess the effects of stimulants as analeptics (restorative agents) in counteracting physical and mental performance decrements and mood deterioration resulting from sleep deprivation. In three field studies, subjects were required to perform various military exercises during partial sleep deprivation conditions. Sleep deprived soldiers treated with 30 or 35 mg amphetamine sulfate (benzedrine) did not significantly improve their times taken to negotiate an obstacle course compared with soldiers treated with placebo, and no significant effect was found for the number of staff problems solved by officers after administration of 40 mg benzedrine compared to officers given placebo. Also, benzedrine was not reported to prevent sleep 48 hours later, nor were there any significant side effects reported (6). However, in another study (7), 7.5 gr caffeine had desirable subjective effects but negligible improvements in sensorimotor coordination; 5 mg desoxyephedrine had insignificant subjective improvements, but significant improvements on sensorimotor measurements; and 10 mg benzedrine had subjective effects equal to those of caffeine and sensorimotor improvements nearly as great as those with deoxyephedrine. In a third study (8), 10-15 mg benzedrine in fatigued subjects compared to placebo severely disturbed the first night of sleep of men performing road marches; however, the drug group reported feeling less fatigue and reported less discomfort compared to those receiving placebo. 15 mg methedrine caused no significant improvement in the total time taken for men to cover a road course. The placebo group, however, complained of more severe fatigue than the methedrine group, and more men dropped out of the march in the placebo group than in the methedrine group. No rebound effects (i.e., sleep disturbances or fatigue) were apparent after drug discontinuation for either compound. Based on these studies, it appears that amphetamine, methedrine, and caffeine have some restorative effects on mood, sensorimotor coordination, and endurance.

There have been some studies in the laboratory on the effects of amphetamine and other stimulants as potential analeptic drugs. The majority have found significant analeptic effects of amphetamine and some other related CNS stimulants on performance and mood during sleep deprivation conditions of up to 72 hours. For instance, after 36 hours of sleep deprivation, there occurred a decrement in sustained performance of a skilled task, which was reduced after administration of 10 mg amphetamine (9). In a 72 hour total sleep deprivation study (10), those measures of performance which were least affected by sleep loss returned to the non-sleep loss level after 15 mg d-amphetamine, while those measures most effected by sleep loss were still far from the non-sleep loss level after drug. Another study in which 10 mg d-amphetamine was given to men deprived of sleep for 24 hours performing a continuous arithmetic task (11) showed that after drug, the d-amphetamine group performed significantly better on the continuous task than the placebo group, and also reported being mentally alert, confident, and having an increased ability to concentrate. In

addition to 15 mg d-amphetamine, two related stimulants--20 mg methylphenidate and 100 mg magnesium pemoline--significantly increased the number of correct responses in a continuous arithmetic task after sleep deprivation when compared to placebo, and d-amphetamine produced significantly greater performance effects than methylphenidate but was not significantly different from magnesium pemoline (12). d-Amphetamine (20 mg) was compared to 20 and 40 mg prolintane, an amphetamine derivative, after 24 hours sleep deprivation (13). d-Amphetamine significantly decreased sleepiness and drowsiness and increased friendliness, energy, nervousness, and night-time insomnia. A more recent assessment of amphetamine as an analeptic (14) found that subjects performed significantly better on a vigilance task when given 10 mg d-amphetamine after 24 hours sleep deprivation than in their pre-tests. d-Amphetamine reversed the effects of sleep deprivation on EEG alpha band activity and beta 2 band activity but did not reverse the effects of sleep deprivation on perceived decreased vigor and increased fatigue.

While these studies have examined a few related stimulants in various sleep deprivation paradigms, there exist several inherent design flaws in most of these experiments, making some of their results contradictory and difficult to relate to modern concepts of sustained operations. Because of these problems, it is impossible to determine from previous sleep deprivation studies whether the significant effects of amphetamine and other stimulants that have been claimed are genuine (i.e. to what extent they may aid in restoring normal alertness and performance). Many critical variables were not controlled, leading to contradictory results. Several experiments used only one dose of drug so that dose response curves could not be established for the stimulant under investigation. Often, appropriate controls were not implemented in the sleep deprivation/drug design--most studies did not use a within subjects and/or repeated measures design, and some did not counterbalance the experimental conditions. All of the field studies allowed some amount of sleep; and may have administered the stimulants too late to counteract fatigue. Some studies have failed to take pre-sleep deprivation baseline measures, and one study failed to use a placebo control. Further, each study used different performance measures, making cross comparisons difficult. Finally, no studies utilized objective measures of alertness, (e.g., multiple sleep latency test) to determine whether a particular stimulant was able to restore normal alertness after sleep deprivation. In addition to these design flaws, there is a critical lack of comparisons among classes of stimulants, such as amphetamines, MAO inhibitors, cholinergic agonists, dopamine precursors, and neuroactive peptides (e.g., TRH).

CANDIDATE AGENTS

Pharmacologic modification of military performance dates back at least to World War II when Soviet troops, particularly pilots, used amphetamines extensively. Reported benefits include decreased fatigue and drowsiness, and improved memory and concentration (15). Amphetamines were also used in Vietnam by US troops particularly for long range reconnaissance patrols to combat fatigue on the return journey (16).

However, central nervous system (CNS) stimulants of a variety of types should be considered, along with other compounds that affect cognition and performance, since these drugs influence different neurotransmitter systems thought to be involved in the control and maintenance of alertness (17). These stimulants are outlined in Table 1, and their respective groups will be considered in turn.

TABLE 1. CANDIDATE PERFORMANCE-ENHANCING COMPOUNDS

1. Amphetamine Derivatives
   - d-amphetamine
   - methamphetamine
   - diethylpropion
   - mazindol
   - phentermine
   - benzphetamine
   - phenmetrazine
   - phendimetrazine
   - phenylpropanolamine

2. Other Stimulants
   - methylphenidate
   - magnesium pemoline
   - caffeine, theophylline
   - pentylenetetrazol*

3. Catecholamine Agonists
   - bromocriptine
   - L-dopa
   - amantadine

4. MAO Inhibitors
   - tranylcypromine
   - deprenyl*

5. Cholinergic Agonists
   - nicotine
   - arecholine*

6. Nootropics
   - piracetam*

7. Metabolic "Enhancers"
   - dihydroergotoxine mesylate
   - cyclandelate

8. Neuropeptides
   - thyrotropin releasing hormone (TRH) and analogs (MK-771)*
   - vasopressin analogs (DDAVP, LVP)*

*Investigational use only.

Amphetamine and Related Compounds

These compounds are potent sympathomimetic amines with prominent CNS stimulating effects in comparison to their peripheral effects. Central effects are thought to be due to stimulation at the reticular activating system as well as direct cortical stimulation (18). These compounds directly release catecholamines from nerve terminals and may have direct agonist effects as well (19,20).

In man the effects of an oral dose of 10 to 30 mg of d-amphetamine are: wakefulness, alertness, decreased sense of fatigue, and elevation of mood, with increased initiative and self confidence. Ability to concentrate is enhanced. Physical endurance is improved (21). In general, the duration of adequate performance before fatigue appears is lengthened and the active effects of fatigue are mitigated (21,22), especially those due to lack of sleep (14,23). Amphetamines also appear to reduce the frequency of attention lapses, and improve the execution of tasks that require sustained attention (22,24).

Amphetamines are not without possible side effects, however, and these can include headaches, palpitations, dizziness, vasomotor disturbances, dysphoria, agitation, confusion, and sometimes disturbances in judgement (22,25). Amphetamines are used clinically for excess sleepiness in narcolepsy, in hyperkinetic children, in some cases of refractory depression, and as anorectic agents (25).

Other Stimulants

Methylphenidate and magnesium pemoline are chemically dissimilar from but functionally similar to amphetamine derivatives (26,27). They act as CNS stimulants without significant peripheral effects. They share many of the same benefits and liabilities as amphetamine. Pemoline has a particularly long half life compared to other stimulants (27). They are both used clinically in attention deficit disorders and appear to improve concentration, accuracy, and focusing of attention (27).

Caffeine is probably the most widely used drug in the western world. The popularity of caffeine-containing beverages is probably due to this compound. Such beverages have been known since ancient times to stimulate and elevate mood as well as to increase the capacity for work (21,28).

Caffeine and theophylline (methylxanthines) are both potent CNS stimulants. Persons ingesting 85-250 mg of caffeine have been reported to experience less drowsiness and fatigue, more rapid and clear flow of thought, and to show increased capacity for sustained intellectual effort. Decreases in reaction time are also seen, although coordination and timing may be impaired (21). At higher doses, methylxanthines produce nervousness, insomnia, tremors, hypertension, and other signs of CNS over-stimulation (29). It should be noted that methylxanthines, including caffeine, have potent peripheral effects including effects on the cardiovascular, bronchial, and urinary systems. Methylxanthines are used clinically for asthma and other pulmonary conditions, and as adjuncts in analgesics and over-the-counter stimulants (29). Caffeine has also been studied experimentally as a model of anxiety in individuals with panic disorders (T. Uhde, personal communication).

Pentylenetetrazol is a nonspecific neural stimulant that has been used to study the actions of anticonvulsants. It may block the inhibitory action of the neurotransmitter GABA in the CNS, thereby increasing excitability (27). It has received trials in regressed geriatric patients with equivocal results (27). It is intriguing because theoretically it may antagonize the sedative effects of benzodiazepines (27).

Catecholamine Agonists

These compounds are either direct or indirect catecholamine agonists which act by directly stimulating catecholamine receptors or by providing catecholamine precursors. L-Dopa is the chemical precursor of dopamine and norepinephrine. When administered with a peripheral decarboxylase inhibitor, it elevates central catecholamines levels and can provide stimulant-like effects (30,31). This result is used clinically to treat the coma of hepatic encephalopathy (which may be a transmitter deficient state). L-Dopa is used primarily in the treatment of Parkinson's disease. Bromocriptine is a direct acting dopamine receptor (D_2) agonist and has also been used in the treatment of hepatic encephalopathy (30,31) and Parkinson's disease. Amantidine, an antiviral agent, appears to stimulate catecholaminergic systems by releasing dopamine (31). It is also reported to have stimulant-like effects and is used clinically in pseudo-parkinsonism as well as Parkinson's disease (31).

MAO Inhibitors

This class of compounds prevents the breakdown of catecholamines by inhibiting the enzyme monoamine oxidase (32). They are used clinically as antidepressants and as an adjunct in the management of Parkinson's disease. Chemically, several of the MAO inhibitors are closely related to amphetamine and have direct stimulant effects of their own. Stimulant effects are seen frequently early in the administration of the nonselective MAO inhibitor tranylcypromine and the MAO-B selective inhibitor deprenyl. Deprenyl has been studied as a possible adjunct in the management of Alzheimer's disease (33) and Parkinson's disease (34) and appears to produce improvement in mood, daily functioning, and some aspects of cognition. It may also potentiate the effect of L-dopa. MAO inhibitors also depress REM sleep and have stimulant-like effects on the EEG (24).

It is notable that most of the drugs mentioned thus far have actions relating to the central catecholaminergic (particularly the dopaminergic) system. They either release, conserve, and replenish catecholamines or directly imitate their actions. It is clear, therefore, that maintenance of alertness and awakeness is mediated at least partially through this system. Whether this system controls cognitive performance as well, however, is less clear.

Cholinergic Agonists

Central cholinergic systems have been widely investigated as mediators of mood, memory, and consciousness (35). Cholinergic drugs are used worldwide as stimulants in the form of tobacco (nicotine) and betel nuts (arecholine). Cholinergic agonists can act to desynchronize and activate the EEG (35), and wake up a sleeping animal. The effects are complex, however, and may be biphasic, leading to sedation with continued administration, which may be a result of the tachyphylaxis that is seen with these compounds.

Nicotine is the presumed active ingredient in tobacco and has a complex peripheral and central pharmacology, stimulating nicotinic-type cholinergic receptors, which have an extensive distribution in the brain (36). In both animal and human studies, nicotine has been shown to improve task acquisition and memory consolidation (37), especially in individuals with poor baseline performance. Nicotine has been shown to increase arousal and attention and as well as to decrease reaction time and prevent time-related performance decrements (37).

Arecholine, although mostly a muscarinic cholinergic agonist, seems to produce at least some of the same effects as nicotine, suggesting some redundancy in central cholinergic systems. Arecholine has been shown to block some cognition-impairing effects of scopolamine in humans (38) and to provide brief cognitive improvement in Alzheimer's disease (39).

The dose-response curves of cholinergic agonists appears to be steep, and overdosage can impair arousal and cognition. The methodology for optimal use of these compounds remains to be fully worked out. Nicotine and arecholine are both under study experimentally as treatments for Alzheimer's disease. The principal investigator (PI) has been conducting extensive trials of intravenous nicotine in normal volunteers and Alzheimer's disease patients in an attempt to assess its utility and establish the precise neurobiologic effects as well as optimal usage patterns (40).

Nootropics

Nootropics are a new class of psychotropic agents developed in the search for gamma amino butyric acid (GABA) analogs. While the first compound, piracetam, failed to have GABA activity, it did appear to affect mentation and consciousness. Piracetam, the representative compound of this group, has been extensively studied in humans and may have cognition enhancing effects (41). It appears to improve consciousness in surgical patients, stimulate memory in some impaired subjects, and perhaps in normal humans as well. The effects are subtle, however, and remain controversial. The pharmacologic basis for these effects are unknown, but may be related to increased metabolic rates and perhaps increased precursor uptake (41). These drugs may be useful themselves, or in combination with other compounds to combat the effects of fatigue.

Neuropeptides

Various peptide chains have been identified as neuromodulators and neurotransmitters, including opiate peptides, substance P, thyrotropin releasing hormone (TRH), and others. Several neuropeptides appear to have direct effects on levels of consciousness and overall emotional state. TRH, a tripeptide, in particular may have activating properties in high doses (42) as well as possibly being euphorigenic (A. Mellow, personal communication). Various forms of arginine vasopressin have been shown to prevent experimentally-induced memory deficits in animals (43) and have been studied in humans with memory impairments as well (44). Although results have been somewhat equivocal in the few human studies that have been done, these compounds have not been examined under conditions of artificially-induced cognitive impairment (i.e. sleep deprivation) in humans. Their peripheral and side effect profiles appear modest, and they may be useful adjuncts either by themselves or in combination with other agents.

In summary, we propose to screen and test a number of candidate compounds for their effects on alertness, cognitive variables, mood, and attention after 48 hours of sleep deprivation with the goal of identifying promising compounds for further development as adjuncts to continuous operations. Later studies will be directed at defining field use parameters for such compounds. It is possible that no single compound will emerge as an ideal candidate and that combinations may be required. What will be unique about this study is the attempt to cross compare a number of candidate agents using a reliable and replicable methodology with direct relevance to continuous operations under controlled conditions. Issues of experimental design and analysis will be resolved so that meaningful conclusions can be drawn about the suitability of various agents for further investigations. We also hope to gain knowledge about the appropriate ways to use these compounds to maximize beneficial effects and minimize unwanted side effects. We also believe that we will be able to gain information about the relative

contribution of a number of central neuronal systems to the variables mentioned above.

We propose to study initially the following drugs (singly) from the previously mentioned classes:

Amphetamine Derivatives:	d-amphetamine
Other Stimulants:	methylphenidate
Cholinergic Agonists:	nicotine
MAO Inhibitors	l-deprenyl, tranylcypromine

Other members of the aforementioned classes, combinations of drugs, and other candidate agents will be submitted for approval as amendments following study of these drugs and initial evaluation of the experimental methodology.

METHODOLOGY

General Discussion

We propose to divide the study into two phases. Phase I will involve screening of candidate compounds using the Multiple Sleep Latency Test (MSLT) (Appendix A) (45), actigraphy, several tests of continuous cognitive performance, and mood and emotional assessments. Agents will be evaluated on the basis of their ability to normalize sleep latency and cognitive parameters without significant changes in the subjective or objective emotional state of the individual after 48 hours of sleep deprivation. A data base will be developed to compare large numbers of compounds on similar measures to increase the validity and reliability of conclusions made about the drugs' possible utility in a military environment. A primary purpose of Phase I is to quickly eliminate unlikely candidates prior to the more extensive commitment and investments of Phase II. A secondary purpose of Phase I to test and refine the methodologies to be used in Phase II.

Phase II of the study will involve taking those compounds that meet the above criteria in Phase I and studying them more comprehensively, with the aim of further defining the cognitive effects, more precisely assessing dose-response effects, pharmacokinetic variables, and methods of administration. The goal in this phase is to further narrow the possible candidate drugs and define how they may be optimally used in a laboratory setting. This will pave the way for actual field studies. Field studies will be more meaningful once many of these important variables are defined. Phase II will be detailed in a separate protocol and will not be further described here.

The exact details of drug administration for Phase I will, of necessity, be somewhat different for each drug. These will be specified below for Phase I trials. In general, the study will use matched groups of subjects for each drug. Each drug will be administered as three doses and control (placebo). Subjects will be assigned into groups so as to balance the design in terms of age, weight, and education level. Sex will be addressed by initially excluding females and later including them as a separate group to be tested with promising compounds. Order of drug administration to each group will be randomized and balanced to eliminate order effects, and the investigators will be blind to the order. Although a within subjects design is theoretically preferable, for efficiency reasons, we feel that it is not practical in a study of this length. With the design we are proposing, dosage becomes a grouping variable rather than a within variable. With properly balanced groups, this should not present analysis problems. Further, previous

work has suggested that the variance on the MSLT of sleep deprived individuals is quite low (46), suggesting that intersubject variability may not be great. Activity and/or sleep as measured by the actigraph prior to the study may be used as a covariate in controlling other confounding baseline variables.

Subject Selection and Evaluation

Initial studies will be conducted in males only, so as to reduce the necessary subject number for initial screening studies and control one source of experimental variability. Later studies will include females as a separate group to examine whether sex differences exist in the response to stimulant drugs.

Diagnostic information will be obtained by a clinical interview and physical exam prior to inclusion in the study. Careful family histories will also be obtained. Subjects with major illnesses will be excluded on the basis of history and laboratory tests assessing psychiatric, hematopoietic, renal, hepatic, and hormonal function. Subjects will also be screened for hepatitis B and exposure to HTLV-III with appropriate blood tests. Pregnancy testing will be performed on all premenopausal females. Females of childbearing age will be cautioned against sexual relations prior to and immediately after the study. Subjects will be screened briefly with standard psychometric tests to establish appropriateness for cognitive testing experiments. All subjects with known sensitivities to or medical contraindications to the use of the specified drugs will be excluded. Criteria for exclusion include significant cardiovascular disease, psychiatric disease, asthma, active peptic ulcer, hyperthyroidism, pyloric stenosis, narrow angle glaucoma, severe prostate hypertrophy, epilepsy, other serious neurologic illness, and pregnancy. All subjects will be drug free prior to beginning the study. Concurrent use of some noncentrally active medications (i.e., diuretics or antibiotics) may be allowed only after careful review by the investigators. Consideration will be given to the effects these medications would have on either subject evaluation procedures or risks of drug interaction during the study. Generally, smokers and heavy coffee drinkers will be excluded from this study.

To assess the level and activity of each individual prior to the study, each subject will wear an actigraph device for 72 hours prior to the beginning of the study. The actigraph is a wristwatch-sized activity monitor which records arm movements and has been shown to be a highly reliable measure of overall activity level (47).

Consent and Preparation

Each subject will receive an oral and written explanation of the purposes, procedures, and potential hazards of this study. A record of the communication of this information and the subject's informed consents will be entered into the subject's medical records.

Source of Subjects

Subjects will be recruited through advertisements in local papers and post publications.

Subject Identification

Subject names and social security numbers will be used on patient files kept by the PI. Subjects will be assigned a subject sequence number (1 - 160) which will be used for data analysis and/or publications.

PROCEDURES

PHASE I - Sleep Latency and Cognitive Performance

A diagram of the procedures is shown in Figure 1. Subjects will be brought into the laboratory at 0800 on day 1, after an overnight fast. Subjects will then give a urine sample and baseline physiologic measurements (height, weight, blood pressure/pulse, temperature). The subjects will then be given an actigraph device to wear on the nondominant wrist as above. This will be worn throughout the study to provide additional measures of motor activity under the various experimental conditions. Breakfast will then be provided. The subjects will then be involved in a number of psychological assessments such as the MMPI, designed to measure general personality variables. They will then be occupied with training and pretesting on the cognitive procedures to be used on day 3. This will be done to assure that performance reaches criterion levels prior to the sleep deprivation phase. The subjects will also undergo three initial sleep latency tests (SLTs) at 2-hour intervals on the morning of both day 1 and day 2, as described below, to establish a baseline mean. The subjects will then be allowed to read, watch TV, or converse as desired. Every two hours throughout the first 48 hours, the subjects will be asked to complete a cognitive work battery on a computer, lasting approximately 30 minutes. Meals will be served at 0800, 1200, and 1800 hours. Subjects will be asked to remain awake throughout the first 48 hours of the study (except for SLTs) and will remain in the large experimental chambers of the Continuous Operations Research Branch.

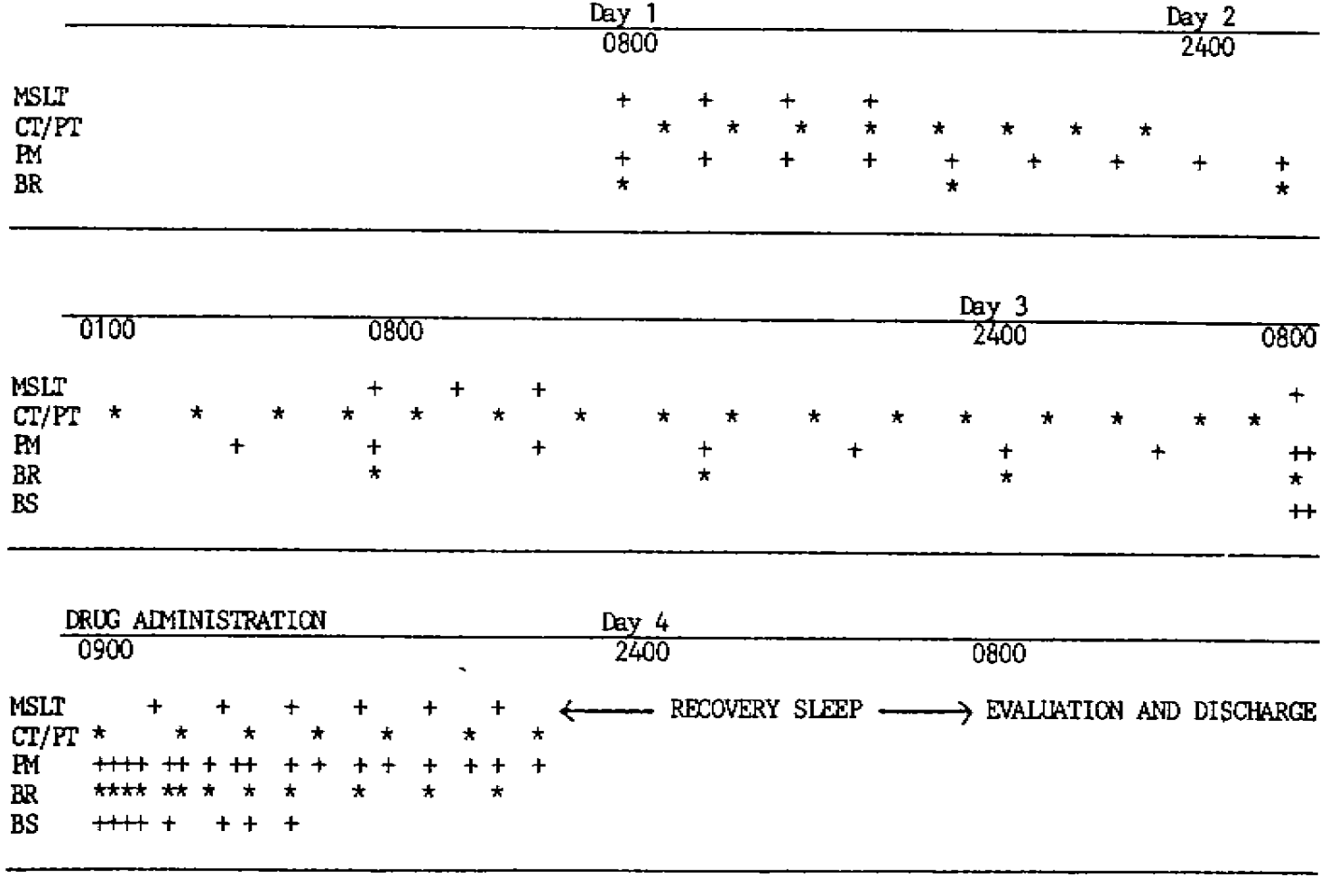
Periodic self and observer ratings of mood, arousal state, and physical effects will be made throughout days 1 and 2 of the study. Measures will include both objective and subjective rating scales. Objective measures will include the NIMH Self Rating Scale and the Brief Psychiatric Rating Scale (BPRS). Subjective measures may include the Profile of Mood States (POMS), the Stanford Sleepiness Scale, Thayer's Activation/Deactivation Check List (automated), and visual analog scales developed for this protocol (Appendix B). Measures of blood pressure, pulse, body temperature, and respirations will be made at regular intervals throughout the study. The subjects will be assisted in remaining awake throughout the first night by regular observation and interaction with a technician and/or an investigator. If a subject does fall asleep, he will be gently awakened. Appropriate diversions will be made available for the subjects.

Beginning at 0800 on day 3, regular measurements of latency to sleep will be made. This measure will be made by using the technique of the MSLT (Appendix 1). The subject will be placed in a darkened room, instructed to lie down, and encouraged to sleep. Continuous EEG will be recorded by standard procedures. The time from the beginning of the test until the appearance of stage 1 sleep criteria on EEG is the sleep latency measure. The maximum length of any one test will be 30 minutes. The amount of sleep will be limited to the first minute of stage 1 so that subjects will not accumulate significant amounts of sleep during the procedure. The procedure will be repeated at intervals of 2 hours throughout day 3 until 2100 hours.

Beginning after the initial MSLT on day 3 and also repeated at 2-hour intervals throughout the day, the subjects will be asked to perform a short performance assessment battery. These tests are designed to be sensitive to fatigue degradation and

FIGURE I STUDY PROTOCOL

Measures: MSLT = Multiple Sleep Latency Test
CT/PT = Cognitive or Performance Test
PM = Physiologic Monitoring
BR = Behavioral Ratings
BS = Blood Sampling



include items from the Walter Reed Automated Performance Assessment Battery (PAB) (Appendix C). The tests include measures of sustained performance, short term memory, concentration, and vigilance.

An intravenous catheter (angiocath) will be inserted into a forearm vein at 0800 and kept patent with a heparin lock using heparin sodium, 20 units/cc. Blood samples will be drawn perodically up to 300 minutes after drug administration for drug levels, plasma catecholamines, and hormones.

Drug administration will take place immediately after the first MSLT and initial PAB assessment have been obtained on day 3 (see below). The route of administration will generally be oral using tablet or elixir, occasionally intravenous or percutaneous depending on the drug (see below). Physiologic measures (BP, pulse, body temperature) will be taken at regular intervals before, during, and after drug administration. EKG may be monitored by telemetry if indicated. The MSLT and PAB will continue to be administered at 2-hour intervals for 12 hours after drug administration to measure changes brought about by total sleep deprivation and the effects of drug administration. Periodic assessments of mood, arousal state, and side effects will continue to be made. Testing will be terminated at 2100 hours of day 3, and the subjects will be allowed to sleep ad lib until the next morning (day 4). All subjects will be clinically evaluated by an investigator to ensure against significant residual effects from the study prior to their leaving the laboratory.

Severe changes in behavior, excess elevations in blood pressure, EKG changes, and/or unusual changes in the level of consciousness will be treated as clinically indicated, and the study may be terminated for that subject (see "Hazards and Precautions", page 16). Blood sampling will be limited to a maximum of 450 cc during any six-week period. Blood that is drawn will be centrifuged, separated, and the plasma stored at -20^{0}C in the Department of Behavioral Biology freezers prior to assay. Urine samples will be similarly stored for later assay for drugs.

Drug Administration

d-Amphetamine

Dextroamphetamine will be given in doses between 2.5 and 25 mg of a 1 mg/ml oral solution. The minimal stimulant dose is considered to be 2.5-5.0 mg (25). 25 to 30 mg is generally considered to be a highly stimulant dose in most individuals and is in the dosage range required for some cases of adult hyperkinesis and narcolepsy (18).

Methylphenidate

Methylphenidate is available as 5 and 10 mg tablets and will be administered in doses of 10 mg to 30 mg orally. The usual adult dose for methylphenidate is 30-60 mg per day (26). At these doses, peripheral effects should be minimal.

Nicotine

Nicotine will be administered as an intravenous infusion of nicotine bitartrate of 15 or 30 μg/cc made up from a stock solution of 1 mg nicotine base per cc diluted in normal saline. Doses will range from 0.125 to 0.75 μg/kg/min for up to 30 minutes. Extensive experience by the PI with studies of intravenous nicotine in nonsmoking normal volunteers and elderly patients has shown that such doses are safe and well tolerated (NIH Protocol 84-M-247, IND 25,517) (40). Nicotine may also be administered as nicotine gum, which is available as 1 mg nicotine base per piece. This results in much slower

absorption characteristics than is seen with intravenous administration (48). Dosage would be 1-2 mg gum/session.

l-Deprenyl

l-Deprenyl is available as 5 mg oral capsules and will be administered in a single dose from 5 mg to 30 mg orally. The usual adult dose of l-deprenyl is between 10 and 100 mg per day. In our experience with l-deprenyl, we have behavioral evidence of activation in this dosage range (33).

Tranylcypromine

Tranylcypromine is available in 5 and 10 mg capsules and will be administered in a single dose from 5 to 30 mg orally. The usual adult dose of tranylcypromine is between 20 and 80 mg per day (49).

Source of Medications and Placebos

All standard medications and placebos will be obtained through the WRAMC Pharmacy Service. Investigational medications will be obtained directly from the manufacturer (l-deprenyl, nicotine). Compounds that are not directly formulated for human use will be so prepared in accordance with standard procedures and FDA requirements for the IND. This will be performed through the Experimental Therapeutics Branch, WRAIR, The National Institute of Health Pharmaceutical Development Service, or through a private laboratory.

Medications will be stored in secured storage containers designed for drug storage in the Department of Behavioral Biology.

Summary of Anticipated Procedures - Phase I

48 Hours of sleep deprivation followed by sleep latency and cognitive testing. Drug administration (double blind, placebo controlled) followed by repeated MSLTs and cognitive testings over 12 hours. Regular monitoring of mood, side effects, physiological parameters. Blood drawn at intervals for hormones and drug levels. Study terminated at 2100 hours on day 3, subject allowed to sleep until 0800, day 4. Estimated blood loss 100 cc per session.

DATA ANALYSIS

Data analysis for MSLT, cognitive performance, physiologic, behavioral, and hormonal measures will be accomplished using a two-way repeated measures analysis of variance (ANOVA). Dosages of drug will be used as grouping variables and time as a within subjects variable. Post hoc comparisons will be accomplished through standard techniques, e.g., Tukey's HSD or Dunnett's test. Baseline measures between groups will be analyzed by a one-way ANOVA. If hormonal data is not normally distributed, appropriate transformations (i.e., log, square root, etc.) will be made before submitting the data to ANOVA. Analysis of covariance (ANCOVA) may be used to adjust data for differences in baseline MSLT, hormonal, cognitive, or educational variables that are not controlled for by grouping.

Continuous measures of activity from the wrist-worn actigraph and body temperature will be subjected to time-series analyses to characterize the inherent circadian rhythm and its changes throughout the course of the experiment. Correlations

with other variables will be made to ascertain the extent of rhythmic correspondence amongst the measures.

Experimental data will be stored indefinitely in individual research folders and on personal computer files as well as archived on magnetic tape in the Department of Behavioral Biology. Analyses will be performed by personnel from the Department of Behavioral Biology.

GENERAL SAFETY CONSIDERATIONS

Studies will be performed at the Department of Behavioral Biology, WRAIR, in experimental chambers designed for long-term studies, close observation, and continuous monitoring (Appendix D). At least one technician (one of the same sex as the subject) will be present at all times, as well as investigators at selected times. Primary investigators will be present for drug administration. Resuscitative capabilities are available and discussed in Appendix E. All personnel are BCLS qualified, and the PI is ACLS qualified. Ambulance facilities are available through the Wheaton Rescue Squad. IV catheters will be placed in a forearm vein and kept patent by use of a heparin lock or normal saline drip. Pulse, blood pressure, and temperature will be monitored at regular intervals throughout the study. EKG and EEG will be monitored at certain times related to MSLT testing or drug administration (see Appendix E for monitoring equipment to be used). Cognitive and performance testing will generally not take longer than 20 minutes per session and will consist of continuous performance tasks, vigilance tasks, and other non-noxious cognitive tasks. These will be repeated at regular intervals throughout the study. Behavior and mood will also be rated frequently. Mental states and symptom changes will be followed closely. If systolic blood pressure exceeds 190 mm hg or heart rate exceeds 85% of age predicted maximum, or if triplets of ventricular premature contractions develop on EKG, the study will be stopped and appropriate clinical assessment and treatment initiated. If unusual physical or behavioral changes occur, the subject will be clinically assessed and appropriate treatment initiated. Drug administration will take place in a sitting or supine position. Toilet facilities are available in the experimental chambers. Subjects will be allowed to sleep at the conclusion of the study and clinically assessed prior to being allowed to leave the laboratory. Although the primary investigators will be blind to each subject's drug dosage, the blind codes will be available at all times in the laboratory so that in the event that the blind needs to be broken for a particular subject for clinical reasons, this can be done immediately.

In general, each subject will participate in only one drug study, although selected individuals may be repeated on different drugs to obtain within subject comparability data. Cumulative blood collection will be carefully monitored so as not to exceed 450 cc during a six-week period.

Hazards and Precautions

d-Amphetamine

Amphetamines have been used clinically since 1935 (25). Their acute toxicity is not great, and toxicity occurs generally only after chronic use of high doses. Oral acute use as planned here presents only minor hazards, all of which are temporary. Possible central side effects include restlessness, dizziness, tremor, irritability, weakness, insomnia, and sometimes euphoria. Extremely rarely, psychosis has been reported, but is most likely to occur within a schizophrenic population, specifically excluded from this study (25). Peripheral side effects include headache, palpitations, flushing, hypertension,

nausea, diarrhea, and abdominal cramps (25). All patients will be closely observed by the investigators for the development of side effects and assessed formally at regular, frequent intervals. Blood pressure, pulse, and EKG will also be monitored. Chlorpromazine (Thorazine) is an effective treatment for amphetamine side effects, both central and peripheral, due to its catecholaminergic blocking effects. Oral and injectable chlorpromazine will be kept on hand in the laboratory for administration by the investigators if clinically indicated.

Methylphenidate

The side effect profile of oral methylphenidate is essentially identical to that discussed above for amphetamine, with the same degree of risk for small oral doses. The treatment for unfavorable side effects is also identical, with chlorpromazine being the agent of choice.

In neither of the above drugs is there any evidence of a risk of subsequent amphetamine abuse from a single dose administration research study (50,51).

Nicotine

Nicotine has been safely given intravenously to humans in several studies in doses equal to or greater than those considered for use here (52,53). In a prior study, we have used doses of up to 1.5μg/kg/min for up to three hours without serious side effects (40). Possible side effects include signs of postganglionic stimulation, such as increased heart rate and blood pressure, coughing, hiccups, nausea, and vomiting. Brief pain at the injection site has also been reported. High doses can produce feelings of anxiety, restlessness, and dysphoria. In human studies, the cardiovascular effects of IV nicotine are modest (54,55) and rapidly reversible. In cardiovascularly healthy subjects, IV nicotine has not been noted to produce pathologic EKG changes (55). In our study of 30 individuals up to the age of 82 with over 80 infusions, no EKG changes have been seen (with continuous monitoring). All side effects are rapidly reversible by terminating the drug infusion. As the half-life of nicotine is short ($t_{1/2}\beta$ = approx. 120 min), blood levels drop rapidly leading to rapid disappearance of all effects. Peak blood levels of nicotine with the dosage envisioned in this study will range from 5 to 20 ng/ml. Smokers generally have peak levels in the 30-60 ng/ml range (56). Mecamylamine is a clinically used oral ganglionic blocker and a specific antagonist of nicotine's effects. It will be kept available for use to counteract any long lasting effects of nicotine. In prior studies, this has not been necessary.

l-Deprenyl

l-Deprenyl has been used in psychiatric patients, Parkinsonian patients, and other groups and normals in many studies (57). It has been given alone in doses up to 100 mg/day and in combination with other drugs, including L-dopa and carbidopa. The incidence of unfavorable side effects in our experience has been very low, but side effects that have been reported with acute and chronic use include: dizziness, weakness, palpitations, fainting, sedation, anxiety, agitation, and hypomania. l-Deprenyl is contraindicated in patients with severe cardiovascular disease, increased intraocular pressure, urinary retention, hyperthyroidism, and seizure disorders. Individuals with these disorders will be excluded from the study. Concurrent use of centrally and peripherally acting sympathomimetic amines, parenterally administered reserpine, guanethidine, or meperidine is generally contraindicated. Subjects will be questioned about the use of such drugs. Foods with a high tyramine content or pressor amine precursors are avoided by patients taking MAO inhibitors on a chronic basis. Although side effects from foods or drugs have been reported only after chronic use of these drugs,

subjects will be warned about consuming these types of foods or drugs (see Appendix F) for a period of one week after the end of the protocol. Should unusual behavioral reactions develop, chlorpromazine (25-50 mg) will be used if clinically indicated. Of note is that despite the lack of dietary restrictions and the concurrent use of other medications, no hypertensive reactions have been reported in the Parkinsonian patients receiving 10 mg/day of l-deprenyl chronically (34).

Tranylcypromine

Tranylcypromine has been used in the pharmacotherapy of depression for over 20 years. It is usually used in doses of between 20 and 80 mg per day, and by itself has few major side effects. Those that have been noted include hypotension, dizziness, anxiety, agitation, sedation, and overstimulation. Like all nonselective MAO inhibitors, it shares the liability of rendering the individual sensitive to the hypertensive effects of tyramine. However, the degree of actual MAO inhibition after a single dose is unlikely to be large enough to cause significant tyramine sensitivity (D. L. Murphy, personal communication). Subjects will be cautioned against taking any sympathomimetic drugs or tyramine-containing foods for one week after the study, however. Dosages in this study will range from 5 to 30 mg orally as a single dose. Further precautions will be observed as with l-deprenyl above.

Sleep Deprivation

Sleep deprivation has been shown to produce changes in mood, arousal state, and cognition (58). From a research perspective, we are seeking these changes so as to examine the ability of various drugs to normalize them. Severe changes of mood, emotions, sensory perception, and cognition have only been produced by long term (greater than 72 hours) sleep deprivation and are not anticipated here. Previous studies here have used up to 72 hours of sleep deprivation without serious side effects (59). All effects of the sleep deprivation in this study will be fully reversed by one night of normal sleep (60). The interaction of drug effects and sleep deprivation should tend to mitigate the latter; however, it is possible that some side effects could be additive. Subjects will be clinically assessed by a physician investigator if this occurs and appropriate steps taken, including medication and/or termination of the study.

Subjects will in some cases undergo the mild discomfort associated with the placement of IV catheters and the mild restriction involved in the evaluation of mood and mental status. Cognitive testing as used in this protocol has been noted to be occasionally frustrating, but no other side effects have been reported.

IND

The PI is coprincipal investigator on an IND at NIH for administration of IV nicotine and mecamylamine. Separate INDs for nicotine and deprenyl will be obtained for this study.

SPECIFIC MEDICAL OR NURSING CARE REQUIREMENTS

Medical care is required to administer medications, insert and remove catheters, perform clinical assessments, and treat any side effects, or other medical difficulties which might develop over the course of the study. These functions will be provided by

physician investigators. Monitoring of blood pressure, pulse rate, and temperature will be provided by physician investigators, and by non-physician employees of the Department of Behavioral Biology.

DEPARTURE FROM PROTOCOL FOR INDIVIDUAL PATIENTS

When Allowed

(1) A subject may remove himself from the protocol at any time.

(2) If a subject develops an acute self-limited illness (e.g., upper respiratory infection) before the start of his scheduled session, he may be rescheduled for another session.

(3) If illness occurs during the course of the study, the subject will be removed from the study. These decisions will be made by the physician monitor and PI.

(4) If a subject is determined to have been using proscribed drugs, tobacco, or alcohol immediately prior to the start of the study, he will not be permitted to take part in the study or will be removed from the study if it is underway.

(5) Any subject who uses proscribed drugs, tobacco, alcohol, or caffeine above the level permitted during the course of the study will be removed from the study.

Who will be Notified

If the protocol is modified, this will be mentioned in the annual progress report. If a toxic side effect occurs, both the Surgeon General's Human Subjects Research Review Board and the WRAIR Office of Research Management will be notified.

MODIFICATION OF PROTOCOL

If modification is deemed beneficial to the project by the investigators, a DF outlining the proposed modification and justification will be sent to The Surgeon General's Human Subjects Research Review Board and the WRAIR Office of Research Management.

DISPOSITION OF UNUSED MEDICATIONS

Unused medications will be turned in to WRAIR Logistics Division for disposal in accordance with regulations.

USE OF INFORMATION AND PUBLICATIONS ARISING FROM STUDY

These studies will be submitted for publication in the open scientific literature.

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clear that a correlation does not always exist between the MSLT and earlier subjective tests (SSS). Thus, the objective sleepiness measured by the MSLT may be thought of as an underlying tendency to fall asleep, masked by concurrent drives and behaviors, and uncovered in neutral or nondemanding situations.

To assess objectively the side effects of the widely utilized sedative-hypnotics, the benzodiazepenes, numerous studies have been conducted using the MSLT as a measure of daytime alertness (3,4,5). Testing with estazolam (6), triazolam (7), and flurazepam (7) in elderly insomniacs and oxazepam (8), flurazepam (8), and midazolam (9) in healthy adults have shown increases in nocturnal sleep time, especially in stage 2. Few daytime effects were seen using estazolam, midazolam and oxazepam. However, daytime alertness increased or showed no change with triazepam, and it decreased with flurazepam ($t_{1/2}$ = 74 hours) due to a carryover effect in normals and insomniacs. The MSLT and performance series indicate that transient insomnia associated with sudden sleep schedule changes is treatable with triazolam. Testing conducted with antihistamines (10) decreased the MSLT and a correlation was found between the mean latency over the day and performance. Administering delta sleep inducing peptide (DSIP) compresses the sleep period and enhances REM sleep, and reduces the tendency for narcoleptics to fall asleep (11). Indeed, an increase in performance and daytime alertness was measured (MSLT) after repeated morning DSIP doses. A study utilizing the anxiolytic buspirone showed no effect on the MSLT in chronic insomniacs (12). To our knowledge, no studies have been done to investigate the effects of stimulants on the MSLT in normal, sleep-deprived subjects.

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APPENDIX B

DATA COLLECTION FORMS

APPENDIX A

DESCRIPTION OF THE MULTIPLE SLEEP LATENCY TEST

The Multiple Sleep Latency Test (MSLT) (1) is an objective measure of an individual's physiological daytime sleep tendency (i.e. readiness to fall asleep). Repeated determinations of sleep latency, recorded as the time between the individual's initial attempt to sleep and the point at which the electroencephalographic patterns of sleep first develop, measure the underlying sleep tendency of the individual in the absence of alerting factors. The MSLT provides information on the underlying arousal state, with irresistable sleepiness at one end of the scale and total alertness at the other end.

The MSLT is administered in a setting intended to promote sleep. Subjects lie in a bed in a quiet, darkened room and are instructed to close their eyes and attempt to fall asleep. The environment is designed to remove as many alerting factors (e.g., light, noise, cold, etc.) as possible to enable the underlying sleep tendency to be measured. If a subject is not sleepy, he will not fall asleep or will experience a delay in its onset, receiving a high MSLT score. In contrast, the sleep-deprived, tired individual will fall asleep quickly, scoring lower. In administering the MSLT, sleep latency is recorded at two hour intervals across the day. Each test is limited to 30 minutes so that subjects will not become bored if they cannot fall asleep. The amount of sleep is limited to the first minute of stage 1, so that subjects will not accumulate significant amounts of sleep during sleep deprivation procedures. The MSLT is sensitive to changes in total sleep time as small as one hour and has a high retest correlation for individuals.

After sleep disorders medicine became formalized in the early 1970's, the MSLT was developed in response for the need for an objective measure of daytime sleepiness (2). The MSLT came to supplement previous subjective measures such as the Stanford Sleepiness Scale (SSS). Since the time of its inception, the MSLT has been used and validated in studies investigating the effect of total sleep deprivation and sleep restriction on daytime sleep tendency. It has been successfully employed in separating diagnostic categories of sleep disorders (e.g., narcolepsy, sleep apnea, excessive daytime somnolence) and evaluating treatment. In addition, the test has been used to compare sleep latency in a number of nonclinical populations including adolescents, young adults and the elderly. Studies have determined that extending sleep increases the sleep latency in young adults, and that depriving sleep decreases the time for the onset of sleep.

A number of studies, however, showing clear deficits or improvements on the MSLT have failed to reveal consistent changes in the ability to perform. Performance measures have the advantage of objectifying the impairment of abilities, especially vigilance and repetitive tasks in this case, but with infrequent testing, motivational effects (rallying for the tests) can obviate much of their utility. Only when the MSLT scores are very low, indicating a pathological degree of sleepiness (i.e. total sleep deprivation, narcolepsy, etc.) has a relationship to performance been documented. When the task is monotonous, repetitive and uninteresting, performance deficits are more likely to appear under sleep loss conditions. Behavioral factors (excitement, hunger, fear, boredom) strongly influence the subjective tests more than the objective tests. It is

Name _____

Date _____

Time _____

Please check physical symptoms which are present now.

For women: menstruating ____yes ____no

For	None	Slight	Moderate	Much
1. Increased appetite				
2. Poor appetite				
3. Dry mouth				
4. Increased salivation				
5. Things taste different				
6. Stiffness				
7. Tremor				
8. Weakness				
9. Tiredness				
10. Headache				
11. Itching				
12. Constipation				
13. Diarrhea				
14. Nausea				
15. Stomachache				
16. Increased need to urinate				
17. Difficulty urinating				
18. Heart pounding				
19. Dizzy				
20. Blurred vision				
21. Decreased sexual thoughts or feelings.				
22. Increased sexual thoughts or feelings				
23. Sweating				
24. Difficulty sleeping last night				
25. Drowsiness				
26. Other Trouble breathing				

NAME _____ DATE _____

SEX: Male (M) Female (F)

IDENTIFICATION

Below is a list of words that describe feelings people have. Please read each one carefully. Then fill in ONE circle under the answer to the right which best describes HOW YOU HAVE BEEN FEELING DURING THE PAST WEEK INCLUDING TODAY.

The numbers refer to these phrases.

0 = Not at all
1 = A little
2 = Moderately
3 = Quite a bit
4 = Extremely

Col (C) O.P. (O)

	NOT AT ALL	A LITTLE	MODERATELY	QUITE A BIT	EXTREMELY
1. Friendly	0	1	2	3	4
2. Tense	0	1	2	3	4
3. Angry	0	1	2	3	4
4. Worn out	0	1	2	3	4
5. Unhappy	0	1	2	3	4
6. Clear-headed	0	1	2	3	4
7. Lively	0	1	2	3	4
8. Confused	0	1	2	3	4
9. Sorry for things done	0	1	2	3	4
10. Shaky	0	1	2	3	4
11. Listless	0	1	2	3	4
12. Peeved	0	1	2	3	4
13. Considerate	0	1	2	3	4
14. Sad	0	1	2	3	4
15. Active	0	1	2	3	4
16. On edge	0	1	2	3	4
17. Grouchy	0	1	2	3	4
18. Blue	0	1	2	3	4
19. Energetic	0	1	2	3	4
20. Panicky	0	1	2	3	4
21. Hopeless	0	1	2	3	4
22. Relaxed	0	1	2	3	4
23. Unworthy	0	1	2	3	4
24. Spiteful	0	1	2	3	4
25. Sympathetic	0	1	2	3	4
26. Uneasy	0	1	2	3	4
27. Restless	0	1	2	3	4
28. Unable to concentrate	0	1	2	3	4
29. Fatigued	0	1	2	3	4
30. Helpful	0	1	2	3	4
31. Annoyed	0	1	2	3	4
32. Discouraged	0	1	2	3	4
33. Resentful	0	1	2	3	4
34. Nervous	0	1	2	3	4
35. Lonely	0	1	2	3	4
36. Miserable	0	1	2	3	4
37. Muddled	0	1	2	3	4
38. Cheerful	0	1	2	3	4
39. Bitter	0	1	2	3	4
40. Exhausted	0	1	2	3	4
41. Anxious	0	1	2	3	4
42. Ready to fight	0	1	2	3	4
43. Good natured	0	1	2	3	4
44. Gloomy	0	1	2	3	4
45. Desperate	0	1	2	3	4
46. Sluggish	0	1	2	3	4
47. Rebellious	0	1	2	3	4
48. Helpless	0	1	2	3	4
49. Weary	0	1	2	3	4
50. Bewildered	0	1	2	3	4
51. Alert	0	1	2	3	4
52. Deceived	0	1	2	3	4
53. Furious	0	1	2	3	4
54. Efficient	0	1	2	3	4
55. Trusting	0	1	2	3	4
56. Full of pep	0	1	2	3	4
57. Bad-tempered	0	1	2	3	4
58. Worthless	0	1	2	3	4
59. Forgetful	0	1	2	3	4
60. Carefree	0	1	2	3	4
61. Terrified	0	1	2	3	4
62. Guilty	0	1	2	3	4
63. Vigorous	0	1	2	3	4
64. Uncertain about things	0	1	2	3	4
65. Bushed	0	1	2	3	4

MAKE SURE YOU HAVE ANSWERED EVERY ITEM.

EDITS POM 021

	NOT PRESENT	MILD	MODERATE	SEVERE	NOT RATABLE
11. SUSPICIOUSNESS - Belief (delusional or otherwise) that others have now, or have had in the past, malicious or discriminatory intent toward the pt. On the basis of verbal report and behavior, rate only those suspicions which are currently held whether they concern past or present circumstances.	1	SEEMS GUARDED 2 3	SAYS DOES NOT TRUST 4 5	PARANOID DELUSIONS 6 7	0
12. HALLUCINATORY BEHAVIOR - HALLUCINATION STATE-MENTS - Perceptions without normal external stimulus correspondence. Rate only those experiences which are reported to have occurred during the rating period and which are described as distinctly different from the thought & imagery processes of normal people.	1	OCCAS. WITH INSIGHT 2 3	OFTEN AND NO INSIGHT 4 5	PERVASIVE 6 7	0
13. MOTOR RETARDATION - BEHAVIOR - Reduction in energy level evidenced in slowed movements & speech, reduced body tone, decreased number of movements. Rate on the basis of observed behavior of the pt only; do not rate on the basis of pt's subjective impression of own energy level.	1	SLOWED 2 3	RETARDED 4 5	CATATONIC 6 7	0
14. UNCOOPERATIVENESS - Evidence of resistance, unfriendliness, resentment, & lack of readiness to cooperate with ward procedures and with others.	1	RESENTS 2 3	RESISTS 4 5	REFUSES 6 7	0
15. UNUSUAL THOUGHT CONTENT - Unusual, odd, strange, or bizarre thought content. Rate here the degree of unusualness, not the degree of disorganization of thought processes.	1	ODD 2 3	BIZARRE 4 5	IMPOSSIBLE 6 7	0
16. BLUNTED AFFECT - Reduced emotional tone, apparent lack of normal feeling or involvement.	1	LOWERED FEELING 2 3	FLAT 4 5	MECHANICAL 6 7	0
17. EXCITEMENT - Heightened emotional tone, increased reactivity, agitation, impulsivity.	1	INCREASED EMOTION 2 3	INTENSE 4 5	OFF THE WALL 6 7	0
18. DISORIENTATION - Confusion or lack of proper association for person, place, or time.	1	MUDDLED 2 3	CONFUSED 4 5	DISORIENTED 6 7	0
19. ELATED MOOD - Overly cheerful, euphoric. Rate only degree of expressed or indicated excessive good feeling; do not infer elation from increased activity or from grandiose statements alone.	1	TOO CHEERFUL 2 3	HIGH 4 5	EUPHORIC 6 7	0
20. MOTOR HYPERACTIVITY - Increase in energy level evidenced in more frequent movements and rapid speech.	1	ENERGETIC 2 3	PRESSURED 4 5	FRENETIC 6 7	0
21. DISTRACTIBILITY - Degree to which observed sequence of speech and acts are interrupted by minimal external stimuli or only partially relevant associations.	1	TROUBLE FOCUSING 2 3	OVERLY RESPONSIVE 4 5	FRAGMENTED 6 7	0
22. HELPLESSNESS, HOPELESSNESS - Expressed feelings of inability to cope; pessimism and despair about future.	1	DOUBTFUL 2 3	GLOOMY 4 5	NO HOPE 6 7	0
23. SOCIAL INCOMPETENCE - Rate how ineffective the pt is in his contact with others. Do not rate isolation or withdrawal. Rate what happens when pt does interact with others. Note instructions for 1 rating.	1	AWKWARD 2 3	INEPT 4 5	LACKS SOCIAL SKILLS 6 7	0
24. LOSS OF FUNCTIONING - Rate general level of functioning. See guidelines - note instructions for 1 rating.	1	MILD LOSS 2 3	MOD. LOSS 4 5	SEVERE LOSS 6 7	0

Imp_____ Dep _____ Ma_____ Psy _____ Anx _____

STIMULANT STUDY DATA SHEET (I)

SUBJECT NO. _____ DATE _____ DRUG _____ DRUG CODE _____

DAY 1							DAY 2							DAY 3					
TIME	SBP	DBP	P	RR	T	SLT	TIME	SBP	DBP	P	RR	T	SLT	TIME	SBP	DBP	P	T	SLT
0800							0400							0400					
1000							0800							0800					
1200							1000							0830					
1600							1200							0900					
2000							1600							0930					
2400							2000							1000					
							2400							1030					
														1100					
														1130					
														1200					
														1230					
														1300					
														1330					
														1400					
														1600					
														1800					
														2000					
														2200					

COMMENTS (NOTE DAY AND TIME):

APPENDIX C

DESCRIPTION OF COGNITIVE TEST BATTERY

The test battery to be used in this study is a subset of The Walter Reed Performance Assessment Battery (1). Test items and visual stimuli are presented on a microcomputer monitor and the subject answers or responds by means of the computer keyboard. Individual tests are automatically generated, administered, recorded and scored. This particular implementation is designed to require less than 30 minutes for its completion, and to use subtasks that are known to be sensitive to stimulants, sleep deprivation, and circadian rhythms. The subtasks include multiple measures of subjective states, two independent measures of time perception, one combined measure of mental arithmetic and sustained attention, and individual tasks to measure choice reaction time, spatial rotation and logical reasoning. These tasks are described in order below.

Subjective Status: This is a "self-rating" task taking approximately 5 minutes to complete. It consists of 101 adjectives to be rated on either a 3-point or 5-point scale, and 7 statements from which one is to be selected. The task is compiled from three previously existing tasks that have been used in sleep-related studies, and which will be identified here as Scales I, II, and III.

Scale I - Subjects are presented with 65 adjectives and are asked to respond on a 5-point scale with the extent to which each adjective reflects their current feelings. The adjectives are derived from Thayer's Activation-Deactivation Check List (2,3), and from Zuckerman's Multiple Affect Check List (4), plus three repeated items for checking internal consistency.

Scale II - A task procedurally identical to the above but consisting of 36 adjectives to be rated on a 3-point scale. The scale yields six factor-analytically derived indices identified as Activity, Fatigue, Happiness, Depression, Anger and Fear (5).

Scale III - The Stanford Sleepiness Scale. A single item single frame 7-point scale specifically designed to measure "sleepiness" (6). This scale has previously been used in conjunction with the multiple sleep latency test (7) and is reproduced in Appendix 2.

Time Perception: Two independent measures of time perception are obtained by using two standard procedures with different interval values. Together they require approximately two minutes to complete.

Interval Production Task - The subject is instructed in the standard placement of his preferred hand on the keyboard, and is required to tap a designated key at what he estimates to be regular one second intervals. No watches or clocks are allowed, and the subject is requested to respond as accurately and as consistently as possible. The task ends after 60 intervals are completed.

Time Estimation Task - A moving object appears to pass behind a barrier and the subject is to estimate when it will reappear. The barrier is a white rectangle filling the bottom third of the screen with a black notch centered along its bottom edge. The object is a small white square that appears at the top center of the screen and descends at a constant rate such that it would coincide with the notch exactly ten seconds later (if

actually allowed to continue). The subject presses a key at the estimated moment of reappearance, whereupon the notch briefly turns white and then the next trial begins. The task ends after six trials are completed.

Sustained Attention: The Serial Addition/Subtraction task is a machine-paced mental arithmetic task requiring sustained attention and concentration. Two randomly selected digits and either a plus or minus sign are displayed sequentially in the same center-screen location, followed by a prompt symbol. The subject performs the indicated addition or subtraction and enters the least significant digit of the result. If the result is negative he first adds ten to it and enters the positive single digit remainder. The digits and signs are presented for 250 milliseconds, separated by 200 milliseconds, with the next trial beginning 500 milliseconds after the response.

This task was adapted from Pauli as used by Wever (8,9) and is known to be sensitive to sleep deprivation effects (10). The task ends after 50 responses and typically takes 3 to 4 minutes.

Choice Reaction Time: Reaction times (RTs) are known to be sensitive to the effects of stimulants (11), sleep deprivation, and circadian rhythms. The classical choice reaction time procedure consists of repeatedly presenting the subject with one of n distinct stimuli to which he is to make one of n responses as rapidly as possible. In the present case the stimuli are the digits 0 through 9 and the response consists of pressing the corresponding key on the keypad. The stimuli are presented one at a time in the center of the screen and remain present until the response occurs. The next stimulus follows 500 milliseconds later. The task ends after 50 responses.

This task was designed to fulfill the standard requirements of a choice RT task while closely resembling the Serial Addition/Subtraction task. The results can therefore be used to correct for certain learning effects common to the two, and for estimating the relative contributions of response execution time to the observed calculation time.

Spatial Rotation: The computer monitor displays the figure of a manikin standing inside either a circle or a square, holding a circle in one hand and a square in the other. The figure may be facing forward or backward, and may be right side up or upside down. The subject must determine which hand holds the matching shape and quickly press a key with his corresponding right or left hand. The 16 possible permutations are presented twice each in random order for a total of 32 trials. The task is adapted from the Manikin task of Benson & Gedye (12) and of Reader, Benel & Rahe (13).

Logical Reasoning: The letter pair AB or BA is presented along with a statement that correctly or incorrectly describes the order of the letters within the pair (eg "B follows A" or "A is not preceded by B"). The subject must quickly decide whether the statement is true or false and press a key accordingly. The 32 possible permutations are presented once each in random order. The task is adapted from Baddeley (14).

APPENDIX C REFERENCES

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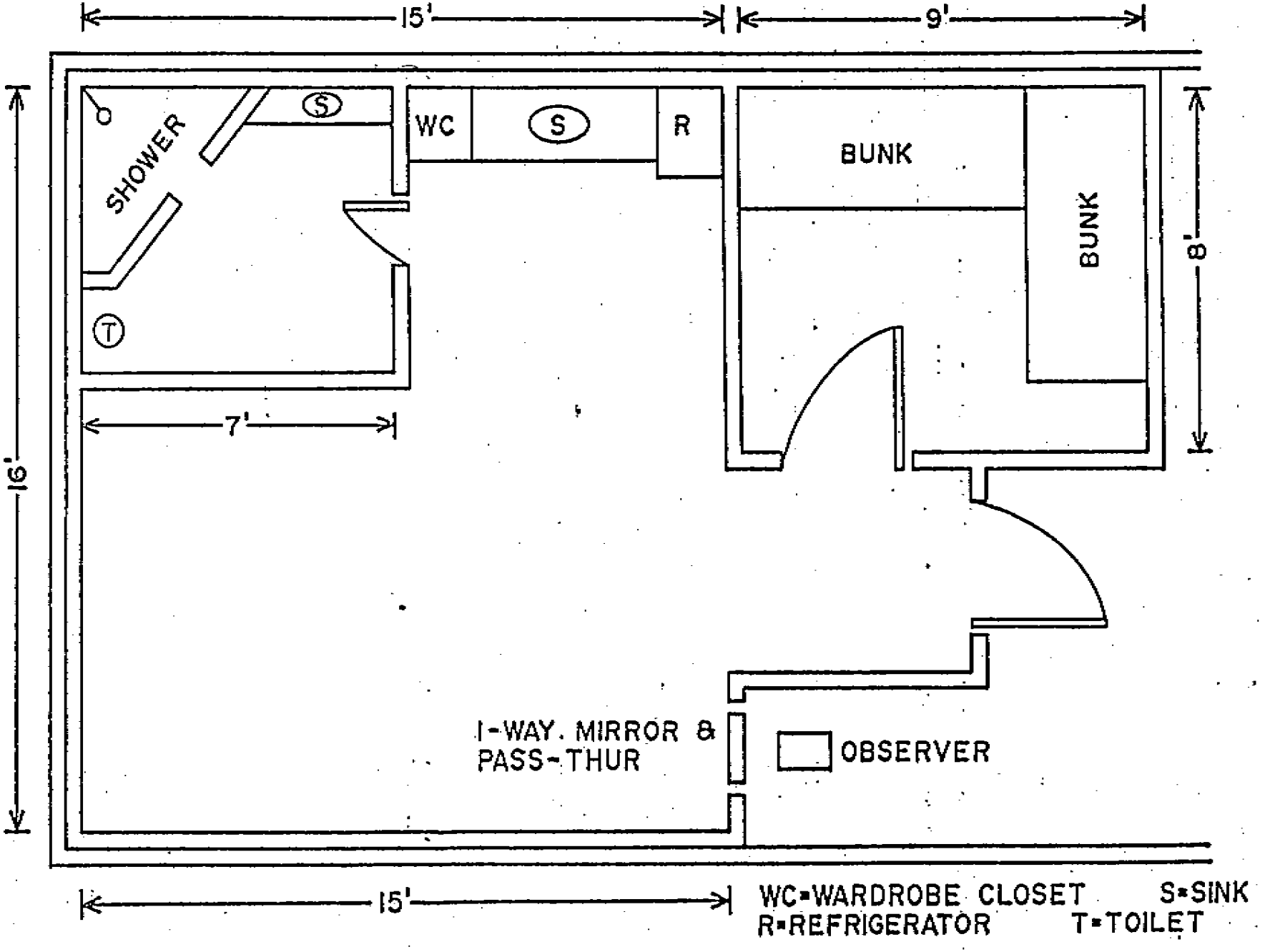
APPENDIX D

CONTROLLED ENVIRONMENT CHAMBERS

The controlled environment chambers are designed to isolate the subjects from all external time cues. The chamber configuration consists of two carpeted rooms approximately 16 x 15 x 8 feet and 9 x 8 x 8 feet joined by a 4 x 4 x 8 feet sound lock. All sections are light proof and are enclosed by two layers of 4 inch acoustical paneling to provide 120 db sound attenuation. To minimize transmission of external vibratory cues, the rooms are built on vibration isolators to provide a "floating" foundation independent of that supporting the parent laboratory building (Bldg. 189) within which they are enclosed. All plumbing is acoustically insulated, and the waste disposal system employs a holding tank designed to isolate it from the parent building's system. All air ducts entering the chambers are connected through flexible couplings to minimize sound transmission while providing for constant temperature and humidity control. The electrical supply passes through a center-tapped transformer to prevent transmission of fluctuations in power due to alterations in external grid demand. Both rooms are lit by standard overhead incandescent lighting fixtures controlled by an external timer.

The large chamber room is designed as the main living area and contains a private bathroom with a sink and shower stall and a kitchen area with a refrigerator, sink, storage cabinets, and a wardrobe. A thru-wall access cabinet connects the chamber to the experimenter monitoring area to permit the exchange of supplies, meals, and data samples. Double doors constructed of 4 inch-thick acoustical panels allow items to be passed in or out of the chamber without permitting actual communication with the subjects inside. A one-way viewing mirror (30 x 24 inches) is located above the access cabinet along with a remotely-controlled television camera mounted in one corner of the room to permit continuous observation of the subjects when needed.

The smaller room is designed as a sleeping area and is equipped with two two-tiered bunk beds to accommodate four persons. There is an intercom but no observation window for this room. During periods of darkness, a low intensity red nightlight can be switched on in both chambers and in the sound lock to provide sufficient light to enable subjects to move about safely if necessary.


15'
9'
16'
8'
7'
15'
SHOWER
S
WC
S
R
BUNK
BUNK
T
1-WAY. MIRROR &
PASS-THUR
OBSERVER
WC=WARDROBE CLOSET
R=REFRIGERATOR
S=SINK
T=TOILET

APPENDIX E

RESUSCITATIVE AND MONITORING EQUIPMENT

PHARMACEUTICALS

Aminophylline
Ammonia (inhalant)
Atropine sulfate
Bretylium tosylate
Calcium chloride
Chlorpromazine
Dexamethasone sodium phosphate
Dextrose (D5W)
Distilled water
Diphenhydramine HCl
Ephedrine sulfate
Epinephrine
Furosemide
Lidocaine HCl
Mecamylamine
Metaraminol bitartrate
Naloxone hydrochloride
Nitroglycerin
Rheomacord
Ringers' lactate
Sodium bicarbonate
Sodium chloride
Verapamil

EMERGENCY MEDICAL SUPPLIES AND EQUIPMENT

Adhesive tape, surgical and tape remover
Airways, oropharyngeal and nasopharyngeal
Aspirator pump
Cannulas, nasal, oxygen
Catheters, assorted types and sizes
Defibrillator with oscilloscope
Endotracheal tubes (assorted types and sizes)
First aid kit
Forceps, endotracheal tube
Gauze
Intravenous injection sets
IV Catheter placement units
Labels (medication added to IV)
Laryngoscope (assorted types and sizes)
Lubricant, surgical
Mask, oxygen
Needle, hypodermic (assorted types and sizes)
Needle, spinal
ophthalmoscope
Prep pads, alcohol

Sphygmomanometer
Sponge, surgical
Spray, adhesive bond
Stethoscope
Stylets (small and large)
Syringes (assorted types and sizes)
Thermometer
Tongue depressors
Tourniquet
Tray, catheter
Tube, stomach
Yankauer surgical suction instrument

MONITORING EQUIPMENT

EKG:	Oxford Medilog 9000 System
BP/P:	Lumiscope 100-046
EEG:	Grass 8-10D Electroencephalograph Oxford Medilog 9000 System
Actigraphy:	Precision Design Actigraph Model AM-16

APPENDIX F

MAO INHIBITOR DRUG INCOMPATIBILITIES

CONTRAINDICATION

Stimulants:	Amphetamines ("pep pills"); cocaine; weight reducing or antiappetite drugs
Decongestants:	Sinus, hay fever, cold tablets; nose sprays or drops, asthma tablets or inhalants, cough preparations (or any products containing ephedrine, phenylephrine, or phenylpropanolamine)
Antihypertensives:	Methyldopa, guanethidine, reserpine
Antidepressants:	Imipramine, desimipramine, chlorimipramine
MAOIs:	Tranylcypromine after other MAOs
Sympathomimetics:	Dopamine, metaraminol

RELATIVELY CONTRAINDICATED (MARKED POTENTIATION)

Narcotics:	Meperidine (pethidine)
Sympathomimetics:	Epinephrine, norepinephrine, isoproteronal
General anesthetics:	All

SOME POTENTIATION POSSIBLE

Narcotics:	Morphine, codeine, etc.
Sedatives:	Alcohol, barbiturates, benzodiazepines
Local anesthetics:	Containing vasoconstrictors
Hypoglycemic agents:	Insulin, tolbutamide, chlorpropamide

INSUFFICIENT KNOWLEDGE

Antidepressants:	Maprotoline, amoxapine, trazodone

MAO INHIBITOR DIETARY RESTRICTIONS

	Examples
Aged, matured cheeses (unpasteurized)	Cheddar, Camembert, Stilton, Bleu, Swiss
Smoked or pickled meats, fish, or poultry	Herring, sausage, corned beef
Aged/putrifying meats, fish, or poultry	Chicken or beef liver, pate, game
Yeast or meat extracts	"Bovril", marmite, brewer's yeast (beware of drinks, soups, or stews made with these products)
Red wines	Chianti, burgundy, sherry, vermouth
Italian broad beans	Fava beans

APPENDIX G

DEFENSE TECHNICAL INFORMATION CENTER SEARCH

CONTROL NO. 049342

PERFORMANCE AND DRUG STIMULANTS

SEARCH CONTROL NO. 049342

PERFORMANCE AND DRUG STIMULANTS (U)

27161
TO: WALTER REED ARMY INST RSCH
WASHINGTON, DC 20307

REQUESTED BY: LTC BELENKY/ 276-3279 3/6/86

THIS REPORT (COMPILATION) IS MARKED TO REFLECT THE HIGHEST CLASSIFICATION OF ANY COMPONENT PART THEREOF. IT SHOULD BE DESTROYED WITHIN 12 MONTHS AS THESE RECORDS ARE UPDATED AT LEAST ANNUALLY.

UNCLASSIFIED

(THIS PAGE IS UNCLASSIFIED)

APPENDIX H

CONSENT TO PARTICIPATE IN A LABORATORY RESEARCH STUDY

WALTER REED ARMY INSTITUTE OF RESEARCH

STUDY TITLE: Pharmacologic Optimization of Alertness in Continuous and Sustained Operations

INTRODUCTION

We invite you to take part in a research study at the Walter Reed Army Institute of Research. It is important that you read and understand several general principles that apply to all who take part in our studies: (a) taking part in the study is entirely voluntary; (b) personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others; (c) you may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. The nature of the study, the risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. You are urged to discuss any questions you have about this study with the investigators who explain it to you.

PURPOSE

All of us have experienced the effects of sleep deprivation and fatigue on our thinking, mood, decision making, and memory. Our thinking becomes fuzzy, memory poor, mood unstable, and decision making abilities impaired. While the neurobiological processes that underlie these changes are not completely understood, nor how sleep reverses them, they are believed to be related to changes in certain chemicals in the brain that act as messengers between nerve cells. In ways not yet completely understood, lack of sleep may cause changes in these chemical systems leading to the above mentioned effects. Certain drugs may act to restore the system more toward normal functioning, at least briefly. These drugs include commonly known stimulants such as amphetamine, and less commonly known compounds such as L-dopa. We hope to study in a detailed way how these drugs act to restore normal alertness and how they improve mental functioning. By doing this, we hope to identify medications that may compensate for lack of sleep without unpleasant side effects. We also hope to understand more about the chemistry of sleep and fatigue and develop better approaches to understanding how the brain works.

PROCEDURE

NOTE: For the particular medication study that you consent to participate in, an appendix will be added to this consent form describing in detail the risks and side effects of that medication. The words "drug" or "medication" refer then to that particular medication unless otherwise specified.

After fasting overnight, and skipping breakfast, you--along with three other subjects--will arrive at the laboratory at about 8:00 a.m. At that time, you will have several general physical measures assessed including blood pressure, pulse, and temperature. You will then have several electrode leads attached to your scalp with a washable paste, be placed in a darkened room, and instructed to try to sleep. As soon as you do fall asleep, you will be awakened and the time measured. This is called the sleep latency test (SLT) and will be repeated twice on Day 1 and at intervals throughout the study. You will then be allowed to have breakfast and subsequently given a number of computerized tests. These will be repeated at 2-hour intervals throughout the duration of the study. The remainder of Day 1 and Day 2 will be spent in the experimental area with reading, watching TV, and games available. Meals will be served at 8 a.m., 12 noon, and 6 p.m. We will ask you to remain in the experimental area all night and to remain awake continuously. You will be assisted in this by engaging in various tasks, diversions, and interaction with technicians and other subjects. Beginning the next morning at approximately 8 a.m., you will perform several SLTs at 2-hour intervals, as well as receive brief tests of your memory, learning, and performance at 2-hour intervals. The same procedure will continue on Day 2 with regular meals, mental tasks, and diversions. We will ask you to remain awake throughout Day 2 and all night.

At approximately 8:30 a.m. on Day 3, an intravenous catheter will be placed in your arm to obtain blood samples. Breakfast will be withheld on the morning of Day 3. At 9:00 a.m., you will receive a medication, either an active drug or a placebo. A placebo is a medication without any known effect, for example, salt water or an inert material. We include this to help distinguish the effects of the drug from that of the procedure itself. The medication will usually be given orally, although for some medications, a second intravenous catheter will be used briefly in a different vein for drug administration. Your blood pressure, pulse, temperature, and respiration will be measured regularly. There will be close observation of your mood and emotional state and you will be asked to fill out ratings of your mood and feeling state. Blood may be withdrawn periodically through the catheter to measure drug levels and hormone responses. The sampling catheter will be withdrawn no later than 300 minutes after drug administration. If there is a second infusion catheter, this will be withdrawn after drug administration is complete, always within 30 minutes. You will be given meals at 12 p.m. and 6 p.m. on Day 3.

The formal testing will terminate at 9 p.m. on Day 3. You will be asked to remain and sleep until 8 a.m. the next morning (Day 4) to recover from the sleep deprivation.

You may be asked to participate in more than one three-day trial. Each trial will be separated by at least 72 hours from any other trial. For each trial you will receive either medication or placebo. The order of administration of the drug or placebo will be determined in such a way so that you will not know which you are receiving. You may receive one of several different doses of the active medication.

Discharge from the laboratory after each trial is anticipated by 8 a.m. on Day 4. We do not expect any continuing effects of the medication; however, if you are experiencing any difficulties at that time, you may be asked to remain for further observation and/or necessary treatment.

POSSIBLE RISKS, INCONVENIENCES, AND SIDE EFFECTS

(For specific information on the drug used in this trial, see the attached appendix.)

If you have serious heart disease, asthma, ulcer disease, active thyroid disease, pyloric stenosis, narrow angle glaucoma, substantial prostate enlargement, epilepsy, or a serious psychiatric disorder, you should not participate in this study.

If you are female and are pregnant or believe that you may be pregnant, you should not participate in this study. You are cautioned against becoming pregnant immediately before or after this study. It is recommended that you refrain from sexual intercourse between the time of your pregnancy screening test and the end of the study. If you do have sexual intercourse, you should use adequate contraception other than oral contraceptives.

Risks from the experimental procedures are minor. It is possible that you may feel emotional and mental changes after 48 hours of sleep deprivation; however, those should not be severe. Prior studies have deprived individuals of sleep up to 72 hours without serious side effects. The recovery sleep at the end of each trial should result in full recovery of any residual effects. The catheter(s) that are placed in your arm vein may produce some discomfort initially and some bruising occurs rarely. Local infection and thrombophlebitis (blood clot) can also occur with intravenous catheters, but are extremely uncommon. The total amount of blood sampling is not expected to exceed 70-100 cc (5-6 tablespoons) per trial. This is far less than the amount for a routine blood donation.

The SLT, EEG recording, physiological monitoring, and mental tests should produce no undue discomfort.

d-AMPHETAMINE

Possible Risks and Side Effects

As you may know, amphetamines have been known to be stimulant drugs for many years. They have been extensively studied and are approved for clinical use. Amphetamines have a broad range of effects. These effects include increased heart rate and blood pressure and evidence of nervous system stimulation, including increased alertness, vigor, energy, and talkativeness. Possible side effects include tremor, nervousness, confusion, restlessness, insomnia, headache, and dryness of the mouth. There has been the extremely rare occurrence of a psychotic reaction with hallucinations. Occasional individuals find amphetamines produce feelings of fatigue.

In the event that side effects become severe, a second medication (chlorpromazine) would be used to reverse the effects of amphetamine.

There is no evidence that exposure to single low doses of amphetamine has any serious possibility of causing drug dependence.

If you have heart disease, epilepsy, psychological problems, high blood pressure, diabetes, thyroid disorder, allergies to amphetamine or similar drugs, or are taking MAO inhibitor or other antidepressants, you should not participate in this study.

METHYLPHENIDATE

Possible Risks and Side Effects

Methylphenidate is a stimulant drug, related to amphetamines. It has been extensively studied over the last 30 years and is used clinically in the treatment of hyperactive children and certain sleep disorders. The effects of this drug are similar to that of amphetamine and include increased heart rate and blood pressure, and evidence of nervous system stimulation including increased alertness, vigor, energy, and talkativeness. Possible side effects include tremor, restlessness, nervousness, confusion, insomnia, headache, and dryness of the mouth. There has been the extremely rare occurrence of a psychotic reaction at this dosage.

In the event that side effects become severe, a second medication (chlorpromazine) would be used to reverse the effects of methylphenidate.

There is no evidence that exposure to single low doses of methylphenidate will lead to the possibility of stimulant drug dependence.

If you have heart disease, epilepsy, glaucoma, psychological difficulties, high blood pressure, diabetes, thyroid disorder, allergies to methylphenidate or similar drugs, or are taking MAO inhibitor or other antidepressants, you should not participate in this study.

NICOTINE

Possible Risks and Side Effects

As you may know, nicotine is contained in cigarettes. Nicotine has a broad range of effects which have been well studied for many years. These effects include increased heart rate and blood pressure, increased sweating, and occasionally tremor. Side effects include dizziness, blurred vision, nervousness, nausea, headache, and vomiting. Occasional patients experience brief pain at the injection site. Nicotine will be administered by an intravenous infusion for up to 30 minutes. The intravenous catheter will then be withdrawn.

Should side effects become severe, the infusion would be discontinued. Side effects that have been seen disappear rapidly after administration of the drug is stopped. However, if side effects persisted, a second medication (mecamylamine) would be administered to reverse the effects of nicotine. Should serious side effects occur, you would not be expected to continue with the study.

If you have heart disease, asthma, ulcer disease, active thyroid disease, pyloric stenosis, uncontrolled high blood pressure, diabetes, narrow angle gluacoma, substantial prostate enlargement, epilepsy, or allergies to nicotine you should not paticipate in this study.

Mecamylamine and nicotine have been administered together without serious side effects. Mecamylamine alone can cause blurred vision, dizziness, dry mouth, abdominal cramps, and slowness in urinating.

L-DEPRENYL/TRANYLCYPROMINE

Possible Risks and Side Effects

l-Deprenyl and tranylcypromine are both similar drugs which inhibit the action of an enzyme in the body (MAO). They are used clinically here and abroad as antidepressants and in the treatment of Parkinson's disease. They are usually given on a chronic basis, but will only be given once during each study session. Acute effects of l-deprenyl or tranylcypromine are modest, but could include a sense of stimulation, alertness, or activation. Blood pressure and pulse may be briefly elevated. Possible acute side effects include uneasiness, a sense of overstimulation, nervousness, insomnia, headache, dizziness, and dryness of the mouth. If they occur, these effects should fade very quickly.

One additional precaution needs to be explained to you. As these drugs when given on a chronic basis inhibit a normally occurring enzyme in the body, they impair the body's ability to deactivate a substance called tyramine, present in certain foods, and certain other drugs that can mimic the action of tyramine. Exposure to these compounds or foods can lead to high blood levels of tyramine and convergent high blood pressure. Patients who are on these drugs chronically are consequently placed on some dietary and medication restrictions. Although the risk of adverse reactions from a single dose is extremely low, we will ask that you restrict your diet for one week after the study is completed and avoid certain medications. These restrictions are listed on the attached sheet. If you do require any medical treatment within one week, you should tell your treating physician that you have had a single dose of an "MAO Inhibitor".

If you have heart disease, epilepsy, psychological problems, high blood pressure, diabetes, thyroid disorder, allergies to MAO inhibitor drugs, or are currently taking antidepressant drugs, you should not participate in this study.

MAO INHIBITOR DRUG INCOMPATIBILITIES

CONTRAINDICATION

Stimulants:	Amphetamines ("pep pills"); cocaine; weight reducing or antiappetite drugs
Decongestants:	Sinus, hay fever, cold tablets; nose sprays or drops, asthma tablets or inhalants, cough preparations (or any products containing ephedrine, phenylephrine, or phenylpropanolamine)
Antihypertensives:	Methyldopa, guanethidine, reserpine
Antidepressants:	Imipramine, desimipramine, chlorimipramine
MAOIs:	Tranylcypromine after other MAOs
Sympathomimetics:	Dopamine, metaraminol

RELATIVELY CONTRAINDICATED (MARKED POTENTIATION)

Narcotics:	Meperidine (pethidine)
Sympathomimetics:	Epinephrine, norepinephrine, isoproterenol
General anesthetics:	All

SOME POTENTIATION POSSIBLE

Narcotics:	Morphine, codeine, etc.
Sedatives:	Alcohol, barbiturates, benzodiazepines
Local anesthetics:	Containing vasoconstrictors
Hypoglycemic agents:	Insulin, tolbutamide, chlorpropamide

INSUFFICIENT KNOWLEDGE

Antidepressants:	Maprotoline, amoxapine, trazodone

MAO INHIBITOR DIETARY RESTRICTIONS

	Examples
Aged, matured cheeses (unpasteurized)	Cheddar, Camembert, Stilton, Bleu, Swiss
Smoked or pickled meats, fish, or poultry	Herring, sausage, corned beef
Aged/putrifying meats, fish, or poultry	Chicken or beef liver, pate, game
Yeast or meat extracts	"Bovril", marmite, brewer's yeast (beware of drinks, soups, or stews made with these products)
Red wines	Chianti, burgundy, sherry, vermouth
Italian broad beans	Fava beans

OTHER PERTINENT INFORMATION

1. Confidentiality: When results of a study such as this are reported in medical journals or at meetings, the identification of those taking part is withheld. Medical records are maintained according to current legal requirements, and are made available for review as required by authorized users only under guidelines established by the Federal Privacy Act.

2. Payments: Payment is at the rate of $300.00 for one three-day study session.

3. Problems or Questions: Should any problem or question arise with regard to your rights as a participant in research, or with regard to any research-related injury, you should contact the principal investigator, Paul Newhouse, M.D., or the other investigators involved in this study, Stephen Vance, M.D., and Gregory Belenky, M.D., at Bldg 189, Forest Glen Annex, WRAIR, Telephone: (301) 427-5521.

For information regarding the rights of research subjects, please contact the Center Judge Advocate Office at (301) 576-4096, 4097.

ADULT SUBJECT'S CONSENT:

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

_____

Volunteer Signature and Date Signed

_____

Witness Signature and Date Signed

_____

Investigator Signature and Date Signed
(Name, Rank, Title, Section)

PRIVACY ACT STATEMENT

The purpose for requesting personal (e.g., health, sleep habits) information is to provide the minimum information necessary to determine if you satisfy the specific criteria for participation in this study.

This information may be used to provide full documentation of investigative studies; conduct further research; teach; compile statistical data; adjudicate claims and determine benefits; and report medical conditions required by law to other federal, state, and local agencies. It may be used for other lawful purposes including law enforcement and litigation. Even though permitted by law, whenever possible, these personal data will not be released without your consent.

The disclosure of requested information is voluntary. If the information is not furnished, and/or not available from other sources, your voluntary participation in this investigational study may be precluded.

I understand that a copy of the Volunteer Consent Sheet, together with a copy of this form, may be placed in my records as evidence of this notification, and additional copies may be retained permanently by the investigator and the U.S. Government. I have received or have declined to accept a copy of the Volunteer Consent Sheet and a copy of this form which I may keep.

_____

Volunteer Signature and Date Signed

APPENDIX H

VOLUNTEER AGREEMENT AFFIDAVIT AND PRIVACY ACT STATEMENT

VOLUNTEER AGREEMENT AFFIDAVIT

For use of this form, see AR 40-38; the proponent agency is the Office of the Surgeon General

THIS FORM IS AFFECTED BY THE PRIVACY ACT OF 1974

1. **AUTHORITY:** 10 USC 3012, 44 USC 3101 and 10 USC 1071-1087.

2. **PRINCIPAL PURPOSE:** To document voluntary participation in the Clinical Investigation and Research Program. SSN and home address will be used for identification and locating purposes.

3. **ROUTINE USES:** The SSN and home address will be used for identification and locating purposes. Information derived from the study will be used to document the study; implementation of medical programs; teaching; adjudication of claims; and for the mandatory reporting of medical condition as required by law. Information may be furnished to Federal, State and local agencies.

4. **MANDATORY OR VOLUNTARY DISCLOSURE:** The furnishing of SSN and home address is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide the information may preclude your voluntary participation in this investigational study.

PART A - VOLUNTEER AFFIDAVIT

VOLUNTEER SUBJECTS IN APPROVED DEPARTMENT OF THE ARMY RESEARCH STUDIES

Volunteers under the provisions of AR 70-25 are authorized all necessary medical care for injury or disease which is the proximate result of their participation in such studies.

I, _____ (last, first, middle), SSN _____ having full capacity to consent and having attained my _____ birthday, do hereby volunteer to participate in

Pharmacologic Optimization of Alertness in Continuous and Sustained Operations (Phase I)
(research study)

under direction of Paul A. Newhouse, M.D., MAJ, MC conducted at Walter Reed Army Institute of Research
(name of institution)

The implications of my voluntary participation; the nature, duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by _____

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights on study-related injury I may contact

Paul Newhouse, M.D., Stephen Vance, M.D., or Gregory Belenky, M.D.

at Bldg. 189, Forest Glen Annex, WRAIR, WRAMC, Telephone: (301) 427-5521.
(name and address of hospital & phone number (include area code))

I understand that I may at any time during the course of this study revoke my consent and withdraw from the study without further penalty or loss of benefits however, I may be ☐ required (military volunteer) or ☒ requested (civilian volunteer) to undergo certain examination if, in the opinion of the attending physician, such examinations are necessary for my health and well-being. My refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled.

PART B - TO BE COMPLETED BY INVESTIGATOR

INSTRUCTIONS FOR ELEMENTS OF INFORMED CONSENT:(Provide a detailed explanation in accordance with Appendix E, AR 40-38 or AR 70-25.)

We invite you to take part in a research study at the Walter Reed Army Institute of Research. It is important that you read and understand several general principles that apply to all who take part in our studies: (a) taking part in the study is entirely voluntary; (b) personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others; (c) you may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. The nature of the study, the risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. You are urged to discuss any questions you have about this study with the investigators who explain it to you.

PURPOSE

All of us have experienced the effects of sleep deprivation and fatigue on our thinking, mood, decision making, and memory. Our thinking becomes fuzzy, memory poor, mood unstable, and decision making abilities impaired. While the neurobiological processes that underlie these changes are not completely understood, nor how sleep reverses them, they are believed to be related to changes in certain chemicals in the brain that act as messengers between nerve cells. In ways not yet completely understood, lack of sleep may cause changes in these chemical systems leading to the above mentioned effects. Certain drugs may act to restore the system more toward normal functioning, at least briefly. These drugs include commonly known stimulants such as amphetamine, and less commonly known compounds such as L-dopa. We hope to study in a detailed way how these drugs act to restore normal alertness and how they improve mental functioning. By doing this, we hope to identify medications that may compensate for lack of sleep without unpleasant side effects. We also hope to understand more about the chemistry of sleep and fatigue and develop better approaches to understanding how the brain works.

PROCEDURE

NOTE: For the particular medication study that you consent to participate in, an appendix will be added to this consent form describing in detail the risks and side effects of that medication. The words "drug" or "medication" refer then to that particular medication unless otherwise specified.

After fasting overnight, and skipping breakfast, you--along with three other subjects--will arrive at the laboratory at about 8:00 a.m. At that time, you will have several general physical measures assessed including blood pressure, pulse, and temperature. You will then have several electrode leads attached to your scalp with a washable paste, be placed in a darkened room, and instructed to try to sleep. As soon as you do fall asleep, you will be awakened and the time measured. This is called the sleep latency test (SLT) and will be repeated twice on Day 1 and at intervals throughout the study. You will then be allowed to have breakfast and subsequently given a number of computerized tests. These will be repeated at 2-hour intervals throughout the duration of the study. The remainder of Day 1 and Day 2 will be spent in the experimental area with reading, watching TV, and games available. Meals will be served at 8 a.m., 12 noon, and 6 p.m. We will ask you to remain in the experimental area all night and to remain awake continuously. You will be assisted in this by engaging in various tasks, diversions, and interaction with technicians and other subjects. Beginning the next morning at approximately 8 a.m., you will perform several SLTs at 2-hour intervals, as well as receive brief tests of your memory, learning, and performance at 2-hour intervals. The same procedure will continue on Day 2 with regular meals, mental tasks, and diversions. We will ask you to remain awake throughout Day 2 and all night.

At approximately 8:30 a.m. on Day 3, an intravenous catheter will be placed in your arm to obtain blood samples. Breakfast will be withheld on the morning of Day 3. At 9:00 a.m., you will receive a medication, either an active drug or a placebo. A placebo is a medication without any known effect, for example, salt water or an inert material. We include this to help distinguish the effects of the drug from that of the procedure itself. The medication will usually be given orally, although for some medications, a second intravenous catheter will be used briefly in a different vein for drug administration. Your blood pressure, pulse, temperature, and respiration will be measured regularly. There will be close observation of your mood and emotional state and you will be asked to fill out ratings of your mood and feeling state. Blood may be withdrawn periodically through the catheter to measure drug levels and hormone responses. The sampling catheter will be withdrawn no later than 300 minutes after drug administration. If there is a second infusion catheter, this will be withdrawn after drug administration is complete, always within 30 minutes. You will be given meals at 12 p.m. and 6 p.m. on Day 3.

The formal testing will terminate at 9 p.m. on Day 3. You will be asked to remain and sleep until 8 a.m. the next morning (Day 4) to recover from the sleep deprivation.

You may be asked to participate in more than one three-day trial. Each trial will be separated by at least 72 hours from any other trial. For each trial you will receive either medication or placebo. The order of administration of the drug or placebo will be determined in such a way so that you will not know which you are receiving. You may receive one of several different doses of the active medication.

Discharge from the laboratory after each trial is anticipated by 8 a.m. on Day 4. We do not expect any continuing effects of the medication; however, if you are experiencing any difficulties at that time, you may be asked to remain for further observation and/or necessary treatment.

POSSIBLE RISKS, INCONVENIENCES, AND SIDE EFFECTS

(For specific information on the drug used in this trial, see the attached appendix.)

If you have serious heart disease, asthma, ulcer disease, active thyroid disease, pyloric stenosis, narrow angle glaucoma, substantial prostate enlargement, epilepsy, or a serious psychiatric disorder, you should not participate in this study.

If you are female and are pregnant or believe that you may be pregnant, you should not participate in this study. You are cautioned against becoming pregnant immediately before or after this study. It is recommended that you refrain from sexual intercourse between the time of your pregnancy screening test and the end of the study. If you do have sexual intercourse, you should use adequate contraception other than oral contraceptives.

SIGNATURE OF VOLUNTEER	DATE SIGNED	SIGNATURE OF LEGAL GUARDIAN (If volunteer is a minor)
PERMANENT ADDRESS OF VOLUNTEER	TYPED OR PRINTED NAME AND SIGNATURE OF WITNESS	DATE SIGNED

Risks from the experimental procedures are minor. It is possible that you may feel emotional and mental changes after 48 hours of sleep deprivation; however, those should not be severe. Prior studies have deprived individuals of sleep up to 72 hours without serious side effects. The recovery sleep at the end of each trial should result in full recovery of any residual effects. The catheter(s) that are placed in your arm vein may produce some discomfort initially and some bruising occurs rarely. Local infection and thrombophlebitis (blood clot) can also occur with intravenous catheters, but are extremely uncommon. The total amount of blood sampling is not expected to exceed 70-100 cc (5-6 tablespoons) per trial. This is far less than the amount for a routine blood donation.

The SLT, EEG recording, physiological monitoring, and mental tests should produce no undue discomfort.

GNATURE OF VOLUNTEER	DATE SIGNED	SIGNATURE OF LEGAL GUARDIAN (If volunteer is a minor)
	H-5	
AMANENT ADDRESS OF VOLUNTEER	TYPED OR PRINTED NAME AND SIGNATURE OF WITNESS	DATE SIGNED

d-AMPHETAMINE

Possible Risks and Side Effects

As you may know, amphetamines have been known to be stimulant drugs for many years. They have been extensively studied and are approved for clinical use. Amphetamines have a broad range of effects. These effects include increased heart rate and blood pressure and evidence of nervous system stimulation, including increased alertness, vigor, energy, and talkativeness. Possible side effects include tremor, nervousness, confusion, restlessness, insomnia, headache, and dryness of the mouth. There has been the extremely rare occurrence of a psychotic reaction with hallucinations. Occasional individuals find amphetamines produce feelings of fatigue.

In the event that side effects become severe, a second medication (chlorpromazine) would be used to reverse the effects of amphetamine.

There is no evidence that exposure to single low doses of amphetamine has any serious possibility of causing drug dependence.

If you have heart disease, epilepsy, psychological problems, high blood pressure, diabetes, thyroid disorder, allergies to amphetamine or similar drugs, or are taking MAO inhibitor or other antidepressants, you should not participate in this study.

SIGNATURE OF VOLUNTEER	DATE SIGNED	SIGNATURE OF LEGAL GUARDIAN (If volunteer is a minor)
PERMANENT ADDRESS OF VOLUNTEER	TYPED OR PRINTED NAME AND SIGNATURE OF WITNESS	DATE SIGNED

METHYLPHENIDATE

Possible Risks and Side Effects

Methylphenidate is a stimulant drug, related to amphetamines. It has been extensively studied over the last 30 years and is used clinically in the treatment of hyperactive children and certain sleep disorders. The effects of this drug are similar to that of amphetamine and include increased heart rate and blood pressure, and evidence of nervous system stimulation including increased alertness, vigor, energy, and talkativeness. Possible side effects include tremor, restlessness, nervousness, confusion, insomnia, headache, and dryness of the mouth. There has been the extremely rare occurrence of a psychotic reaction at this dosage.

In the event that side effects become severe, a second medication (chlorpromazine) would be used to reverse the effects of methylphenidate.

There is no evidence that exposure to single low doses of methylphenidate will lead to the possibility of stimulant drug dependence.

If you have heart disease, epilepsy, glaucoma, psychological difficulties, high blood pressure, diabetes, thyroid disorder, allergies to methylphenidate or similar drugs, or are taking MAO inhibitor or other antidepressants, you should not participate in this study.

SIGNATURE OF VOLUNTEER	DATE SIGNED	SIGNATURE OF LEGAL GUARDIAN (If volunteer is a minor)
PERMANENT ADDRESS OF VOLUNTEER	TYPED OR PRINTED NAME AND SIGNATURE OF WITNESS	DATE SIGNED

NICOTINE

Possible Risks and Side Effects

As you may know, nicotine is contained in cigarettes. Nicotine has a broad range of effects which have been well studied for many years. These effects include increased heart rate and blood pressure, increased sweating, and occasionally tremor. Side effects include dizziness, blurred vision, nervousness, nausea, headache, and vomiting. Occasional patients experience brief pain at the injection site. Nicotine will be administered by an intravenous infusion for up to 30 minutes. The intravenous catheter will then be withdrawn.

Should side effects become severe, the infusion would be discontinued. Side effects that have been seen disappear rapidly after administration of the drug is stopped. However, if side effects persisted, a second medication (mecamylamine) would be administered to reverse the effects of nicotine. Should serious side effects occur, you would not be expected to continue with the study.

If you have heart disease, asthma, ulcer disease, active thyroid disease, pyloric stenosis, uncontrolled high blood pressure, diabetes, narrow angle gluacoma, substantial prostate enlargement, epilepsy, or allergies to nicotine you should not paticipate in this study.

Mecamylamine and nicotine have been administered together without serious side effects. Mecamylamine alone can cause blurred vision, dizziness, dry mouth, abdominal cramps, and slowness in urinating.

L-DEPRENYL/TRANYLCYPROMINE

Possible Risks and Side Effects

l-Deprenyl and tranylcypromine are both similar drugs which inhibit the action of an enzyme in the body (MAO). They are used clinically here and abroad as antidepressants and in the treatment of Parkinson's disease. They are usually given on a chronic basis, but will only be given once during each study session. Acute effects of l-deprenyl or tranylcypromine are modest, but could include a sense of stimulation, alertness, or activation. Blood pressure and pulse may be briefly elevated. Possible acute side effects include uneasiness, a sense of overstimulation, nervousness, insomnia, headache, dizziness, and dryness of the mouth. If they occur, these effects should fade very quickly.

One additional precaution needs to be explained to you. As these drugs when given on a chronic basis inhibit a normally occurring enzyme in the body, they impair the body's ability to deactivate a substance called tyramine, present in certain foods, and certain other drugs that can mimic the action of tyramine. Exposure to these compounds or foods can lead to high blood levels of tyramine and convergent high blood pressure. Patients who are on these drugs chronically are consequently placed on some dietary and medication restrictions. Although the risk of adverse reactions from a single dose is extremely low, we will ask that you restrict your diet for one week after the study is completed and avoid certain medications. These restrictions are listed on the attached sheet. If you do require any medical treatment within one week, you should tell your treating physician that you have had a single dose of an "MAO Inhibitor".

If you have heart disease, epilepsy, psychological problems, high blood pressure, diabetes, thyroid disorder, allergies to MAO inhibitor drugs, or are currently taking antidepressant drugs, you should not participate in this study.

MAO INHIBITOR DRUG INCOMPATIBILITIES

CONTRAINDICATION

Stimulants:	Amphetamines ("pep pills"); cocaine; weight reducing or antiappetite drugs
Decongestants:	Sinus, hay fever, cold tablets; nose sprays or drops, asthma tablets or inhalants, cough preparations (or any products containing ephedrine, phenylephrine, or phenylpropanolamine)
Antihypertensives:	Methyldopa, guanethidine, reserpine
Antidepressants:	Imipramine, desimipramine, chlorimipramine
MAOIs:	Tranylcypromine after other MAOs
Sympathomimetics:	Dopamine, metaraminol

RELATIVELY CONTRAINDICATED (MARKED POTENTIATION)

Narcotics:	Meperidine (pethidine)
Sympathomimetics:	Epinephrine, norepinephrine, isoproterenol
General anesthetics:	All

SOME POTENTIATION POSSIBLE

Narcotics:	Morphine, codeine, etc.
Sedatives:	Alcohol, barbiturates, benzodiazepines
Local anesthetics:	Containing vasoconstrictors
Hypoglycemic agents:	Insulin, tolbutamide, chlorpropamide

INSUFFICIENT KNOWLEDGE

Antidepressants:	Maprotoline, amoxapine, trazodone

MAO INHIBITOR DIETARY RESTRICTIONS

	Examples
Aged, matured cheeses (unpasteurized)	Cheddar, Camembert, Stilton, Bleu, Swiss
Smoked or pickled meats, fish, or poultry	Herring, sausage, corned beef
Aged/putrifying meats, fish, or poultry	Chicken or beef liver, pate, game
Yeast or meat extracts	"Bovril", marmite, brewer's yeast (beware of drinks, soups, or stews made with these products)
Red wines	Chianti, burgundy, sherry, vermouth
Italian broad beans	Fava beans

NATURE OF VOLUNTEER	DATE SIGNED	SIGNATURE OF LEGAL GUARDIAN (If volunteer is a minor)
	H-11	
PERMANENT ADDRESS OF VOLUNTEER	TYPED OR PRINTED NAME AND SIGNATURE OF WITNESS	DATE SIGNED

OTHER PERTINENT INFORMATION

1. Confidentiality: When results of a study such as this are reported in medical journals or at meetings, the identification of those taking part is withheld. Medical records are maintained according to current legal requirements, and are made available for review as required by authorized users only under guidelines established by the Federal Privacy Act.

2. Payments: Payment is at the rate of $300.00 for one three-day study session.

3. For information regarding the rights of research subjects, please contact the Center Judge Advocate Office at (301) 576-4096, 4097.

INATURE OF VOLUNTEER	DATE SIGNED	SIGNATURE OF LEGAL GUARDIAN *(If volunteer is a minor)*
IMANENT ADDRESS OF VOLUNTEER	TYPED OR PRINTED NAME AND SIGNATURE OF WITNESS	DATE SIGNED

PRIVACY ACT STATEMENT

The purpose for requesting personal (e.g., health, sleep habits) information is to provide the minimum information necessary to determine if you satisfy the specific criteria for participation in this study.

This information may be used to provide full documentation of investigative studies; conduct further research; teach; compile statistical data; adjudicate claims and determine benefits; and report medical conditions required by law to other federal, state, and local agencies. It may be used for other lawful purposes including law enforcement and litigation. Even though permitted by law, whenever possible, these personal data will not be released without your consent.

The disclosure of requested information is voluntary. If the information is not furnished, and/or not available from other sources, your voluntary participation in this investigational study may be precluded.

I understand that a copy of the Volunteer Consent Sheet, together with a copy of this form, may be placed in my records as evidence of this notification, and additional copies may be retained permanently by the investigator and the U.S. Government. I have received or have declined to accept a copy of the Volunteer Consent Sheet and a copy of this form which I may keep.

_____

Volunteer Signature and Date Signed

TRANSMITTAL SLIP 15 June 83

TO: (Name, office symbol, room number, building, Agency/Post)	Initials	Date
1. COL Tynan		
2.		
3.		
4.		
5.		

Action	File	Note and Return
Approval	For Clearance	Per Conversation
As Requested	For Correction	Prepare Reply
Circulate	For Your Information	See Me
Comment	Investigate	Signature
Coordination	Justify	

REMARKS

Fred:

Attached are chapter outlines of psychopharm document for your review. If you wish to make critical comments for feedback to authors, would you return suc comments (handwritten are fine) & the outlines to me by 30 JUNE?. Each outline will also be reviewed by myself & one other committee membe

DO NOT use this form as a RECORD of approvals, concurrences, disposal clearances, and similar actions

FROM: (Name, org. symbol, Agency/Post)	Room No.—Bldg.
[signature]	Phone No.

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OSITION FORM

e AR 340-15; the proponent agency is TAGO.

YMBOL	SUBJECT
-UWI-C	Comments on Sleep chapter outline

chopharm Study Group FROM Chairman, DATE 6 July 84 CMT 1
Sleep Sub Group Psychopharm Study Group

The attached comments on your sleep chapter outline were obtained from multiple reviewers and are forwarded for your consideration.

Vince O'Donnell
CPT, MSC
Chairman

CPT Vince O'Donnell, Dept. Behav. Biology
LTC G.L. Belenky, Dept. Behav. Biology
Dr. Frederick Hegge, Dept. Behav. Biology
COL Frank Jones, Dept. Milit. Psychiatry
Dr. Jean Kant, Dept. Med. Neurosciences
CPT John Leu, Dept. Med. Neurosciences
Dr. Frank Tortella, Dept. Med. Neurosciences
CPT Jeffrey Witkin, Dept. Med. Neurosciences
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