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A Comparison of the Efficacy of Modafinil and Dextroamphetamine as Alertness Promoting Agents in Aviators Performing Extended Operations

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14. ABSTRACT

Successful military operations depend on maintaining continuous day-night operations. Stimulants are easy to use and popular for sustaining performance because their utility is not dependent on environmental or scheduling modifications. Eighteen pilots each completed 15 helicopter flights and other evaluations during two 40 hr periods of sustained wakefulness during which they received 2 of 3 experimental conditions: 3 doses at 4 hr intervals of modafinil (100mg), dextroamphetamine (5mg), or placebo. Statistical results showed that the stimulants maintained alertness, feelings of well-being, cognitive function, judgment, risk perception, and situation awareness of sleep-deprived aviators consistently better than placebo and without side effects of aeromedical concern. Like previous research, this study strongly suggests that these drugs can maintain acceptable levels of mood and performance during sleep deprivation. The results also confirm that modafinil is well tolerated and appears to be a good alternative to dextroampheatmine for countering the debilitating mood and cognitive effects of sleep loss during sustained operations.

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Introduction

Military doctrine can require Army aviation units to operate around the clock during times of conflict. The success of military operations depends on maintaining the speed and momentum of continuous day-night operations (Department of the Army, 1997). Army personnel deployed during Operation Desert Storm confirmed the difficulties associated with operational fatigue and indicated that sleep deprivation was a problem for a number of personnel even though the actual combat period was short (Caldwell, 1992). Cornum (1992) further highlighted the problem in U.S. Air Force F-15C pilots flying air combat patrol missions during Desert Storm who suffered significant circadian rhythm disruptions and fatigue from continuous sustained operations. He further noted that effective crew rest or sleep management strategies could not have been implemented due to operational constraints.

Much research has been conducted on potential strategies for sustaining military performance in situations where sleep deprivation may be a factor. Some of the current strategies include manipulating the timing and duration of sleep periods (Akerstedt & Torsvall, 1985; Bonnet, 1990; 1991) via sleep management programs or the administration of hypnotics (Babkoff & Krueger, 1992). However, these countermeasures can only work in situations where some flexibility exists in terms of personnel staffing and scheduling. During times of intense operations, administrative and behavioral interventions may not be sufficient to satisfactorily preserve performance. Even in situations where Soldiers do receive enough sleep, they may not be able to maintain appropriate levels of vigilance during long periods of overnight duty without some form of assistance. There may be times when the only viable alternative is to sustain performance through the use of stimulants.

Background

Stimulants are easy to use and popular for sustaining performance because their utility is not dependent upon environmental manipulations or scheduling modifications. This is why drugs such as dextroamphetamine have been used in several military conflicts (Miller, 1997; Emmonson & Vanderbeek, 1993). Of the alertness-promoting compounds currently available, caffeine, dextroamphetamine, and modafinil have been shown to be effective in a variety of situations and appear to hold the most promise for use in aviation operations (Akerstedt & Ficca, 1997). The current edition of the U.S. Army Flight Surgeon's Aeromedical Checklists (2008) authorizes the use of dextroamphetamine for sustained flight operations. It provides the following guidance:

> DEXEDRINE: May use in dosages of 5 mg or 10 mg not to exceed 30 mg in 24 hour period. May not use to prevent sleep for longer than 64 continuous hours. Be aware of the after effects of sustained use of stimulants due to its long half- life of 10.25 hours. For example, aviators have required two 8-hour night sleep periods following 64 hours of continuous wakefulness using Dexedrine to recover near normal sleep architecture.

Previous research indicating the potential of modafinil for use in aviation applications led to the joint funding of the present study by the U.S. Special Operations Command Biomedical

Initiative Steering Committee (SOCOM BISC) and the U.S. Army Medical Research and Materiel Command (USAMRMC). Despite a robust body of laboratory evidence showing modafinil to be a very well tolerated drug, the SOCOM BISC's goal for funding this study was to establish the efficacy and safety of modafinil during actual flying operations, thus providing the face or operational validity desired to approve the use of modafinil for actual military flight operations and field conditions.

To date, the usefulness of modafinil, specifically for aviation settings, has been evaluated in three controlled aviation simulation studies (Caldwell et al., 2000b; Caldwell et al., 2004; LeDuc et al., 2009). Caldwell et al. (2000b) found that 3 daily doses of 200 mg (given at 2300, 0300, and 0700 during a 40-hour period of continuous wakefulness) maintained flight performance at rested levels and attenuated the effects of 40 hours of continuous wakefulness on fatigue, confusion, and physiological arousal. There were negligible effects on temperature, heart rate and blood pressure. No adverse behavioral effects were noted however vertigo, nausea, and dizziness were reported as side effects in some subjects. The frequency of these side effects is shown in table 1.

Table 1.
Side effects observed in the Caldwell et al. (2000b) six subject simulator study of the efficacy of modafinil (3 x 200 mg split doses for a total of 600 mg).

Symptom	Modafinil Condition	Placebo Condition
Nausea	18 instances reported by 4 subjects	4 instances reported by 1 subject*
Vertigo	10 instances reported by 4 subjects	1 instance reported by 1 subject*
Nervousness	7 instances reported by 3 subjects	0 instances reported
Dizziness	5 instances reported by 3 subjects	1 instance reported by 1 subject

* The same individual reported this symptom under both drug conditions.

In a subsequent simulator study, Leduc et al. (2009) found evidence that lower doses of modafinil (3 x 100 mg versus Caldwell's 3 x 200 mg) could maintain alertness without causing the side effects reported by Caldwell et al. (2000b) that would be incompatible with flying duties or other demanding military jobs. Results from the LeDuc et al. study support the idea that the side effects reported by volunteers in the Caldwell et al. study were most likely the result of the modafinil dose (as suggested by a study by Buguet et al., 2003). Statistical comparisons showed that side effects reported by LeDuc's modafinil group were either equal to or less than those reported by the placebo control group (see figures 1 and 2).

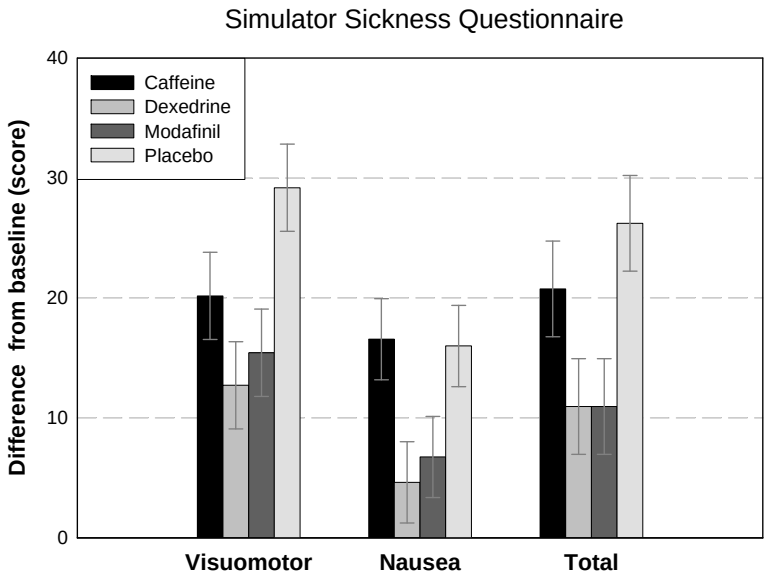

Figure 1. Self reports of simulator sickness (LeDuc et al., 2009).

As depicted in figure 1, self-reported eye strain, nausea, and total symptom severity were elevated in all groups. However, ratings in the placebo and caffeine groups were significantly higher than in the dextroamphetamine and modafinil groups. It further appears that both dextroamphetamine and modafinil may have protected against the increase in nausea (figures 1 and 2). This current effort, an in-flight study using a real helicopter, employed the same lower doses of the drugs as did LeDuc et al. (2009) (3 x 5 mg dextroamphetamine and 3 x 100 mg modafinil).

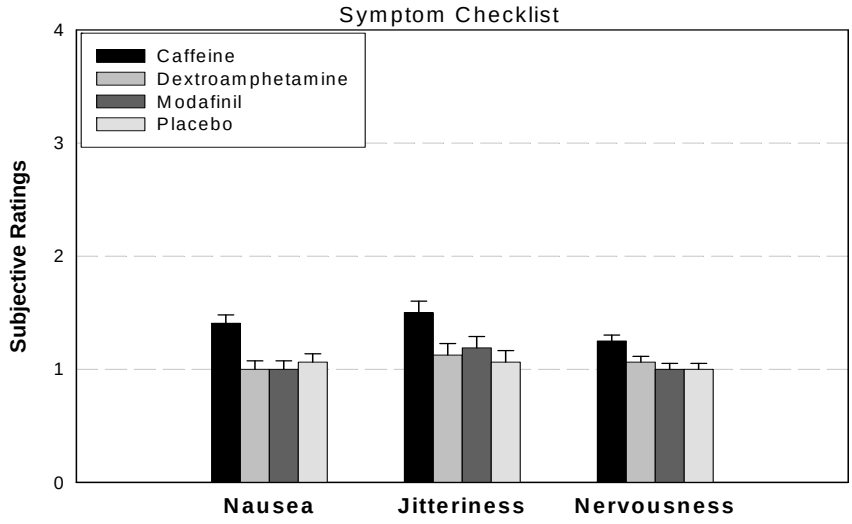

Figure 2. Self reports of symptoms produced by drug administration from the symptom checklist (LeDuc et al., 2009).

Drug information

See appendix A for drug (product) monographs. In addition, elimination kinetics of dextroamphetamine and modafinil are detailed in the Results section below.

Dextroamphetamine

Dextroamphetamine (d-alpha-methylphenthylamine) is a synthetic stimulant that has been marketed in the United States (U.S.) under the trade name Dexedrine® (SmithKline Beecham) since the 1960s. Dextroamphetamine is approved by the FDA for two indications: 1) treatment of the symptoms of the sleep disorder narcolepsy (excessive daytime sleepiness and uncontrollable sleep bouts); 2) treatment of the symptoms of attention-deficit disorder with hyperactivity (ADHD), including hyperactivity, distractibility, limited attention span, emotional lability, and impulsivity. The stimulant effects of dextroamphetamine occur through widespread dopaminergic (DA) action, including high-affinity binding to the DA receptor and blocking of DA reuptake. Laboratory investigations have shown that single doses (20 mg) of dextroamphetamine can return cognitive performance to baseline levels and maintain this recovery after 48 hours of total sleep deprivation (Newhouse et al., 1989). Multiple 10-mg doses of dextroamphetamine, administered prophylactically, will sustain the performance of pilots for as long as 64 hours (Caldwell et al., 1999b; Caldwell et al., 2000a). U.S. Air Force EF-111A Raven jet crews were administered 5 mg dextroamphetamine during a strike on Libya in April of 1986, and were able to overcome the fatigue of the mission and the sleep deprivation that occurred in preparation for the mission (Senechal, 1988). F-15C pilots, flying lengthy combat air patrol missions during Operation Desert Shield/Storm while suffering from sleep deprivation and circadian disruption, also benefited from the use of 5 mg tablets of dextroamphetamine (Cornum, 1992). It is authorized for use in sustaining performance by the aircrews of all three U.S. military services.

Modafinil

Modafinil is a relatively new psychostimulant that holds promise for sustaining performance during continuous operations. Modafinil (2-[(diphenyl-methyl)-sulfiny] acetamide), a synthetic stimulant, has been available in the United States as a schedule IV drug under the trade name Provigil® (Cephalon, Inc.) since late 1998. Modafinil is approved by the FDA for treating symptoms of narcolepsy and for use in shift work disorder. Modafinil is believed to exert its stimulant effects by acting as an antagonist to the dopamine reuptake transporter. Modafinil may also act to increase the extracellular levels of dopamine (Wisor et al., 2001), although the mechanism(s) by which this occurs remain unclear. In contrast to dextroamphetamine, modafinil displays very low affinity for dopamine uptake binding sites (Mignot, Nishino, Guilleminault, & Dement, 1994). In 2003, the U.S. Air Force authorized the use of modafinil for certain missions. Doses of 200 mg (not to exceed 400 mg within 24 hours) can be administered to pilots of two-seater bomber missions greater than 12 hours in duration and for F-15C missions longer than eight hours. To date, modafinil has not been approved for single-seat operations (BNET, 2010).

Hypotheses and objectives

The intent of this work was to evaluate the positive and negative effects of lower doses of modafinil and dextroamphetamine on crew behavior and performance under both in-flight and laboratory conditions. This assessment includes comparisons of modafinil (100 mg) and dextroamphetamine (5 mg) to placebo.

Hypothesis 1. Continuous sleep deprivation of 40 hours will impair flight performance, cognitive skills, vigilance, judgment, alertness, mood, situational awareness, and decision-making, and increase risk taking.

Hypothesis 2. Compared to placebo, modafinil and dextroamphetamine will yield significantly better performance on tests of flight performance, cognitive abilities, vigilance, judgment and risk taking, alertness, mood, situational awareness, and decision-making.

Hypothesis 3. Volunteers will not experience negative symptoms or serious side effects during flight when 3 doses of 100 mg of modafinil or 3 doses of 5 mg of dextroamphetamine administered at 4-hour intervals during the course of the 40 hour sustained operations scenario.

Objective 1. Determine the degree to which 3 doses of 100 mg of modafinil or 3 doses of 5 mg of dextroamphetamine administered at 4-hour intervals sustains flight performance, cognitive skills, vigilance, judgment and risk taking in a friend/foe task, alertness, mood, situational awareness, and decision-making throughout 40 hours of continuous wakefulness.

Objective 2. Determine whether there are operationally significant side effects associated with administration of 3 doses of 100 mg of modafinil or 3 doses of 5 mg of dextroamphetamine administered at 4-hour intervals during the course of the 40 hour sustained operations scenario.

Objective 3. Compared to a placebo condition, evaluate whether performance can fully recover after a full night of sleep following 40 hour period of wakefulness during which 3 doses of 100 mg of modafinil or 3 doses of 5 mg of dextroamphetamine administered at 4-hour intervals are taken.

Objective 4. Compare the effects of 3 doses of 100 mg of modafinil and 3 doses of 5 mg dextroamphetamine administered at 4-hour intervals to previous work conducted at USAARL (200 mg modafinil [Caldwell et al., 1999a], 10 mg dextroamphetamine [Caldwell et al., 1999b] and 100mg modafinil and 5 mg dextroamphetamine [LeDuc et al., 2009]) in order to provide more clear guidance regarding dosage levels and timing strategies.

Objective 5. Determine the most effective agent in maintaining alertness in aviators by comparing 3 doses of 100 mg of modafinil and 3 doses of 5 mg of dextroamphetamine administered at 4-hour intervals during the course of a 40 hour sustained operations scenario.

Methods

Demographics

Eighteen UH-60 rated aviators were recruited for this research (17 male, 1 female; reflecting the population ratios from which volunteers were drawn of approximately 90-95% male). Fifteen participants were members of active Army units while three were members of the Army

National Guard. The population of volunteers was composed of UH-60 Black Hawk helicopter rated aviators, having flown within the previous 60 days (current in the aircraft), between the ages of 19 and 50. An upper limit of 50 was imposed based on research showing that total sleep time and other sleep parameters associated with cognitive performance independent of sleep deprivation and/or drug administration can change significantly in older individuals (e.g., Van Cauter, Leproult, and Plat, 2000), possibly introducing a substantial source of error variance into the study. This population's age ranged from 22 to 38 years of age with a mean of 29.5 years. Body weight ranged from 127 to 234 pounds with an average weight of 183 pounds. Specific flight experience data (flight hours flown) were not collected, however, based on the distribution of participant military ranks (from Warrant Officer 1 to Major), flight experience likely ranged from less than 500 hours to over 2000 hours.

All volunteers freely gave their informed consent and completed the study. Volunteers received no monetary compensation for participation although costs associated with travel to and from the U.S. Army Aeromedical Research Laboratory (USAARL) were reimbursed. During their participation, all volunteers were placed in a "temporary duty" or TDY status at USAARL.

Medical screening

Potential participants were medically screened by a study physician (flight surgeon) for disqualifying acute and chronic health and/or mental conditions (see exclusion criteria, appendix B). They were also excluded if they related any history of a sleep disorder or recent daily caffeine intake exceeding 600 mg, herbal supplements or remedies containing caffeine, or reported use of any drug which, based on its known pharmacokinetics, would not have been cleared from the body by 48 hours prior to participation. Volunteers were neither allowed to consume caffeine during the test week nor take any medications or dietary supplements without permission from the study flight surgeon.

Study design

This study employed a balanced, incomplete block (split-plot) design (6 condition groups [table 2], 3 per group, for a total of 18 subjects) in which two participants at a time experienced two 40-hour sleep-deprivation periods. During one deprivation period, subjects were given modafinil (3 doses of 100 mg), dextroamphetamine (3 doses of 5 mg) or placebo (3 doses) at 4-hour intervals.

Table 2.
Condition groups (three subjects per group).

	1st Condition	2nd Condition
Condition Group 1	modafinil	placebo
Condition Group 2	placebo	modafinil
Condition Group 3	dextroamphetamine	placebo
Condition Group 4	placebo	dextroamphetamine
Condition Group 5	modafinil	dextroamphetamine
Condition Group 6	dextroamphetamine	modafinil

For economic and staffing considerations, qualified and interested individuals were to be scheduled to participate in pairs in one of nine study sessions (each lasting one week for a total of nine weeks). The original plan was to schedule two subjects (Participants A and B) in a pseudo-random fashion to one of the nine drug orders (table 3) with the pairing order randomized by the medical monitor (who is not involved in data collection) prior to commencement of the study. The planned pairings in table 3 ensured that each drug condition (modafinil, dextroamphetamine, or placebo) was administered first in six of the deprivation periods and second in six of the deprivation periods. Due to recruitment and scheduling challenges, a change to the protocol was requested and approved which allowed for one participant to be tested per week when two could not be recruited and scheduled together. This occurred four times. Therefore, the result was that although the study required 11 weeklong sessions instead of nine, the drug order remained the same (table 4). In illustration, during the third weeklong session, Subject 5 participated without a partner and received modafinil first and then dextroamphetamine. In the next weeklong session, Subject 6 also participated alone and received dextroamphetamine followed by placebo as called for by the original drug order plan. It is important to note that whenever two participants experienced the same sleep deprivation period together, each was assessed as an individual, not as a team. In other words, the performance of one was independent of the performance of the other. Therefore, it was of no consequence whether one participant was on one drug condition while the other was on another or whether a participant was partnered with another or participated alone during their session.

Table 3.
Original drug order plan.

	Session	Participant A	Participant B
M = modafinil D = dextroamphetamine P = placebo	1	MD	DM
	2	MD	PM
	3	MD	DP
	4	PD	DM
	5	PD	MP
	6	PD	DP
	7	DP	MP
	8	DM	PM
	9	MP	PM

Table 4.
Actual drug order plan.

	Session	Participant A	Participant B
M = modafinil D = dextroamphetamine P = placebo	1	MD	DM
	2	MD	PM
	3	MD	
	4		DP
	5	PD	DM
	6	PD	MP
	7	PD	DP
	8	DP	MP
	9	DM	PM
	10	MP	
	11		PM

Procedure

The protocol was approved by the USAMRMC Human Subjects Research Review Board (HSRRB). Table 5 shows the detailed schedule of activities that occurred throughout a typical week of testing. The schedule was designed to test sleep deprivation, initial drug effects, and then drug sustained effects over time. Drug dosing occurred every 4 hours in order to replicate the dosing procedures in several previous studies involving modafinil and dextroamphetamine (Caldwell et al., 1994; 1996; 1998; 1999a; 1999b; Leduc et al., 2009).

At 1500 hours (hrs) on Day 1, volunteers reported to USAARL. From 1500 to 1800 hrs, they were given time to read the informed consent statement, ask questions, and sign the document if they wished to participate. Each volunteer provided written informed consent before participating. The medical exam included the collection of vital signs. Eating and drinking was permitted at any time throughout the duration of the study except when the volunteers were being tested. Throughout the sleep laboratory, ambient lighting was maintained at approximately 500 lux (except during sleep periods, when bedroom lights were turned off), and ambient room temperature was maintained at approximately 23 degrees Celsius. An Actiwatch® was issued to each participant. Each Actiwatch® was identifiable by serial number and matched to the subject number. The donning of each Actiwatch® on the subject's non-dominant wrist was supervised by the research team to ensure proper placement. The Actiwatch® remained on the arm for the duration of the study. At 1800 hrs, volunteers were allowed to participate in physical training (PT) until 1900 hrs when they showered and had dinner. At 2000 hrs, they were given instructions, familiarization, and practice on the EST (Engagement Skills Trainer) 2000 (small arms simulator) and other psychological, physiological, and cognitive (PPC) computerized tasks (table 6). At approximately 2245, each volunteer was escorted to his/her own comfortable, sound-attenuated bedroom where they were allowed to sleep undisturbed from 2300 to 0700 hrs on Day 2.

On Day 2, volunteers were awakened at 0700 hrs and allowed time for personal hygiene and to eat a meal. The female volunteer was escorted to the Lyster Army Health Clinic (LAHC) where a urine sample was provided to ensure she was not pregnant. Practice on all tests began at 0900 hrs and continued throughout the day until 2230 hrs. At approximately 2245 hrs, each volunteer was escorted to his/her bedroom where they were allowed to sleep undisturbed from 2300 to 0700 hrs on Day 3. Baseline testing, including flight testing in the actual aircraft, began at 0900 hrs and continued throughout the day until 2230 hrs on Day 3. At 16 hours post wake (2300 hrs), volunteers were administered the first of three split dose of placebo, dextroamphetamine, or modafinil. Sleep deprivation data collection began at 2310 hrs. The second split dose was administered at 0300 hrs and the last split dose was given at 0700 hrs. Testing continued throughout the day and evening. At approximately 2245 hrs, each volunteer was escorted to his/her bedroom where they were allowed to sleep undisturbed from 2300 to 0700 hrs on Day 5.

Following personal hygiene and breakfast, testing resumed at 0900 hrs on Day 5 and continued through the evening. At 16 hours post wake (2300 hrs), volunteers received the first of three split dose of placebo, dextroamphetamine, or modafinil. The second sleep deprivation data collection period began at 2310 hrs. The second split dose was administered at 0300 and the last split dose was given at 0700 hrs. Testing continued throughout Day 6 and into the evening. At approximately 2245 hrs, each volunteer was escorted to his/her bedroom where they were allowed to sleep undisturbed from 2300 to 0700 hrs on Day 7.

At 0700 hrs on Day 7, volunteers were awakened, allowed time for personal hygiene and fed breakfast. Post-recovery sleep testing resumed at 0900 hrs and continued until 1300 hrs. Following completion of tests and lunch, volunteers were administered a brief medical examination by the study physician prior to being cleared for release from the study. During the medical exam, vital signs were taken (heart rate, blood pressure, and temperature) and the volunteer was asked about any symptoms or complaints he or she might have. In every case, the study physician found the volunteers to be in good health, with no significant symptoms or complaints, and cleared the volunteer for release from the study. Volunteers were then debriefed and released at 1500 hrs on Day 7.

Table 5.
Testing schedule.*

	SUN	MON	TUE	WED	THU	FRI	SAT
	In-Proc./ Day 1	Training/Day 2	Baseline 1/Day 3	Testing 1/Day 4	Baseline 2/Day 5	Testing 2/Day 6	Recovery/Day 7
23:00		Sleep	Sleep	**Dose A** PPC Testing	Sleep	**Dose B** PPC Testing	Sleep
00:00				Aircraft Flight Testing		Aircraft Flight Testing	
01:00							
02:00				EST 2000 Testing		EST 2000 Testing	
03:00				**Dose A** PPC Testing		**Dose B** PPC Testing	
04:00				Aircraft Flight Testing		Aircraft Flight Testing	
05:00							
06:00				EST 2000 Testing		EST 2000 Testing	
07:00		Wake/Shower	Wake/Shower	**Dose A** PPC Testing	Wake/Shower	**Dose B** PPC Testing	Wake/Shower
08:00		Breakfast (US)	Breakfast	Breakfast	Breakfast	Breakfast	Breakfast
09:00		EST 2000 Practice	EST 2000 Baseline	Aircraft Flight Testing	EST 2000 Testing	Aircraft Flight Testing	EST 2000 Testing
10:00		PPC Practice	PPC Baseline	EST 2000 Testing	PPC Testing	EST 2000 Testing	PPC Testing
11:00		Aircraft Flight Practice	Aircraft Flight Baseline	PPC Testing	Simulator Flight Testing	PPC Testing	Simulator Flight Testing
12:00							
13:00		Lunch	Lunch	Lunch	Lunch	Lunch	Lunch
14:00		EST 2000 Practice	EST 2000 Baseline	EST 2000 Testing	EST 2000 Baseline	EST 2000 Testing	Med exam: release
15:00	- Consent - Medical exam - Actiwatch placement - Lab tour	PPC Practice	PPC Baseline	PPC Testing	PPC Testing	PPC Testing	
16:00		Aircraft Flight Practice	Aircraft Flight Baseline	Aircraft Flight Testing	Simulator Flight Testing	Aircraft Flight Testing	
17:00							
18:00	PT	PT	PT	PT	PT	PT	
19:00	Shower/ Dinner	Shower/ Dinner	Shower/ Dinner	Shower/ Dinner	Shower/ Dinner	Shower/ Dinner	
20:00	EST 2000 Zeroing	EST 2000 Practice	EST 2000 Baseline	EST 2000 Testing	EST 2000 Baseline	EST 2000 Testing	
21:00	PPC Practice with instructions	PPC Practice	PPC Baseline	PPC Testing	PPC Testing	PPC Testing	
22:00		Break	Break	Break	Break	Break	

* PT = Physical Training; PPC = Psychological, Physiological, Cognitive; US = urine sample (females only)

Table 6.
Psychological, physiological, and cognitive (PPC) tests.

Test	Duration (minutes)
Vital Signs (oral temp, blood pressure, heart rate)	5
Symptom Checklist (SC)	2
Motion Sickness Questionnaire (MSQ)	5
Evaluation of Risk (EVAR)	5
Visual Analogue Scale (VAS)	3
Profile of Mood States (POMS)	3
Balloon Analog Risk Test (BART)	8
Psychomotor Vigilance Task (PVT)	10
Iowa Gambling Task (IGT)	20
Cambridge Neuropsychological Test Automated Battery (CANTAB)	
- Rapid Visual Information Processing (RVP)	7
- Stockings of Cambridge (SOC)	10
- Spatial Working Memory (SWM)	8
Total time	86

Materials

Physiological measures

Vital signs

Oral temperature, blood pressure, and heart rate were recorded upon arrival on Day 1, then during each PPC period per tables 5 and 6. For oral temperature, blood pressure, and heart rate, an IVAC Model 4200 VitalCheck was used. These measurements were taken to monitor general health status as well as to determine whether stimulant agents exerted thermoregulatory and cardiovascular effects.

Urinalysis

A urine sample was collected from the sole female volunteer during the breakfast hour of Day 2 to be used for urine pregnancy screening. Negative results were returned well before any drug administration occurred on Day 4. As all volunteers were on flight status, it was predetermined to be unnecessary to perform urine drug screens.

Actiwatch® activity monitoring system

Volunteer activity data was collected through the use of the Actiwatch® activity monitoring system. The Actiwatch® is a small, lightweight, limb-worn, device which utilizes an accelerometer to monitor the occurrence and degree of motion. The sensor integrates the degree

and speed of motion and produces an electrical current that varies in proportional magnitude at a sampling rate of up to 32 Hertz (Hz). It contains an omnidirectional sensor and is thus, sensitive to motion in all directions. Once collected, the data is wirelessly downloaded to a reader that is connected to a personal computer. Accompanying Actiwatch® software allows the manipulation, analysis, and presentation of the data.

Questionnaires

Symptom Checklist (SC)

The two-minute SC (Appendix B) was administered during each PPC period per tables 5 and 6 to determine if volunteers were currently experiencing a series of symptoms. These symptoms correspond to adverse effects most frequently reported following administration of modafinil and dextroamphetamine as per product monographs (Appendix A), as well as those adverse effects leading to discontinuation of the agents as cited in the product monographs.

Motion Sickness Questionnaire (MSQ)

Subjective sickness symptoms were measured using the MSQ (Kellogg, Kennedy, & Graybiel, 1965; Appendix C). The MSQ is a self-report form consisting of 28 items that are rated by the participant in terms of severity on a 4-point scale. The MSQ yields four scores: a nausea, oculomotor, disorientation, and total motion sickness score. Nausea scores were derived from the self assessment of general discomfort, increased salivation, sweating, nausea, difficulty concentrating, stomach awareness, and confusion. Oculomotor disturbance scores are derived from self assessment of general discomfort, fatigue, headache, eyestrain, difficulty focusing and concentrating, and blurred vision. Disorientation scores combine reports of focusing difficulties, nausea, fullness of the head, blurred vision, dizziness with eyes open and/or closed, and vertigo. The total symptom severity score is an aggregate of all of the symptoms. Administered during each PPC period, it took approximately five minutes to complete.

Evaluation of Risks Questionnaire (EVAR)

Impairments in judgment are often apparent in situations where an individual engages in behavior where the risks far outweigh the probable advantages. The propensity to engage in or avoid risky behavior and situations was assessed by a brief 24-item paper and pencil questionnaire (Appendix D) that has been used effectively to measure individual variability in risk assessment in previous research with Special Operations Forces (Sicard et al., 2001). Individuals marked a point along a 100 (millimeter) mm bipolar visual analogue scale to indicate their preference for various types of risky activities. Administration time was approximately five minutes during each PPC period.

Visual Analogue Scale (VAS)

The VAS (Appendix E) consists of eight 100 mm lines centered over the adjectives ‘alert/able to concentrate’, ‘anxious’, ‘energetic’, ‘feel confident’, ‘irritable’, ‘jittery/nervous’,

‘sleepy’, and ‘talkative’ (Penetar et al., 1993) to measure subjective alertness and mood. The extremes of each line correspond to ratings of ‘not at all’ and ‘extremely.’ Scores consist of the distance of the participant’s mark from the left end of the line in mm. The task was presented via computer during the PPC periods and took approximately three minutes (Appendix I).

Profile of Mood States (POMS)

The POMS (McNair, Lorr, & Droppleman, 1992; Appendix F) is a 65-item adjective checklist that measures current mood states along six subscales: tension-anxiety, anger-hostility, depression-dejection, vigor-activity, fatigue-inertia, and confusion-bewilderment. It took approximately three minutes to take during each PPC period. Volunteers rated themselves from 1 (not at all) to 5 (extremely) for each mood-related adjective.

Computerized performance tests

Psychomotor vigilance task (PVT)

During each PPC, participants completed a 10-minute PVT. Using a handheld device, a pushbutton response to the visual stimulus (presented with an inter-stimulus duration of 1-10 seconds) was required. Data consisted of simple reaction time from stimulus onset to response, number of lapses (responses greater than 500 [milliseconds] ms), and number of anticipatory “false” responses.

Balloon Analog Risk Test (BART)

The BART is an eight minute computer-based risk assessment test which requires the subject to pump balloons to gain play dollars. If the balloon bursts, no money is gained. It was administered during each PPC period.

Iowa Gambling Task (IGT)

The IGT is a 20-minute computerized test administered during the PPC period involving the simple task of choosing cards from decks with differing pay/loss ratios. It measures the ability to make cost/benefit analyses and the adjustment of risk to one’s own benefit. It is a well-established test of the ability to properly assess risk.

Cambridge Neuropsychological Test Automated Battery (CANTAB)

The CANTAB employs touch-screen technology and rapid, non-invasive, language-independent cognitive tests. It is well validated and suitable for repeated measures testing. The following subtests were chosen based upon a review of published reports that have used CANTAB to assess stimulant effects. In addition, these subtests have proven their sensitivity in previous USAARL stimulant studies. These selected CANTAB subtests were administered during the PPC period and took a total of 25 minutes.

Rapid Visual Information Processing (RVP). The RVP is a 7-minute subtest of visual sustained attention with a small working memory component. A white box is displayed in the center of the computer screen, inside which are digits (from 2 to 9) displayed in a pseudo-random order, at the rate of 100 digits per minute. The subject must detect consecutive odd or even sequences of digits (for example, 2-4-6) and respond by pressing the touch pad.

Stockings of Cambridge (SOC). This is a test of spatial planning based upon the 'Tower of London' test. The subject is shown two displays containing three colored balls. The displays can easily be perceived as stacks of colored balls held in stockings or socks suspended from a beam. This arrangement assists subjects to come to grips with some of the rules of the problems which involve 3-D concepts, and to fit in with the verbal instructions. The subject must use the balls in the lower display to copy the pattern shown in the upper one. The subtest took 10 minutes to complete.

Spatial Working Memory (SWM). This is a test of the subject's ability to retain spatial information and to manipulate remembered items in working memory. It is a self-ordered task, which also assesses heuristic strategy. A trial begins with a number of colored squares (boxes) being shown on the screen. The overall aim is that the subject should find a blue 'counter' in each of the boxes and use them to fill up an empty column on the right hand side of the screen. The subject must touch each box in turn until one opens with a blue 'counter' inside (a search). Returning to an empty box already sampled on this search is an error. It was an eight minute subtest.

Engagement and Skills Trainer (EST2000) marksmanship performance

The EST2000 is the Army's primary small arms weapons simulator (figure 3). It is designed for use as a military firing range simulator and can be used to program friend/foe scenarios. This allows for the assessment of weapons accuracy and friend/foe detection in sleep deprived volunteers in a controlled environment without the use of live ammunition. The weapons are slightly modified to interface with the system but still maintain their form, fit, feel, and function. The USAARL EST 2000 includes five firing position lanes. The usual parameters of number of rounds fired, number of hits, misses, friends killed, foe killed, and accuracy of fire, are augmented by USAARL's special data collection software which also allows shot radius (accuracy in the form of distance of the shot from center of mass of the target), reaction time (latency of trigger pull from the time of target presentation), and root mean square distance from target center of mass as a measure of aiming drift. The simulations took approximately 40 minutes.

Figure 3. USAARL Engagement and Skills Trainer (EST2000) firing range.

Flight Performance

This study is characterized as an *in-flight* study and all data collection flights were originally planned to occur in an actual UH-60A Black Hawk helicopter. An unforeseen tripling of worldwide oil prices made the cost of the original plan cost prohibitive. As a strategy to preserve the research effort and still evaluate flight performance under mostly actual flight conditions, three of the flights, all occurring during the drug recovery periods, were changed to flights performed in the USAARL's NUH-60 Black Hawk Research Flight Simulator (AEROMED). The same research flight profile was followed regardless of whether the flight took place in the USAARL NUH-60 Black Hawk Research Flight Simulator (figure 3) or in the USAARL JUH-60 Black Hawk Research Helicopter (figure 4). Repetition of the exact flight route in either the simulator or aircraft was possible due to the simulator's geo-specific visual database (satellite imagery of actual geographical areas), which allows the pilot to see the same geographic scenes as in the real world. In other words, this visual database allowed the simulator operator to present to the pilot the same visual scenery of the 200-mile area surrounding Fort Rucker, AL, where the data collection flight was conducted. Hence, participants saw the same visual environment (i.e., terrain, airfields, streets, population centers) in the simulator as they did when flying the actual aircraft.

Flight evaluations involved a variety of flight maneuvers (table 7). The same maneuver sequence was used for every flight. This set of standardized visual and instrument precision maneuvers formed a flight profile designed to provide a systematic method for detecting changes in flight performance as a function both of time and the subject's alertness. There were ten standardized maneuvers in the profile: stationary hover, an instrument takeoff, two straight-and-levels, one standard-rate turn, one climbing turn, one intercept turn, two segments of an instrument landing system (ILS) approach, and one missed approach procedure. Participants

were instructed to maintain prescribed flight standards (airspeed, heading, altitude, roll, etc.) depending on the individual flight maneuvers listed in table 7.

Table 7.
Flight maneuvers.

#	MANEUVER DESCRIP-TION	HEADING /TRACK* (degrees)	ALT (feet)	RATE OF CLIMB/ DESCENT (feet per min)	AIR SPEED (knots indicated)	TIME (mins)	MEASURES	START/STOP MANEUVER
1	Stationary Hover	200	10 AGL (above ground level)	0	0	2	Heading, Altitude	Start: Established hover Stop: 2 minutes
2	Instrument Takeoff	200	10 AGL to 800 MSL (mean sea level)	+500	0 to 80	1	Climb rate, Airspeed	Start: Collective Increase for Takeoff Stop: Collective Reduction for 800 MSL
3	Straight and Level 1	210 (Dalton-Beaver Dam)	800 MSL	0	120	2	Heading, Altitude, Airspeed	Start: Hdg 240 Stop: 2 mins
4	Straight and Level 2	130 (Beaver Dam-High Falls)	800 MSL	0	120	3	Heading, Altitude, Airspeed	Start: Hdg 130 Stop: 3 mins
5	Left Standard Rate Turn	From 130, full 360 degree turn	800 MSL	0	120	2	Altitude, Airspeed, Turn rate	Start: At start of turn Stop: At roll out
6	Climbing Right Turn	130 to 310	800- 2000 MSL	+1000	120	2.2	Rate of Climb, Airspeed	Start: Upon turn from heading 130/310 and coll. Increase for climb Stop: Level 2000’
7	13 DME (Distance Measuring Equipment) Intercept Turn	From 310 to localizer intercept	2000 MSL	0	120	3	Altitude, Airspeed	Start: At start of turn Stop: Roll out on localizer
8	Instrument Landing System	061*	2000 MSL	0	120	3	Altitude, Airspeed, Localizer Course	Start: Established 061 course Stop: At GS intercept point
9	Instrument Landing System	061*	2000 MSL to 498 MSL	-540	120	2.8	Airspeed, Localizer Course	Start: Glide slope intercept Stop: Middle marker
10	Missed Approach	061	498 MSL to 800 MSL	+500	120	1	Airspeed, Heading	Start: Collective increase at execution of MAP Stop: 800 MSL

Whenever a volunteer pilot was flying the aircraft, a well-rested, pilot-in-command, USAARL research safety instructor pilot was in the left front seat of the aircraft with access to the flight controls. This was to ensure the safe operation of the aircraft when the sleep-deprived volunteer pilot was on the flight controls. The USAARL research pilot always retained final decision authority during all phases of the flight profile. The volunteer pilot performed the duties of co-pilot from the right front seat and took directions from the USAARL research pilot who directed the performance of the flight maneuvers as specified in the research flight profile.

When two volunteers participated during the same week, the first volunteer pilot to fly was driven the five minute drive to Lowe Army Heliport (LOR) (the airfield where the USAARL aircraft is based and maintained). Here the volunteer joined the USAARL research pilot who had prepared the helicopter for flight. The USAARL research pilot would fly the helicopter from LOR to the USAARL helipad (a three minute flight; located in front of the laboratory). After landing, the USAARL research pilot would transfer the controls to the volunteer pilot who would begin performing the flight maneuvers per the flight profile. Upon completion of the maneuvers, the USAARL pilot would land the aircraft once again at the USAARL helipad. The first volunteer would disembark and be replaced by the second volunteer pilot. When ready, the flight profile would be repeated and performance data collected for the second pilot. Upon completion of the maneuvers, the USAARL pilot would take the flight controls and fly the helicopter to LOR for landing and termination. After aircraft shutdown, the second volunteer pilot was transported, by car, back to the USAARL for follow-on testing.

The extent to which each pilot performed the standard maneuvers listed in table 7 was determined by computerized scoring. The scoring calculated RMS errors (among other calculations) for the measures within each of the flight maneuvers to express how well participants maintained specific headings, altitudes, airspeeds, and other parameters. Each flight profile lasted approximately 35 minutes.

NUH60 Black Hawk Research Flight Simulator

All simulator flights were conducted in the USAARL NUH-60 Black Hawk Research Flight Simulator (AEROMED) (figure 4). The AEROMED is a unique flight simulator instrumented for research data collection. It consists of a compartment containing a cockpit, an instructor/ operator station, and an observer station. It is a six-degree-of-freedom motion system which is equipped with a system of six-Dell precision 450 personal computer (PC) visual image generator that simulates natural helicopter environment surroundings for day, dusk, and night with blowing sand or snow. The AEROMED's Research Data Acquisition System (RDAS) is used to collect the flight performance data and consists of a Dell Latitude laptop computer that can sample and store up to 128 variables of flight parameters at a rate of 30 frames per second. Flight performance data were recorded while the volunteer was the pilot on the controls and marked at precise intervals by a USAARL research aviator using the RDAS. The research aviator operated the simulator and supervised all aspects of the flight from the rear of the simulator compartment, acting as air traffic control and, if needed, as a copilot. Finally, the RDAS was used to calculate scores for a variety of measures within each of the flight maneuvers to express how well

participants maintained specific headings, altitudes, airspeeds, and other parameters (see Caldwell et al., 1994, for a detailed discussion).

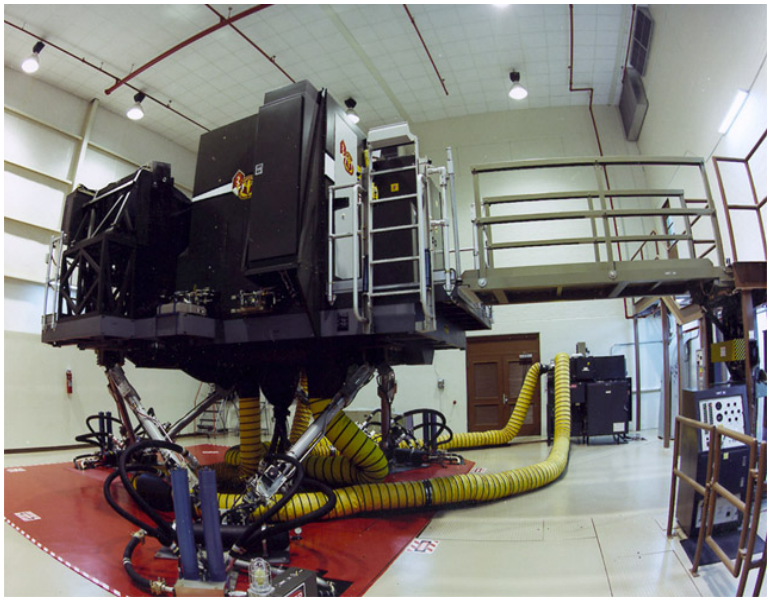

Figure 4. USAARL NUH-60 Black Hawk Research Flight Simulator (AEROMED).

JUH-60 Black Hawk Research Helicopter

The USAARL JUH-60 Black Hawk Research Helicopter (figure 5) is uniquely equipped with an instrumentation package, called the Aeromedical Instrumentation System (AIS), to measure and record pilot performance. The AIS consists of an aircraft wiring harness, a multi-channel signal conditioner, an analog-to-digital converter, and a computer for storing flight data. Permanently installed in the aircraft, the wiring harness connects to the aircraft's flight control, pitot-static, navigation, and other electronic systems. The signal conditioner is located on a removable floor-mounted rack in the rear cabin area. Signal output from the conditioner is converted to digital form by a data acquisition unit and stored in the computer's memory. The analog to digital converter is a Measurement Computing USB (universal serial bus) 2533 with 64 single-ended analog input channels, 16-bit resolution, and 1 MHz throughput. All 32 AIS channels are routed to the analog to digital converter where they are converted and sent to a laptop PC via a USB. Scaling is performed by the PC with calibration values determined prior to the flight. The data is stored as a Microsoft Excel ".csv" file. The channels recorded, recording time, and data file names are all user defined.

Figure 5. USAARL JUH-60 Black Hawk Research Helicopter.

Results

On Day 1, participants were provided with test instructions and practice on all non-flight questionnaire and performance tests. On Day 2, they were allowed a full day of practice on all tests, including two practice flights in the actual helicopter. Preliminary analyses of baseline data from the Day 3 sessions showed that there were pre-existing treatment group differences on several of the subjective and objective test measures, despite the randomization of individuals into the treatment groups. (These group differences are easily seen on most figures depicting baseline data.) To account for these pre-existing differences, data were transformed to baseline adjusted scores for each individual as follows: the measures collected during the baseline test period on the baseline day (Day 3, prior to any drug administration or sleep deprivation) were averaged for each test by individual. This score was subtracted from that volunteer's test scores during the experimental period to remove the pre-existing pre-treatment group biases. In addition to the baseline testing period and for the purposes of comparing the effects of each test condition on the resulting subjective and objective baseline adjusted data, the study schedule was divided into three main testing periods: the drug administration period, the post-drug administration period, and the drug recovery periods (figure 6). With the exception of vital signs data, all data collected within a specific testing period were averaged for comparisons with the other testing periods. The drug administration (testing) period or session is characterized as the ten hours (2300 hrs through 00900 hrs) during which the 3 doses of one of the test substances (dextroamphetamine, modafinil, or placebo) were in active administration every four hours. The post-drug administration (testing) period or session represents the thirteen and one-half hours beginning two hours (0900 hrs) following the final drug dose (given at 0700 hrs) through 2230 hrs. The drug recovery (testing) period is defined as the testing conducted from 0900 hrs through 1300 hrs following a full night of recovery sleep.

In most cases, the two drug administration test days' baseline adjusted scores were subjected to mixed measures ANOVAs using the between-subjects factor, drug group, with three levels (dextroamphetamine, modafinil and placebo), and one within-subject factor, testing periods. In addition, the effects of a full night's recovery sleep were analyzed by comparing test day performance scores and self reports to those of the recovery days (Days 5 and 7). Actigraphy data were analyzed using between-subjects, multivariate analyses of variance (MANOVA) of eight output variables (e.g., sleep time, sleep efficiency, and sleep latency).

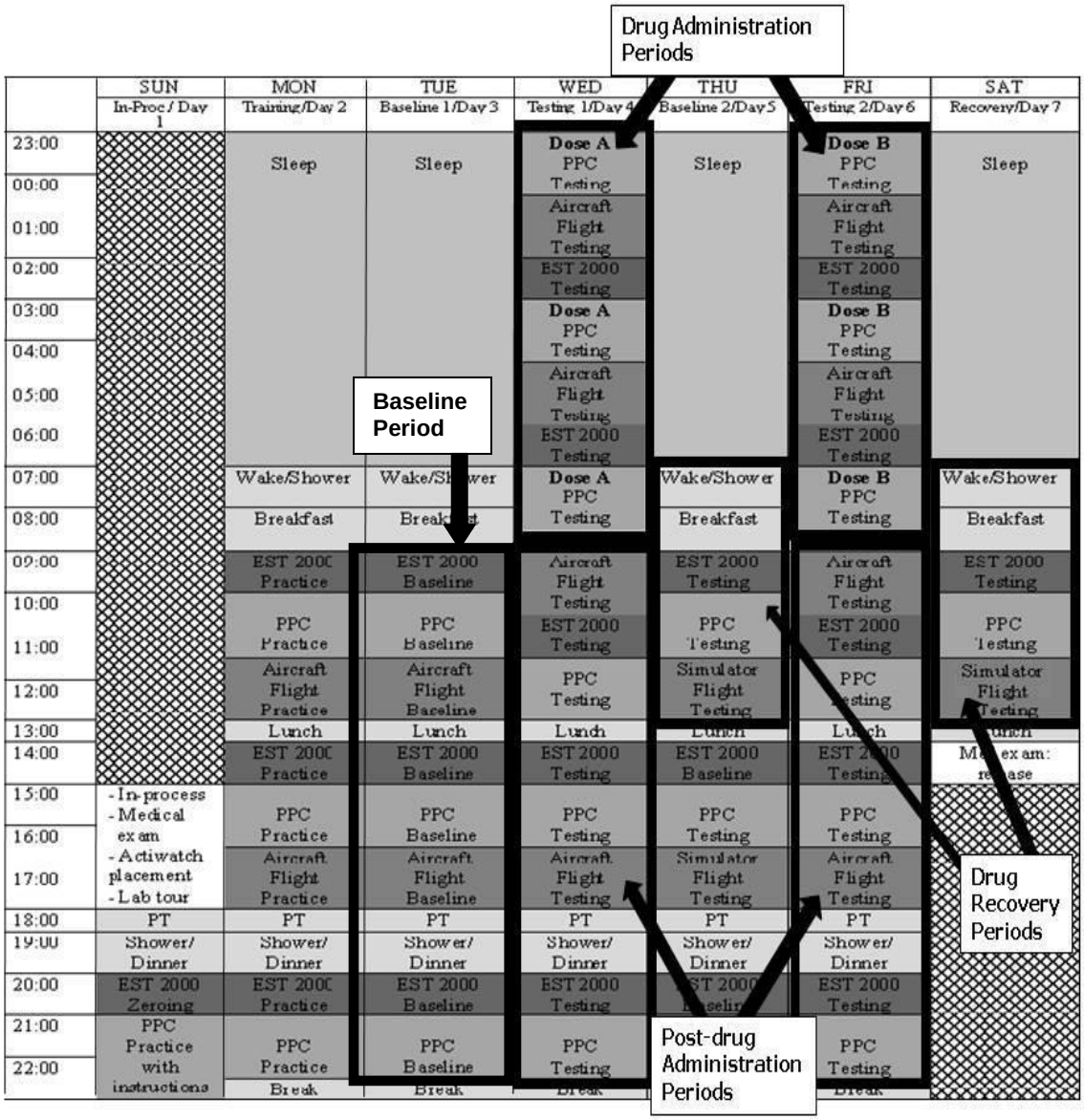

Figure 6. Testing periods used for comparing and analyzing for drug effects.

Additionally, line graphs representing subjective and objective session data are provided for comparison.

Grouping of test measures

The purpose of grouping and then averaging the tests within the three testing sessions or periods (drug administration, post-drug administration, and recovery) was to present an assessment that would be operationally relevant by providing military medical authorities and commanders a better characterization of drug effects during a period of active dosing versus the period post dosing (characterized by a peak and steady decline of drug serum concentrations) versus the period of recovery following a full night (eight hours) of sleep. In addition, for the purposes of analysis, the construct helped minimize the variability of drug and session differences due to the many data points and the many variables affecting serum concentration following oral administration. For modafinil, the variables affecting serum concentration include food (which delays emptying and absorption, but does not affect the time to maximum concentration [T_{max}]), albumin (60 percent protein bound), hepatic function, renal function, ethnicity (genetic mutations and/or deficiencies in the cytochrome enzyme CYP3A4), gender (area under the curve [AUC] slightly lower in males), and concomitant medications utilizing cytochrome CYP enzymes for metabolism (Microdex, 2010). For dextroamphetamine, the variables include food (no effect on absorption, but extends time to T_{max}), urine pH (increased clearance with acidic pH), hepatic function, renal function, and concomitant medications utilizing cytochrome CYP enzymes for metabolism (Microdex, 2010).

Figures 7 and 8 illustrate estimated total serum concentrations during the study's two testing periods and provide insight into drug effect expectations over time.

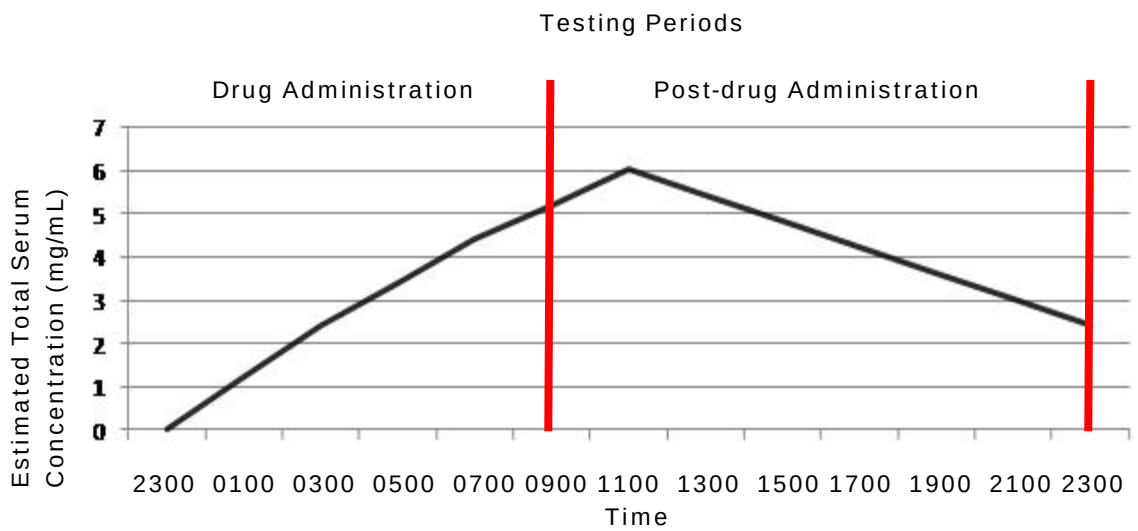

Figure 7. Modafinil estimated total serum concentration (mg/mL) for three oral doses (100 mg) at 2300, 0300, and 0700. (Based on mean peak concentration of 4.82 mg/mL at 2.3 hr following single 200 mg oral dose in healthy subjects, and $T_{1/2}$ of 15 hrs. with zero-order elimination kinetics [Micromedex, 2010; Dunn, 2010]).

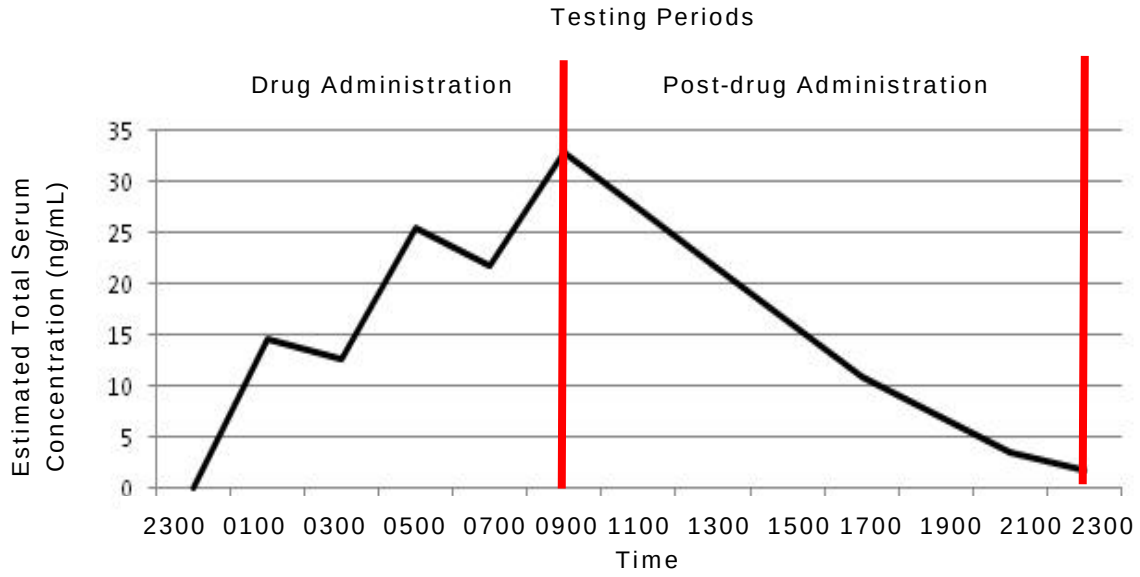

Figure 8. Dextroamphetamine estimated total serum concentration (ng/mL) for three oral doses (5 mg) at 2300, 0300, and 0700. (Based on mean peak concentration of 29.2 ng/mL at 2 hr following single 10 mg oral dose in healthy subjects and $T_{1/2}$ of 10.2 hr with zero-order elimination kinetics [Micromedex, 2010; Dunn, 2010]).

Physiological measures

Vital signs

Vital sign measurements were comprised of four dependent measures: heart rate, oral temperature, systolic blood pressure and diastolic blood pressure. The data were analyzed using 5 (session) x 3 (drug) mixed model ANOVAs. The variable session was the within-subjects factor and its five levels were at 2300, 0300, 0700, and 1200 during the drug administration phases, and a recovery session at 1400 on Day 7. The variable drug was the between-subjects factor and its three levels were modafinil, dextroamphetamine, and placebo. The scores were baseline adjusted. For the heart rate, oral temperature and systolic blood pressure measures, the assumption of sphericity was violated and a Greenhouse-Geisser correction was used.

Heart rate

There were no significant main effects for either the session (F[2.701, 72.939] = 2.039, p = 0.122) or drug (F[2, 27] =0.004, p = 0.996) variables with regard to participants' heart rate data (figure 9). In addition, there was no significant interaction. Figure 10 presents the score means by drug condition and session.

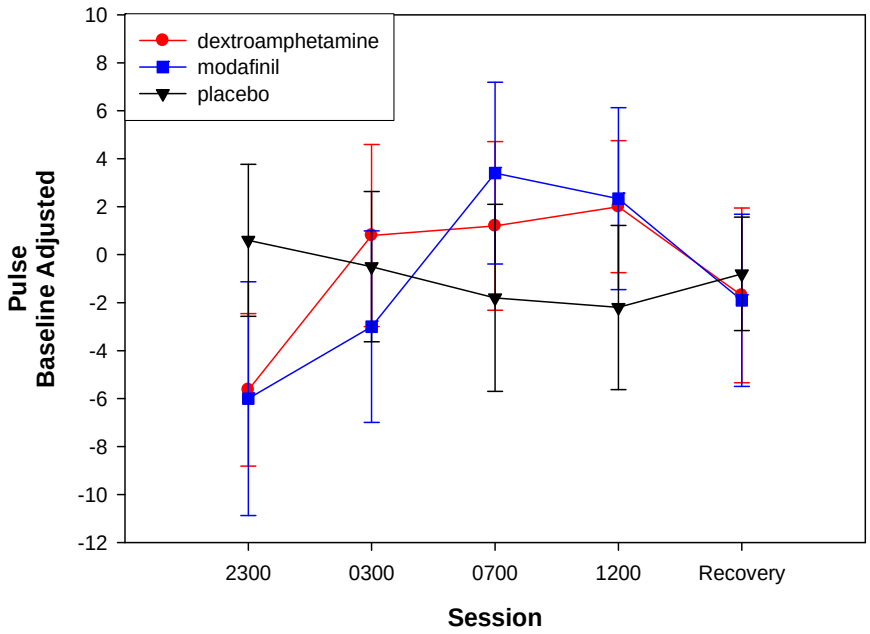

Figure 9. Heart rate (pulse) comparisons by drug and session (baseline adjusted).

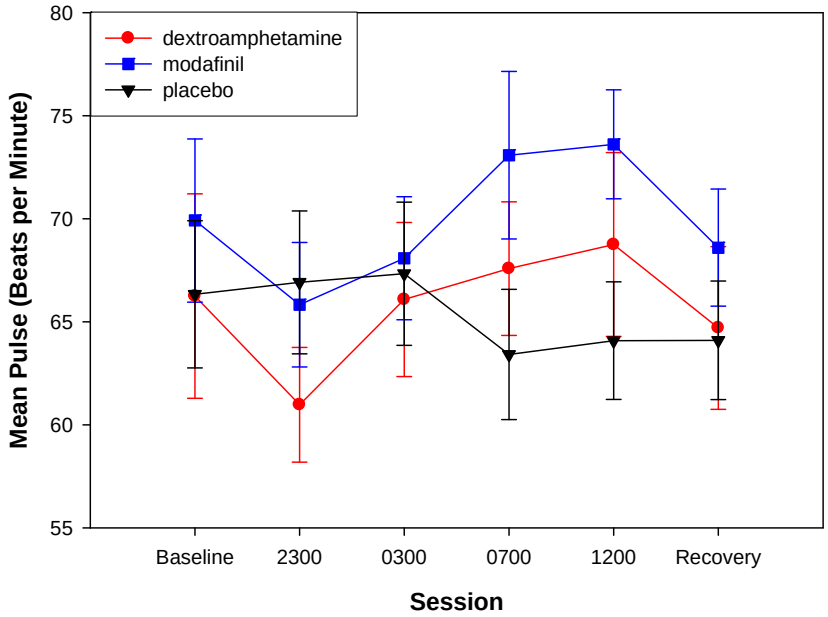

Figure 10. Mean heart (pulse) rate by drug and session.

Oral temperature

There were no significant main effects for either the session ($F[3.131, 84.547] = 2.246$, $p = 0.086$) or drug ($F[2, 27] = 0.052$, $p = 0.949$) variables with regard to participants' temperature data (figure 11). In addition, there was no significant interaction. Figure 12 presents the score means by drug condition and session.

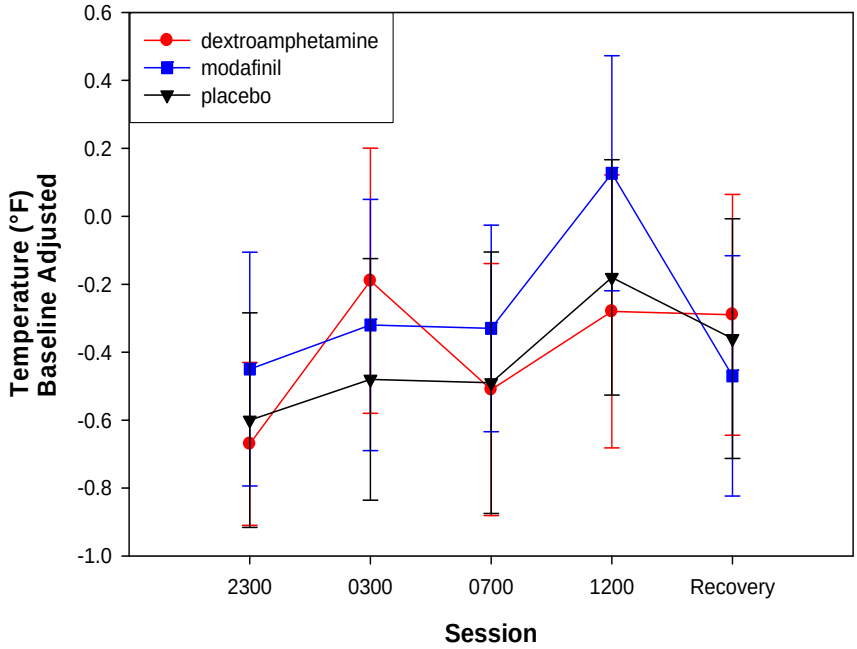

Figure 11. Temperature comparisons by drug and session (baseline adjusted).

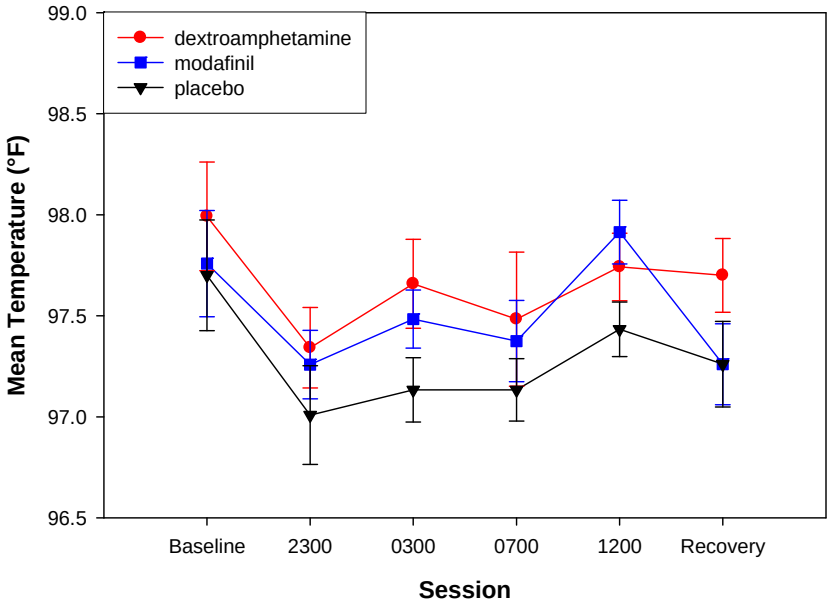

Figure 12. Mean temperature by drug and session.

Systolic blood pressure

There were no significant main effects for either the session ($F[3.396, 91.691] = 1.932$, $p = 0.122$) or drug ($F[2, 27] = 2.672$, $p = 0.087$) variables with regard to participants' systolic blood pressure data (figure 13). In addition, there was no significant interaction. Figure 14 presents the score means by drug condition and session.

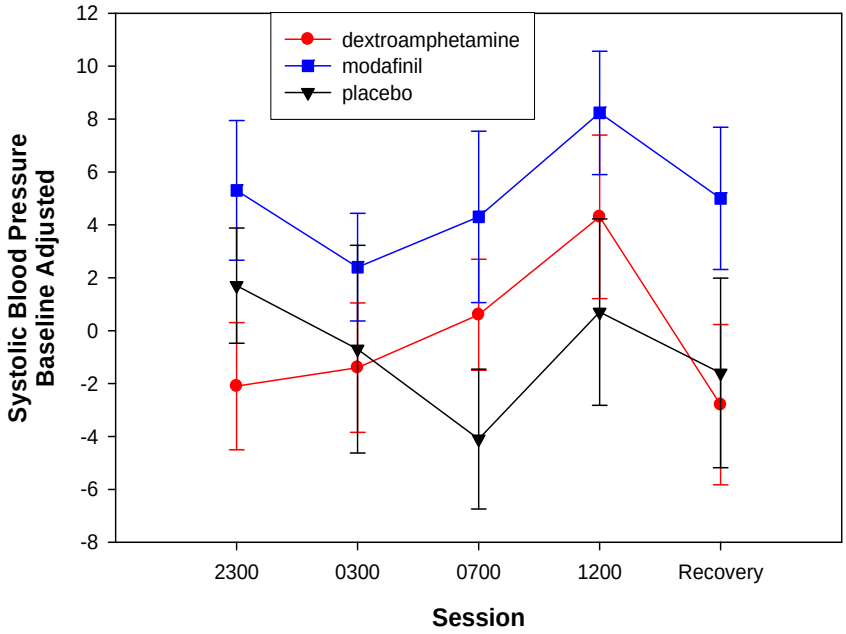

Figure 13. Systolic blood pressure comparisons by drug and session (baseline adjusted).

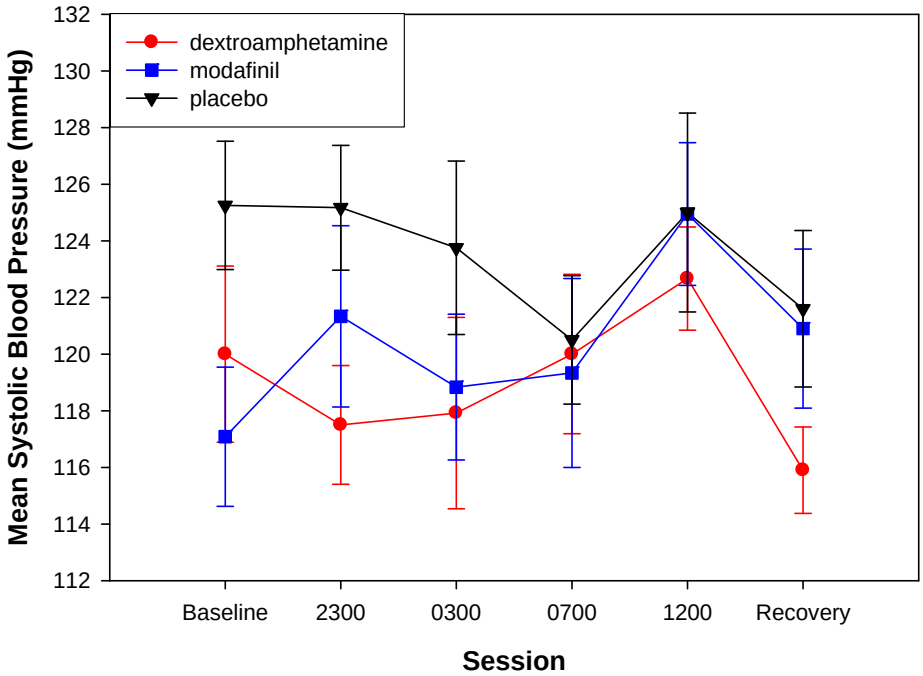

Figure 14. Mean systolic blood pressure by drug and session.

Diastolic blood pressure

There was a significant main effect for session ($F[4,108] = 5.651$, $p < 0.001$) (figure 15)**.** Results from the pairwise comparisons are presented in table 8. The main effect of drug with regard to the diastolic blood pressure data was not significant ($F[2,27] = 1.890$, $p = 0.171$). In addition, the interaction between session and drug was not significant ($F[8, 108] = 1.036$, $p = 0.414$). Figure 16 presents the score means by drug condition and session.

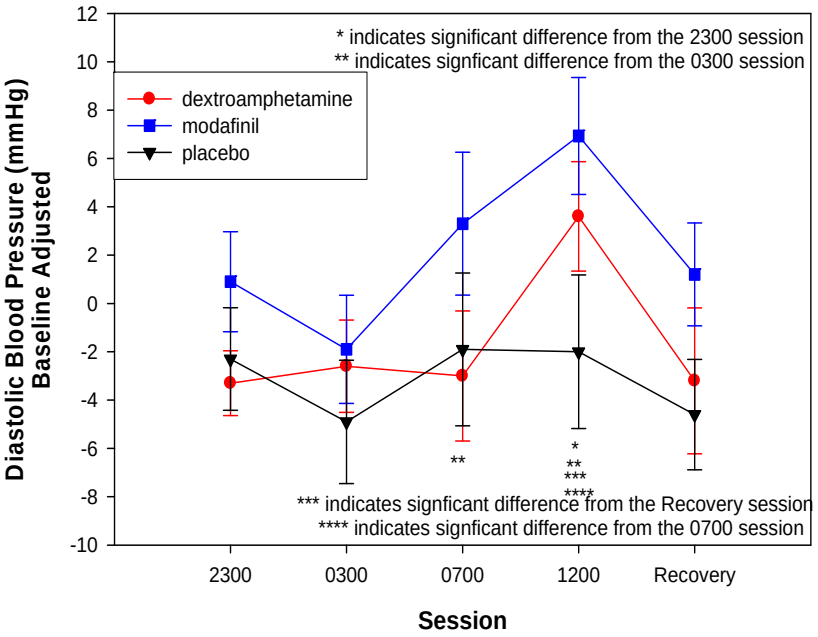

Figure 15. Diastolic blood pressure comparisons by drug and session (baseline adjusted).

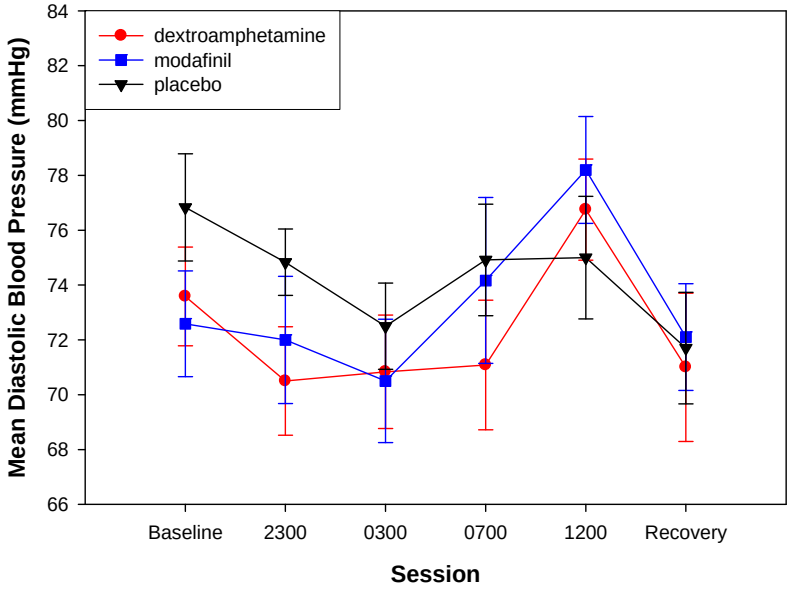

Figure 16. Mean diastolic blood pressure by drug and session.

Table 8.
Pairwise comparisons for diastolic blood pressure data.

Session	Comparison	Mean Difference	*p* value
2300	0300	1.567	0.203
	0700	-1.033	0.471
	1200*	-4.411	0.007
	1400	0.633	0.669
0300	2300	-1.567	0.203
	0700*	-2.6	0.048
	1200*	-5.978	0.00
	1400	-0.933	0.422
0700	2300	1.033	0.471
	0300*	2.6	0.048
	1200*	-3.378	0.021
	1400	1.67	0.328
1200	2300*	4.411	0.007
	0300*	5.978	0.00
	0700*	3.378	0.021
	1400*	5.044	0.00
1400	2300	-0.633	0.699
	0300	0.933	0.422
	0700	-1.667	0.328
	1200*	-5.044	0.00

* indicates statistically significant

Actiwatch® activity monitoring system

All participants wore actiwatches for the duration of the study. Actigraphy data for one participant was invalid and therefore, could not be included in the analysis, resulting in a total of 11 modafinil, 12 dextroamphetamine, and 11 placebo participants. Eight output variables were exported from the Actiware® software program and subjected to a between-subjects multivariate analysis of variance (MANOVA):actual sleep time (minutes), sleep efficiency (percent), sleep latency (minutes), number of sleep bouts, mean sleep bout time (minutes), immobile minutes, number of immobile phases, and mean length of immobility (minutes). Three time periods were defined for this analysis: the baseline sleep period (which occurred on Day 3 from 2300 hrs – 0800 hrs), the wakeful periods (which occurred on Days 4 and 6 from 2300 hrs – 0800 hrs), and the recovery sleep periods (which occurred on Days 5 and 7 from 2300 hrs – 0800 hrs).

Analysis of sleep periods

The comparison sleep periods are labeled baseline, modafinil recovery, dextroamphetamine recovery, and placebo recovery. The initial night of sleep at the laboratory was not included in the analysis given that participants were adjusting to the environment which may have impacted their sleep. The results of the MANOVA showed a significant main effect of drug between groups, $F(24, 126) = 1.73$, $p = .028$. Subsequent univariate ANOVAs showed significant between-subjects effects for actual sleep time (minutes), $F(3, 47) = 4.06$, $p = .012$; sleep efficiency (percent), $F(3, 47) = 4.08$, $p = .012$; and number of sleep bouts, $F(3, 47) = 3.40$, $p = .025$. Independent samples t-tests showed significant differences in actual sleep time between modafinil recovery and placebo recovery sleep periods, $t(20) = -2.24$, $p = .037$, and placebo recovery and baseline sleep periods, $t(26) = 3.12$, $p = .004$ (table 9); in sleep efficiency between modafinil recovery and placebo recovery sleep periods, $t(20) = -2.175$, $p = .042$, and placebo recovery and baseline sleep periods, $t(26) = 3.12$, $p =.004$ (table 10); and in the number of sleep bouts between placebo recovery and baseline sleep periods, $t(26) = -2.85$, p = .009 (table 11).

Table 9.
Significant results of independent samples *t*-tests for mean actual sleep time (minutes).

Paired Comparisons	*N*	Mean	SE*	*t* value	*p* level
1. Modafinil recovery	11	438.91	4.32	-2.24	.037
1. Placebo recovery	11	453.91	5.11		
2. Placebo recovery	11	453.91	5.11	3.12	.004
2. Baseline sleep	17	424.53	6.80		

* SE is standard error of the mean.

Table 10.
Significant results of independent samples *t*-tests for mean sleep efficiency (percentage).

Paired Comparisons	*N*	Mean	SE*	*t* value	*p* level
1. Modafinil recovery	11	91.55	0.90	-2.18	.042
1. Placebo recovery	11	94.58	1.06		
2. Placebo recovery	11	94.58	1.06	3.12	.004
2. Baseline sleep	17	88.45	1.42		

* SE is standard error of the mean.

Table 11.
Significant results of independent samples *t*-tests for mean number of sleep bouts.

Paired Comparisons	*N*	Mean	SE*	*t* value	*p* level
1. Modafinil recovery	11	13.73	2.73	-2.85	.009
1. Placebo recovery	17	24.29	2.41		

* SE is standard error of the mean.

Analysis of wake periods

During the defined wake periods participants had received doses of modafinil, dextroamphetamine, or placebo. The results of the MANOVA were not significant, $F(16, 50) = .79$, $p = .69$, thus, indicating no differences in activity levels between drug groups. To demonstrate that participants were active during these wake periods, the proportion of minutes that participants were immobile during each 8-hour sleep and wake period was calculated. It is expected that participants will be immobile for some time even during wake periods (e.g., watching television, reading). A paired samples *t*-test comparing the mean proportion of immobile minutes during sleep periods to that during wake periods for each participant showed a significant difference such that participants were immobile for a greater proportion of time during sleep periods (mean proportion was .76) than wake periods (mean proportion was .09), $t(16) = -10.54$, $p < .001$.

Questionnaires

Symptom Checklist (SC)

The SC data is comprised of 12 dependent measures: nervousness, excitation, aggression, headache, happiness or elation, pain in abdomen or stomach area, dry mouth, pounding heart, racing heartbeat, tremor, nausea, and jitteriness. The data were analyzed using 3 (session) x 3 (drug) mixed model ANOVAs. The variable *session* was the within-subjects factor and its three levels were the drug administration period, the post-drug administration period, and the drug recovery period. The variable *drug* was the between-subjects factor and its three levels were modafinil, dextroamphetamine, and placebo. The scores were baseline adjusted.

SC Dry Mouth score

There was a significant main effect of session for the dry mouth measure of the SC ($F[2,66] = 3.668$, $p = 0.031$) (figure 17). Pairwise comparisons revealed participants reported significantly more dry mouth during the drug administration period than during the recovery period ($p = 0.012$). There was no main effect of drug or significant interaction with regard to the dry mouth data. Figure 18 presents the score means by drug condition and session.

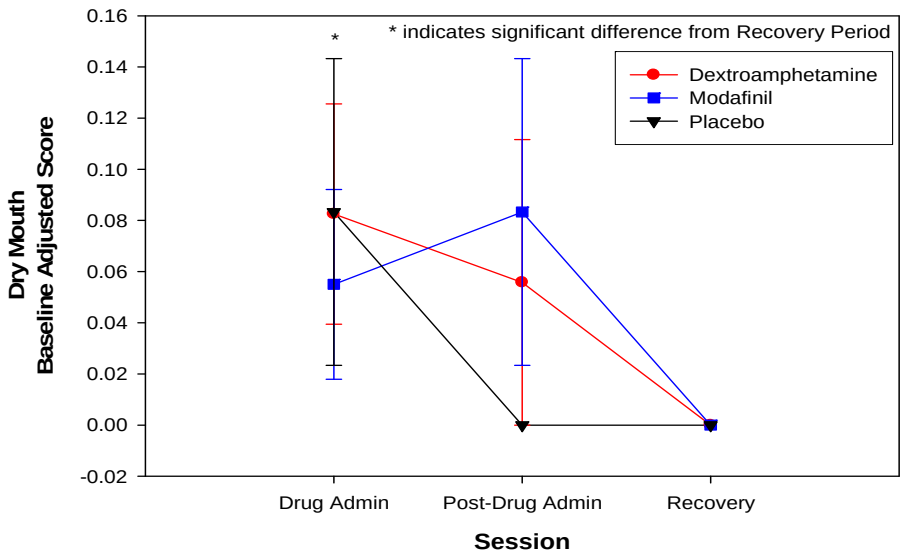

Figure 17. SC Dry Mouth comparisons by drug and session (baseline adjusted).

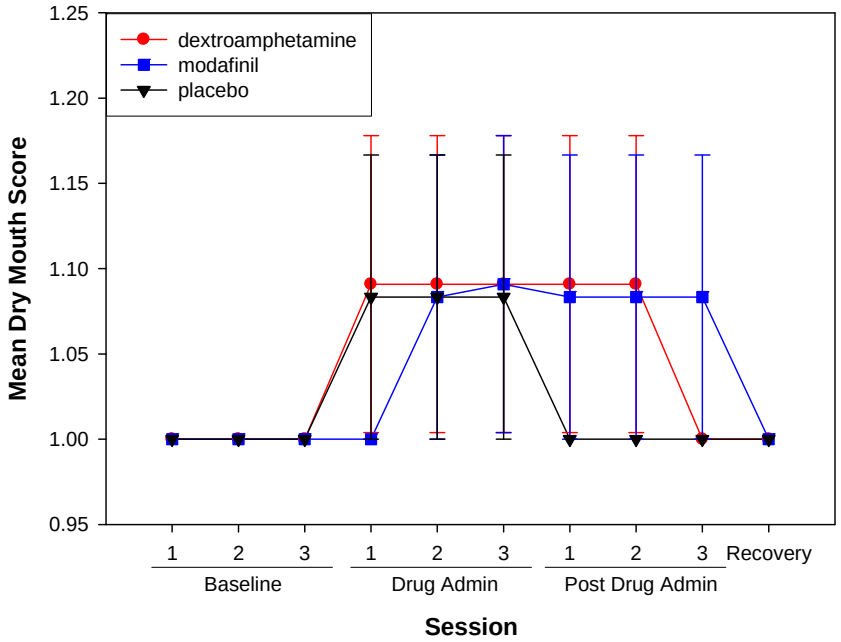

Figure 18. Mean SC Dry Mouth score by drug and session.

SC Jitteriness score

There was also a significant main effect of session for the jitteriness measure of the SC (F[1.483, 48.935] = 5.713, p = 0.011) (figure 19). Pairwise comparisons revealed participants reported significantly more jitteriness during the drug administration (p = 0.008) and post drug administration period (p = 0.01) than during the recovery period. For the jitteriness dependent measure, the assumption of sphericity was violated and a Greenhouse-Geisser correction was used. There was no main effect of drug or significant interaction with regard to the jitteriness data. Figure 20 presents the score means by drug condition and session.

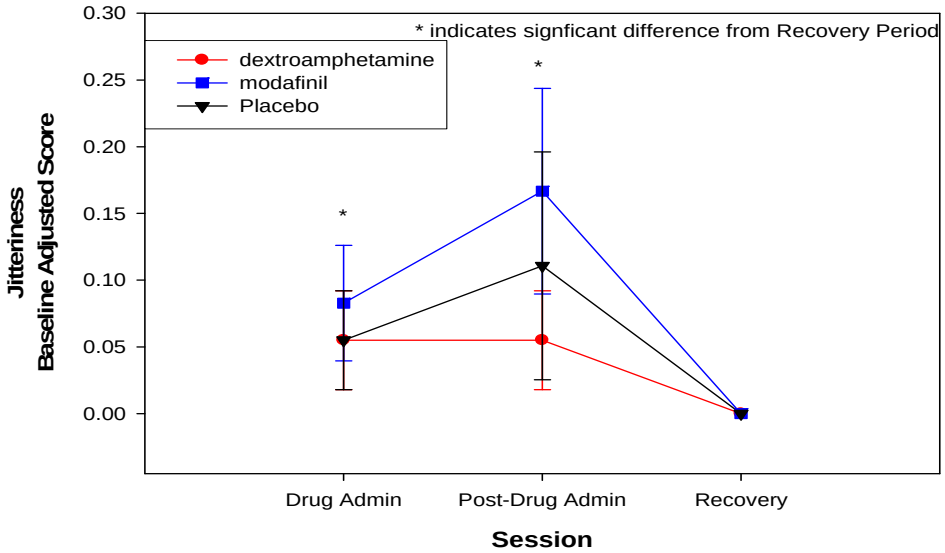

Figure 19. SC Jitteriness comparisons by drug and session (baseline adjusted).

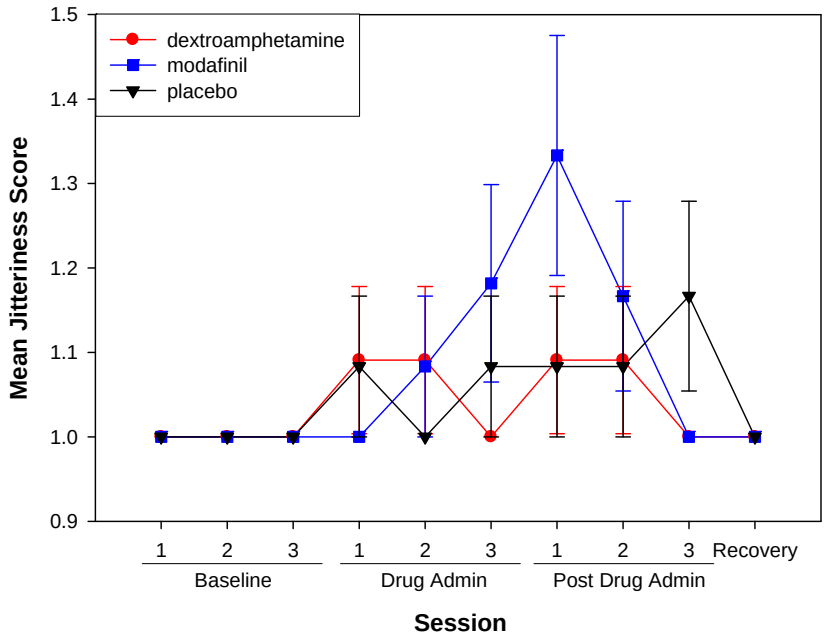

Figure 20. Mean SC Jitteriness score by drug and session.

Other SC measures

There were no significant main effects or interactions for nervousness, excitation, headache, happiness or elation, pain in abdomen or stomach area, pounding heart, racing heartbeat, tremor, nausea, or aggression. Graphs and *p* values of non-significant SC measures and scores can be viewed in Appendix G.

Motion Sickness Questionnaire (MSQ)

The MSQ was administered during each PPC period. Participants' responses on the MSQ questions loaded onto factors indicating symptoms of nausea, oculomotor, disorientation, and total symptom severity. The data were analyzed using 3 (session) x 3 (drug) mixed model ANOVAs. The variable *session* was the within-subjects factor and its three levels were the drug administration period, the post-drug administration period, and the drug recovery period. The variable *drug group* was the between-subjects factor and its three levels were modafinil, dextroamphetamine, and placebo. The scores were baseline adjusted. For all four dependent measures, the assumption of sphericity was violated and a Greenhouse-Geisser correction was used.

MSQ Nausea score

For nausea, there was a main effect of session ($F[1.564, 51.600] = 40.481$, $p < 0.001$). Pairwise comparisons revealed participants reported significantly higher nausea scores during the post drug administration period than during the drug administration period ($p < 0.001$) and the recovery period ($p < 0.001$). Also, participants reported significantly higher nausea scores during drug administration than during the recovery period ($p < 0.001$).

There was a main effect of drug ($F[2,33] = 9.627$, $p = 0.001$). Pairwise comparisons revealed participants reported significantly higher nausea scores under the placebo condition than under the modafinil ($p = 0.001$) and dextroamphetamine ($p < 0.001$) conditions. There was also a significant interaction between session and drug ($F[3.127, 51.600] = 5.131$, $p = 0.003$). To investigate the significant interaction, independent t-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied ($p = 0.0083$). Results for the t-tests are presented in table 12. During the drug administration period, mean MSQ nausea scores for the placebo group were significantly higher than those for both the dextroamphetamine ($p = 0.003$) and modafinil ($p = 0.002$) groups (figure 21). In addition, during the post drug administration period, mean MSQ nausea scores for the placebo group were significantly higher than those of the dextroamphetamine ($p = 0.002$) group. Figure 22 presents the score means by drug condition and session.

Table 12.
Post hoc results for MSQ Nausea scores.

Nausea	During Drug Administration periods	*p* value	During Post Drug Administration	*p* value
	Modafinil vs. Placebo	0.002	Modafinil vs. Placebo	0.018
	Placebo vs. Dextroamphetamine	0.003	Placebo vs. Dextroamphetamine	0.002
	Modafinil vs. Dextroamphetamine	0.652	Modafinil vs. Dextroamphetamine	0.352

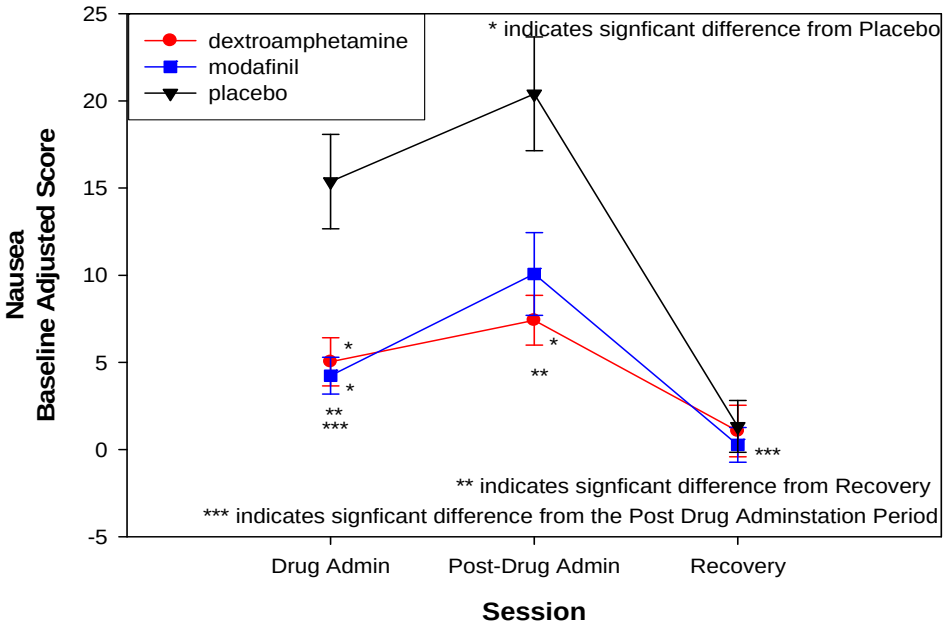

Figure 21. MSQ Nausea score comparisons by drug and session (baseline adjusted).

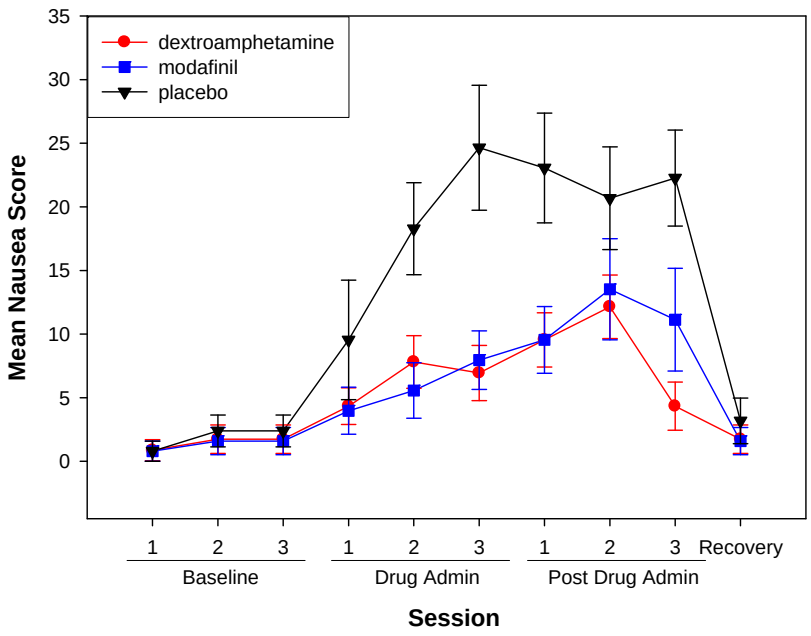

Figure 22. Mean MSQ Nausea scores by drug and session.

MSQ Oculomotor score

For the oculomotor dependent variable, there was a main effect of session (F[1.453, 47.943] = 44.446 , $p < 0.001$). Pairwise comparisons revealed participants reported significantly higher oculomotor scores during the post drug administration period than during the drug administration period ($p < 0.001$) and the recovery period ($p < 0.001$). Also, participants reported significantly higher oculomotor scores during drug administration than during the recovery period ($p < 0.001$). There was a main effect of drug (F[2,33] = 5.994, $p = 0.006$). Pairwise comparisons revealed participants reported significantly higher oculomotor scores under the placebo condition than under the modafinil ($p = 0.021$) and dextroamphetamine conditions ($p = 0.002$).

There was also a significant interaction between session and drug (F[2.906, 47.943] = 5.309, $p = 0.003$). To investigate the significant interaction, independent t-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied (p = 0.0083). Results for the t-tests are presented in table 13. During the drug administration period, the placebo group reported a significantly higher mean MSQ oculomotor score than both the dextroamphetamine ($p = 0.001$) and modafinil ($p = 0.003$) groups (figure 23). In addition, during the post drug administration period, the placebo group reported a significantly higher mean MSQ oculomotor score than the dextroamphetamine ($p = 0.003$) group. Figure 24 presents the score means by drug condition and session.

Table 13.
Post hoc results for MSQ Oculomotor scores.

Oculomotor	During Drug Administration periods	*p* value	During Post Drug Administration	*p* value
	Modafinil vs. Placebo	0.003	Modafinil vs. Placebo	0.101
	Placebo vs. Dextroamphetamine	0.001	Placebo vs. Dextroamphetamine	0.003
	Modafinil vs. Dextroamphetamine	0.765	Modafinil vs. Dextroamphetamine	0.078

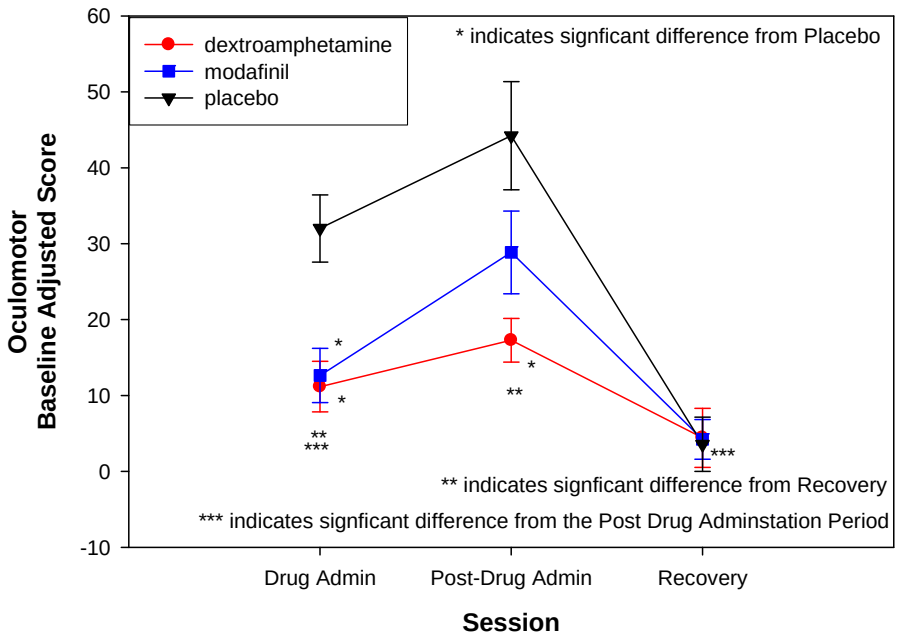

Figure 23. MSQ Oculomotor score comparisons by drug and session (baseline adjusted).

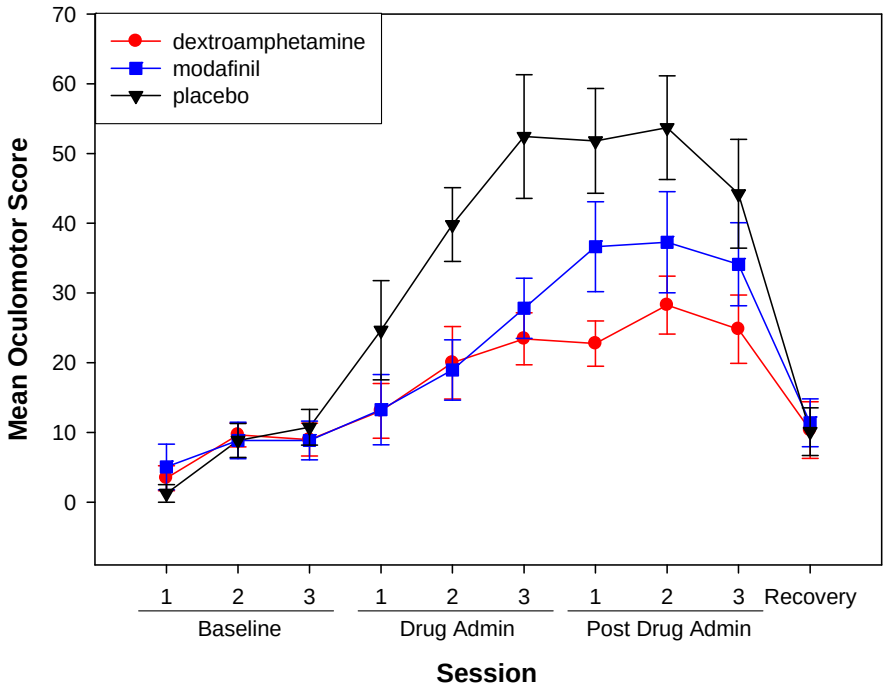

Figure 24. Mean MSQ Oculomotor scores by drug and session.

MSQ Disorientation score

There was significant main effect of session for the MSQ disorientation scores (F[1.662, 54.853] = 17.664, $p < 0.001$). Pairwise comparisons revealed participants reported significantly higher disorientation scores during both the drug administration period ($p = 0.005$) and post drug administration period ($p < 0.001$) than the recovery period. Also, participants reported significantly higher disorientation scores during the post drug administration period than during the drug administration period ($p = 0.001$). The main effect of drug was not significant (F[2,33] = 2.464, $p = 0.101$).

There was a significant interaction between session and drug (F[3.324, 54.853] = 3.360, p = 0.021). To investigate, independent t-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied ($p = 0.0083$). Results for the t-tests are presented in table 14. During the drug administration period, the placebo group reported significantly higher mean MSQ disorientation scores than the dextroamphetamine group ($p = 0.005$) (figure 25). Figure 26 presents the score means by drug condition and session.

Table 14.
Post hoc results for MSQ Disorientation scores.

Disorientation	During Drug Administration periods	*p* value	During Post Drug Administration	*p* value
	Modafinil vs. Placebo	0.133	Modafinil vs. Placebo	0.515
	Placebo vs. Dextroamphetamine	0.005	Placebo vs. Dextroamphetamine	0.041
	Modafinil vs. Dextroamphetamine	0.068	Modafinil vs. Dextroamphetamine	0.088

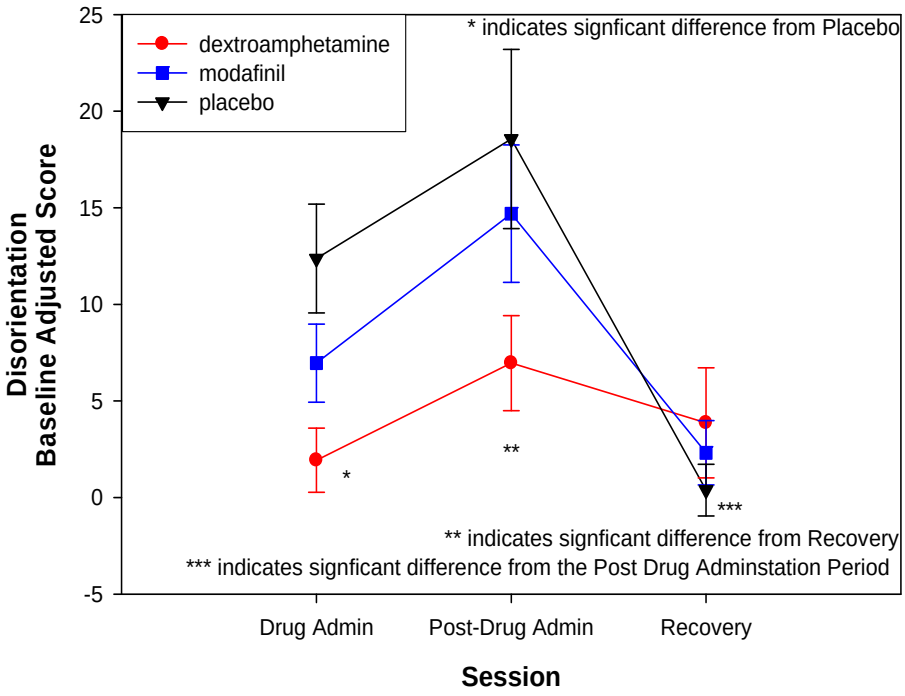

Figure 25. MSQ Disorientation score comparisons by drug and session (baseline adjusted).

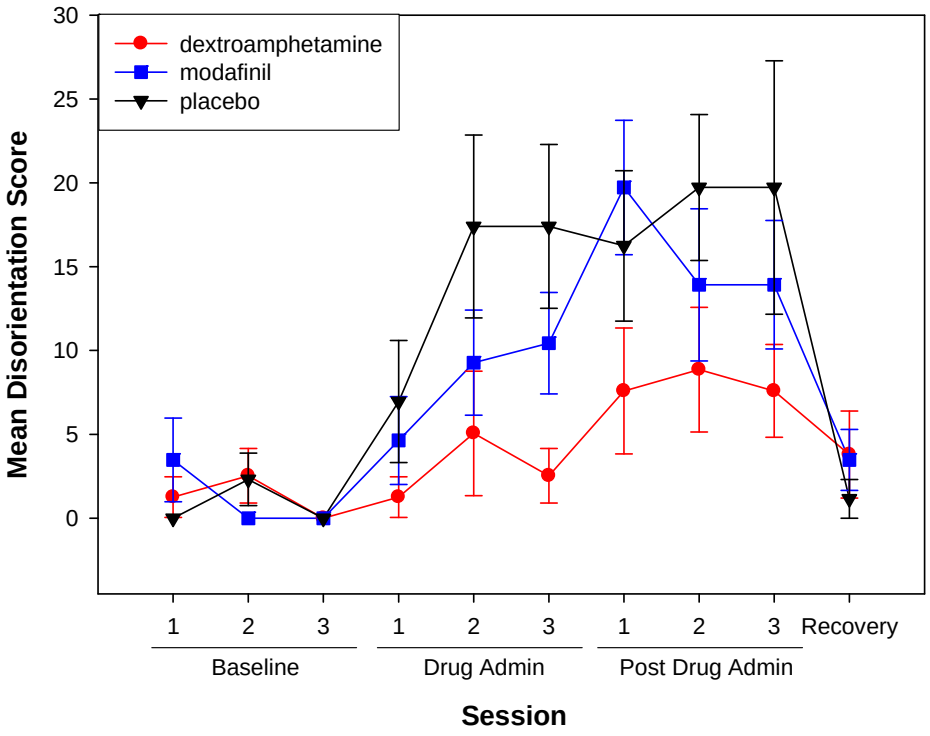

Figure 26. Mean MSQ Disorientation scores by drug and session.

MSQ Total score

There was a significant main effect of session for the total MSQ scores ($F[1.428, 47.119] = 45.085$, $p < 0.001$). Pairwise comparisons revealed participants reported higher total MSQ scores during both the drug administration period ($p < 0.001$) and post drug administration period ($p < 0.001$) than during the recovery period. Also, participants reported significantly higher total MSQ scores during the post drug administration period than the drug administration period ($p < 0.001$). There was also a significant main effect of drug ($F[2,33] = 6.515$, $p = 0.004$). Pairwise comparisons revealed participants reported significantly higher total MSQ scores under the placebo condition than under the modafinil ($p = 0.015$) and dextroamphetamine ($p = 0.001$) conditions.

There was a significant interaction between session and drug ($F[2.856, 47.119] = 5.769$, $p = 0.002$). To investigate, independent t-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied ($p = 0.0083$). Results for the t-tests are presented in table 15. During the drug administration period, the placebo group reported significantly higher total MSQ scores than both the dextroamphetamine ($p = 0.001$) and modafinil group ($p = 0.002$) (figure 27). In addition, during the post drug administration period, the placebo group reported significantly higher total MSQ scores than the dextroamphetamine group ($p = 0.004$). Figure 28 presents the score means by drug condition and session.

Table 15.
Post hoc results for MSQ Total scores.

Total	During Drug Administration periods	*p* value	During Post Drug Administration	*p* value
	Modafinil vs. Placebo	0.002	Modafinil vs. Placebo	0.093
	Placebo vs. Dextroamphetamine	0.001	Placebo vs. Dextroamphetamine	0.004
	Modafinil vs. Dextroamphetamine	0.611	Modafinil vs. Dextroamphetamine	0.088

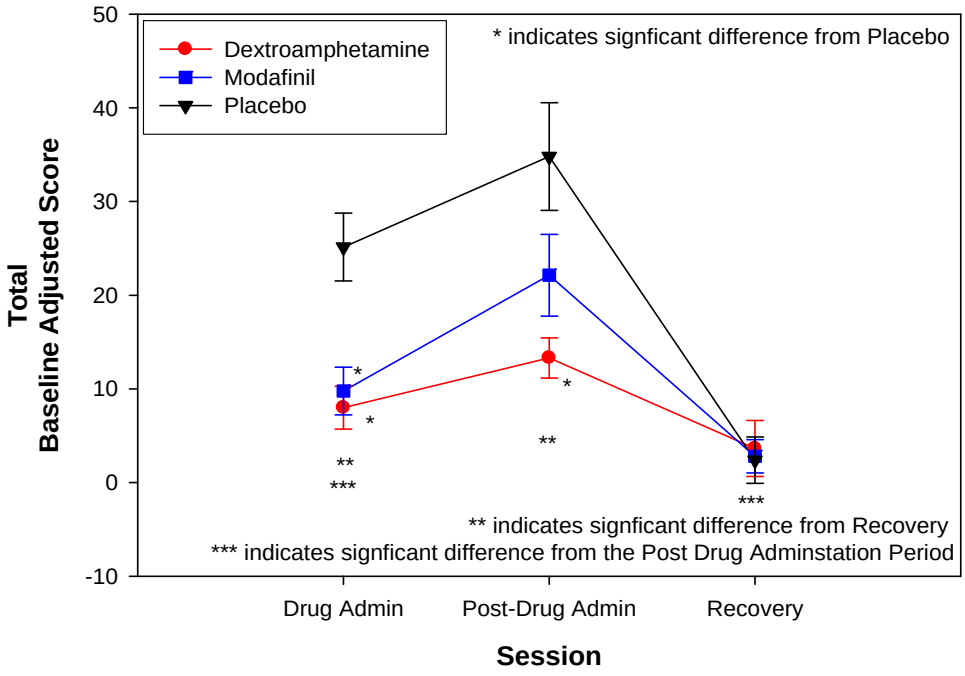

Figure 27. MSQ Total score comparisons by drug and session (baseline adjusted).

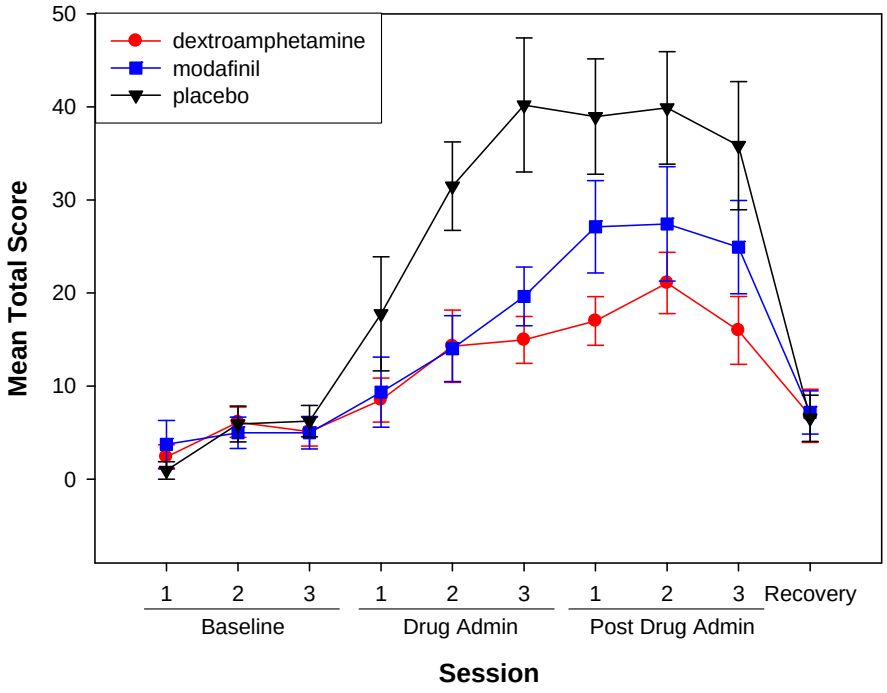

Figure 28. Mean MSQ Total scores by drug and session.

Evaluation of Risks Questionnaire (EVAR)

The EVAR measured the propensity to engage in or avoid risky behavior and situations where participants marked a point along a 100 mm bipolar visual analogue scale to indicate their preference for various types of risky activities. The EVAR was administered during each PPC period. The EVAR contains four dependent measures: control, confidence, risk, and total score. These data were analyzed using a 3 (session, within subjects variable) x 3 (drug, between subjects variable) mixed model ANOVA. The three levels of session were the drug administration period, the post-drug administration period, and the recovery period. The three levels of drug were modafinil, dextroamphetamine, and placebo. All scores were baseline adjusted. The control, risk, and total scores were Greenhouse-Geisser corrected due to a violation of an assumption of sphericity. The confidence scores did not violate the assumption of sphericity.

EVAR Control score

A higher score indicates a higher desire for control. A significant main effect existed for session ($F[1.544, 50.947] = 4.073$, $p = 0.032$), but not for drug ($F[2, 33] = 0.837$, $p = 0.442$) or the interaction between session and drug ($F[3.088, 50.947] = 0.506$, $p = 0.685$) (figure 29). Bonferroni corrected pairwise comparisons (alpha = 0.016) were conducted for the main effect of session and indicated that drug administration and recovery sessions approached significance ($p = 0.017$) (a lower amount of total control was indicated compared to the recovery session), while

drug administration and post-drug administration sessions (p = 0.25) and post-drug administration and recovery sessions (p = 0.192) were not significant. Figure 30 presents the score means by drug and session.

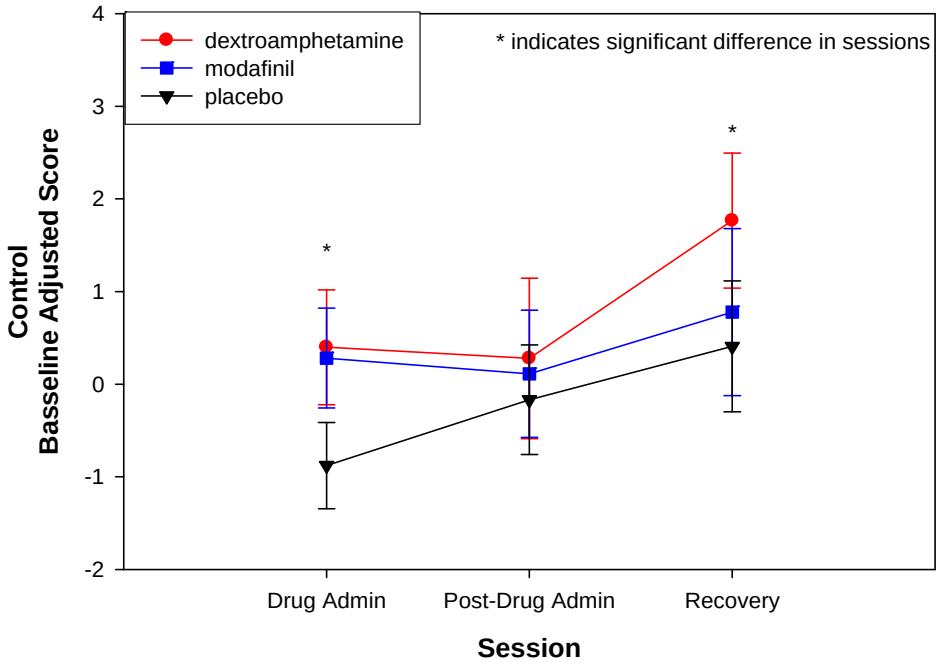

Figure 29. EVAR Control score comparisons by drug and session (baseline adjusted).

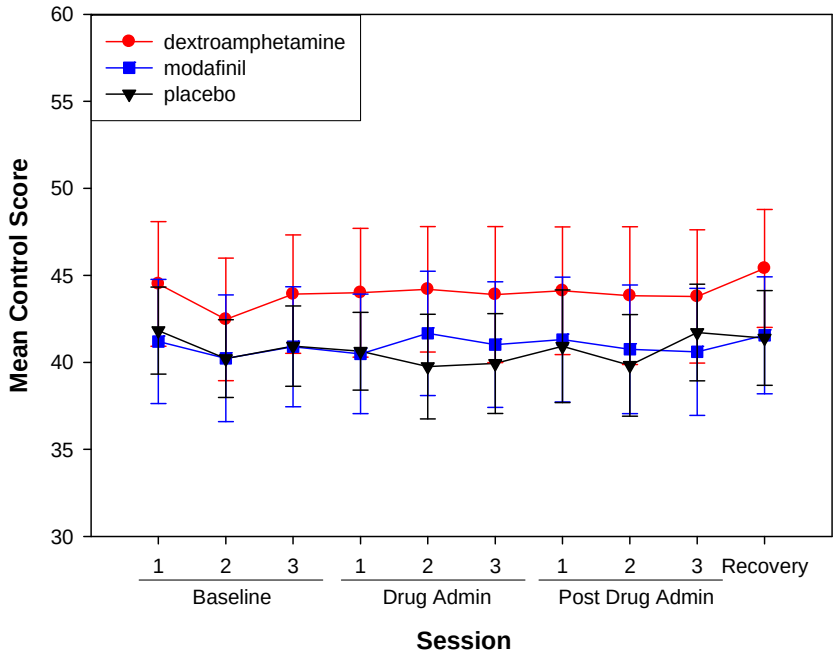

Figure 30. Mean EVAR Control scores by drug and session.

EVAR Confidence score

A higher score indicates a higher confidence. A significant main effect existed for session ($F[2, 66] = 6.122$, $p = 0.004$). During the drug administration and post-drug administration session, a significantly lower amount of total confidence was demonstrated compared to the recovery session. There were no significant main effects for drug ($F[2, 33] = 0.412$, $p = 0.666$) or the interaction between session and drug ($F[4, 66] = 0.845$, $p = 0.502$) (figure 31). Bonferroni corrected pairwise comparisons (alpha = 0.016) were conducted for the main effect of session and indicated that the recovery session was significantly different from both the drug administration session ($p = 0.009$) and the post-drug administration session ($p = 0.01$). The drug administration and post-drug administration were not significantly different ($p = 0.32$). Figure 32 presents the score means by drug condition and session.

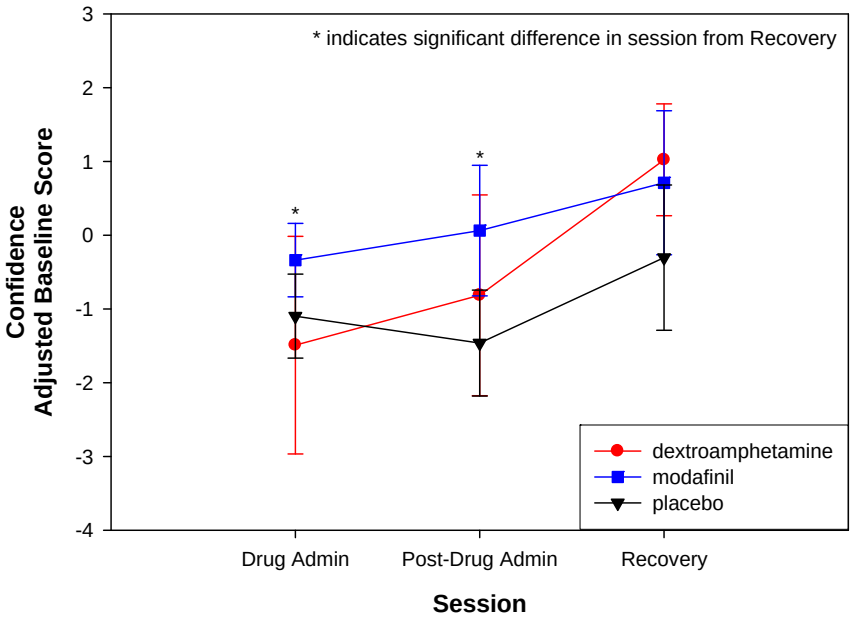

Figure 31. EVAR Confidence score comparisons by drug and session (baseline adjusted).

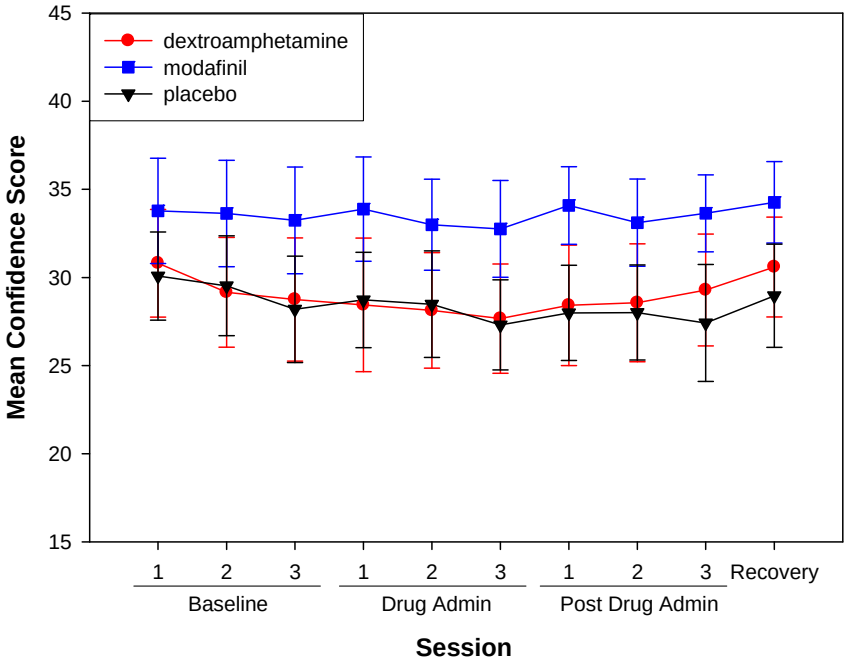

Figure 32. Mean EVAR Confidence scores by drug and session.

EVAR Risk score

A higher score is a higher risk propensity. A significant main effect existed for session (F[1.3, 42.907] = 6.494, p = 0.009). During the drug administration and post-drug administration sessions, a significantly lower amount of total risk propensity was demonstrated compared to the recovery session. There were no significant main effects for drug (F[2, 33] = 0.463, p = 0.634) or the interaction between session and drug (F[2.6, 42.907] = 1.638, p = 0.2) (figure 33). Bonferroni corrected pairwise comparisons (alpha = 0.016) were conducted for the main effect of session and indicated that the recovery session was significantly different from both the drug administration session (p = 0.012) and the post-drug administration session (p = 0.011). The drug administration and post-drug administration were not significant different (p = 0.283). Figure 34 presents the score means by drug condition and session.

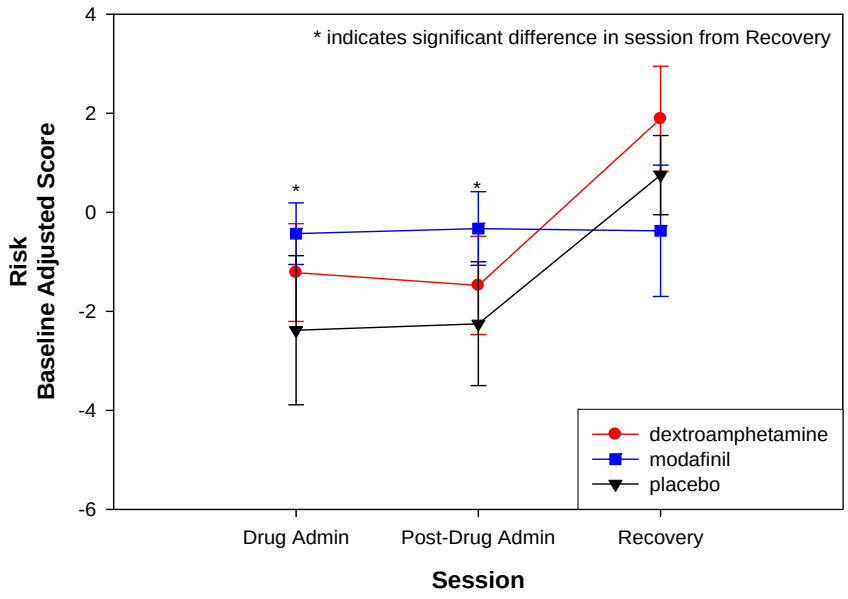

Figure 33. EVAR Risk score comparisons by drug and session (baseline adjusted).

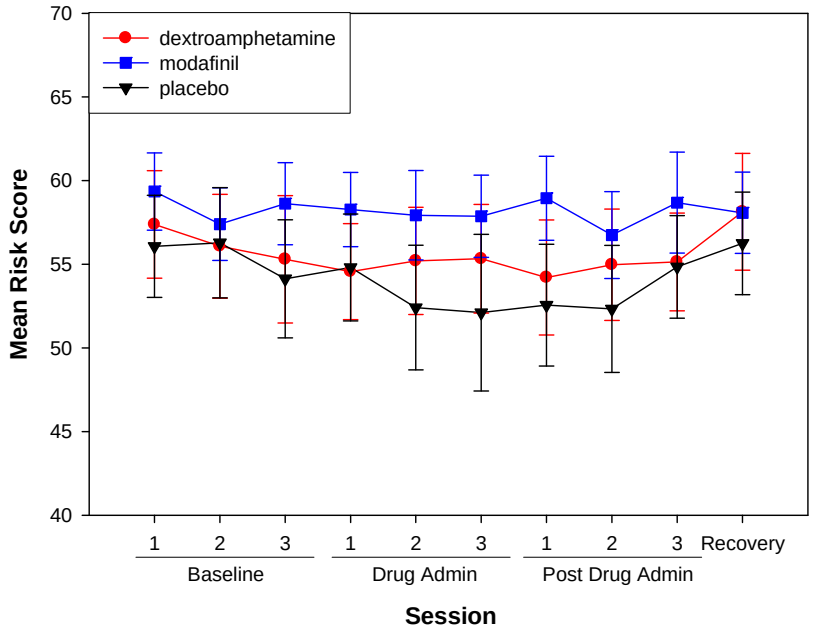

Figure 34. Mean EVAR Risk scores by drug and session.

EVAR Total score

A significant main effect existed for session (F[1.267, 41.818] = 9.119, p = 0.002), but not for drug (F[2, 33] = 0.315, p = 0.707) or the interaction between session and drug (F[2.534, 41.818] = 2.016, p = 0.135) (figure 35). Bonferroni corrected pairwise comparisons (alpha = 0.016) were conducted for the main effect of session and indicated that the recovery session was significantly different from both the drug administration session (p = 0.004) and the post-drug

administration session (p = 0.003). The drug administration and post-drug administration were not significant different (p = 0.293). Figure 36 presents the score means by drug condition and session.

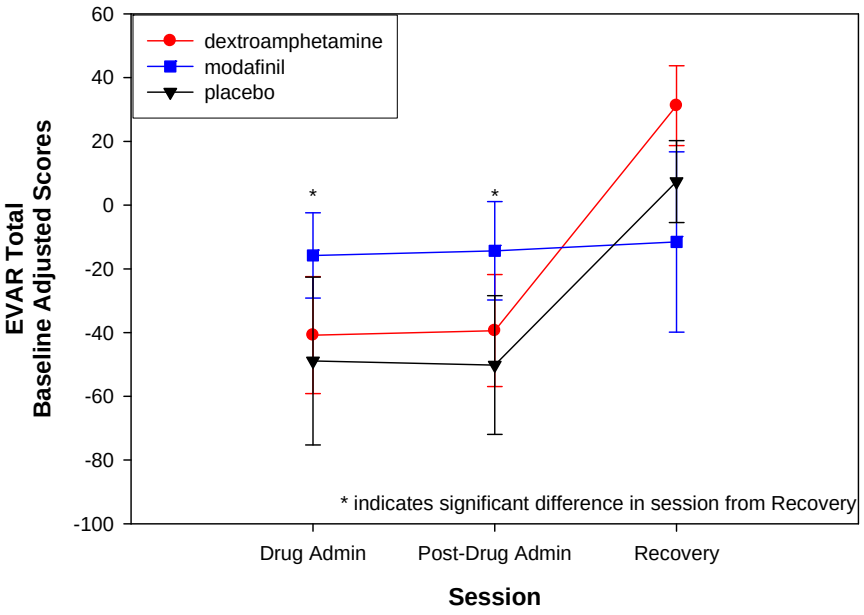

Figure 35. EVAR Total score comparisons by drug and session (baseline adjusted).

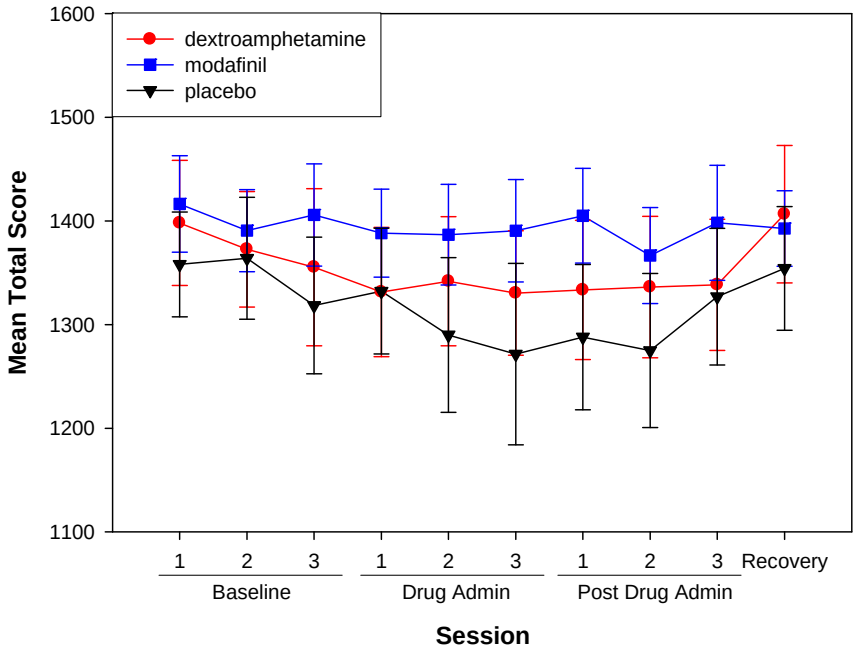

Figure 36. Mean EVAR Total scores by drug and session.

Visual Analog Scale (VAS)

The VAS contains eight dependent measures, Talkative, Sleepy, Nervous, Irritable, Confidence, Energetic, Anxious, and Alert. The higher the score, the more the subject feels of a given measure. This data were analyzed using a 3 (session, within subjects variable) x 3 (drug, between subjects variable) mixed model ANOVA. The three levels of session were the drug administration phase, the post-drug administration phase, and the recovery session. The three levels of drug were modafinil, dextroamphetamine, and placebo. All scores were baseline adjusted and were Greenhouse-Geisser corrected due to the assumption of sphericity being violated, except for the Nervous and Irritable scores, which did not violate the assumption of sphericity.

VAS Talkative score

A significant main effect existed for session ($F[1.398, 46.12] = 19.850$, $p < 0.001$) (drug administration and post-drug administration sessions scored lower in talkative levels than the recovery session) and the interaction between session and drug ($F[2.795, 46.120] = 2.689$, $p = 0.039$), but not for drug ($F[2, 33] = 2.450$, $p = 0.102$) (figure 37). Bonferroni corrected pairwise comparisons were conducted for the main effect of session (alpha = 0.016), determining a significant difference existed between the recovery session and both other sessions (drug administration, $p < 0.001$, and post-drug administration, $p < 0.001$), but no significant difference existed between drug administration and post-drug administration ($p = 0.238$). For the interaction, a significant difference existed between modafinil and dextroamphetamine ($p = 0.008$), but no other conditions were significantly different (table 16). Figure 38 presents the score means by drug condition and session.

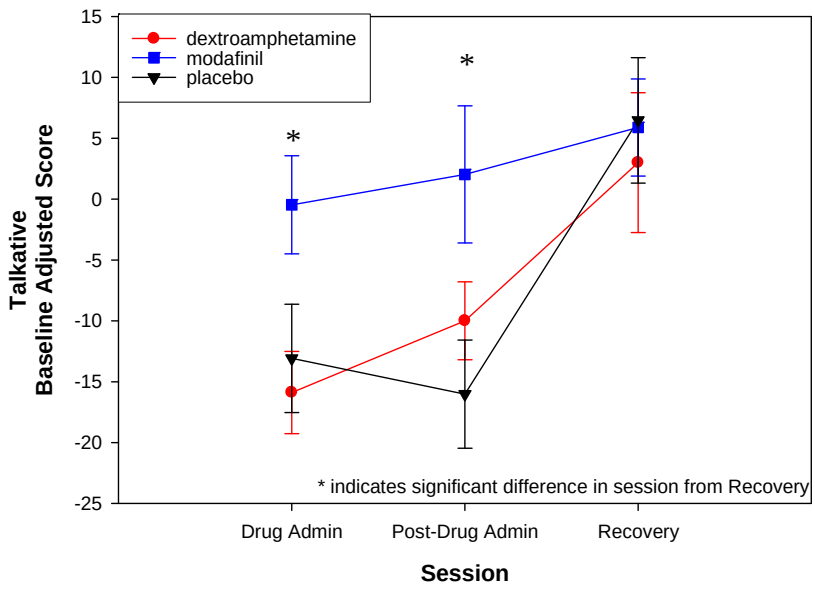

Figure 37. VAS Talkative score comparisons by drug and session (baseline adjusted).

Table 16.
VAS Talkative score interactions between drugs (two-tailed results).

Drug Administration	Modafinil vs. Placebo	$p = 0.047$
	Dextroamphetamine vs. Placebo	$p = 0.620$
	Modafinil vs. Dextroamphetamine	$p = 0.008$
Post-Drug Administration	Modafinil vs. Placebo	$p = 0.020$
	Dextroamphetamine vs. Placebo	$p = 0.283$
	Modafinil vs. Dextroamphetamine	$p = 0.076$
Recovery	Modafinil vs. Placebo	$p = 0.929$
	Dextroamphetamine vs. Placebo	$p = 0.657$
	Modafinil vs. Dextroamphetamine	$p = 0.684$

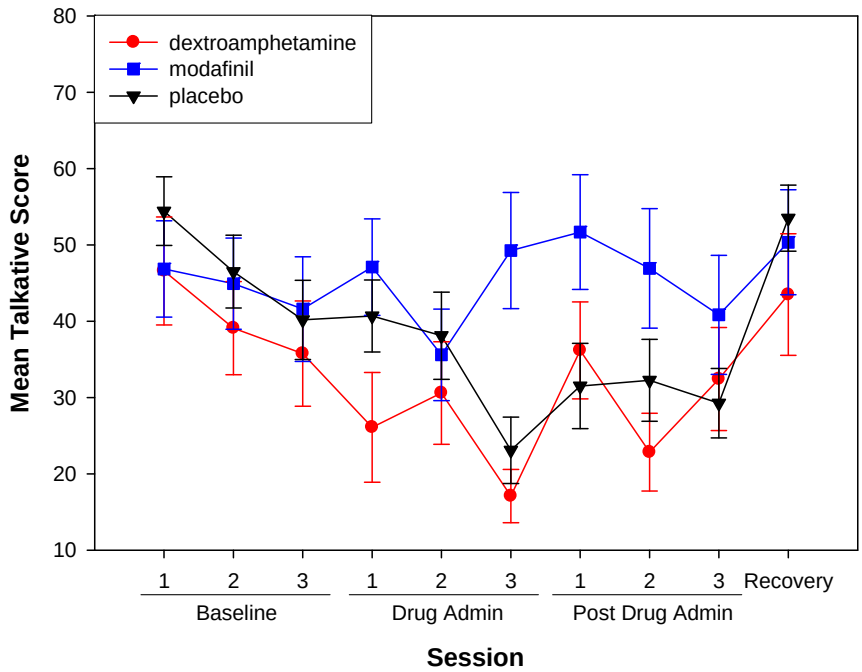

Figure 38. Mean VAS Talkative scores by drug and session.

VAS Sleepy score

A significant main effect existed for session ($F[1.442, 47.575] = 29.405$, $p < 0.001$) (each session was significantly different from the others), drug ($F[2, 33] = 3.666$, $p = 0.036$) (placebo and modafinil groups were significantly different from each other), and the interaction between session and drug ($F[2.883, 47.575] = 3.600$, $p = 0.010$) (figure 39). Bonferroni corrected pairwise comparisons were conducted for the main effect of session (alpha = 0.016), drug (alpha = 0.016) and the interaction between session and drug (alpha = 0.008). For session, all sessions were significantly different from each other (drug administration vs. post-drug administration $p <$ 0.001, drug administration vs. recovery p < 0.001, and post-drug administration vs. recovery $p <$

0.001). For drug, a significant difference existed between modafinil and placebo ($p = 0.014$), but no other conditions were significantly different (modafinil vs. dextroamphetamine, $p = 0.330$, and dextroamphetamine vs. placebo, $p = 0.097$). Table 17 presents the interactions between drugs. Figure 40 presents the score means by drug condition and session.

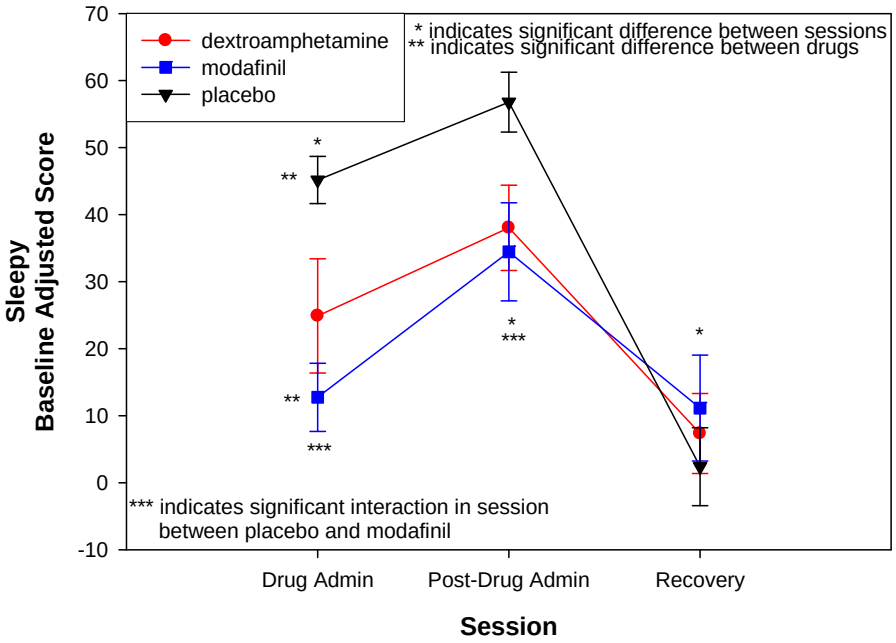

Figure 39. VAS Sleepy score comparisons by drug and session (baseline adjusted).

Table 17.
VAS Sleepy score interactions between drugs (two-tailed results).

Drug Administration	Modafinil vs. Placebo	$p < 0.001$
	Dextroamphetamine vs. Placebo	$p = 0.039$
	Modafinil vs. Dextroamphetamine	$p = 0.235$
Post-Drug Administration	Modafinil vs. Placebo	$p = 0.016$
	Dextroamphetamine vs. Placebo	$p = 0.024$
	Modafinil vs. Dextroamphetamine	$p = 0.715$
Recovery	Modafinil vs. Placebo	$p = 0.382$
	Dextroamphetamine vs. Placebo	$p = 0.559$
	Modafinil vs. Dextroamphetamine	$p = 0.704$

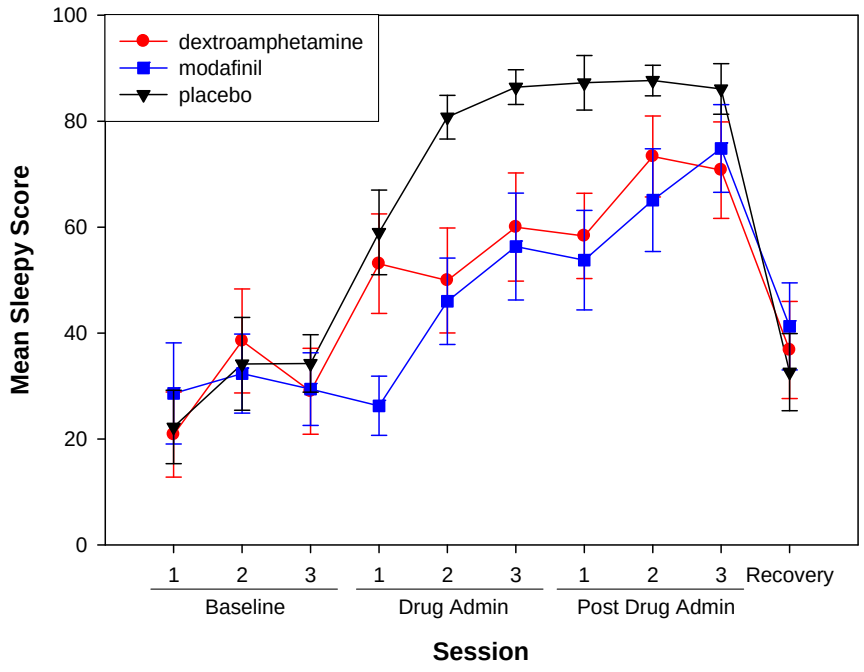

Figure 40. Mean VAS Sleepy scores by drug and session.

VAS Jitteriness/Nervous score

A main effect for session existed ($F[2, 66] = 9.347$, $p < 0.001$) (scores were higher for both drug and post-drug administration sessions than they were for the recovery session), but not for drug ($F[2, 33] = 0.891$, $p = 0.426$) and the interaction between session and drug ($F[4, 66] = 0.492$, $p = 0.741$) (figure 41). Bonferroni corrected pairwise comparisons were conducted for the main effect of session (alpha = 0.016), with a significant difference existing between the recovery session and both the drug administration ($p = 0.001$) and post-drug administration ($p < 0.001$), but no significant difference existed between drug administration and post-drug administration ($p = 0.398$). Figure 42 presents the score means by drug condition and session.

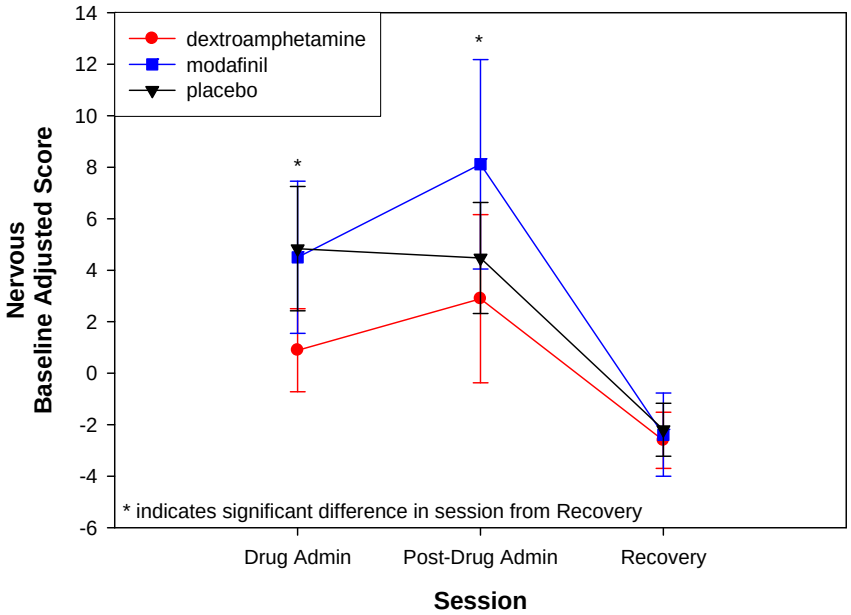

Figure 41. VAS Jitteriness/Nervous score comparisons by drug and session (baseline adjusted).

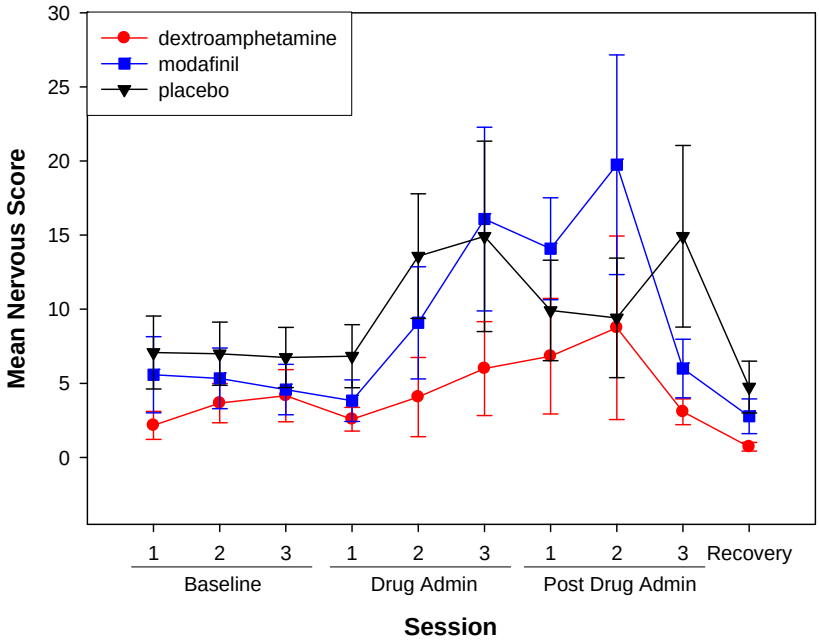

Figure 42. Mean VAS Jitteriness/Nervous scores by drug and session.

VAS Irritable score

No significant differences were found in irritable scores for session ($F[2, 66] = 2.862$, $p = 0.064$), drug ($F[2, 33] = 2.668$, $p = 0.112$), or the interaction between session and drug ($F[4, 66] = 1.953$, $p = 0.112$) (figure 43). Figure 44 presents the score means by drug condition and session.

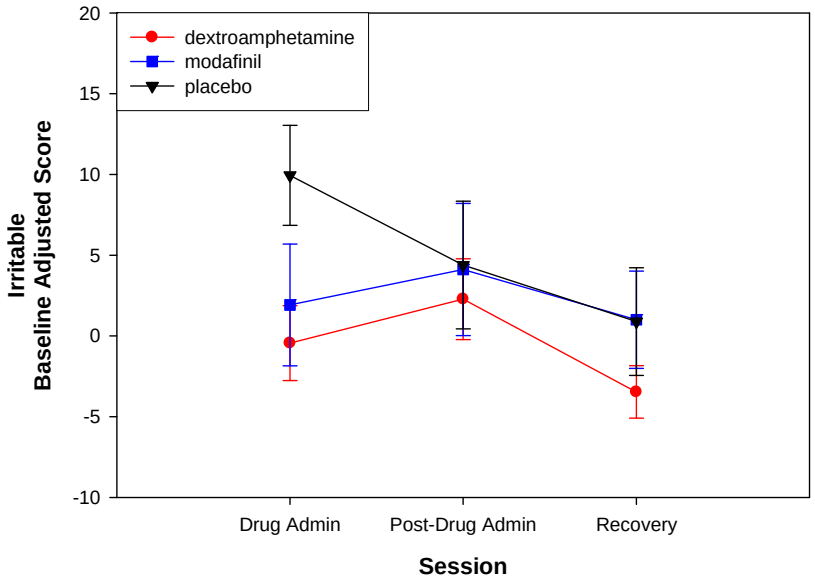

Figure 43. VAS Irritable score comparisons by drug and session (baseline adjusted).

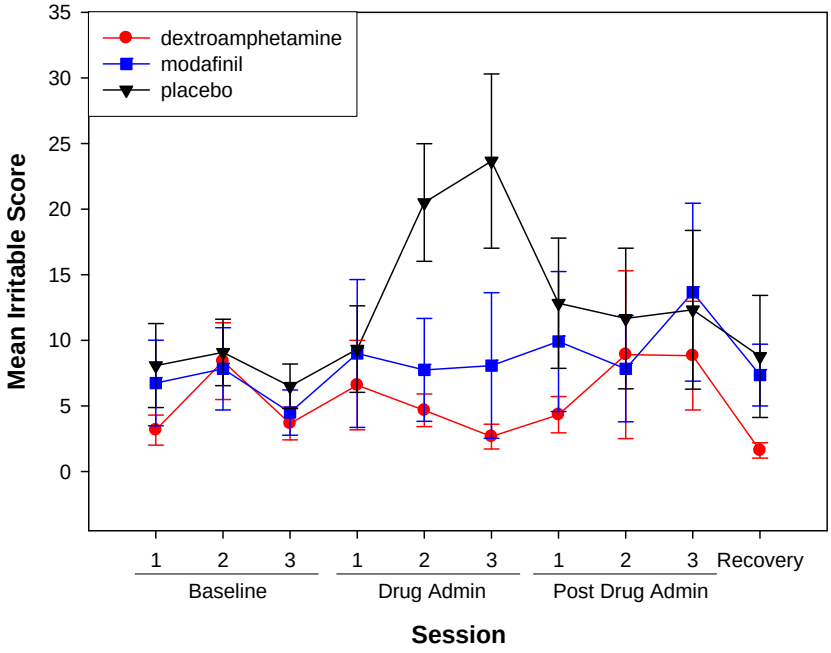

Figure 44. Mean VAS Irritable scores by drug and session.

VAS Confidence score

A main effect of session ($F[2, 66] = 12.263$, $p < 0.001$) existed (each session was significantly different from the others), but not for drug ($F[2, 33] = 2.627$, $p = 0.087$) and the interaction between session and drug ($F[4, 66] = 0.874$, $p = 0.485$) (figure 45). Bonferroni corrected pairwise comparisons were conducted for the main effect of session (alpha = 0.016), with a significant difference existing between all sessions (drug administration vs. post-drug administration, $p = 0.007$, drug administration vs. recovery, $p = 0.016$, and post-drug administration vs. recovery, $p < 0.001$). Figure 46 presents the score means by drug condition and session.

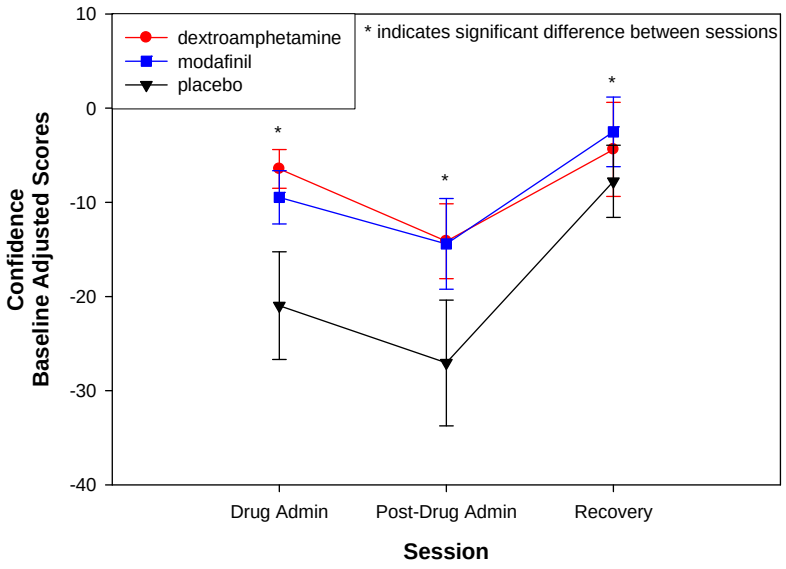

Figure 45. VAS Confidence score comparisons by drug and session (baseline adjusted).

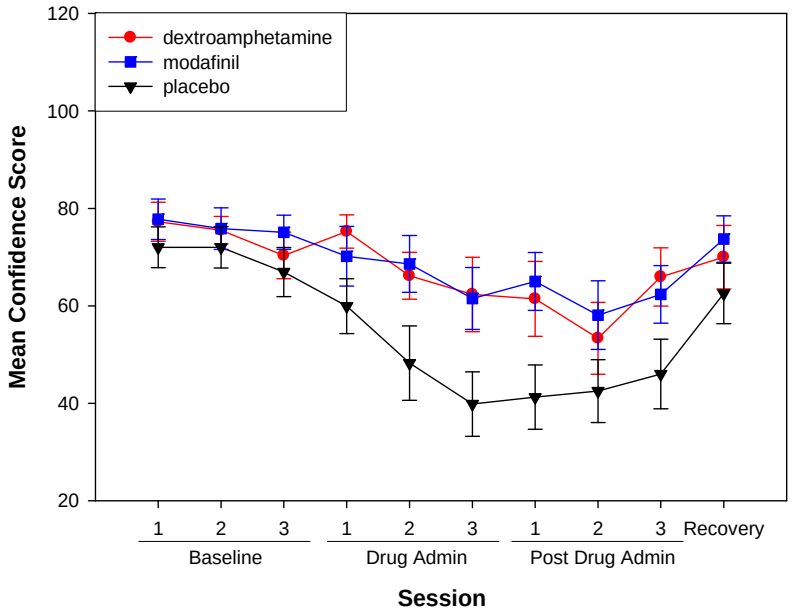

Figure 46. Mean VAS Confidence scores by drug and session.

VAS Energetic score

A main effect of session ($F[1.242, 40.999] = 33.962$, $p < 0.001$) was significant (each session was significantly different), but not for drug ($F[2, 33] = 2.886$, $p = 0.070$) or the interaction between session and drug ($F[2.485, 33.962] = 1.953$, $p = 0.112$) (figure 47). Bonferroni corrected pairwise comparisons were conducted for the main effect of session (alpha = 0.016). For session, a significant difference existed between all sessions (all three comparisons $p <$ 0.001). Figure 48 presents the score means by drug condition and session.

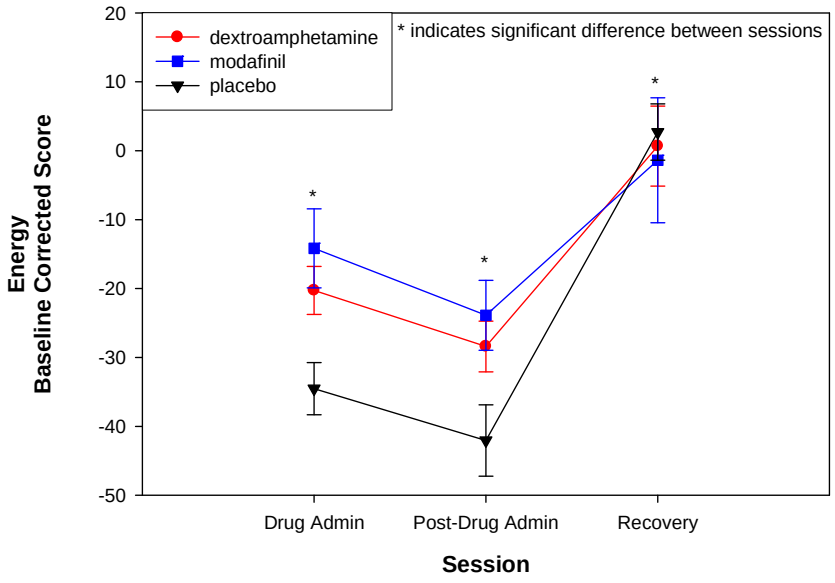

Figure 47. VAS Energetic score comparisons by drug and session (baseline adjusted).

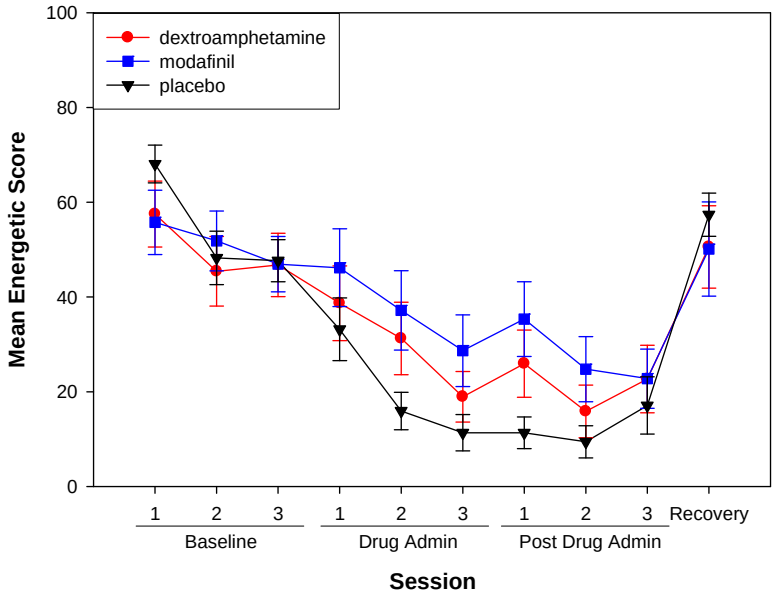

Figure 48. Mean VAS Energetic scores by drug and session.

VAS Anxious score

No significant differences were found in anxious scores for session (F[1.472, 48.570] = 1.720, p = 0.187), drug (F[2, 33] = 0.873, p = 0.427), or the interaction between session and drug (F[2.944, 48.570] = 0.462, p = 0.763) (figure 49). Figure 50 presents the score means by drug condition and session.

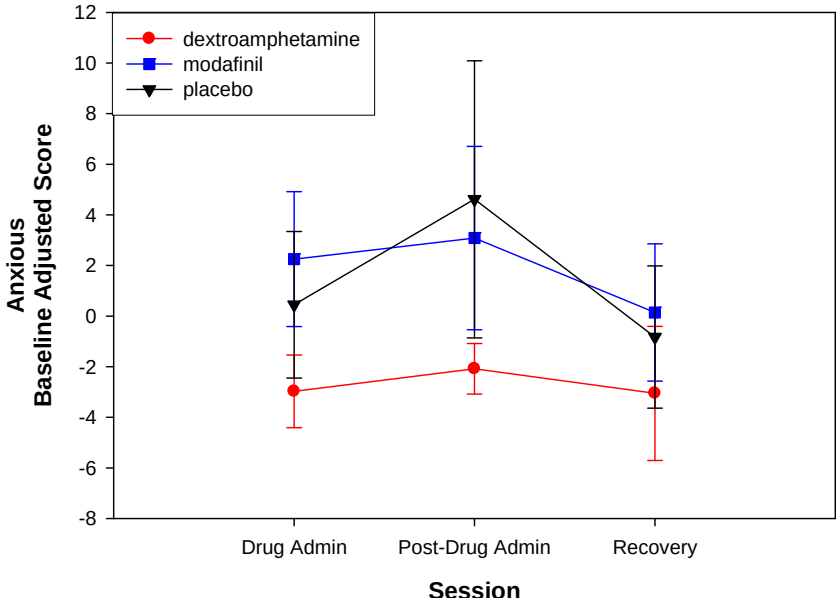

Figure 49. VAS Anxious score comparisons by drug and session (baseline adjusted).

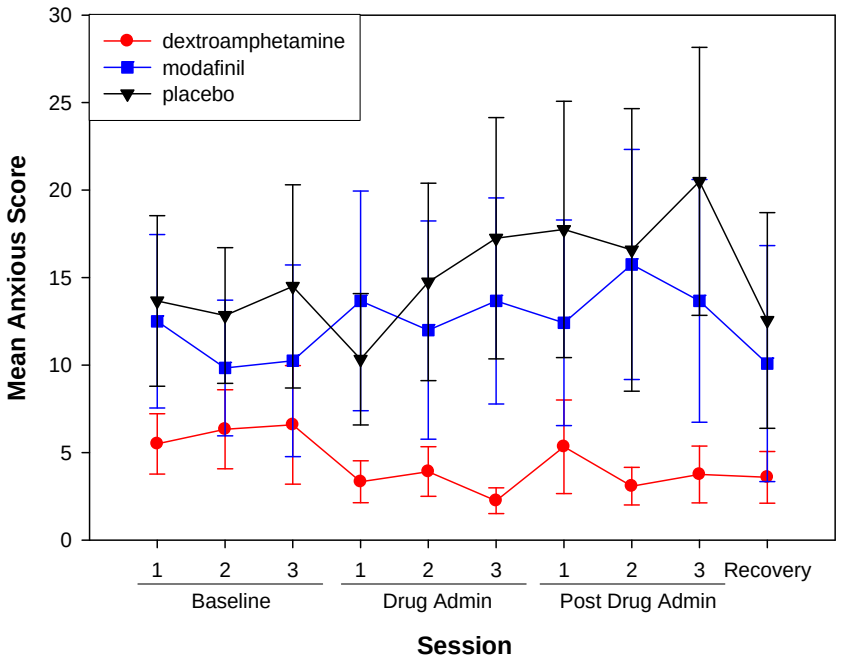

Figure 50. Mean VAS Anxious scores by drug and session.

VAS Alert score

A main effect existed for session (F[1.621, 53.509] = 41.377, $p < 0.001$) with each session significantly different from the others and the interaction between session and drug (F[3.243, 41.377] = 6.626, $p = 0.001$), but not for drug (F[2, 33] = 3.707, $p = 0.053$) (figure 51). Bonferroni corrected pairwise comparisons were conducted for the main effect of session and the interaction between session and drug (alphas of 0.016 and 0.008 respectively). For session, all sessions were significantly different (all $p < 0.001$). Table 18 presents the interactions between drugs. Figure 52 presents the score means by drug condition and session.

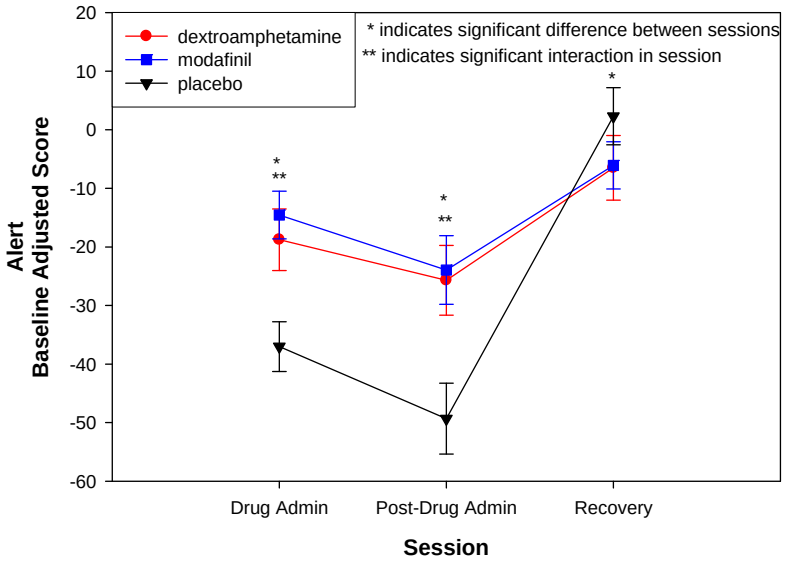

Figure 51. VAS Alert score comparisons by drug and session (baseline adjusted).

Table 18.
VAS Alert score interactions between drugs (two-tailed results).

Drug Administration	Modafinil vs. Placebo	$p = 0.001$
	Dextroamphetamine vs. Placebo	$p = 0.013$
	Modafinil vs. Dextroamphetamine	$p = 0.532$
Post-Drug Administration	Modafinil vs. Placebo	$p = 0.006$
	Dextroamphetamine vs. Placebo	$p = 0.011$
	Modafinil vs. Dextroamphetamine	$p = 0.836$
Recovery	Modafinil vs. Placebo	$p = 0.198$
	Dextroamphetamine vs. Placebo	$p = 0.244$
	Modafinil vs. Dextroamphetamine	$p = 0.952$

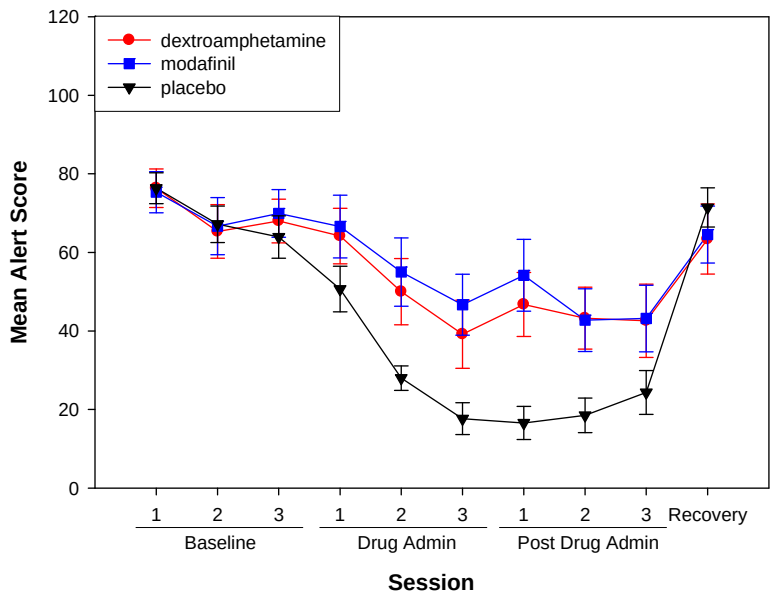

Figure 52. Mean VAS Alert scores by drug and session.

Profile of Mood States (POMS)

The POMS contains six dependent measures: Fatigue, Confusion, Tension, Depression, Anger, and Vigor. The higher the score, the more the subject feels of a given measure. These data were analyzed using a 3 (session, within subjects variable) x 3 (drug, between subjects variable) mixed model ANOVA. The three levels of session were the drug administration phase, the post-drug administration phase, and the recovery session. The three levels of drug were modafinil, dextroamphetamine, and placebo. All scores were baseline adjusted and were Greenhouse-Geisser corrected due to the assumption of sphericity being violated, except for the Depression scores, which did not violate the assumption of sphericity.

POMS Fatigue score

A significant main effect existed for both session ($F[1.309, 43.185] = 3.632$, $p < 0.001$) and the interaction between session and drug ($F[2.617, 43.185] = 3.632$, $p = 0.025$), while the main effect of drug was not significant ($F[2, 33] = 2.512$, $p = 0.097$) (figure 53). Bonferroni corrected pairwise comparisons (alpha = 0.016) were conducted for the main effect of session and indicated that each session was significantly different from all other sessions (drug administration vs. post-drug administration, $p < 0.001$, drug administration vs. recovery, $p = 0.002$, post-drug administration vs. recovery, $p < 0.001$). Bonferroni corrected pairwise comparisons (alpha = 0.008) were also conducted on the main effect of the interaction between session and drug conditions (table 19). A significant interaction was determined between the placebo and modafinil groups during drug administration session. Figure 52 presents the score means by drug condition and session.

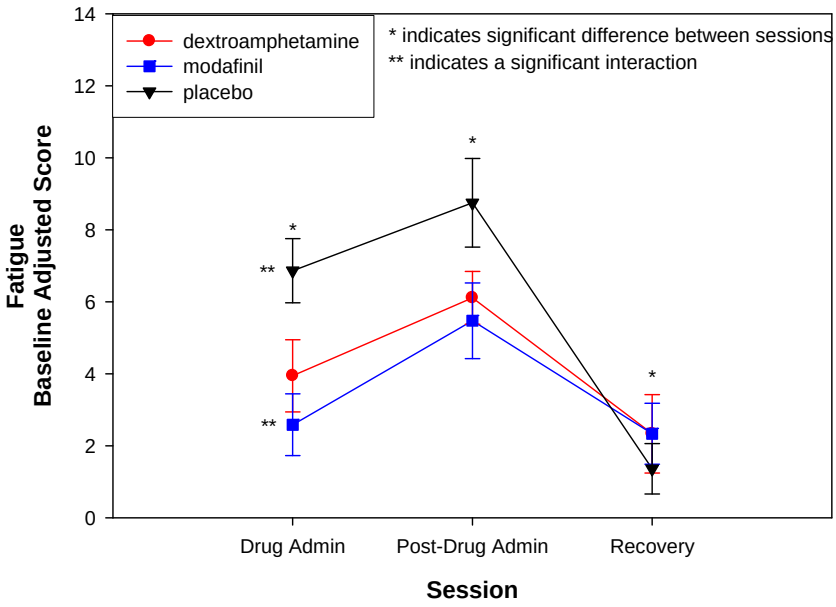

Figure 53. POMS Fatigue score comparisons by drug and session (baseline adjusted).

Table 19.
POMS Fatigue score interactions between drugs (two-tailed results).

Drug Administration	Modafinil vs. Placebo	$p = 0.002$
	Dextroamphetamine vs. Placebo	$p = 0.041$
	Modafinil vs. Dextroamphetamine	$p = 0.623$
Post-Drug Administration	Modafinil vs. Placebo	$p = 0.055$
	Dextroamphetamine vs. Placebo	$p = 0.079$
	Modafinil vs. Dextroamphetamine	$p = 0.623$
Recovery	Modafinil vs. Placebo	$p = 0.386$
	Dextroamphetamine vs. Placebo	$p = 0.461$
	Modafinil vs. Dextroamphetamine	$p = 1.0$

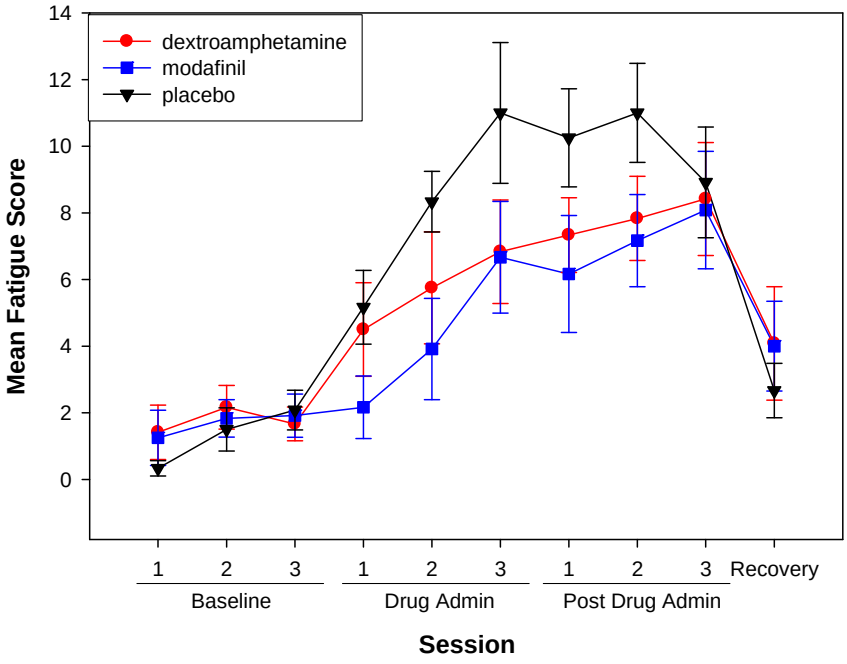

Figure 54. Mean POMS Fatigue scores by drug and session.

POMS Confusion score

A significant main effect existed for both session (F[2.315, 51.823] = 3.717, p = 0.041) and the interaction between session and drug (F[3.141, 51.823] = 4.02, p = 0.011), while the main effect of drug was not significant (F[2, 33] = 1.088, p = 0.349) (figure 55). Bonferroni corrected pairwise comparisons (alpha = 0.016) were conducted for the main effect of session, but no comparisons were found to be significant (drug administration vs. post-drug administration, p = 0.028, drug administration vs. recovery, p = 0.425, post-drug administration vs. recovery, p = 0.040). Bonferroni corrected pairwise comparisons (alpha = 0.008) were also conducted on the main effect of the interaction between session and drug conditions (table 20). Figure 56 presents the score means by drug condition and session.

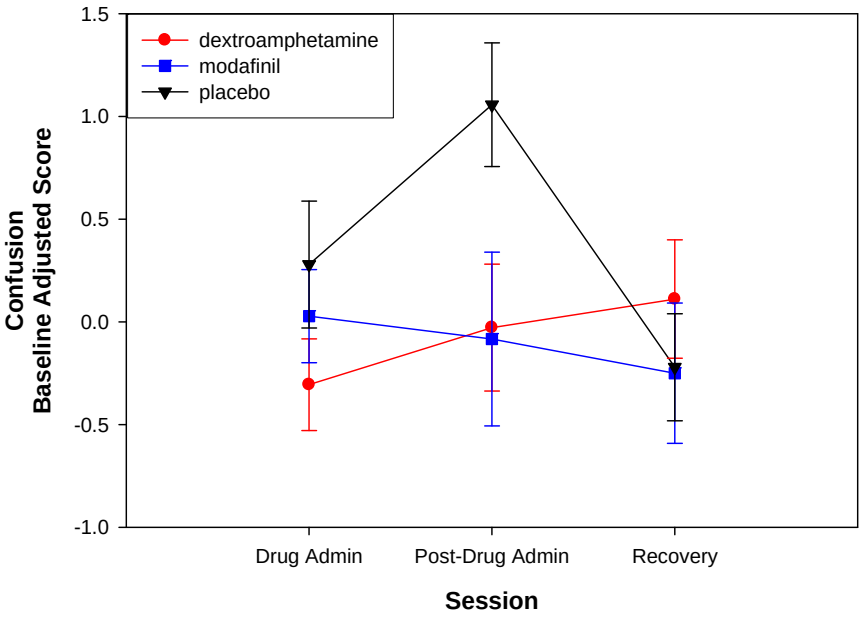

Figure 55. POMS Confusion score comparisons by drug and session (baseline adjusted).

Table 20.
POMS Confusion score interactions between drugs (two-tailed results).

Drug Administration	Modafinil vs. Placebo	$p = 0.519$
	Dextroamphetamine vs. Placebo	$p = 0.139$
	Modafinil vs. Dextroamphetamine	$p = 0.306$
Post-Drug Administration	Modafinil vs. Placebo	$p = 0.039$
	Dextroamphetamine vs. Placebo	$p = 0.02$
	Modafinil vs. Dextroamphetamine	$p = 0.916$
Recovery	Modafinil vs. Placebo	$p = 0.946$
	Dextroamphetamine vs. Placebo	$p = 0.402$
	Modafinil vs. Dextroamphetamine	$p = 0.428$

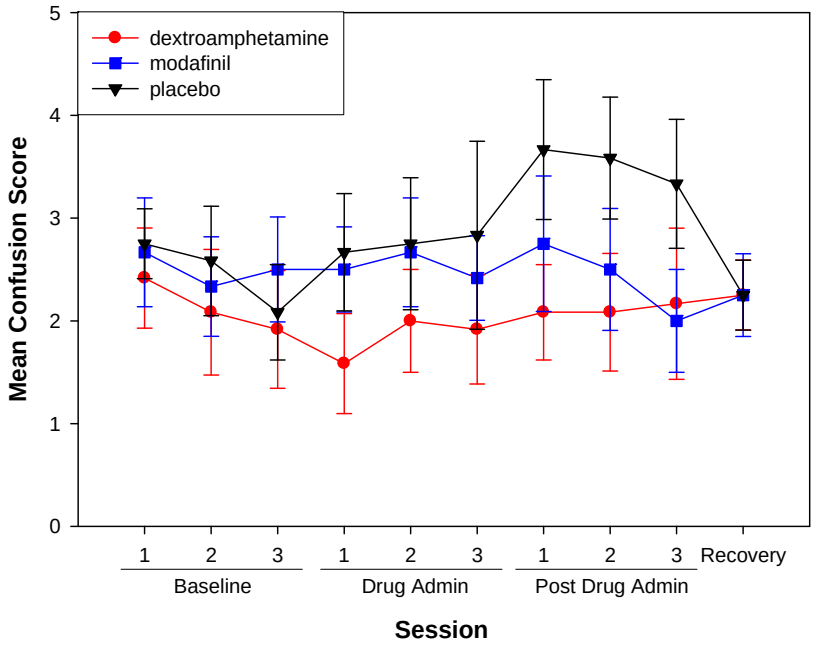

Figure 56. Mean POMS Confusion scores by drug and session.

POMS Tension score

A significant main effect existed for both session ($F[1.582, 52.197] = 27.304$, $p < 0.001$) and the interaction between session and drug ($F[3.163, 52.197] = 4.395$, $p = 0.007$), while the main effect of drug was not significant ($F[2, 33] = 0.295$, $p = 0.747$) (figure 57). Bonferroni corrected pairwise comparisons (alpha = 0.016) were conducted for the main effect of session and indicated that each session was significantly different from all other sessions (drug administration vs. post-drug administration, $p = 0.001$, drug administration vs. recovery, $p < 0.001$, post-drug administration vs. recovery, $p < 0.001$). Bonferroni corrected pairwise comparisons (alpha = 0.008) were also conducted on the main effect of the interaction between session and drug conditions (table 21). Figure 58 presents the score means by drug condition and session.

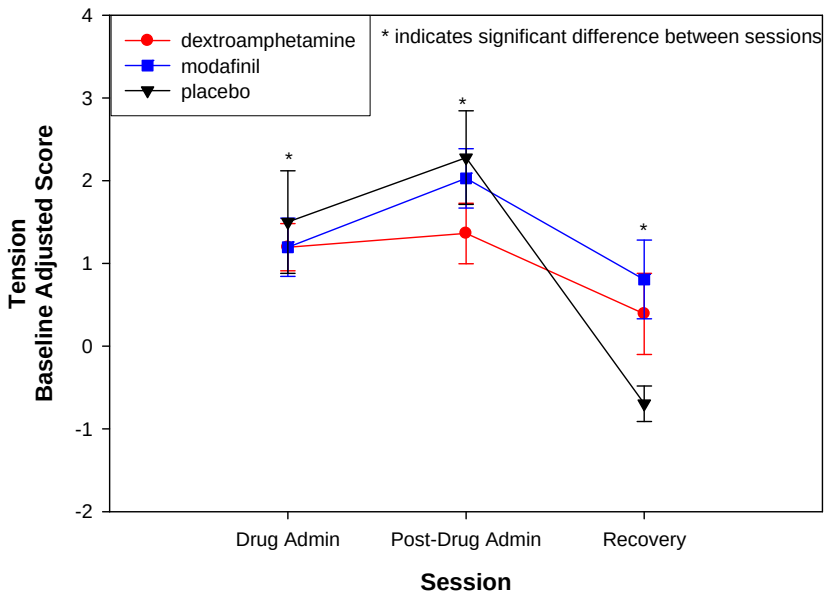

Figure 57. POMS Tension score comparisons by drug and session (baseline adjusted).

Table 21.
POMS Tension score interactions between drugs (two-tailed results).

Drug Administration	Modafinil vs. Placebo	$p = 0.673$
	Dextroamphetamine vs. Placebo	$p = 0.66$
	Modafinil vs. Dextroamphetamine	$p = 0.999$
Post-Drug Administration	Modafinil vs. Placebo	$p = 0.713$
	Dextroamphetamine vs. Placebo	$p = 0.188$
	Modafinil vs. Dextroamphetamine	$p = 0.207$
Recovery	Modafinil vs. Placebo	$p = 0.009$
	Dextroamphetamine vs. Placebo	$p = 0.054$
	Modafinil vs. Dextroamphetamine	$p = 0.548$

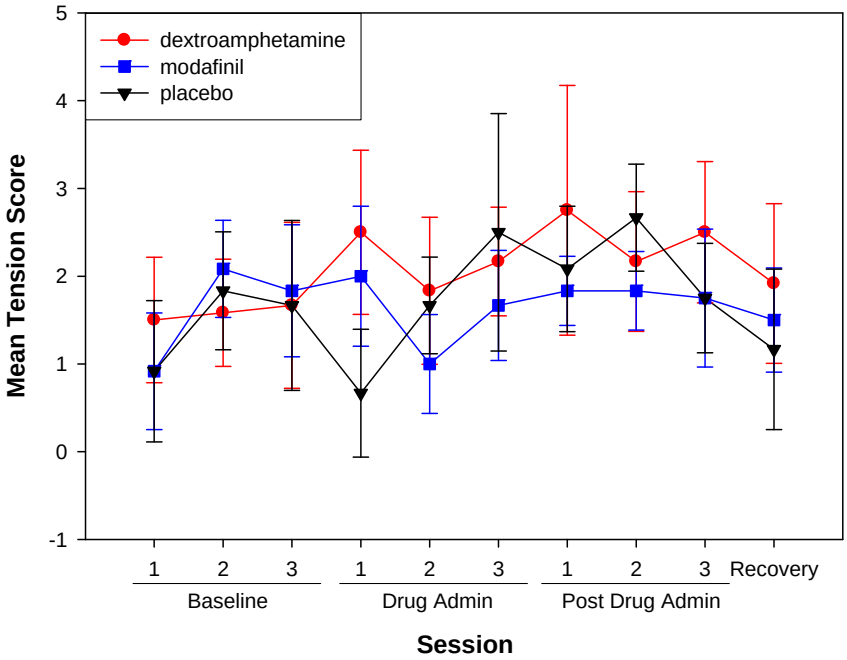

Figure 58. Mean POMS Tension scores by drug and session.

POMS Depression Score

A significant main effect existed for both session ($F[2, 66] = 8.414$, $p = 0.001$) and drug ($F[2, 33] = 3.478$, $p = 0.043$), but not for the interaction between session and drug ($F[4, 66] = 1.724$, $p = 0.155$) (figure 59). Bonferroni corrected pairwise comparisons (alpha = 0.016) were conducted for the main effect of both session and drug. For session, the recovery session was significantly different from both the drug administration ($p = 0.009$) and the post-drug administration ($p = 0.001$) sessions, but the difference between drug administration and post-drug administration sessions were not significantly different ($p = 0.287$). For drug comparisons, both modafinil and dextroamphetamine approached a significant difference from placebo ($p = 0.03$ and $p = 0.028$ respectively), while the difference between modafinil and dextroamphetamine was not significantly different ($p = 0.48$). Figure 60 presents the score means by drug condition and session.

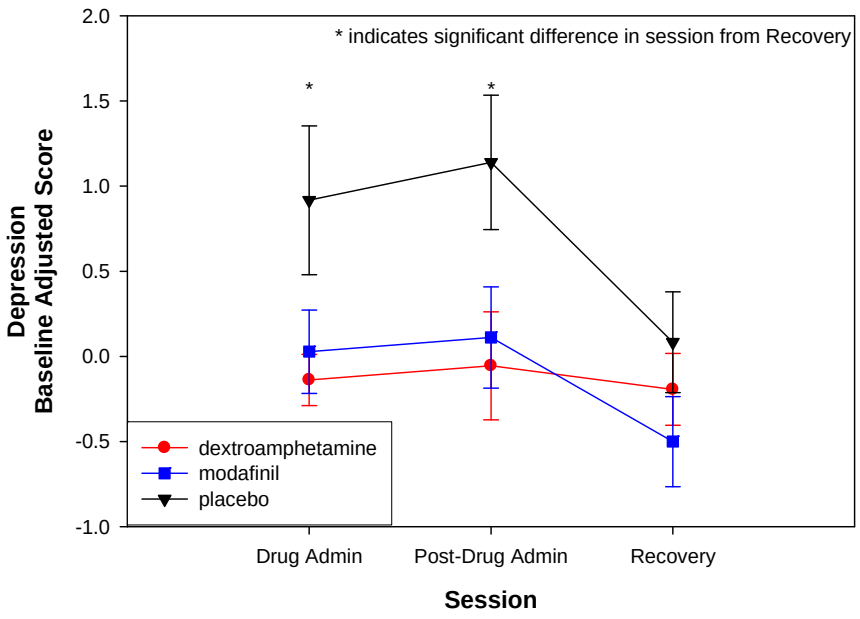

Figure 59. POMS Depression score comparisons by drug and session (baseline adjusted).

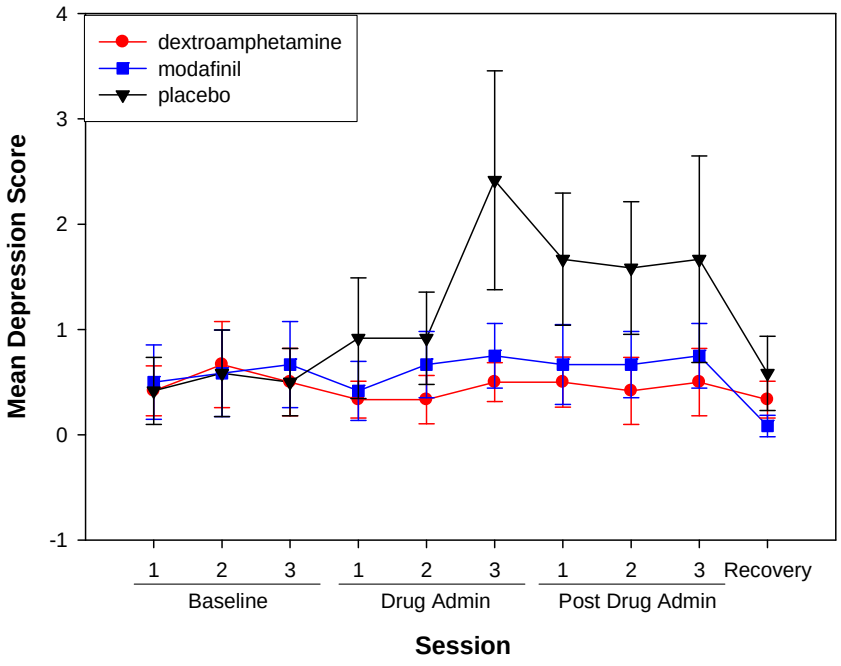

Figure 60. Mean POMS Depression scores by drug and session.

POMS Anger Score

No significant differences were found in anger scores for session ($F[1.599, 52.752] = 1.776$, $p = 0.185$), drug ($F[2, 33] = 0.464$, $p = 0.633$), or the interaction between session and drug ($F[3.197, 52.752] = 1.099$, $p = 0.36$) (figure 61). Figure 62 presents the score means by drug condition and session.

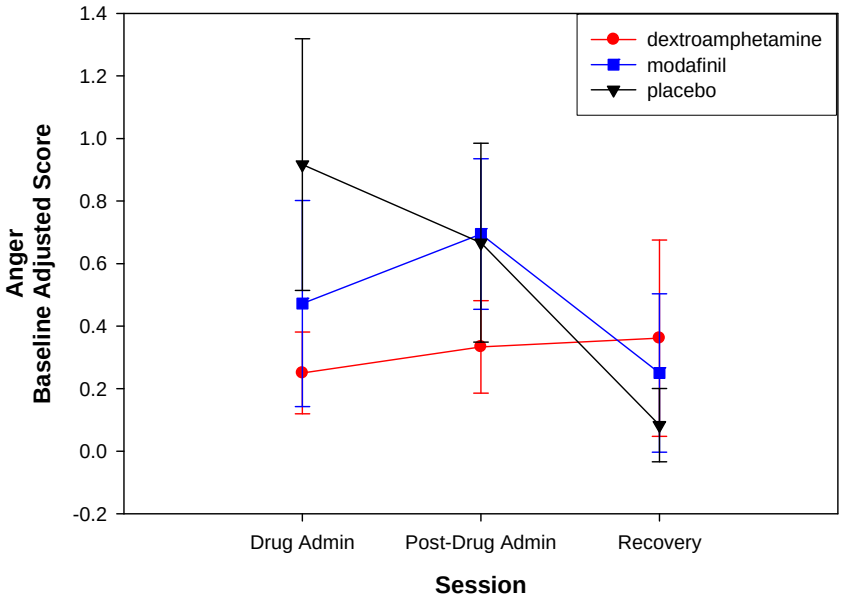

Figure 61. POMS Anger score comparisons by drug and session (baseline adjusted).

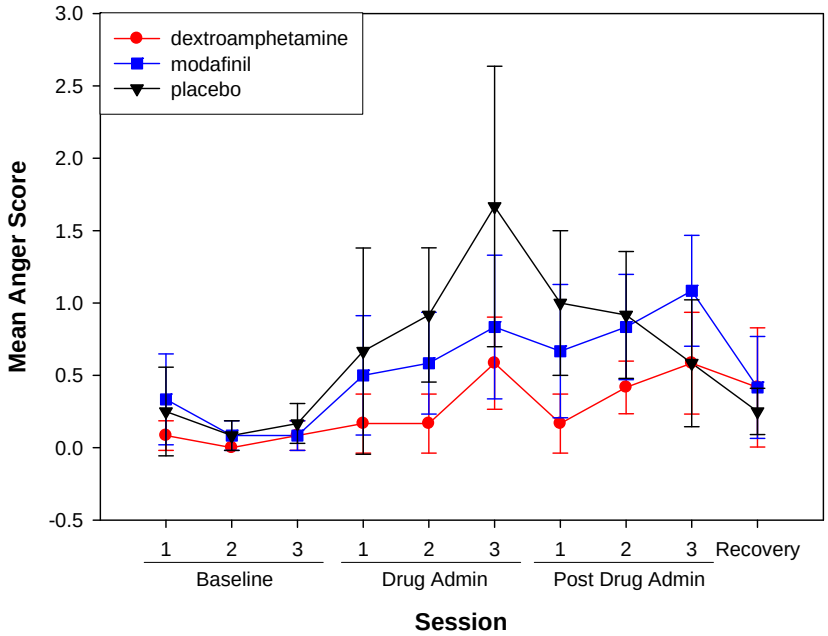

Figure 62. Mean POMS Anger scores by drug and session.

POMS Vigor score

A significant main effect of session ($F[1.401, 46.242] = 42.503$, $p < 0.001$) and the interaction between session and drug ($F[2.803, 46.242] = 4.194$, $p = 0.012$), but not for drug ($F[2, 33] = 2.478$, $p = 0.099$) (figure 63). Bonferroni corrected pairwise comparisons were conducted for the main effect of both session (alpha = 0.016) and the interaction between session and drug (alpha = 0.008). For session, each session was significantly different from all other sessions (drug administration vs. post- drug administration $p < 0.001$, drug administration vs. recovery $p < 0.001$, and post-drug administration vs. recovery $p < 0.001$). Table 22 presents the interactions between drugs. Figure 64 presents the score means by drug condition and session.

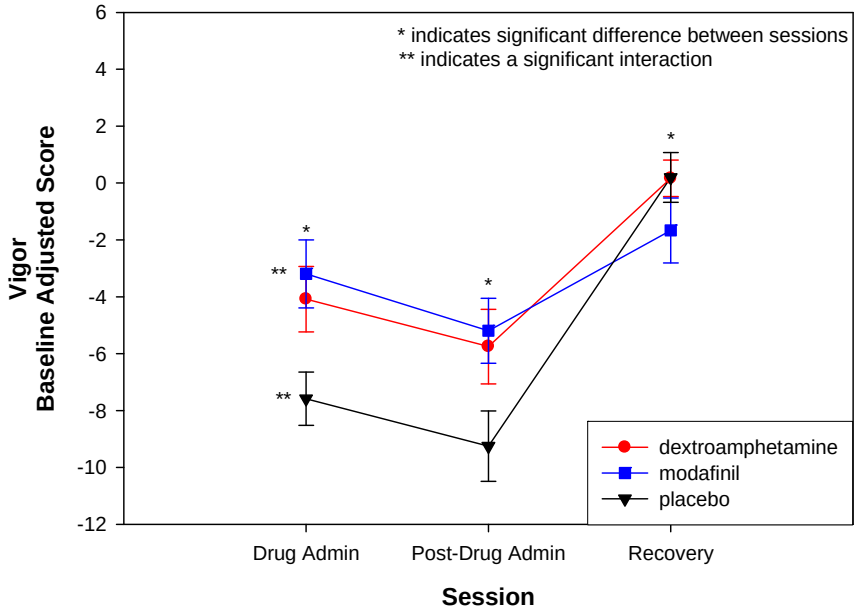

Figure 63. POMS Vigor score comparisons by drug and session (baseline adjusted).

Table 22.
POMS Vigor score interactions between drugs (two-tailed results).

Drug Administration	Modafinil vs. Placebo	$p = 0.009$
	Dextroamphetamine vs. Placebo	$p = 0.027$
	Modafinil vs. Dextroamphetamine	$p = 0.597$
Post-Drug Administration	Modafinil vs. Placebo	$p = 0.025$
	Dextroamphetamine vs. Placebo	$p = 0.065$
	Modafinil vs. Dextroamphetamine	$p = 0.752$
Recovery	Modafinil vs. Placebo	$p = 0.209$
	Dextroamphetamine vs. Placebo	$p = 0.979$
	Modafinil vs. Dextroamphetamine	$p = 0.175$

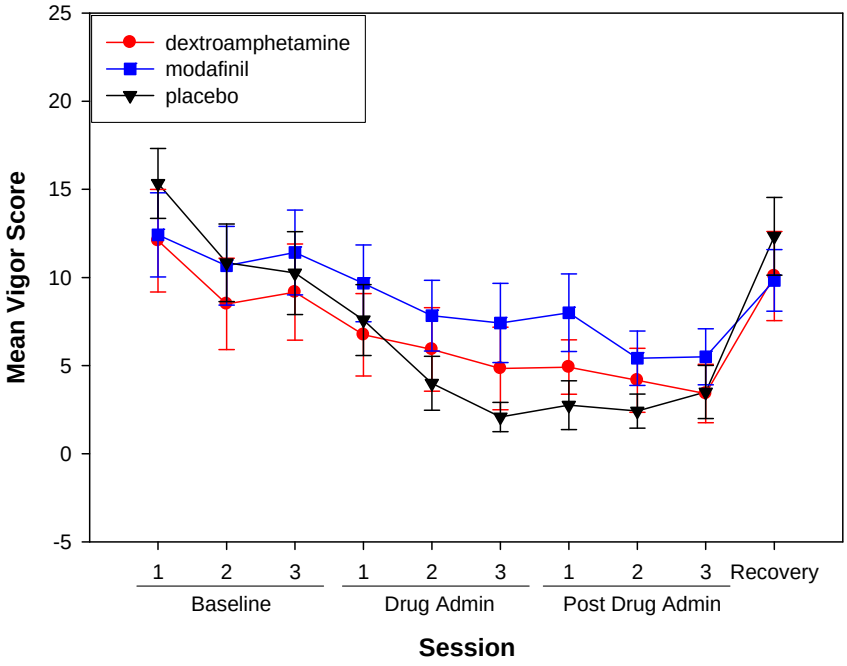

Figure 64. Mean POMS Vigor scores by drug and session.

Performance Tests

Psychomotor Vigilance Task (PVT)

The PVT data are comprised of three dependent measures: reaction time, major lapses, and minor lapses. The data were analyzed using 3 (session) x 3 (drug) mixed model ANOVAs. The variable *session* was the within-subjects factor and its three levels were the drug administration phase, the post-drug administration phase, and a recovery session. The variable *drug* was the between-subjects factor and its three levels were modafinil, dextroamphetamine, and placebo. The scores were baseline adjusted. For all three dependent measures, the assumption of sphericity was violated and a Greenhouse-Geisser correction was used. It should be noted that PVT data were available for only 16 of the 18 participants, resulting in a total of 10 modafinil participant conditions, 11 dextroamphetamine participant conditions, and 11 placebo participant conditions.

PVT Reaction Time

There was a significant main effect of session ($F[1.298, 37.632] = 4.795$, $p = 0.026$) (figure 65). Pairwise comparisons revealed that the mean reaction time during the drug administration sessions were significantly faster than those during the post drug administration sessions ($p = 0.022$). In addition, mean reaction times during the recovery period were significantly faster than those during the post drug administration period ($p = 0.013$). The main effect of drug was not significant ($F[2, 29] = 1.678$, $p = 0.204$). However, there was a significant interaction

between drug and session (F[2.595, 37.632] = 3.517, p = 0.029). To investigate the significant interaction, independent t-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied (p = 0.0083). Results for the t-tests are presented in table 23. During both the drug administration and post drug administration periods, modafinil and dextroamphetamine were not significantly different. Figure 66 presents the reaction time means by drug condition and session.

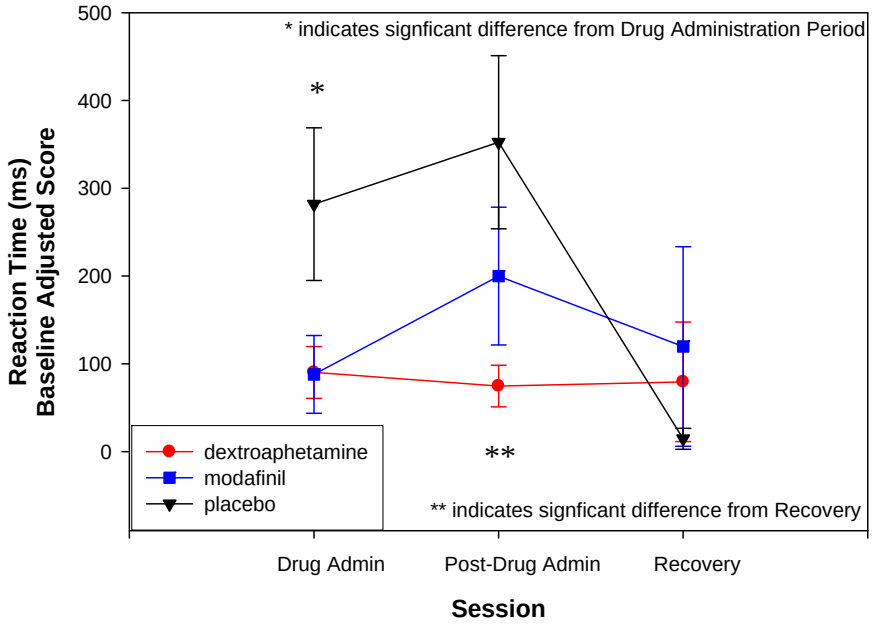

Figure 65. PVT Reaction Time comparisons by drug and session (baseline adjusted).

Table 23.
Post hoc results for PVT reaction time data.

During Drug Administration periods	p value	During Post Drug Administration	p value
Modafinil vs. Placebo	0.069	Modafinil vs. Placebo	0.247
Placebo vs. Dextroamphetamine	0.058	Placebo vs. Dextroamphetamine	0.019
Modafinil vs. Dextroamphetamine	0.967	Modafinil vs. Dextroamphetamine	0.156

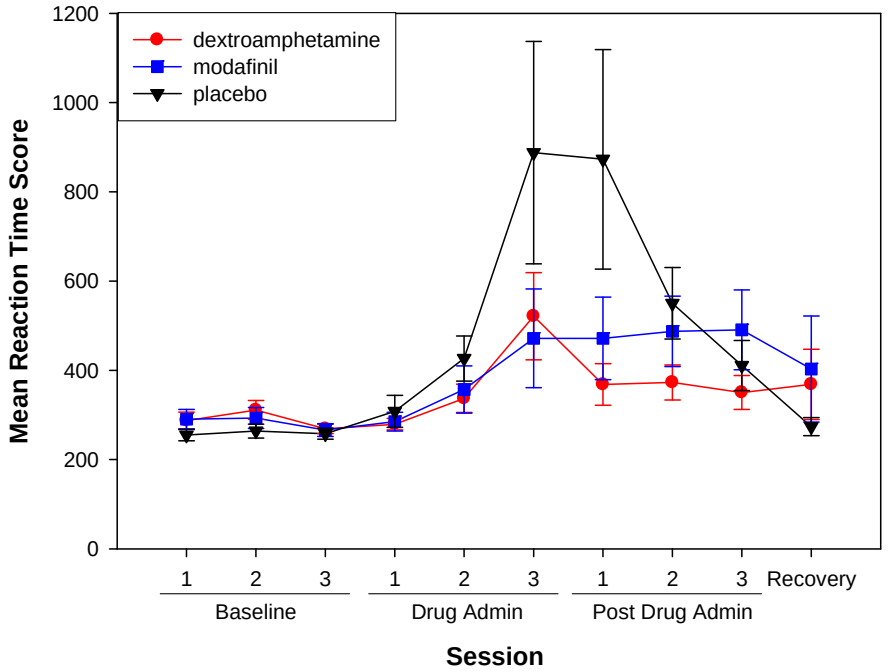

Figure 66. Mean PVT Reaction Time by drug and session.

PVT Major Lapses

A major lapse is defined as a response over 3 seconds. There was a significant main effect of session ($F[1.487, 43.124] = 4.634$, $p = 0.024$) (figure 67). Pairwise comparisons revealed there were significantly more major lapses during the post drug administration period than during both the drug administration period ($p = 0.007$) and the recovery period ($p = 0.012$). The main effect of drug was not significant ($F[2, 29] = 0.457$, $p = 0.637$). In addition, the interaction between drug and session was also not significant ($F[2.974, 43.124] = 2.760$, $p = 0.054$). Figure 68 presents the major lapse means by drug condition and session.

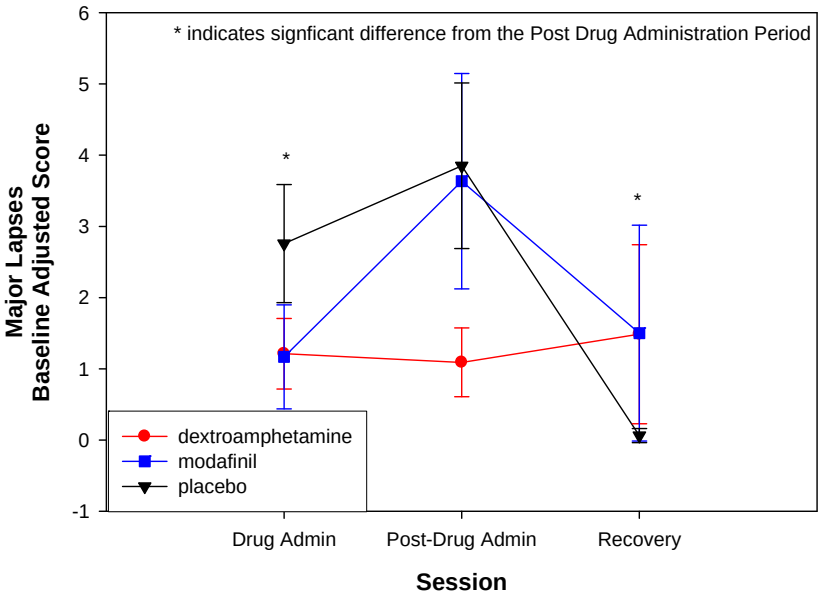

Figure 67. PVT Major Lapses comparisons by drug and session (baseline adjusted).

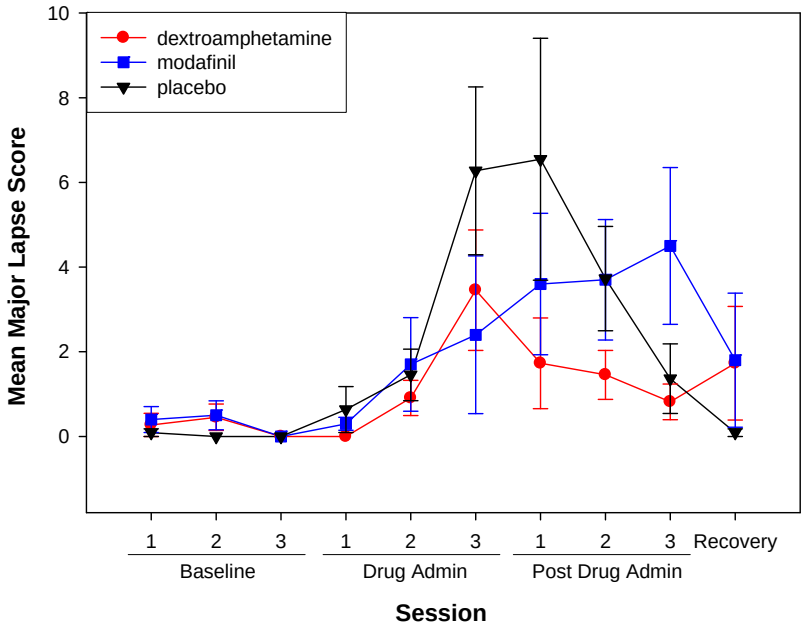

Figure 68. Mean PVT Major Lapses by drug and session.

PVT Minor Lapses

A minor lapse is defined as a response over 500 milliseconds. There was a significant main effect of session (F[1.608, 46.644] = 20.215, p <0.001) (figure 69). Pairwise comparisons revealed there were significantly more minor lapses during the post drug administration period than during both the drug administration period (p = 0.003) and the recovery period (p < 0.001). In addition, there were significantly more minor lapses during the drug administration period than during the recovery period (p = 0.001). The main effect of drug was not significant (F[2, 29] = 2.492, p = 0.100). However, there was a significant interaction between drug and session (F[3.217, 46.644] = 3.665, p = 0.017). To investigate the significant interaction, independent t-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied (p = 0.0083). Results for the t tests are presented in table 24. During the post drug administration period, the placebo group produced significantly more lapses than the dextroamphetamine group (p = 0.007). Figure 70 presents the minor lapse means by drug condition and session.

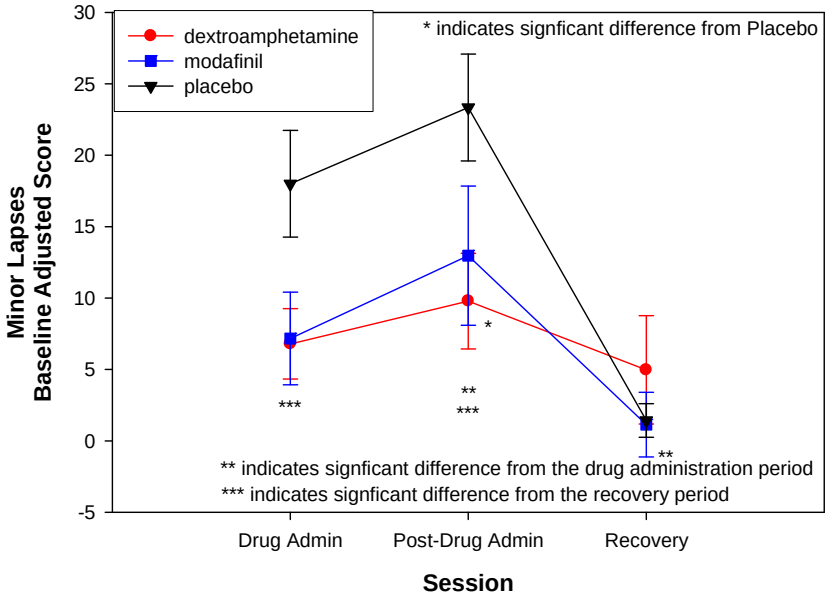

Figure 69. PVT Minor Lapses comparisons by drug and session (baseline adjusted).

Table 24.
Post hoc results for PVT minor lapse data.

During Drug Administration periods	p value	During Post Drug Administration	p value
Modafinil vs. Placebo	0.043	Modafinil vs. Placebo	0.104
Placebo vs. Dextroamphetamine	0.021	Placebo vs. Dextroamphetamine	0.007 (one tailed)
Modafinil vs. Dextroamphetamine	0.926	Modafinil vs. Dextroamphetamine	0.591

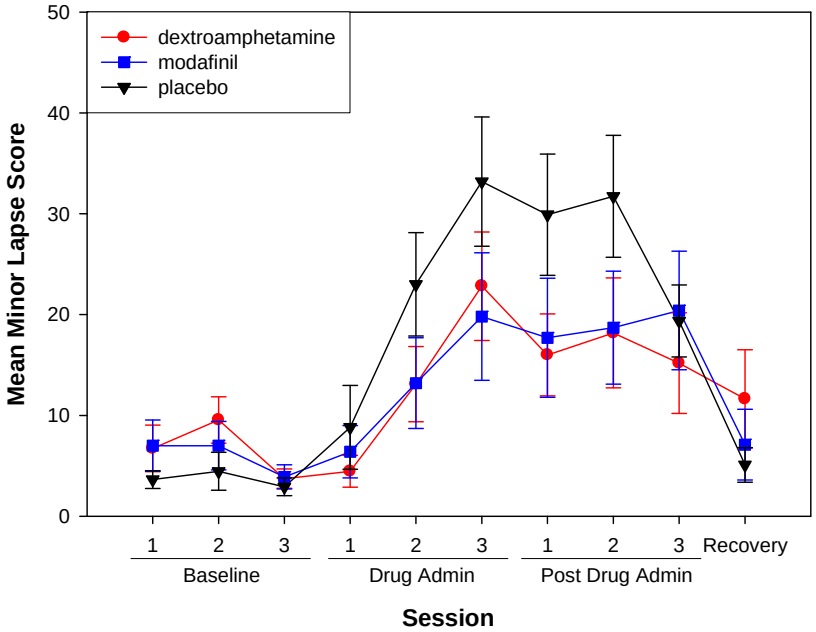

Figure 70. Mean PVT Minor Lapses by drug and session.

Balloon Analog Risk Test (BART)

The BART contains a single dependent measure, the average pump counts per trial of non popped balloons. Higher pump counts equal greater risk taking behavior. These data were analyzed using a 3 (session, within subjects variable) x 3 (drug, between subjects variable) mixed model ANOVA. The three levels of session were the drug administration phase, the post-drug administration phase, and the recovery session. The three levels of drug were modafinil, dextroamphetamine, and placebo. All scores were baseline adjusted and Greenhouse-Geisser corrected due to the assumption of sphericity being violated. Analysis of the data revealed one participant did not complete the task correctly and data were missing from two other participants.

A significant main effect existed for session ($F[1.603, 46.484] = 6.570$, $p = 0.003$) and the interaction between session and drug conditions ($F[3.206, 46.484] = 3.329$, $p = 0.025$), but not for drug ($F[2, 29] = 1.409$, $p = 0.263$) (figure 71). Bonferroni corrected pairwise comparisons (alpha = 0.016) were conducted for the main effect of session and the interaction of drug and session (alpha = 0.008). For session, a significant difference between recovery and the post-drug administration period existed ($p < 0.001$) (table 25). There were significantly fewer pump counts during the post-drug administration sessions than during the recovery session, suggesting risk aversion during the post-drug administration sessions. Figure 72 presents the score means by drug condition and session.

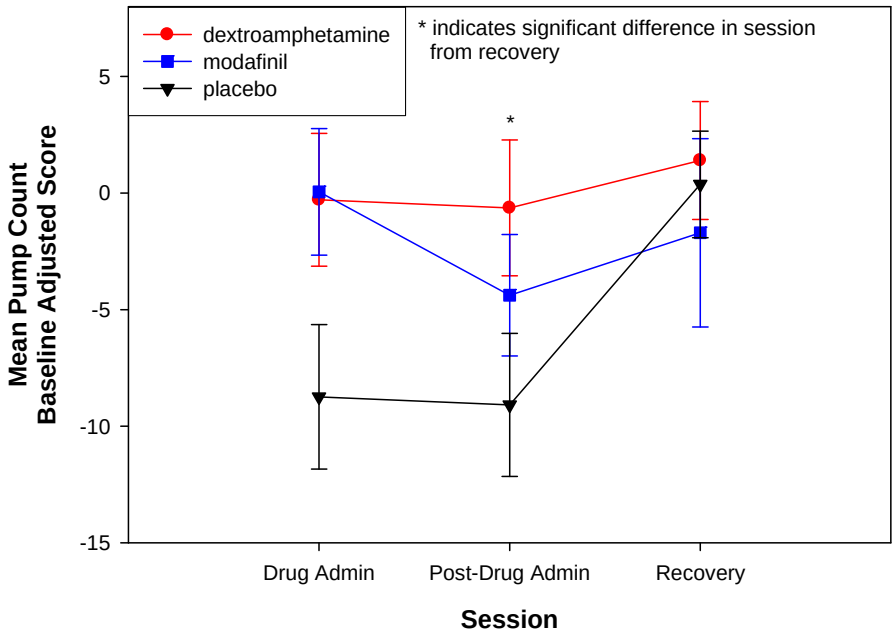

Figure 71. BART mean pump count score comparisons by drug and session (baseline adjusted).

Table 25.
BART mean pump count score interactions between drugs (two-tailed results).

Drug Administration	Modafinil vs. Placebo	$p = 0.014$
	Dextroamphetamine vs. Placebo	$p = 0.019$
	Modafinil vs. Dextroamphetamine	$p = 0.100$
Post-Drug Administration	Modafinil vs. Placebo	$p = 0.042$
	Dextroamphetamine vs. Placebo	$p = 0.009$
	Modafinil vs. Dextroamphetamine	$p = 0.050$
Recovery	Modafinil vs. Placebo	$p = 0.243$
	Dextroamphetamine vs. Placebo	$p = 0.053$
	Modafinil vs. Dextroamphetamine	$p = 0.250$

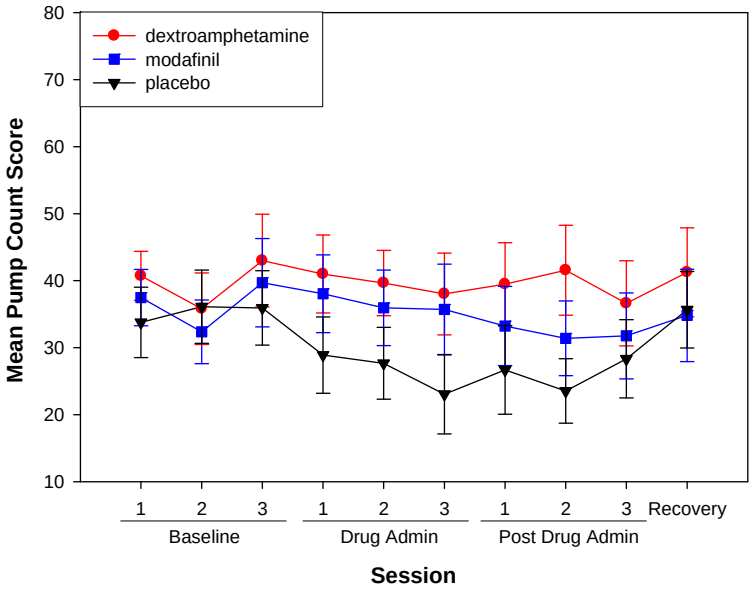

Figure 72. Mean BART pump count scores by drug and session.

Iowa Gambling Task (IGT)

The IGT contains a single dependent measure, the ratio of good to bad cards selected throughout the trial. A higher score is equal to lower risk taking. These data were analyzed using a 3 (session, within subjects variable) x 3 (drug, between subjects variable) mixed model ANOVA. The three levels of session were the drug administration phase, the post-drug administration phase, and the recovery session. The three levels of drug were modafinil, dextroamphetamine, and placebo. All scores were baseline adjusted.

There were no significant main effects for session ($F[1.995, 53.852] = 0.581$, $p = 0.563$), for drug ($F[2, 27] = 0.0569$, $p = 0.573$), and the interaction between session and drug conditions ($F[3.989, 53.852] = 0.564$, $p = 0.690$) (figure 73). Figure 74 presents the score means by drug condition and session.

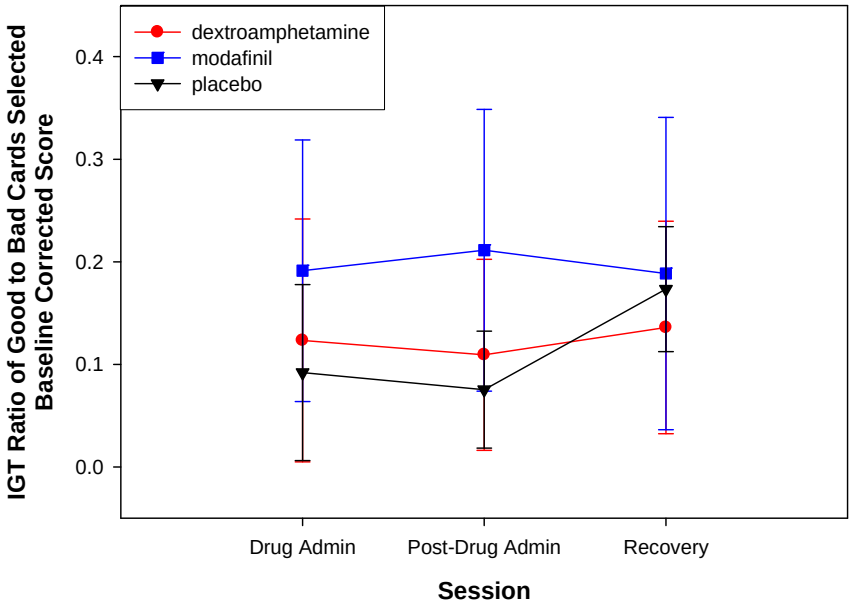

Figure 73. IGT ratio of good to bad cards selected score comparisons by drug and session (baseline adjusted).

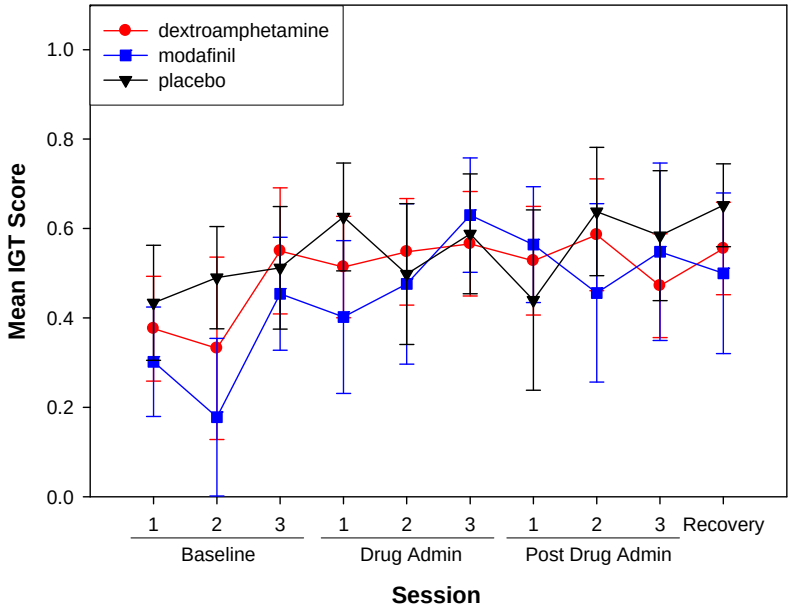

Figure 74. Mean IGT scores by drug and session.

Cambridge Neuropsychological Test Automated Battery (CANTAB)

The CANTAB uses touch-screen technology to deliver rapid, non-invasive, language-independent cognitive tests. It is well validated and suitable for repeated measures testing. The following subtests were chosen based upon a review of the open literature papers that have used CANTAB to assess the effects of stimulants. Each test generated numerous derivative measures, however, only the primary measures or those most salient to the current study are discussed here.

Rapid Visual Processing (RVP)

The RVP, a test of visual sustained attention, contains three dependent measures: hit probability (the ratio of correctly detecting the target stimuli), false alarm probability (the ratio of incorrectly rejecting the distraction stimuli), and the A' (a prime) value score (the measure of performance in detecting sequences). These data were analyzed using a 3 (session, within subjects variable) x 3 (drug, between subjects variable) mixed model ANOVA. The three levels of session were the drug administration phase, the post-drug administration phase, and the recovery session. The three levels of drug were modafinil, dextroamphetamine, and placebo. All scores were baseline adjusted and Greenhouse-Geisser corrected due to the assumption of sphericity being violated.

RVP Hit Probability. A higher hit probability equals higher detection of stimuli. A significant main effect existed for session ($F[2, 60] = 4.446$, $p = 0.016$) and the interaction of session and drug ($F[4, 60] = 2.604$, $p = 0.045$, but not for drug ($F[2, 30] = 2.014$, $p = 0.151$) (figure 75). Bonferroni corrected pairwise comparisons (alpha = 0.016) were conducted for the main effect of session and indicated a significant difference between recovery and the post-drug administration ($p = 0.013$). For interaction, both modafinil and dextroamphetamine are significantly different than placebo in both the drug and post-drug administration periods (table 26). Figure 76 presents the score means by drug condition and session.

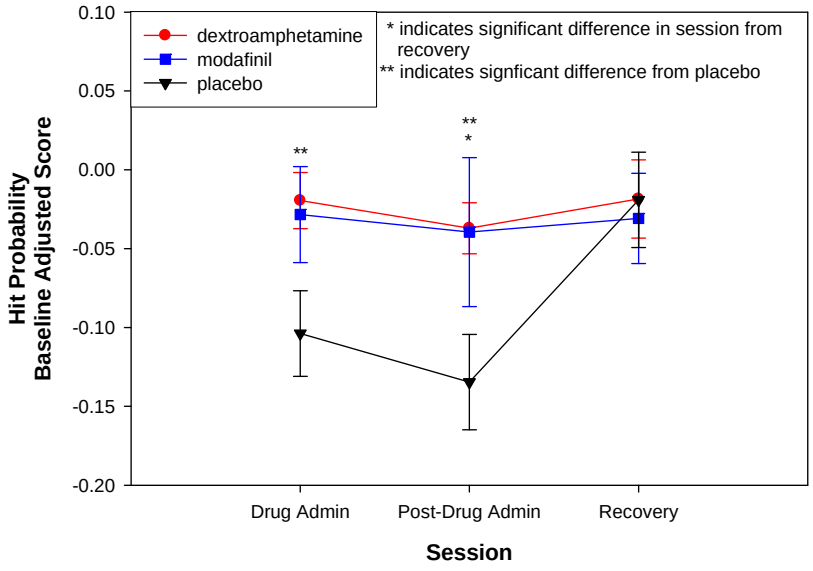

Figure 75. RVP Hit Probability score comparisons by drug and session (baseline adjusted).

Table 26.
Hit probability score interactions between drugs (two-tailed results).

Drug Administration	Modafinil vs. Placebo	$p = 0.010$
	Dextroamphetamine vs. Placebo	$p = 0.003$
	Modafinil vs. Dextroamphetamine	$p = 0.141$
Post-Drug Administration	Modafinil vs. Placebo	$p = 0.012$
	Dextroamphetamine vs. Placebo	$p = 0.001$
	Modafinil vs. Dextroamphetamine	$p = 0.160$
Recovery	Modafinil vs. Placebo	$p = 0.130$
	Dextroamphetamine vs. Placebo	$p = 0.163$
	Modafinil vs. Dextroamphetamine	$p = 0.126$

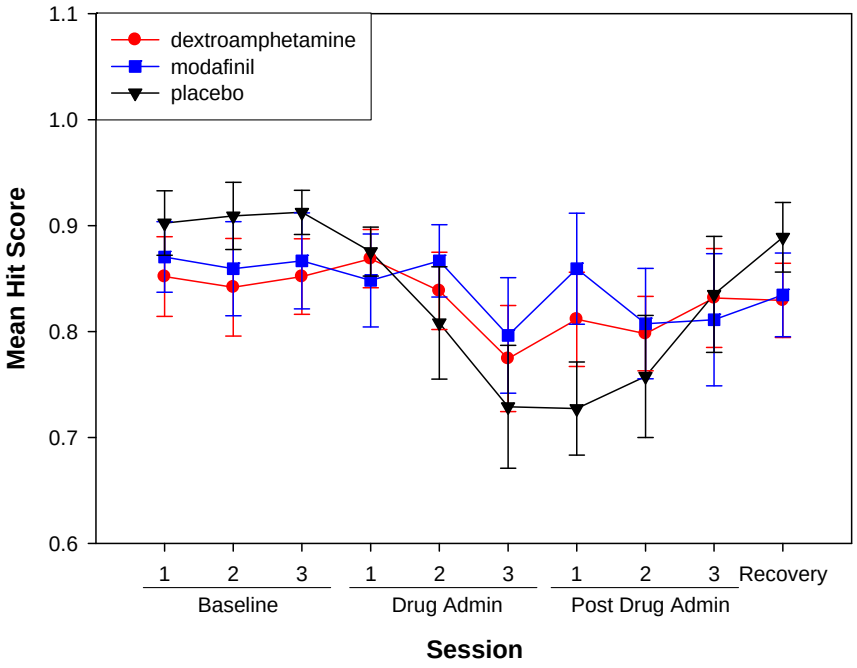

Figure 76. Mean RVP Hit Probability scores by drug and session.

False Alarm Probability. No significant main effects existed for session ($F[1.478, 44.336] = 2.968$, $p = 0.059$), drug ($F[2, 30] = 1.191$, $p = 0.318$), or the interaction between session and drug ($F[2.956, 44.336] = 0.255$, $p = 0.855$) (figure 77). Figure 78 presents the score means by drug condition and session.

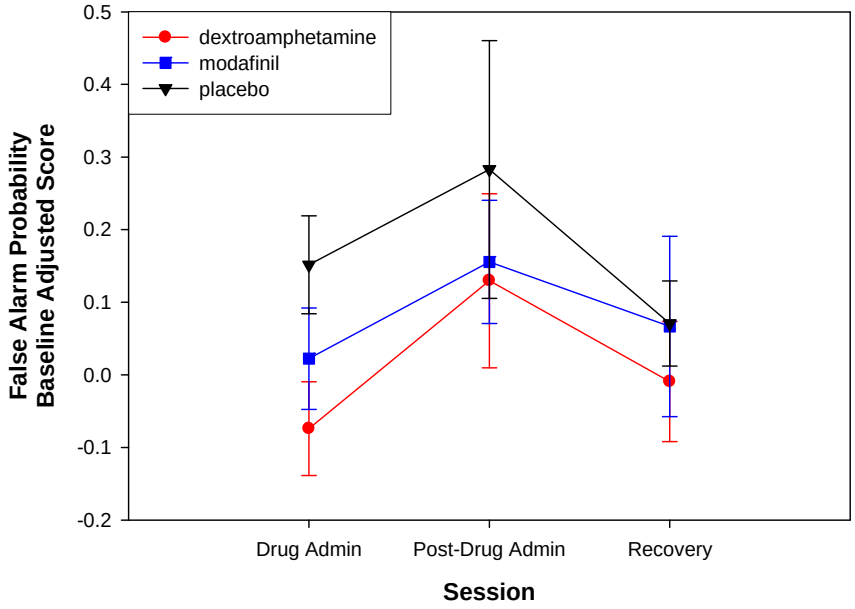

Figure 77. RVP False Alarm Probability score comparisons by drug and session (baseline adjusted).

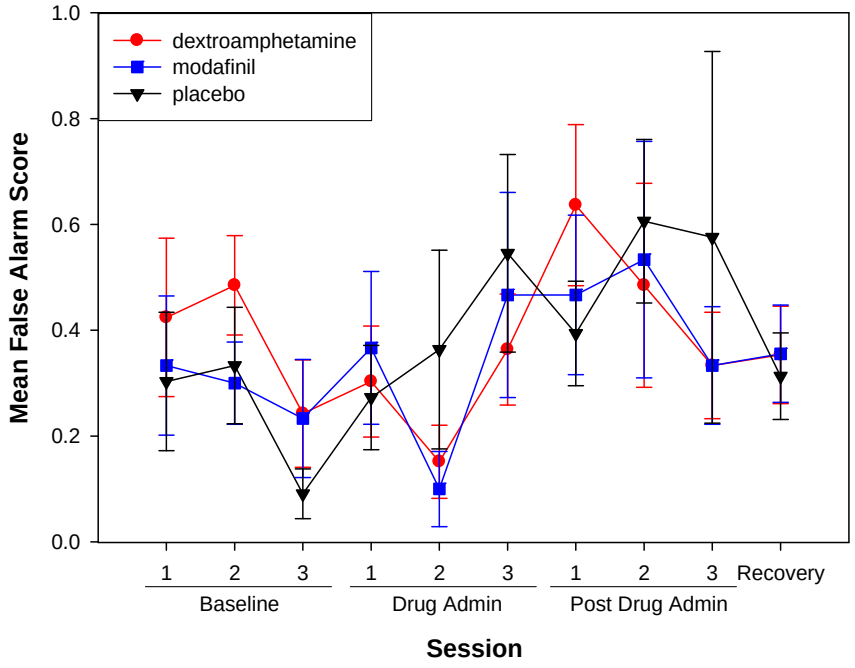

Figure 78. Mean RVP False Alarm Probability scores by drug and session.

A' value. This test provides a measure of the ability to detect sequences. A significant main effect existed for session ($F[1.612, 46.745] = 4.231$, $p = 0.019$), but not for drug ($F[2, 29] = 1.906$, $p = 0.167$) or the interaction between session and drug ($F[3.224, 46.775] = 2.389$, $p = 0.077$) (figure 79). Bonferroni corrected pairwise comparisons (alpha = 0.016) were conducted for the main effect of session and indicated significant difference was approached between drug administration and recovery periods ($p = 0.017$). Figure 80 presents the score means by drug condition and session.

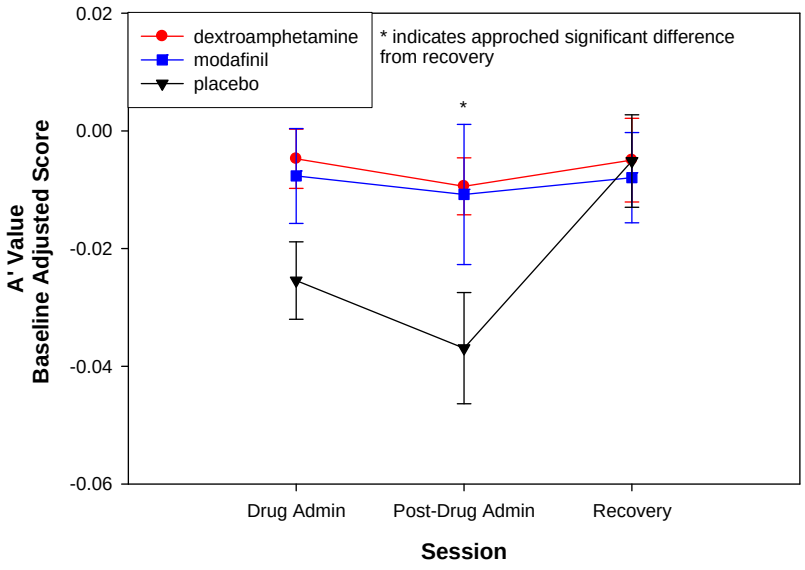

Figure 79. RVP A' Value comparisons by drug and session (baseline adjusted).

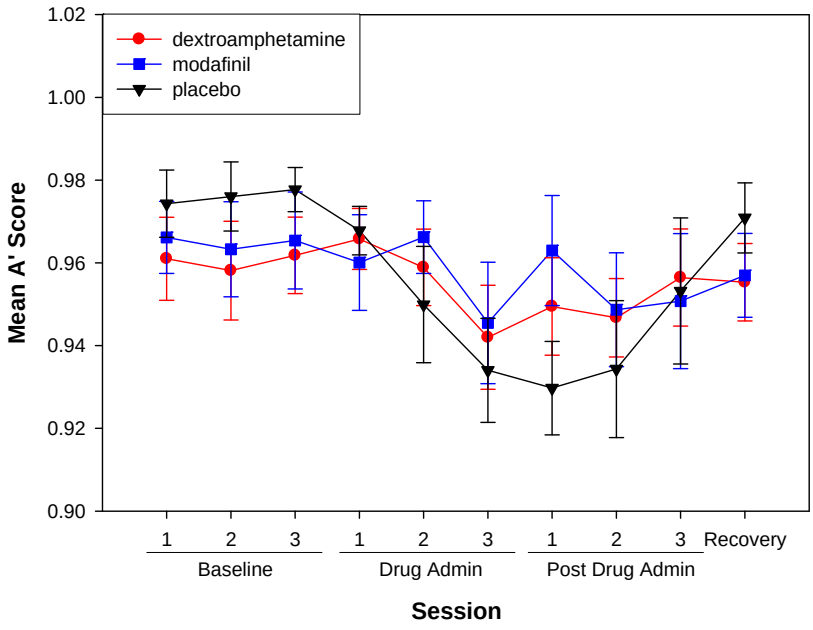

Figure 80. Mean RVP A' Values by drug and session.

Stockings of Cambridge (SOC)

The SOC is a test of spatial reasoning based upon the 'Tower of London' test. The subject was shown two displays containing three colored balls. The subject used the balls in the lower display to copy the pattern shown in the upper one. The SOC contains two dependent measures: the thinking reaction time (reaction time prior to first move), and the mean moves required to solve each task. Although the task had trials which could be solved in three, four, or five moves, only the five move trials were used for analysis since they were the most difficult. These data were analyzed using a 3 (session, within subjects variable) x 3 (drug, between subjects variable) mixed model ANOVA. The three levels of session were the drug administration phase, the post-drug administration phase, and the recovery session. The three levels of drug were modafinil, dextroamphetamine, and placebo. All scores were baseline adjusted and only the thinking reaction time scores were Greenhouse-Geisser corrected due to the assumption of sphericity being violated.

SOC Thinking Reaction Time. A significant main effect existed for session ($F[2, 66] = 25.505$, $p < 0.001$), but not for drug ($F[2, 33] = 0.470$, $p = 0.629$) or the interaction between session and drug ($F[4, 66] = 1.463$, $p = 0.224$) (figure 81). Bonferroni corrected pairwise comparisons (alpha = 0.016) were conducted for the main effect of session and indicated a significant difference between recovery and the other two sessions (drug administration $p < 0.001$, post-drug administration $p < 0.001$), but no significant difference existed between drug administration and post-drug administration ($p = 0.086$). Figure 82 presents the score means by drug condition and session.

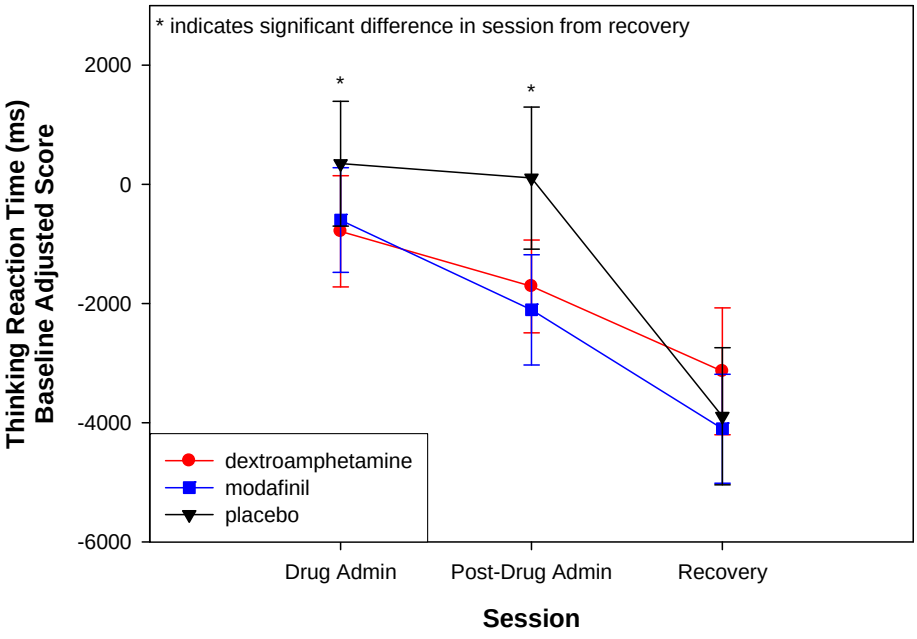

Figure 81. SOC Thinking Reaction Time (ms) comparisons by drug and session (baseline adjusted).

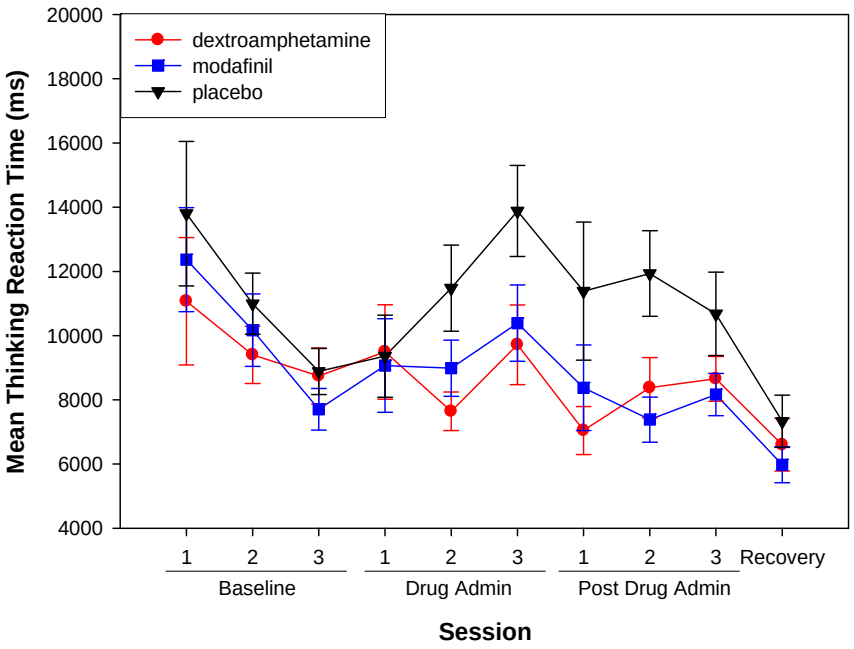

Figure 82. Mean SOC Thinking Reaction Time (ms) by drug and session.

SOC Mean Moves to Solve. No significant main effects existed for session ($F[2, 66] = 0.781$, $p = 0.462$), drug ($F[2, 33] = 0.309$, $p = 0.736$), or the interaction between session and drug ($F[4, 66] = 0.537$, $p = 0.709$) (figure 83). Figure 82 presents the moves to solve means by drug condition and session.

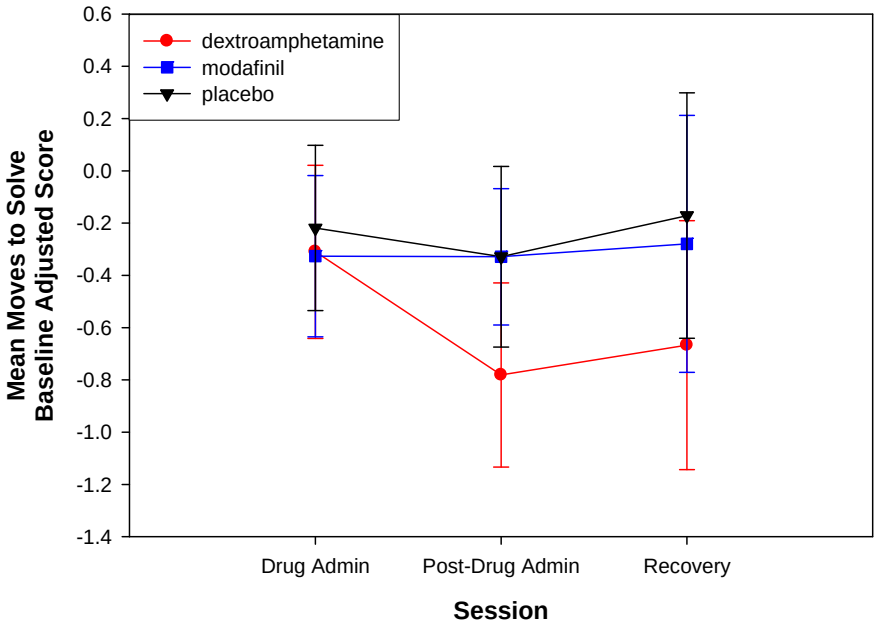

Figure 83. SOC Mean Moves to Solve comparisons by drug and session (baseline adjusted).

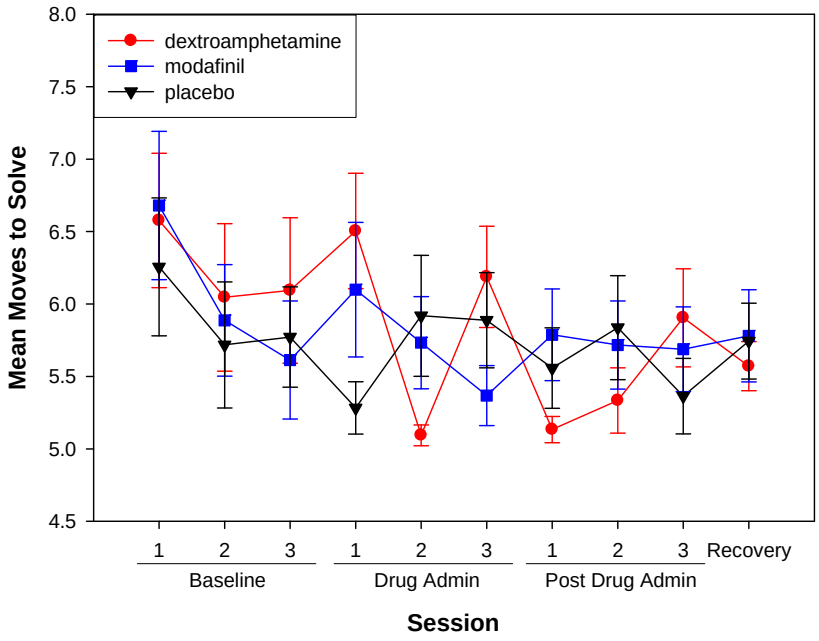

Figure 84. Mean SOC Moves to Solve by drug and session.

Spatial Working Memory (SWM)

The SWM contains three dependent measures, the total errors committed during the task, the total use of a procedural strategy used during the task, and the thinking reaction time to first move for the task. These data were analyzed using a 3 (session, within subjects variable) x 3 (drug, between subjects variable) mixed model ANOVA. The three levels of session were the drug administration phase, the post-drug administration phase, and the recovery session. The three levels of drug were modafinil, dextroamphetamine, and placebo. All scores were baseline adjusted and only the scores for thinking reaction time were Greenhouse-Geisser corrected due to the assumption of sphericity being violated.

SWM Total Errors. A significant main effect existed for session ($F[2, 62] = 9.285$, $p < 0.001$), but not for drug ($F[2, 31] = 1.548$, $p = 0.229$) or the interaction between session and drug ($F[4, 62] = 1.111$, $p = 0.359$) (figure 85). Bonferroni corrected pairwise comparisons (alpha = 0.016) were conducted for the main effect of session and indicated a significant difference between recovery and the other two sessions (drug administration $p = 0.005$, post-drug administration $p < 0.001$), but no significant difference existed between drug administration and post-drug administration ($p = 0.175$). Figure 86 presents the total error means by drug condition and session.

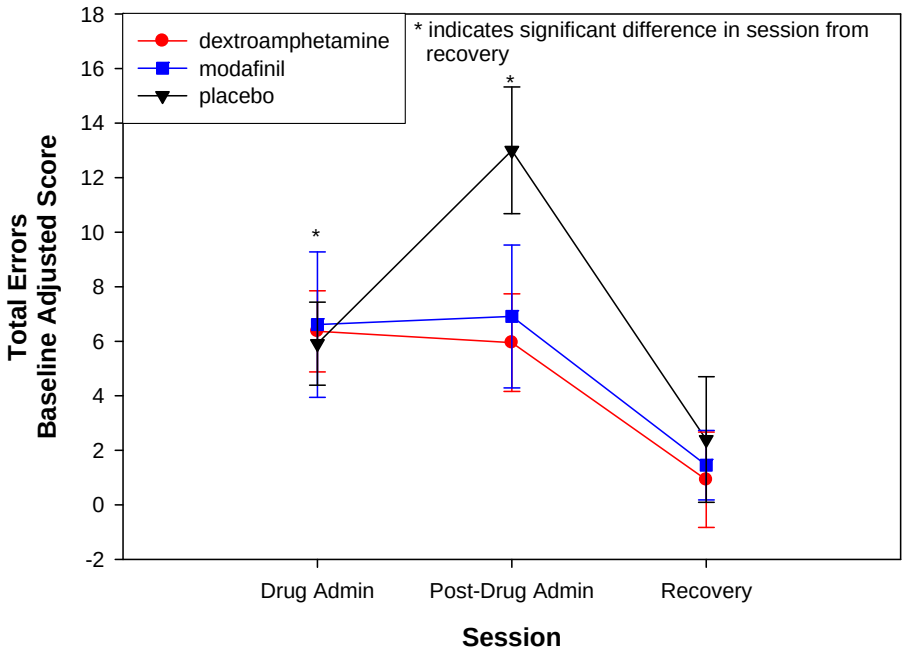

Figure 85. SWM Total Errors comparisons by drug and session (baseline adjusted).

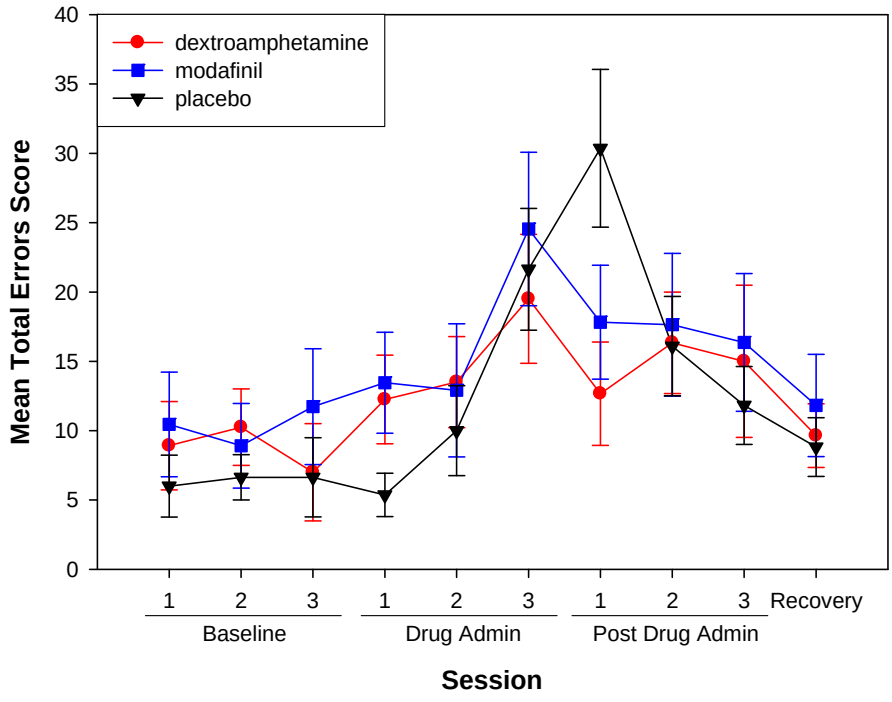

Figure 86. Mean Total Error by drug and session.

SWM Strategy Use. For this measure, a low score indicates high strategy use. A significant main effect existed for session ($F[2, 62] = 4.296$, $p = 0.018$), but not for drug ($F[2, 31] = 0.039$, $p = 0.962$), or for the interaction between session and drug ($F[4, 62] = 0.302$, $p = 0.875$) (figure 87). Bonferroni corrected pairwise comparisons (alpha = 0.016) were conducted for the main effect of session and indicated a significant difference between post-drug administration and recovery ($p = 0.008$). Differences between drug administration and post drug administration ($p = 0.123$) and between drug administration and recovery ($p = 0.171$) were not significant. Figure 88 presents the score means by drug condition and session.

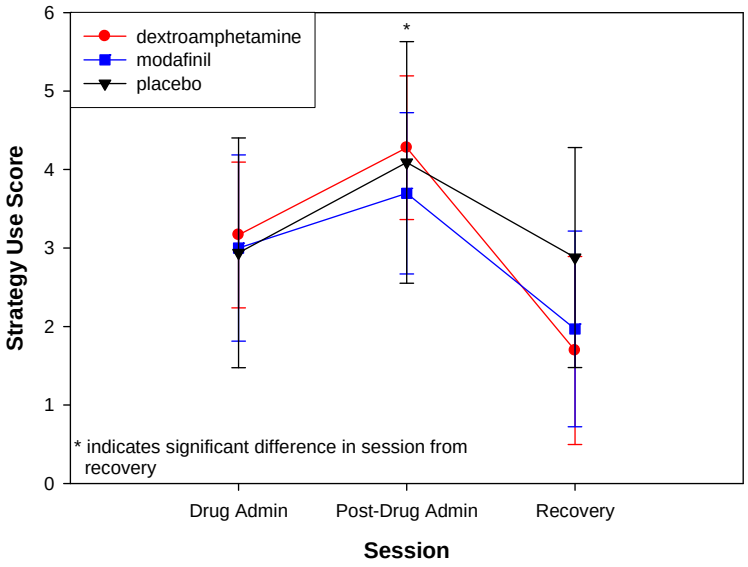

Figure 87. SWM Strategy Use score comparisons by drug and session (baseline adjusted).

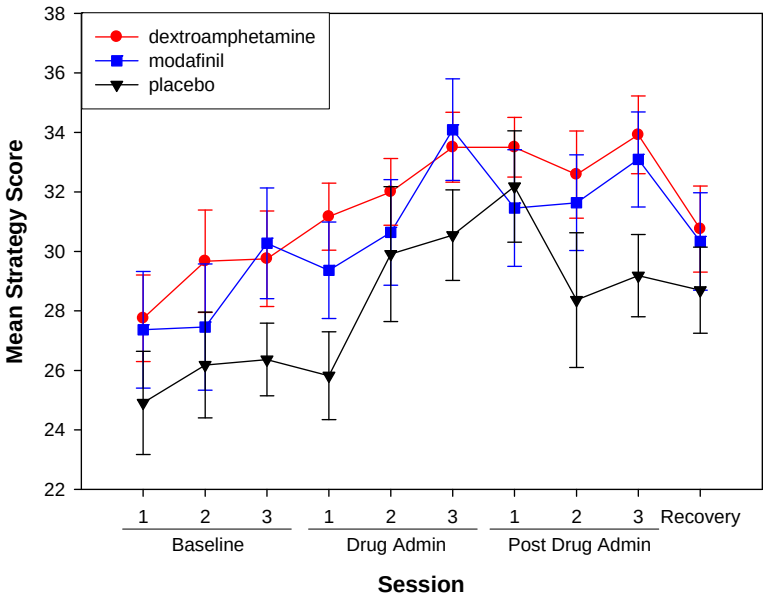

Figure 88. Mean Strategy Use score by drug and session.

SWM Reaction Time to First Move. No significant main effects existed for session ($F[2, 62] = 2.502$, $p = 0.090$), drug ($F[2, 31] = 0.353$, $p = 0.705$), or the interaction between session and drug ($F[4, 62] = 0.393$, $p = 0.813$) (figure 89). Figure 90 presents the reaction time (ms) to first move means by drug condition and session.

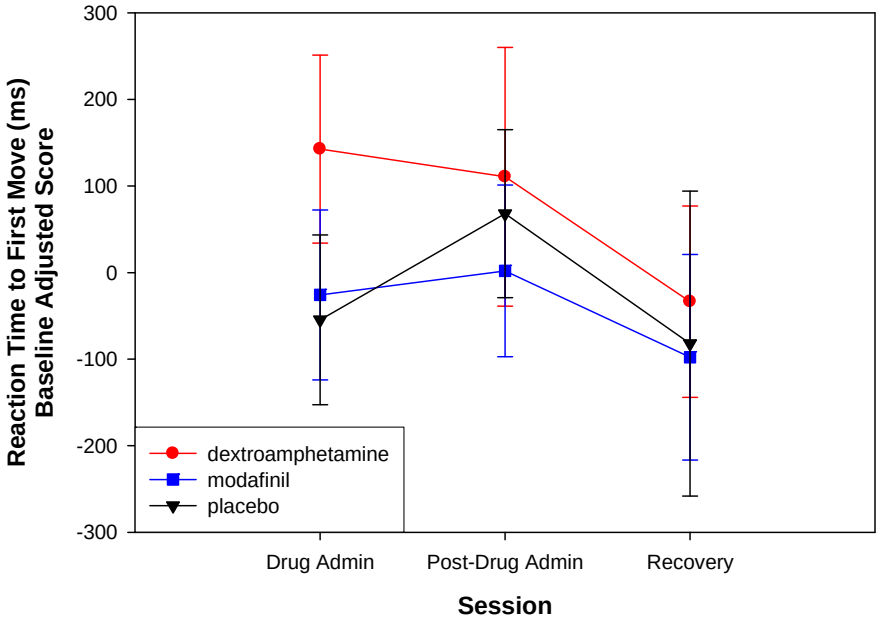

Figure 89. SWM Reaction Time to First Move comparisons by drug and session (baseline adjusted).

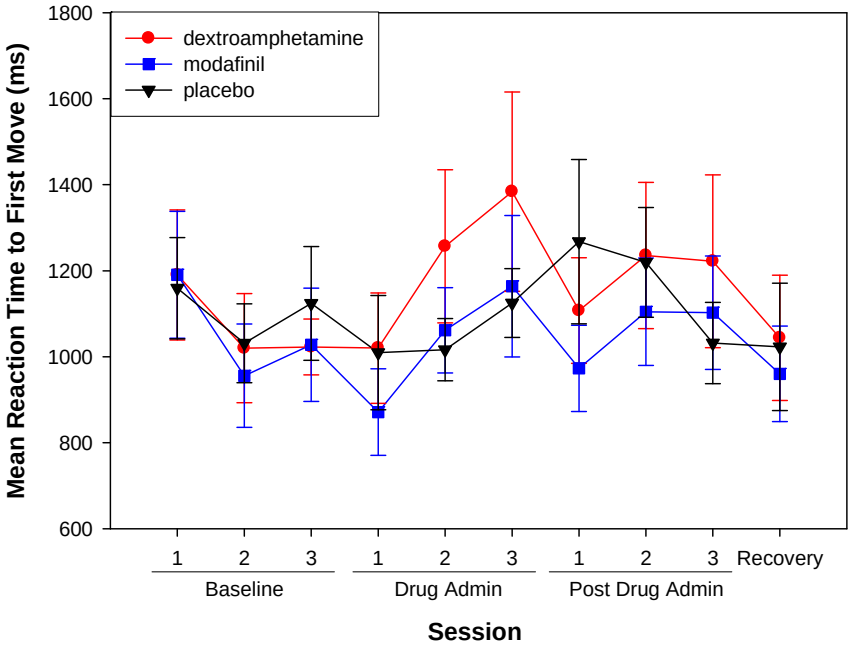

Figure 90. Mean Reaction Time to First Move by drug and session.

EST 2000 marksmanship performance

The EST 2000 data are divided into two main categories: M16 rifle and 9mm pistol. Both categories are comprised of three dependent measures: accuracy (# of hits), reaction time, and shot distance from the center of target (radius).

Firing performance: M16 rifle

The M16 task was performed in three shooting positions: prone supported, prone unsupported, and kneeling.

Prone supported position. The data were analyzed using 3 (session) x 3 (drug) x 6 (range) mixed model ANOVAs. The variable *session* was a within-subjects factor and its three levels were the drug administration period, the post-drug administration period, and the recovery period. In addition, the variable *range* was a within-subjects factor and its six levels were 50, 100, 150, 200, 250, and 300 meters. The variable *drug* was the between-subjects factor and its three levels were modafinil, dextroamphetamine, and placebo. The scores were baseline corrected.

Accuracy. There were no significant main effects for session ($F[2, 66] = 0.435$, $p = 0.649$), range ($F[3.736, 123.293] = 2.005$, $p = 0.103$), or drug ($F[2, 33] = 0.878$, $p = 0.425$). There were no significant interactions for session x drug ($F[4, 66] = 0.421$, $p = 0.793$), range x drug ($F[7.472, 123.293] = 0.358$, $p = 0.933$), session x range ($F[6.169, 203.590] = 1.844$, $p = 0.090$), or session x range x drug ($F[12.339, 203.590] = 0.823$, $p = 0.630$). It should be noted that the assumption of sphericity was violated and a Greenhouse-Geisser correction was used for the range, range x drug, and session x range effect.

Reaction time. There were no significant main effects for session ($F[1.14, 37.636] = 0.284$, $p = 0.627$), range ($F[1.245, 41.082] = 0.517$, $p = 0.515$), or drug ($F[2,33] = 0.878$, $p = 0.425$). There were no significant interactions for session x drug ($F[2.281, 37.636] = 1.039$, $p = 0.372$), range x drug ($F[2.49, 41.082] = 1.031$, $p = 0.379$), session x range ($F[1.059, 34.962] = 1.068$, $p = 0.313$), or session x range x drug ($F[2.119, 34.962] = 0.977$, $p = 0.391$). It should be noted that the assumption of sphericity was violated and a Greenhouse-Geisser correction was used for the session, range and session x range effect.

Shot distance. There were no significant main effects for session ($F[2, 66] = 1.909$, $p = 0.156$), range ($F[2.086, 68.828] = 0.128$, $p = 0.729$, or drug ($F[2,33] = 0.396$, $p = 0.676$). There were no significant interactions for session x drug ($F[4, 66] = 0.856$, $p = 0.495$), range x drug ($F[4.171, 68.828] = 0.128$, $p = 0.975$), session x range ($F[5.411, 178.557] = 0.730$, $p = 0.227$), or session x range x drug ($F[10.822, 178.557] = 0.730$, $p = 0.707$). It should be noted that the assumption of sphericity was violated and a Greenhouse-Geisser correction was used for the range and session x range effect.

Prone unsupported position. The data were analyzed using 3 (session) x 3 (drug) x 4 (range) mixed model ANOVAs. The variable *session* was a within-subjects factor and its three levels were the drug administration period, the post-drug administration period, and the recovery period. In addition, the variable *range* was a within-subjects factor and its four levels were 150, 200, 250, and 300 meters. The variable *drug* was the between-subjects factor and its three levels were modafinil, dextroamphetamine, and placebo. The scores were baseline corrected.

Accuracy. There were no significant main effects for session ($F[2, 66] = 0.314$, $p = 0.732$), range ($F[3, 99] = 1.424$, $p = 0.240$, or drug ($F[2,33] = 0.759$, $p = 0.476$). There were no significant interactions for session x drug ($F[4, 66] = 0.282$, $p = 0.888$), range x drug ($F[6, 99] = 0.964$, $p = 0.975$), session x range ($F[6, 198] = 1.652$, $p = 0.135$), or session x range x drug ($F[12, 198] = 0.638$, $p = 0.808$).

Reaction time. There was a significant main effect for session ($F[2, 66] = 3.152$, $p = 0.049$) such that the pairwise comparisons for this main effect showed that the baseline corrected reaction time at drug administration period was significantly lower than that at post-drug administration period ($p = 0.013$; figure 91). There were no significant main effects for range ($F[1.786, 58.949] = 2.800$, $p = 0.075$), or drug ($F[2,33] = 0.625$, $p = 0.541$). There was a significant interaction for session x range ($F[2.94, 97.016] = 4.842$, $p = 0.004$) such that baseline adjusted reaction times were lower for further distances than shorter distances during the drug administration period (figure 92). There were no significant interactions for session x drug ($F[4, 66] = 1.600$, $p = 0.191$), range x drug ($F[3.573, 58.949] = 0.684$, $p = 0.590$), or session x range x drug ($F[5.880, 97.016] = 0.760$, $p = 0.600$). It should be noted that the assumption of sphericity was violated and a Greenhouse-Geisser correction was used for the range and session x range effect. It is suspected that the level of arousal associated with this task contributed to these effects similar to those found for the in-flight data.

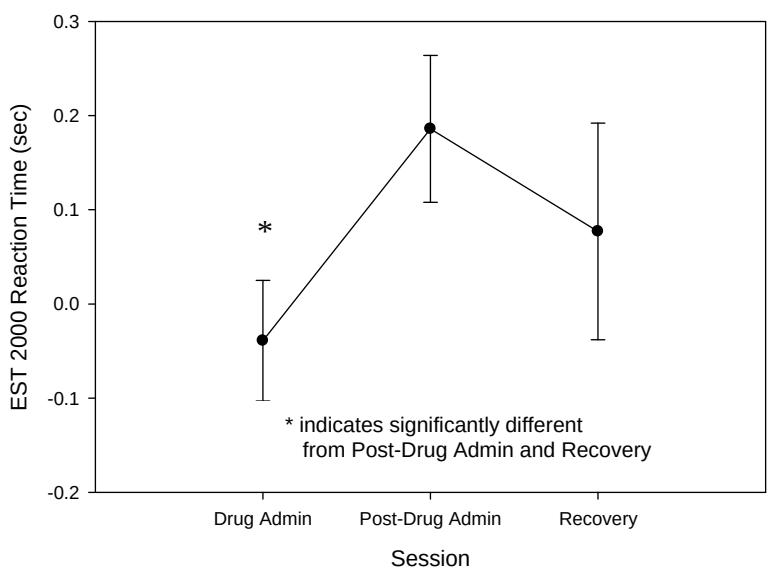

Figure 91. Mean reaction time to fire during the EST 2000 M16 task in the prone unsupported position by session.

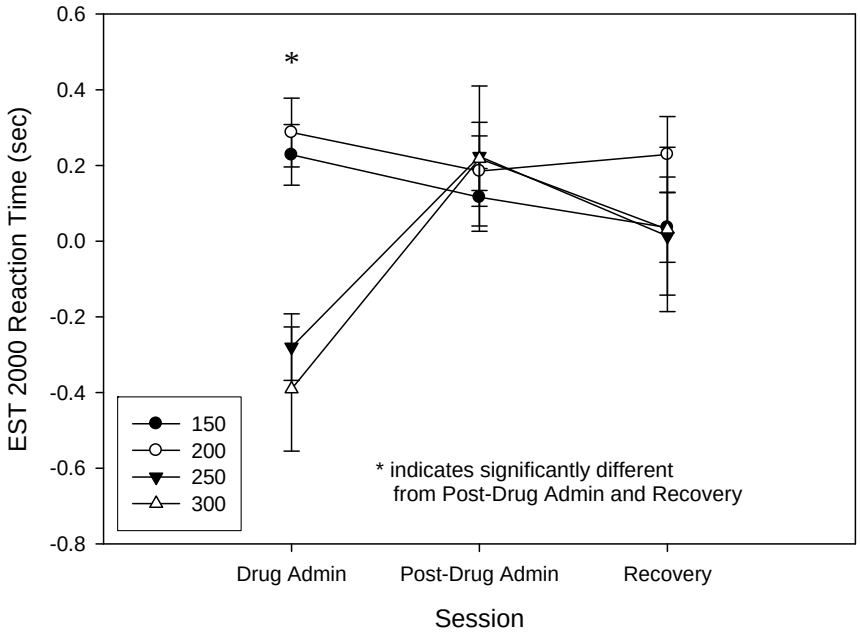

Figure 92. Mean reaction time to fire during the EST 2000 M16 task in the prone unsupported position by session and target distance (range in meters).

Shot distance. There were no significant main effects for session (F[2, 66] = 1.041, p = 0.359), range (F[1.419, 46.823] = 1.453, p = 0.729, or drug (F[2,33] = 1.397, p = 0.262). There were no significant interactions for session x drug (F[4, 66] = 1.061, p = 0.383), range x drug (F[2.838, 46.823] = 0.851, p = 0.468), session x range (F[3.102, 102.369] = 1.382, p = 0.252), or session x range x drug (F[6.204, 102.369] = 0.740, p = 0.623). It should be noted that the assumption of sphericity was violated and a Greenhouse-Geisser correction was used for the range and session x range effect.

Kneeling position. The data were analyzed using 3 (session) x 3 (drug) x 3 (range) mixed model ANOVAs. The variable *session* was a within-subjects factor and its three levels were the drug administration period, the post-drug administration period, and the recovery period. In addition, the variable *range* was a within-subjects factor and its three levels were 50, 100, and 150 meters. The variable *drug* was the between-subjects factor and its three levels were modafinil, dextroamphetamine, and placebo. The scores were baseline corrected.

Accuracy. One subject was excluded from this analysis due to incomplete data. There were no significant main effects for session (F[2,64] = 0.229, p = 0.796), range (F[2,64] = 1.581, p = 0.214, or drug (F[2,32] = 0.103, p = 0.902. There were no significant interactions for session x drug (F[4, 64] = 0.287, p = 0.885), range x drug (F[4, 64] = 0.577, p = 0.680), session x range (F[4, 128] = 1.283, p = 0.280), or session x range x drug (F[8, 128] = 0.878, p = 0.537).

Reaction time. Two subjects were excluded from this analysis due to incomplete data. There were no significant main effects for session (F[2,62] = 1.755, p = 0.181), range (F[2,62] = 0.065,

p = 0.937, or drug (F[2,31] = 0.276, p = 0.760. There were no significant interactions for session x drug (F[4, 62] = 0.185, p = 0.945), or range x drug (F[4, 62] = 0.210, p = 0.932). There was a significant two-way interaction of session x range (F[4, 124] = 2.960, p = 0.022; figure 93) and a significant three-way interaction of session x range x drug (F[8, 124] = 2.844, p = .006; figures 94 through 96). The results patterns of these two interactions are suspected to be a result of the nature of the task and difficulty associated with the kneeling position.

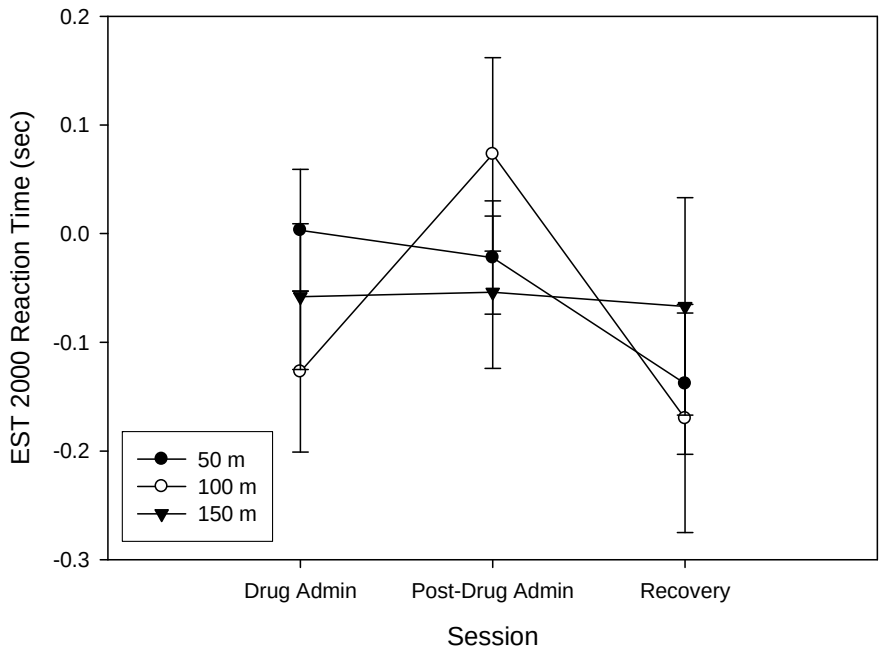

Figure 93. Mean reaction time to fire during the EST 2000 M16 task in the kneeling position by session and target distance (range in meters).

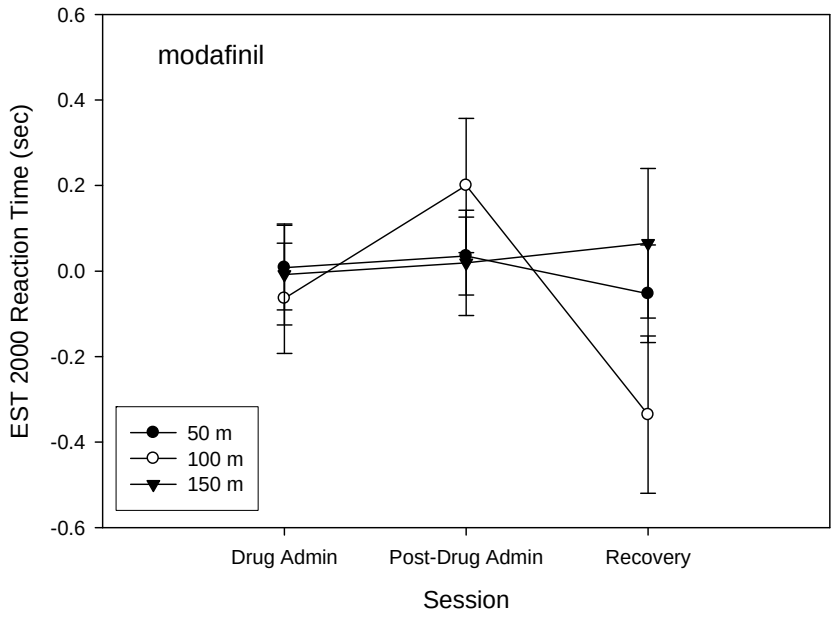

Figure 94. Mean reaction time to fire during the EST 2000 M16 task in the kneeling position by session and target distance (range in meters) in the modafinil condition.

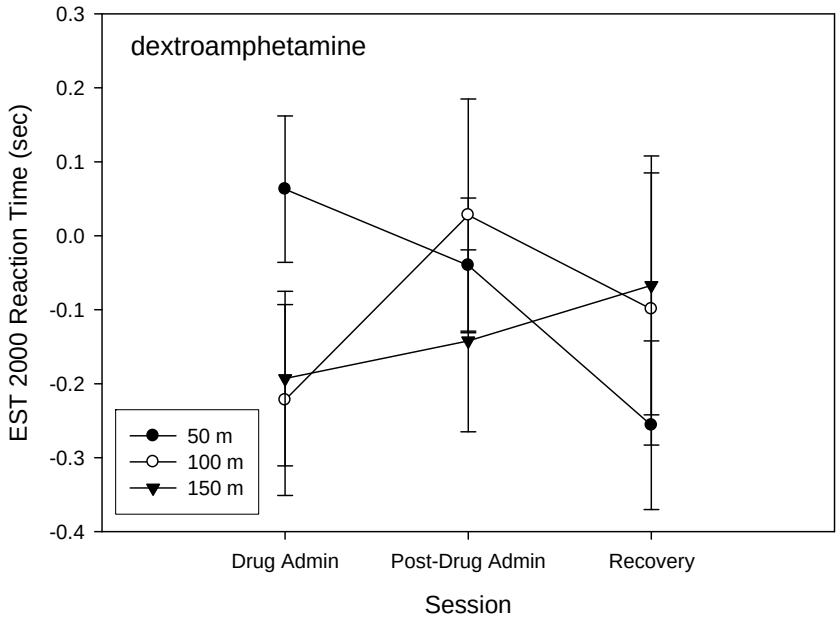

Figure 95. Mean reaction time to fire during the EST 2000 M16 task in the kneeling position by session and target distance (range in meters) in the dextroamphetamine condition

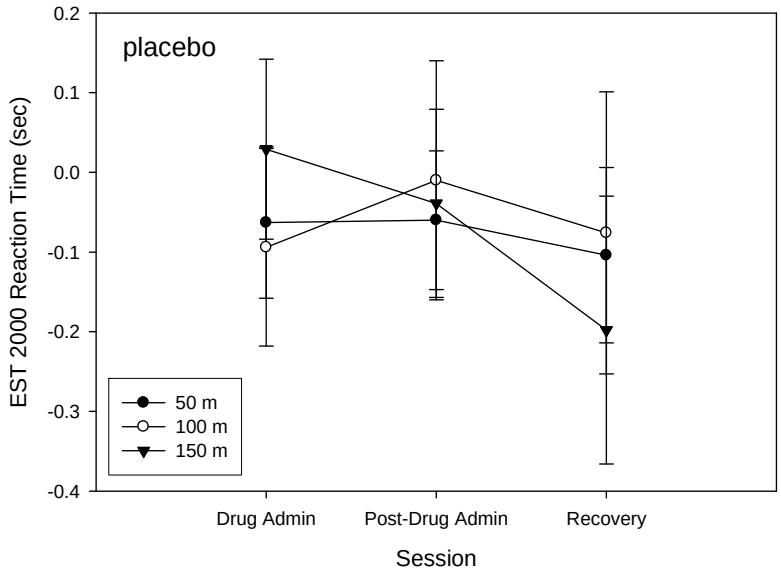

Figure 96. Mean reaction time to fire during the EST 2000 M16 task in the kneeling position by session and target distance (range in meters) in the placebo condition.

Shot distance. For both within subjects factors, the assumption of sphericity was violated and a Greenhouse-Geisser correction was used. There was a significant main effect for range (F[1.626, 53.659] =5.514, p = 0.010). Pairwise comparisons revealed participants' baseline corrected shot radius were significantly larger for the 150 meter targets than for the 50 meter targets (p = 0.015) as would be expected given the varying level of difficulty associated with target distance. (figure 97).

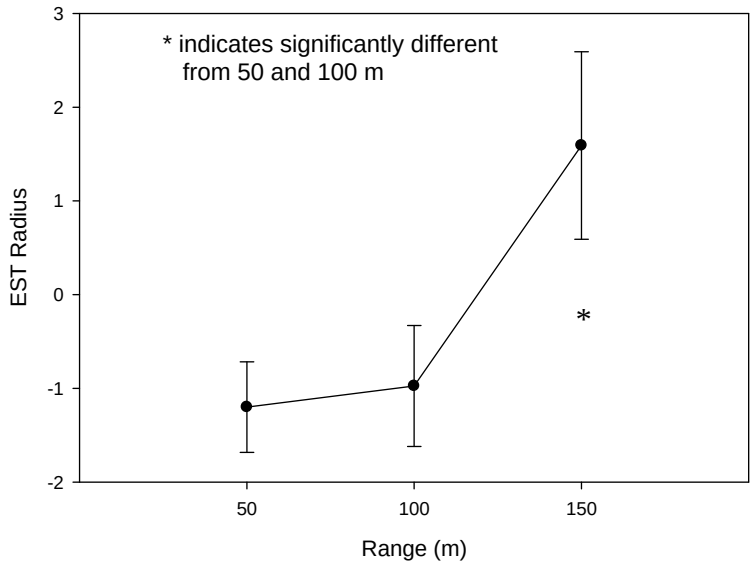

Figure 97. Mean distance from center of target (radius) during the EST 2000 M16 task in the kneeling position by target distance (range in meters).

There were no significant main effects for either the session (F[1.693, 55.864] = 0.061, p = 0.916) or drug (F[2, 33] =0.087, p = 0.917) variables with regard to participants' kneeling radius data. In addition, there was no significant interactions for session x drug (F[3.386, 55.864] = 0.495, p = 0.709), range x drug (F[3.252, 53.659] = 0.738, p = 0.544), session x range (F[2.041, 67.345] = 0.692, p = 0.163), or session x range x drug (F[4.082, 67.345] = 1.547, p = 0.198).

Firing performance: 9mm pistol

The 9mm task was performed in a standing position and its dependent measures were accuracy (# of hits), reaction time, and shot distance from the center of target (radius). The data were analyzed using 3 (session) x 3 (drug) mixed model ANOVAs. The variable *session* was a within-subjects factor and its three levels were the drug administration period, the post-drug administration period, and a recovery period. The variable *drug* was the between-subjects factor and its three levels were modafinil, dextroamphetamine, and placebo. The scores were baseline corrected.

Accuracy. There were no significant main effects for session (F[1.281, 42.278] = 0.481, p = 0.538) or drug (F[2,33] = 0.246, p = 0.784). In addition, the interaction was not significant (F[2.562, 42.278] = 0.471, p = 0.674). It should be noted that the assumption of sphericity was violated and a Greenhouse-Geisser correction was used.

Reaction time. There were no significant main effects for session (F[2,64] = 0.161, p = 0.851) or drug (F[2,32] = 0.154, p = 0.858). In addition, the interaction was not significant (F[4,64] = 1.364, p = 0.256).

Shot distance. There were no significant main effects for session (F[1.494, 47.810] = 1.160, p = 0.309) or drug (F[2,32] = 0.755, p = 0.478). In addition, the interaction was not significant (F[2.988, 47.810] = 0.786, p = 0.507). It should be noted that the assumption of sphericity was violated and a Greenhouse-Geisser correction was used.

Flight performance

The flight data consisted of ten standard maneuvers: stationary hover, instrument takeoff, straight and level flight 1, straight and level flight 2, standard rate turn, climbing (right) turn, intercept turn, ILS (instrument landing system) level flight segment, ILS approach (descent), and a missed approach. Root mean square error (RMSE) means for selected measures (e.g., heading, altitude, climb rate) for each maneuver (see table 7) were analyzed using a 3 (session, within subjects variable) x 3 (drug, between subjects variable) mixed model ANOVA. The three levels of session were the drug administration period, the post-drug administration period, and the recovery period. The three levels of drug were modafinil, dextroamphetamine, and placebo. The means of the root mean square errors (RMSE) for each maneuver component were used to assess the level of performance (control errors) during each flight task. All scores were baseline adjusted for any naturally occurring differences due to ability or experience. Maneuvers 1 through 5, including the instrument takeoff, were performed under visual meteorological conditions (VMC) while maneuvers 6 through 10 were sometimes conducted under instrument

meteorological conditions (IMC) when cloud ceilings were as low as 1500 feet above the ground.

Recall that flights in either the simulator or aircraft were effectively the same due to the simulator's geo-specific visual database. Occasionally, a data collection flight originally planned for the actual aircraft was forced to be conducted in the flight simulator due to adverse weather conditions that exceeded the weather abort criteria established by the research safety pilots and approved by the USAMRMC HSRRB. This occurred 23 percent of the time (40 out of a total of 180 flights originally scheduled for the actual aircraft) over the nine weeks of data collection. For data analysis purposes, flight performance data, whether collected during a simulator or actual aircraft flight, were regarded and treated the same.

Flight maneuvers

Hover. During the hover task, participants were instructed to maintain an altitude of ten feet above the ground and a magnetic heading of 210 degrees. For altitude maintenance, a significant main effect existed for session ($F[2, 66] = 51.908$, $p < 0.001$) with significantly more errors holding a constant altitude during the drug and post-drug administration sessions than during the recovery period. There were no significant main effects for drug ($F[2, 33] = 2.543$, $p = 0.12$) or the interaction between session and drug ($F[4, 66] = 1.357$, $p = 0.258$) (figure 98). Figure 99 presents the hover altitude RMSE means by drug and session.

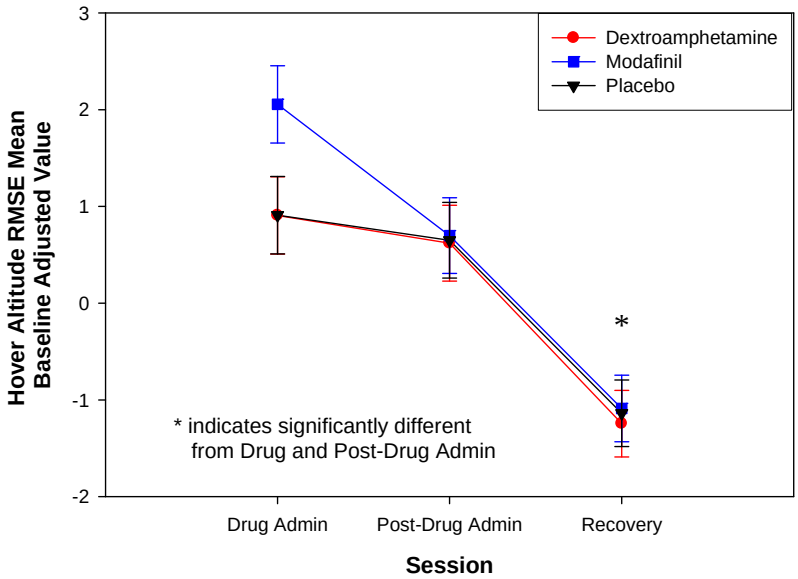

Figure 98. Hover altitude RMSE mean comparisons by drug and session (baseline adjusted).

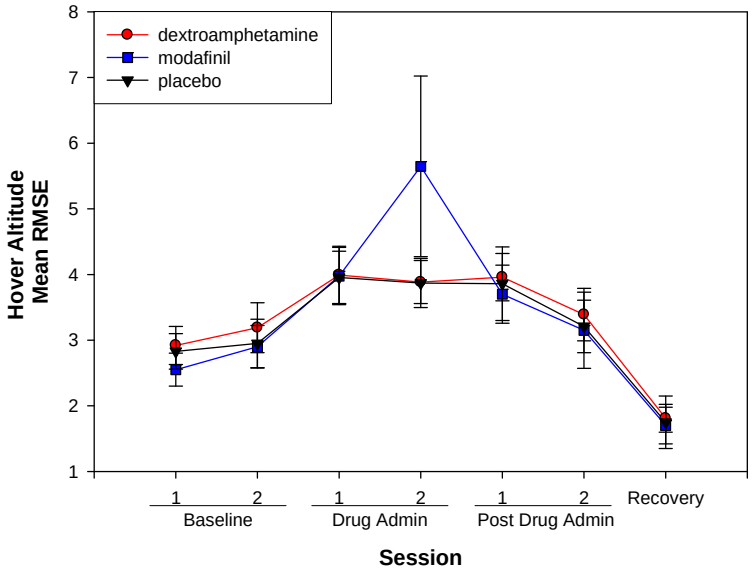

Figure 99. Hover altitude RMSE means by drug and session.

As for heading performance at a hover, no significant main effects were found for session ($F[2, 66] = 1.748$, $p = 0.182$), drug ($F[2, 33] = 0.731$, $p = 0.489$), or the interaction between session and drug ($F[4, 66] = 1.421$, $p = 0.237$) (figure 100). Figure 101 presents the hover heading RMSE means by drug and session.

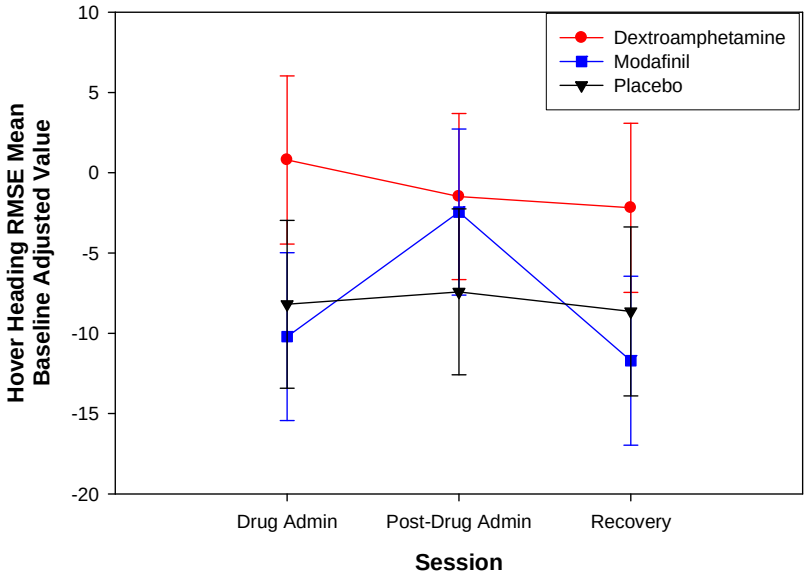

Figure 100. Hover heading RMSE mean comparisons by drug and session (baseline adjusted).

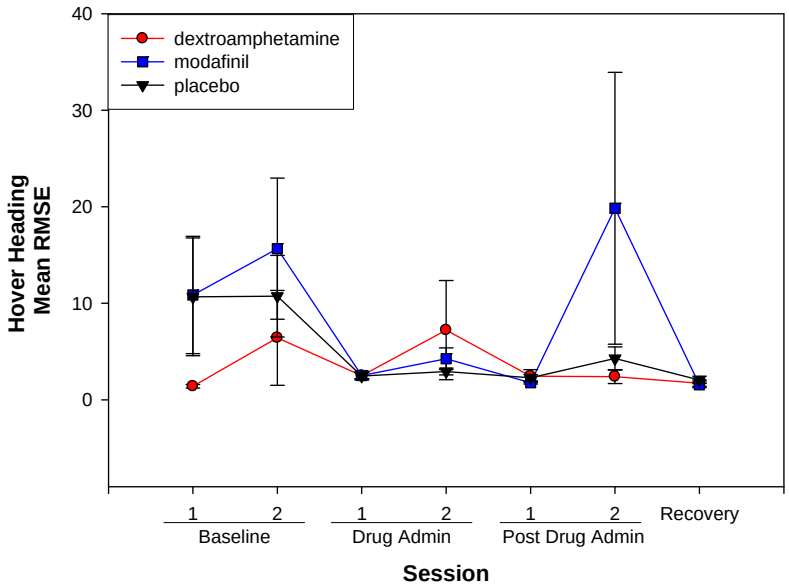

Figure 101. Hover heading RMSE means by drug and session.

Instrument Takeoff. During the takeoff task, participants were instructed to maintain a magnetic heading of 210 degrees and a climb rate of 1000 feet per minute. For heading, no significant main effects were found for session ($F[2, 66] = 2.438$, $p = 0.095$), drug ($F[2, 33] = 1.217$, $p = 0.309$), or the interaction between session and drug ($F[4, 66] = 0.538$, $p = 0.708$) (figure 102). Figure 103 presents the instrument takeoff heading RMSE means by drug and session.

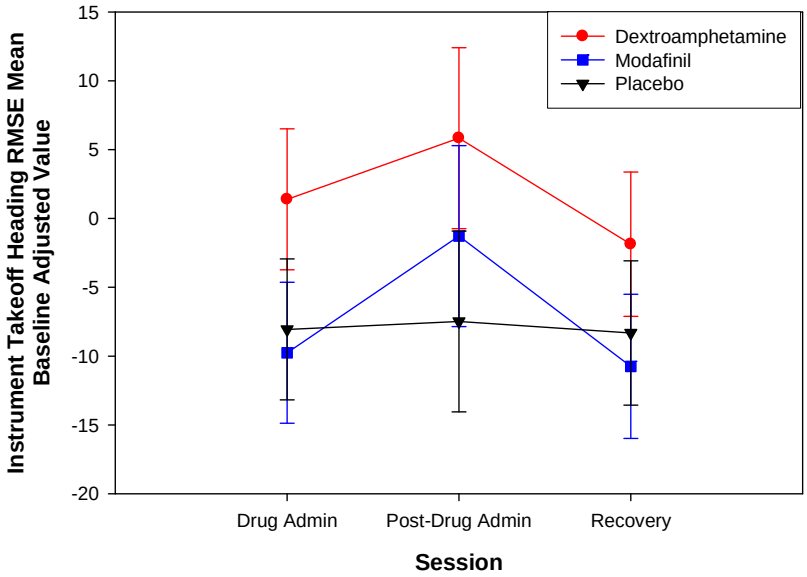

Figure 102. Instrument Takeoff heading RMSE mean comparisons by drug and session (baseline adjusted).

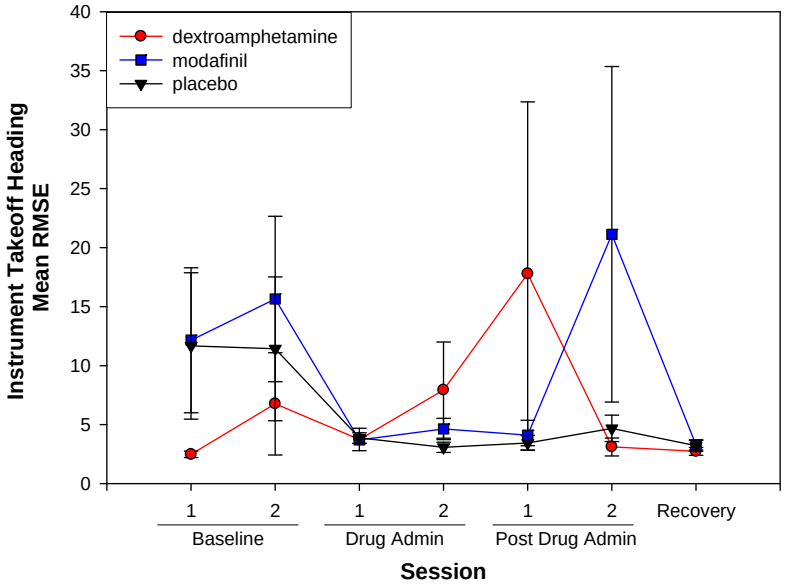

Figure 103. Instrument Takeoff heading RMSE means by drug and session.

As for maintaining a climb rate, a significant main effect existed for session ($F[2, 66] = 8.302$, $p < 0.001$) with significantly more errors in climb performance during the recovery session than during the drug and post-drug administration sessions, but not for drug ($F[2, 33] = 1.562$, $p = 0.220$), or the interaction between session and drug ($F[4, 66] = 0.505$, $p = 0.732$) (figure 104). Figure 105 presents the instrument takeoff climb rate RMSE means by drug and session.

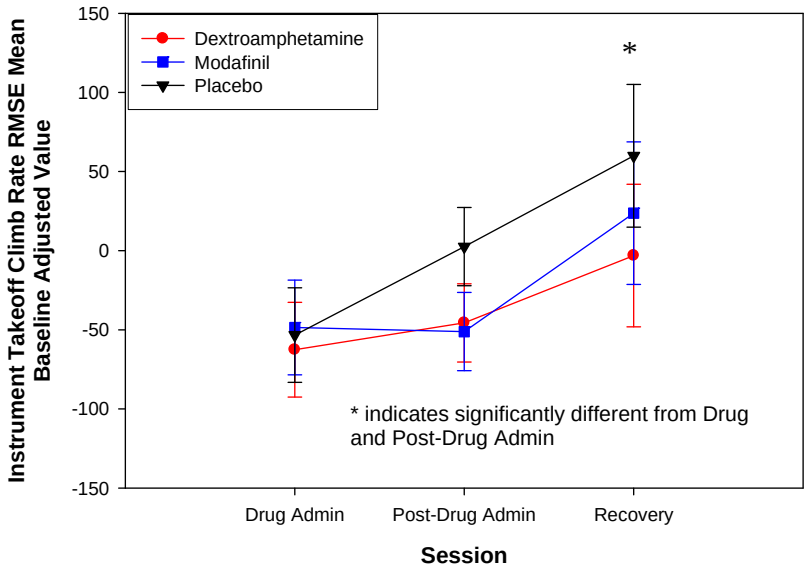

Figure 104. Instrument Takeoff climb rate RMSE mean comparisons by drug and session (baseline adjusted).

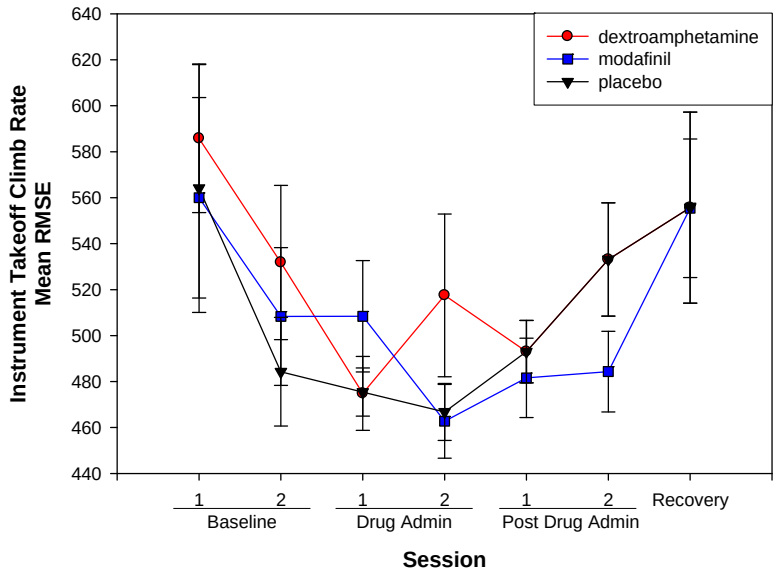

Figure 105. Instrument Takeoff climb rate RMSE means by drug and session.

Straight and Level Flight. During the two consecutive straight and level segments, participants were instructed to first maintain a magnetic heading of 210 degrees and then one of 130 degrees. Since there was no change in the altitude and airspeed requirements during these segments, the data were combined and analyzed as if it were one task. Participants were also tasked to maintain an indicated airspeed of 120 knots and an altitude of 800 feet MSL.

For both headings (210 and 130, respectively), no significant main effects were found for session ($F[2, 66] = 1.063$, $p = 0.351$ and $F[2, 66] = 2.928$, $p = 0.060$), drug ($F[2, 33] = 3.298$, $p = 0.078$ and $F[2, 33] = 1.271$, $p = 0.294$), or the interaction between session and drug ($F[4, 66] = 0.992$, $p = 0.418$ and $F[4, 66] = 0.601$, $p = 0.663$) (figures 106 and 108). Figures 107 and 109 present the straight and level heading RMSE means by drug and session for 210 and 130 degrees, respectively.

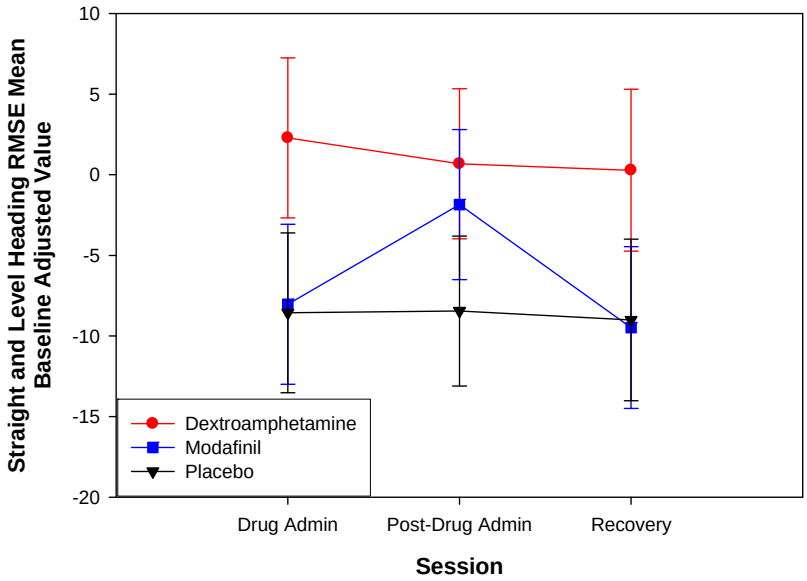

Figure 106. Straight and Level heading (210 degrees) RMSE mean comparisons by drug and session (baseline adjusted).

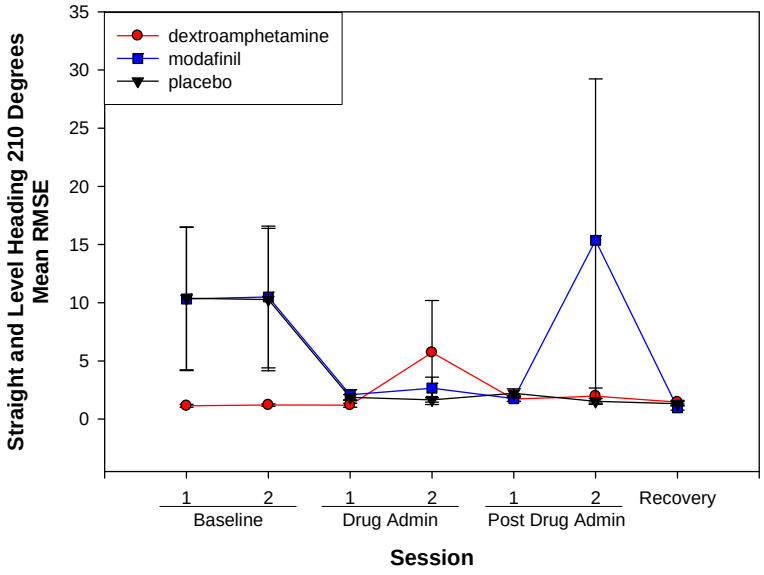

Figure 107. Straight and Level heading (210 degrees) RMSE means by drug and session.

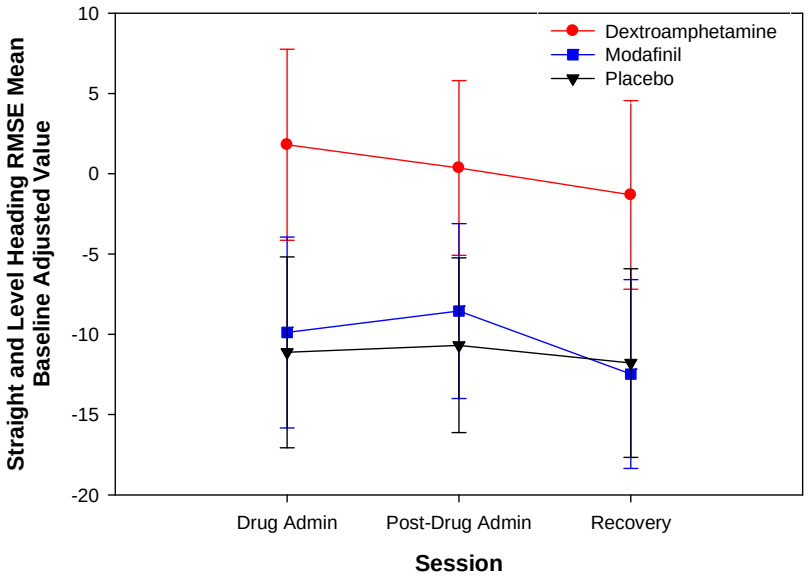

Figure 108. Straight and Level heading (130 degrees) RMSE mean comparisons by drug and session (baseline adjusted).

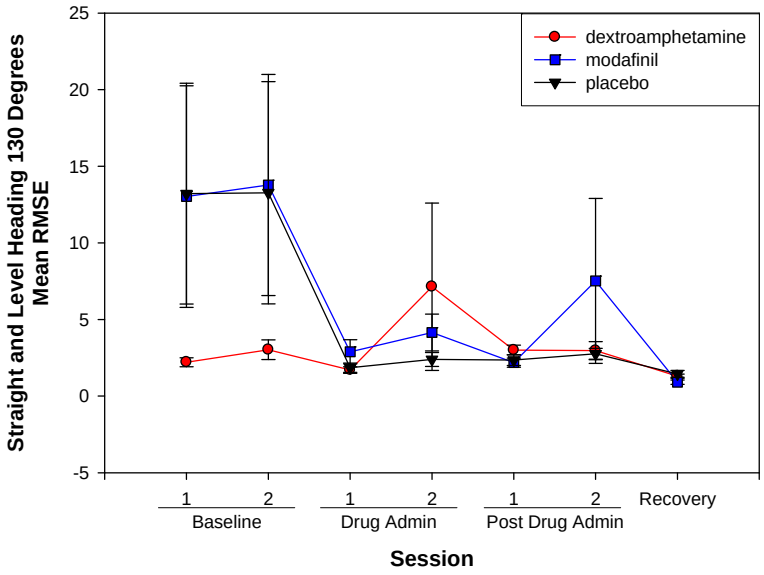

Figure 109. Straight and Level heading (130 degrees) RMSE means by drug and session.

As for airspeed, a significant main effect existed for session ($F[2, 66] = 46.565$, $p < 0.001$) with significantly more precision in maintaining airspeed during the recovery session than during the drug and post-drug administration sessions. There were no significant main effects for drug ($F[2, 33] = 0.319$, $p = 0.729$) or the interaction between session and drug ($F[4, 66] = 0.261$, $p = 0.902$) (figure 110). Figure 111 presents the straight and level airspeed RMSE means by drug and session.

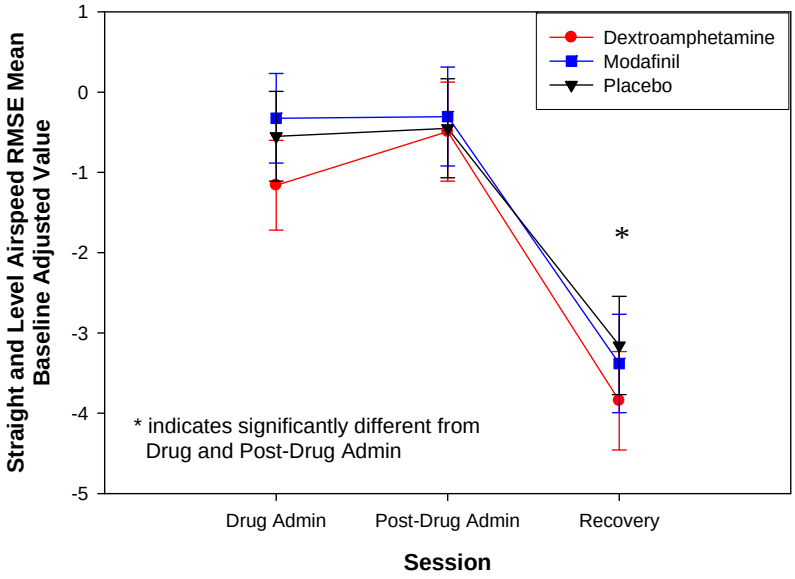

Figure 110. Straight and Level airspeed RMSE mean comparisons by drug and session (baseline adjusted).

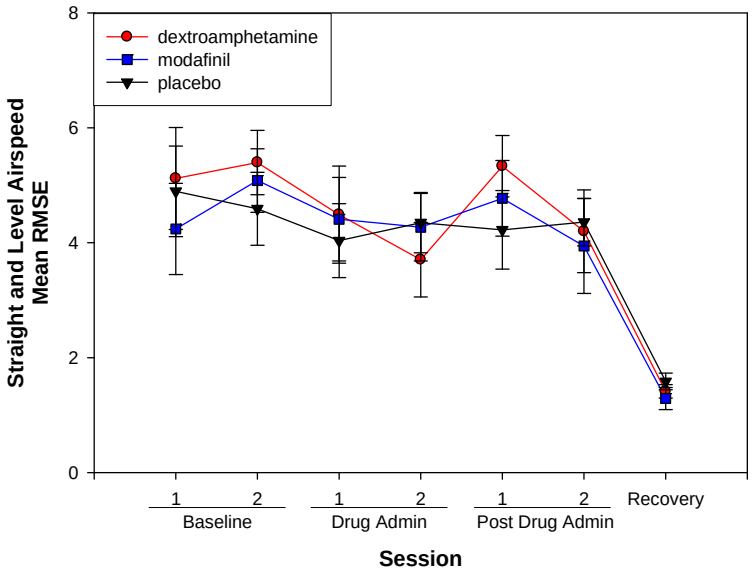

Figure 111. Straight and Level airspeed RMSE means by drug and session.

As for maintaining altitude during straight and level flight, a significant main effect existed for session ($F[2, 66] = 45.878$, $p < 0.001$). Performance during the recovery session showed significantly more precision than performance during the drug and post-drug administration sessions. There were no significant main effects for drug ($F[2, 33] = 0.033$, $p = 0.967$) or the interaction between session and drug ($F[4, 66] = 0.730$, $p = 0.575$) (figure 112). Figure 113 presents the straight and level altitude RMSE means by drug and session.

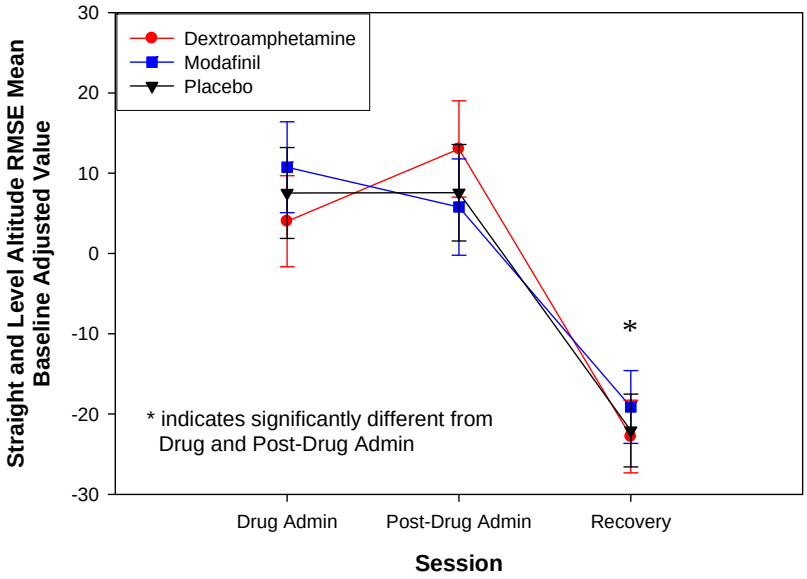

Figure 112. Straight and Level altitude RMSE mean comparisons by drug and session (baseline adjusted).

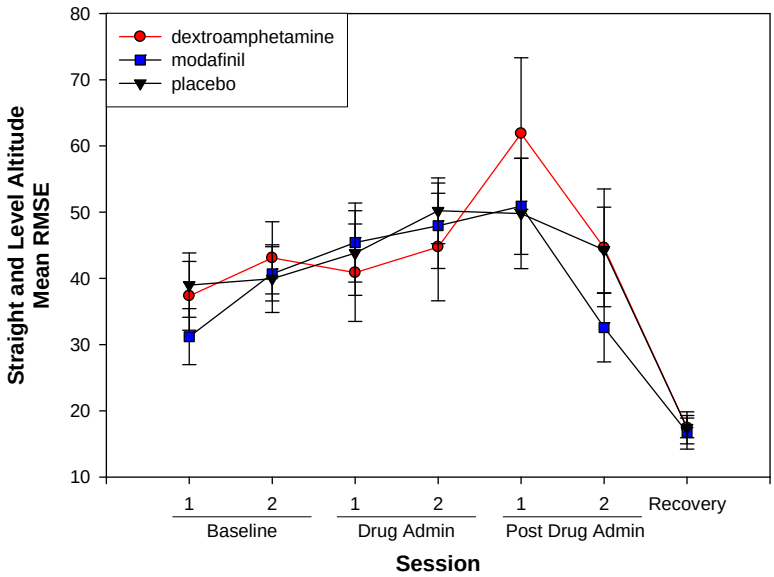

Figure 113. Straight and Level altitude RMSE means by drug and session.

Left Standard Rate Turn. During the standard rate turn to the left, participants were required to maintain a constant turn rate of three degrees per second, an indicated airspeed of 120 knots, and an altitude of 800 feet MSL. For the turn rate, a significant main effect existed for session ($F[2, 66] = 98.129$, $p < 0.001$) with significantly more precision in maintaining a constant turn rate during the recovery session than during the drug and post-drug administration sessions. No significant main effects were noted for drug ($F[2, 33] = 0.643$, $p = 0.532$) or the interaction between session and drug ($F[4, 66] = 0.718$, $p = 0.583$) (figure 114). Figure 115 presents the left standard turn rate RMSE means by drug and session.

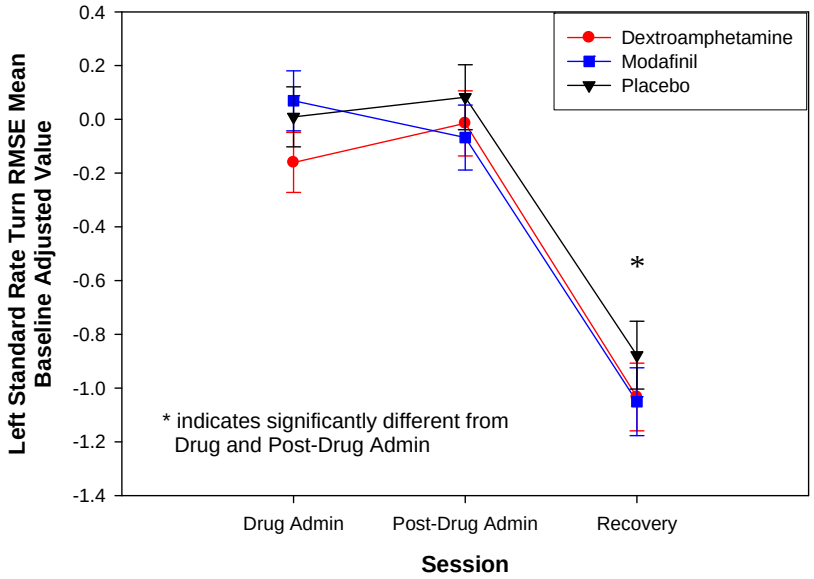

Figure 114. Left Standard Rate Turn turn rate RMSE mean comparisons by drug and session (baseline adjusted).

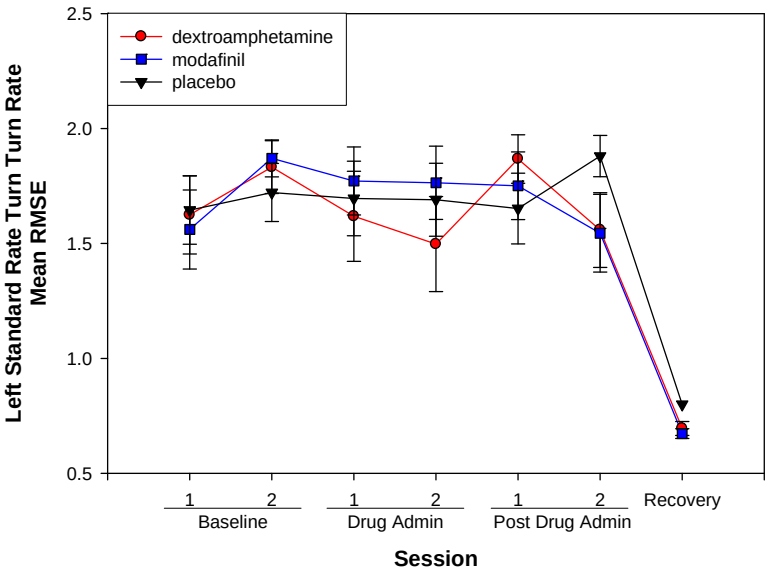

Figure 115. Left Standard Rate Turn turn rate RMSE means by drug and session.

In maintaining airspeed, a significant main effect existed for session ($F[2, 66] = 41.970$, $p < 0.001$) with significantly more precision in performance during the recovery session than during the drug and post-drug administration sessions. No significant main effects were noted for drug ($F[2, 33] = 0.788$, $p = 0.463$) or the interaction between session and drug ($F[4, 66] = 0.438$, $p = 0.781$) (figure 116). Figure 117 presents the left standard rate turn airspeed RMSE means by drug and session.

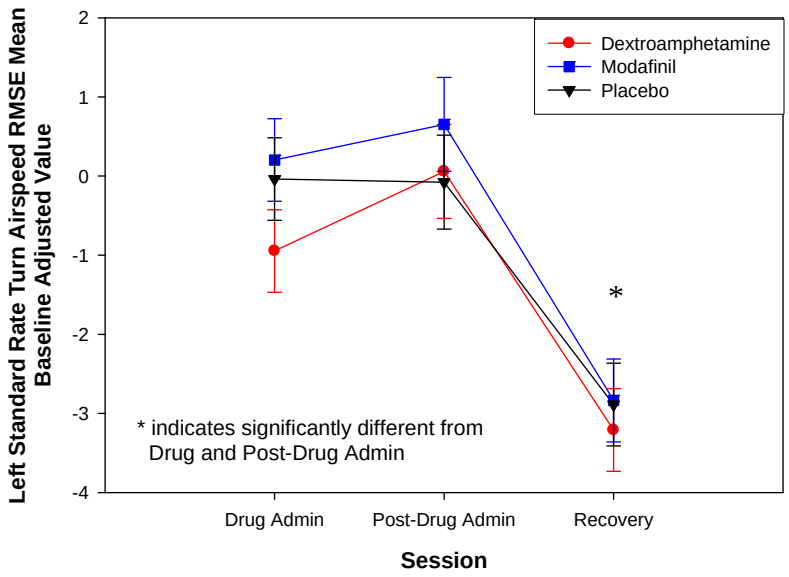

Figure 116. Left Standard Rate Turn airspeed RMSE mean comparisons by drug and session (baseline adjusted).

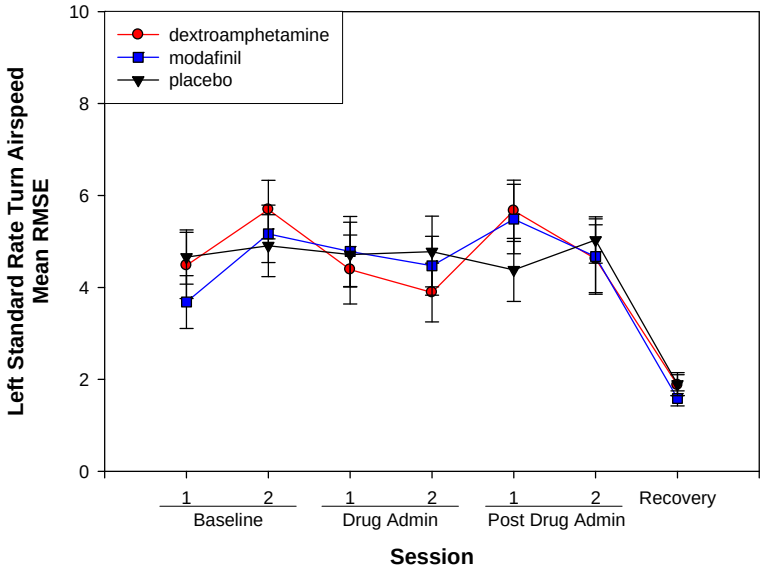

Figure 117. Left Standard Rate Turn airspeed RMSE means by drug and session.

For altitude, a significant main effect existed for session ($F[2, 66] = 46.342$, $p < 0.001$) with significantly more precision in altitude maintenance during the recovery session than during the drug and post-drug administration sessions. No significant main effects were noted for drug ($F[2, 33] = 0.160$, $p = 0.853$) or the interaction between session and drug ($F[4, 66] = 1.077$, $p = 0.375$) (figure 118). Figure 119 presents the left standard rate turn altitude RMSE means by drug and session.

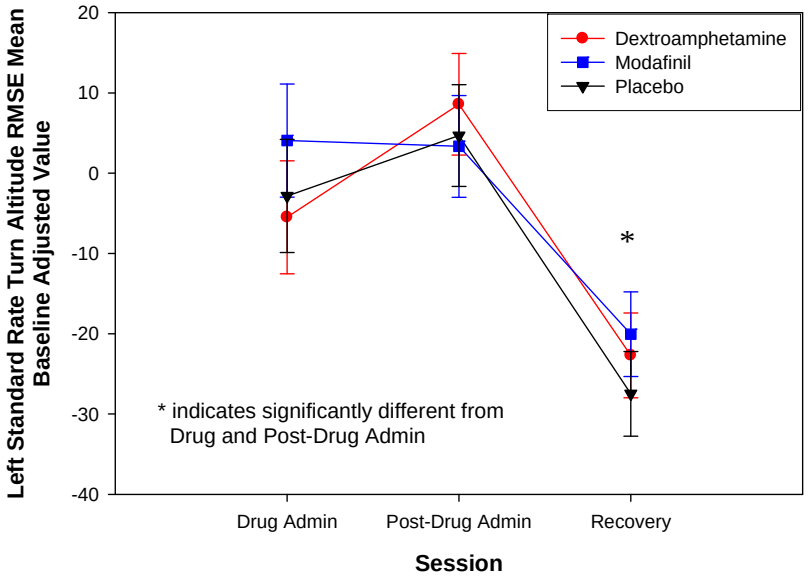

Figure 118. Left Standard Rate Turn altitude RMSE mean comparisons by drug and session (baseline adjusted).

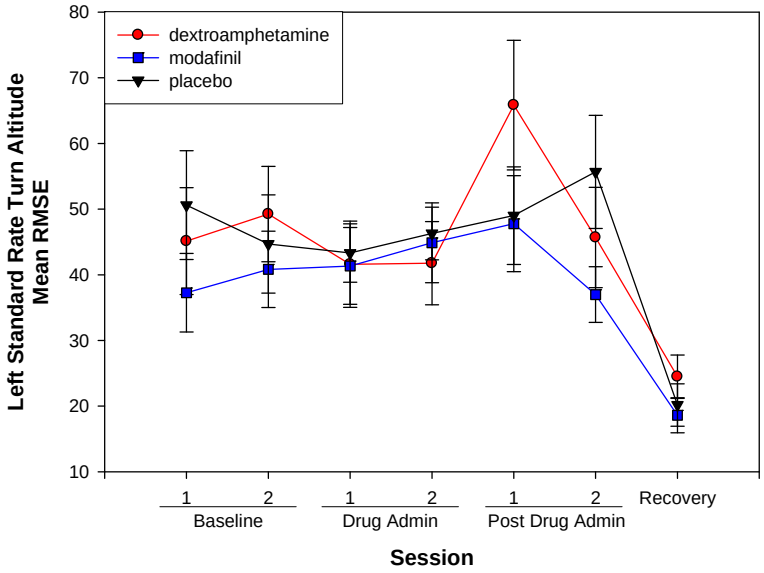

Figure 119. Left Standard Rate Turn altitude RMSE means by drug and session.

Climbing Right Turn. During this maneuver, participants were required to maintain a climb rate of 1000 feet per minute and an indicated airspeed of 120 knots. For the climb rate, no significant main effects were found for session ($F[2, 66] = 0.439$, $p = 0.647$), for drug ($F[2, 33] = 0.131$, $p = 0.116$), or the interaction between session and drug ($F[4, 66] = 1.641$, $p = 0.174$) (figure 120). Figure 121 presents the climbing right turn climb rate RMSE means by drug and session.

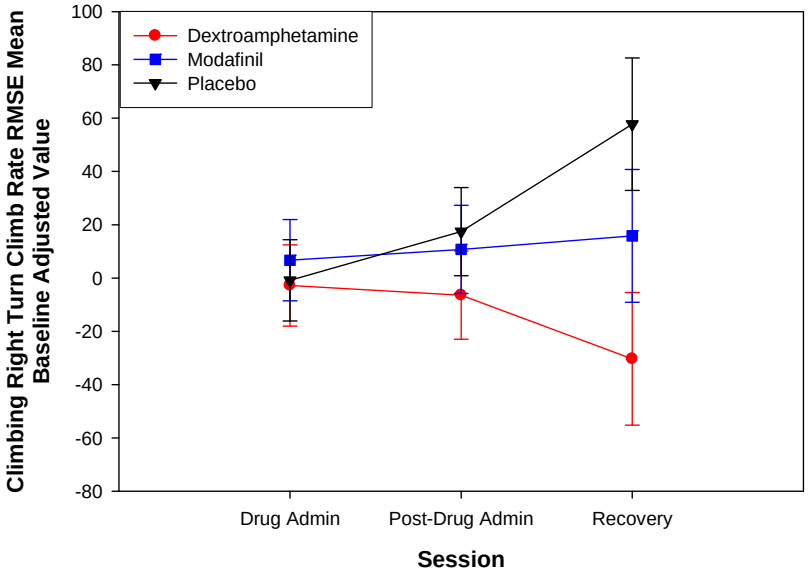

Figure 120. Climbing Right Turn climb rate RMSE mean comparisons by drug and session (baseline adjusted).

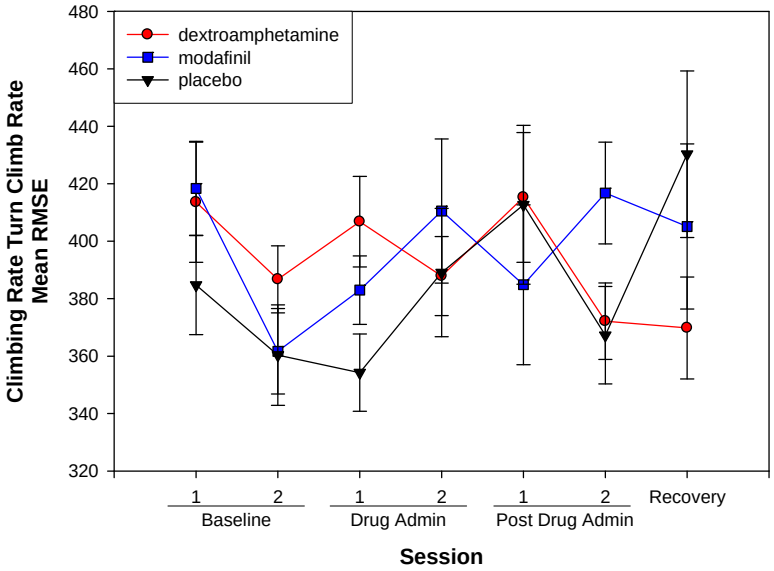

Figure 121. Climbing Right Turn climb rate RMSE means by drug and session.

As for their performance maintaining airspeed, a significant main effect existed for session ($F[2, 66] = 3.463$, $p = 0.037$) with significantly more precision in airspeed maintenance during the recovery session than during the drug and post-drug administration sessions. No significant main effects were noted for drug ($F[2, 33] = 0.066$, $p = 0.936$) or the interaction between session and drug ($F[4, 66] = 0.719$, $p = 0.582$) (figure 122). Figure 123 presents the climbing right turn airspeed RMSE means by drug and session.

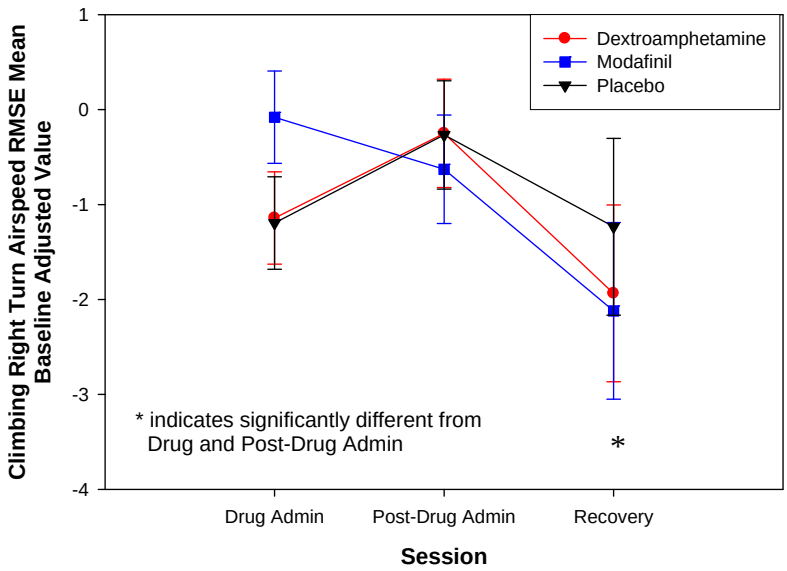

Figure 122. Climbing Right Turn airspeed RMSE mean comparisons by drug and session (baseline adjusted).

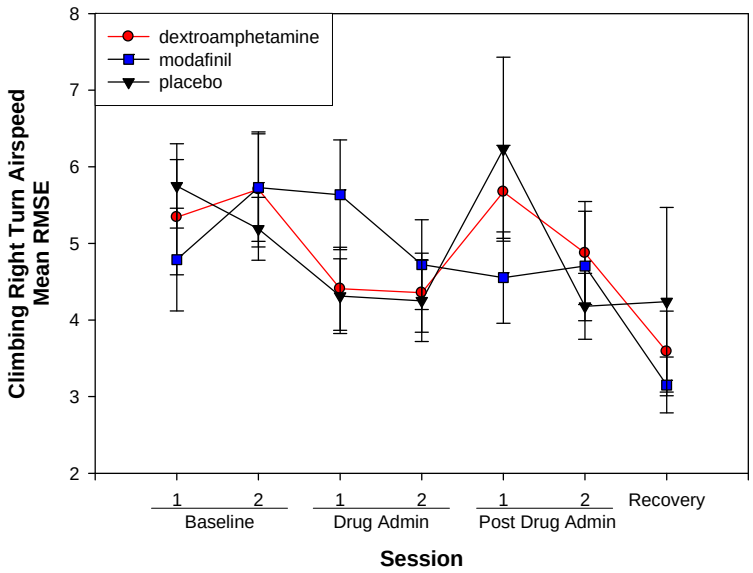

Figure 123. Climbing Right Turn airspeed RMSE means by drug and session.

DME (Distance Measuring Equipment) Arc. During the DME arc, participants were required to maintain a constant altitude of 2000 feet MSL and an indicated airspeed of 120 knots. For altitude performance, a significant main effect existed for session ($F[2, 66] = 28.476$, $p < 0.001$) with significantly more precision in altitude performance during the recovery session than during the drug and post-drug administration sessions. No significant main effects existed for drug ($F[2, 33] = 0.024$, $p = 0.976$) or the interaction between session and drug ($F[4, 66] = 0.730$, $p = 0.575$) (figure 124). Figure 125 presents the DME arc altitude RMSE means by drug and session.

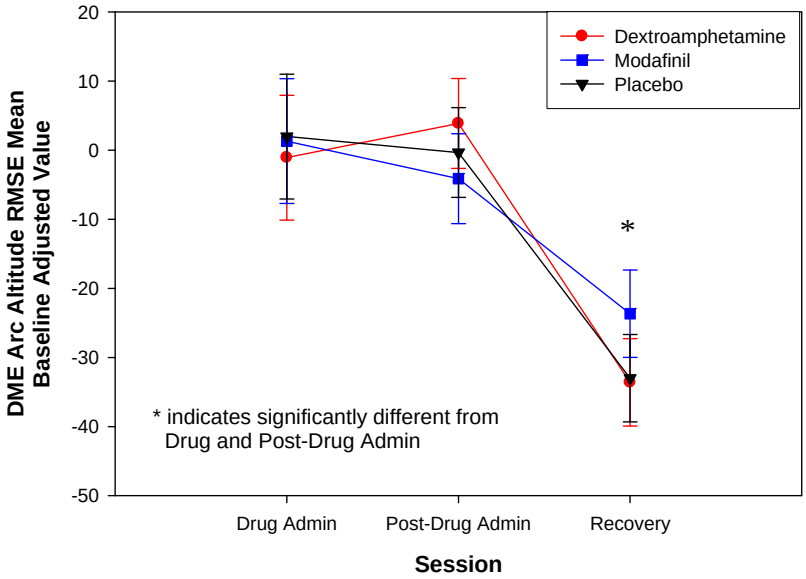

Figure 124. DME Arc altitude RMSE mean comparisons by drug and session (baseline adjusted).

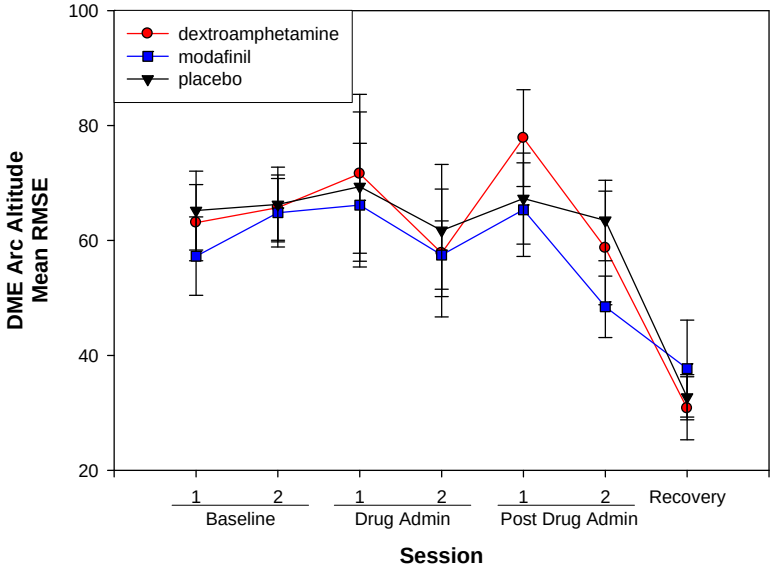

Figure 125. DME Arc altitude RMSE means by drug and session.

For airspeed, a significant main effect existed for session ($F[2, 66] = 27.688$, $p < 0.001$) with significantly more precision in airspeed maintenance during the recovery session than during the drug and post-drug administration sessions. No significant main effects were noted for drug ($F[2, 33] = 0.007$, $p = 0.993$) or the interaction between session and drug ($F[4, 66] = 0.952$, $p = 0.440$) (figure 126). Figure 127 presents the DME arc airspeed RMSE means by drug and session.

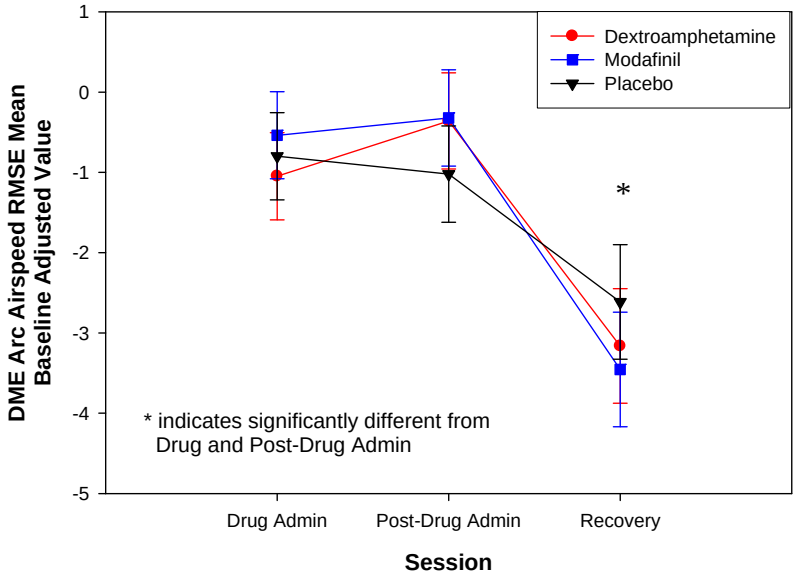

Figure 126. DME Arc airspeed RMSE mean comparisons by drug and session (baseline adjusted).

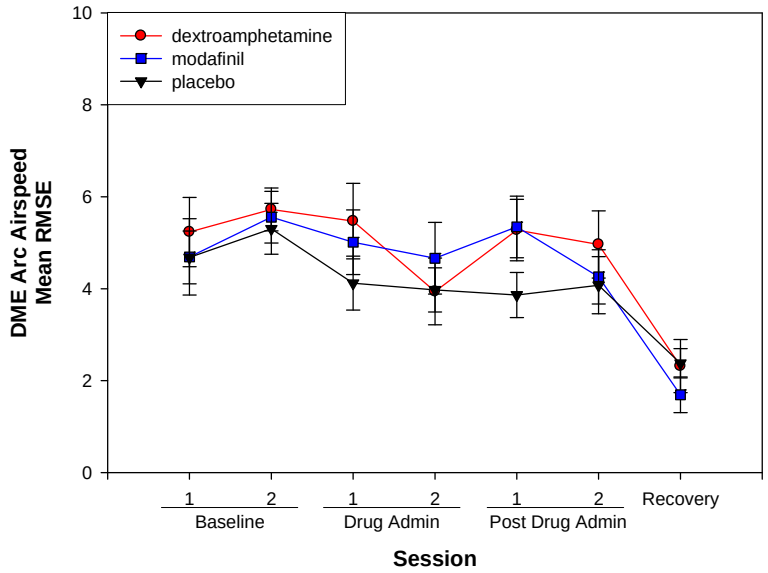

Figure 127. DME Arc airspeed RMSE means by drug and session.

ILS (Instrument Landing System) Approach. During the ILS Approach, participants were required to maintain an altitude of 2000 feet MSL until glideslope intercept, an indicated airspeed of 120 knots, and a track along the localizer (the course component of an ILS). As for altitude, a significant main effect existed for session ($F[2, 66] = 40.773$, $p < 0.001$) with significantly more precision in altitude maintenance during the recovery session than during the drug and post-drug administration sessions. No significant main effects were noted for drug ($F[2, 33] = 1.282$, $p = 0.291$) or the interaction between session and drug ($F[4, 66] = 0.671$, $p = 0.615$) (figure 128). Figure 129 presents the ILS approach altitude RMSE means by drug and session.

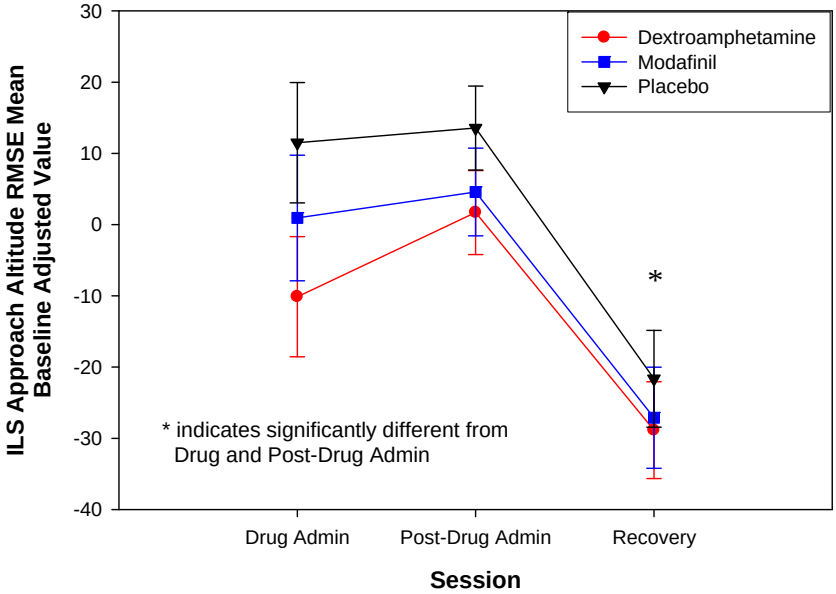

Figure 128. ILS Approach altitude RMSE mean comparisons by drug and session (baseline adjusted).

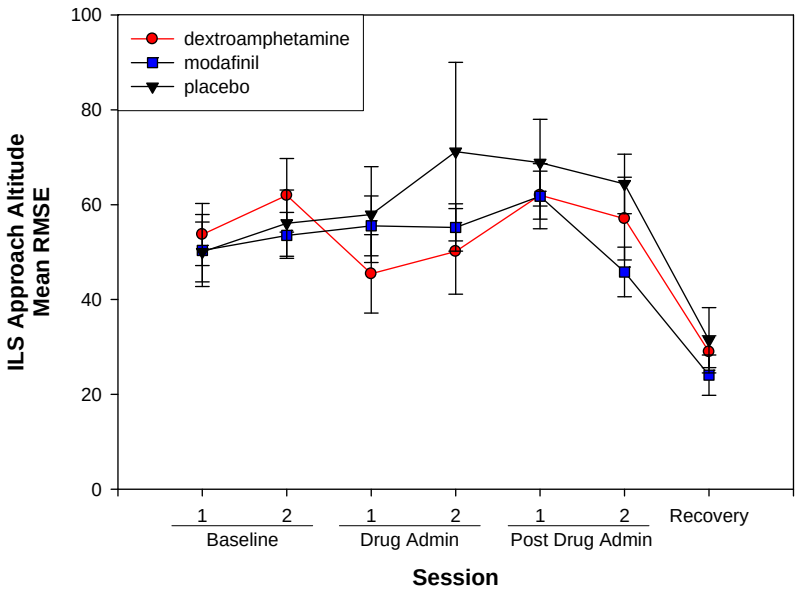

Figure 129. ILS Approach altitude RMSE means by drug and session.

As for airspeed performance, a significant main effect existed for session ($F[2, 66] = 16.447$, $p > 0.001$) with significantly more precision in airspeed maintenance during the recovery session than during the drug and post-drug administration sessions. No significant main effects were noted for drug ($F[2, 33] = 0.215$, $p = 0.808$) or the interaction between session and drug ($F[4, 66] = 0.831$, $p = 0.510$) (figure 130). Figure 131 presents the ILS approach airspeed RMSE means by drug and session.

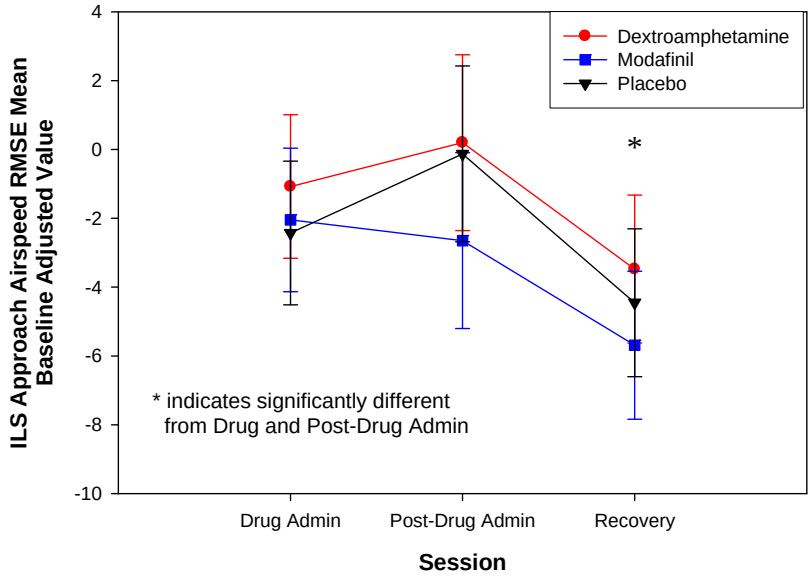

Figure 130. ILS Approach airspeed RMSE mean comparisons by drug and session (baseline adjusted).

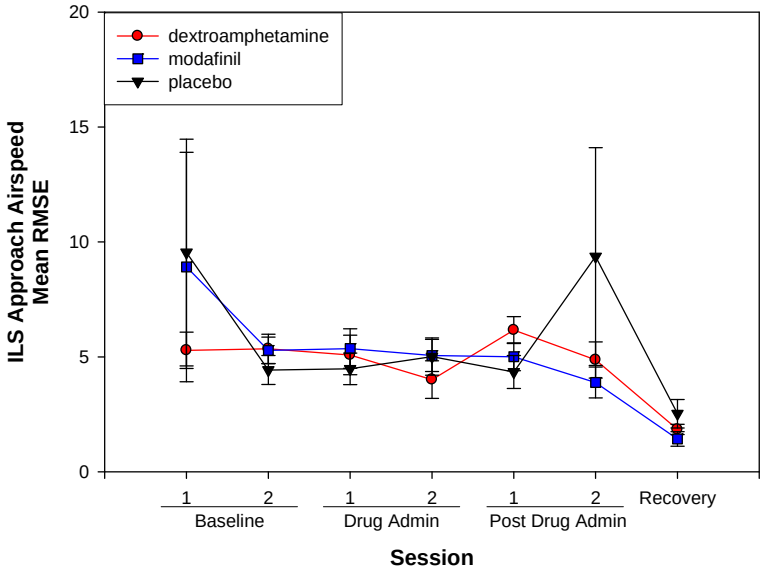

Figure 131. ILS Approach airspeed RMSE means by drug and session.

As for tracking the localizer course, a significant main effect was found for session ($F[2, 66] = 18.303$, $p < .001$) with significantly more precision in maintaining the desired course during the recovery session than the drug administration or post-drug administration sessions. No significant main effect was noted for drug ($F[2, 33] = 1.017$, $p = 0.373$), or the interaction between session and drug ($F[4, 66] = 0.197$, $p = 0.939$) (figure 132). Figure 133 presents the ILS approach course RMSE means by drug and session.

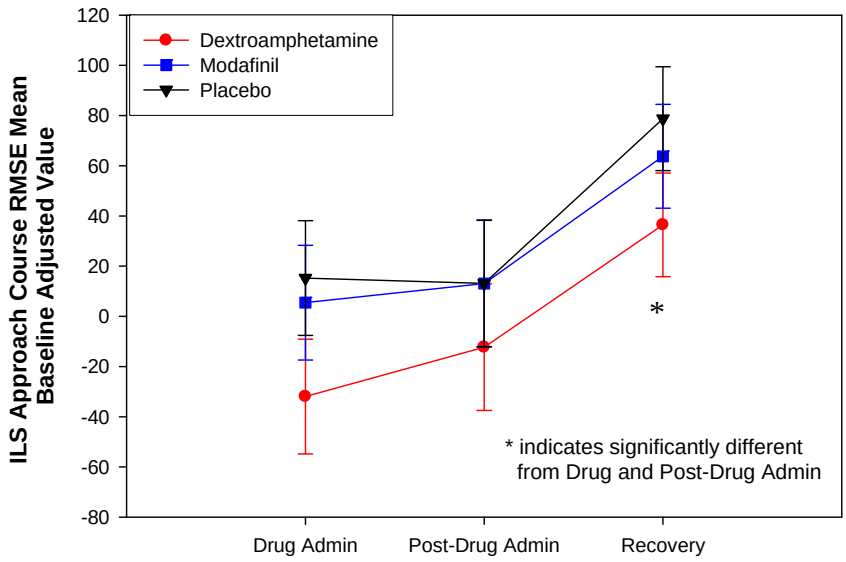

Figure 132. ILS Approach course RMSE mean comparisons by drug and session (baseline adjusted).

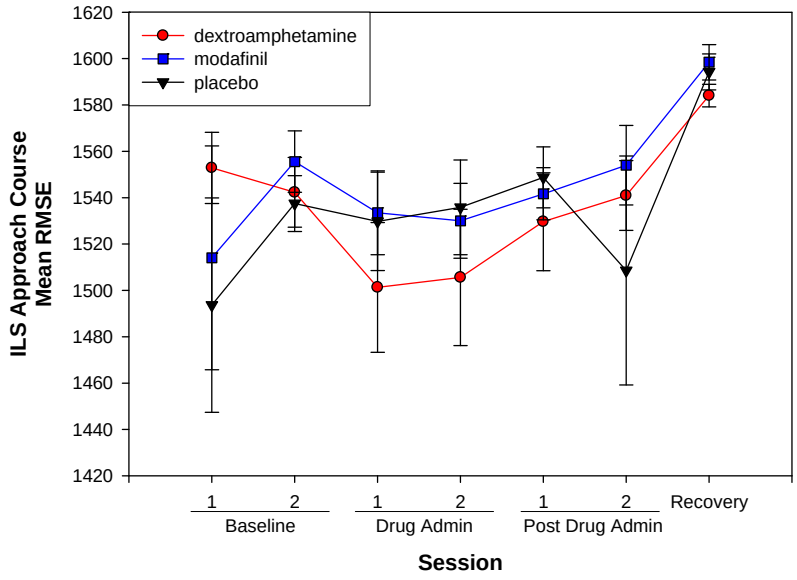

Figure 133. ILS Approach course RMSE means by drug and session.

Missed Approach. During the Missed Approach, participants were required to maintain a magnetic heading of 061 degrees and an indicated airspeed of 120 knots. As for heading maintenance, no significant main effects were found for session ($F[2, 66] = 1.301$, $p = 0.279$), for drug ($F[2, 33] = 1.042$, $p = 0.364$), or the interaction between session and drug ($F[4, 66] = 0.397$, $p = 0.810$) (figure 134). Figure 135 presents the missed approach heading RMSE means by drug and session.

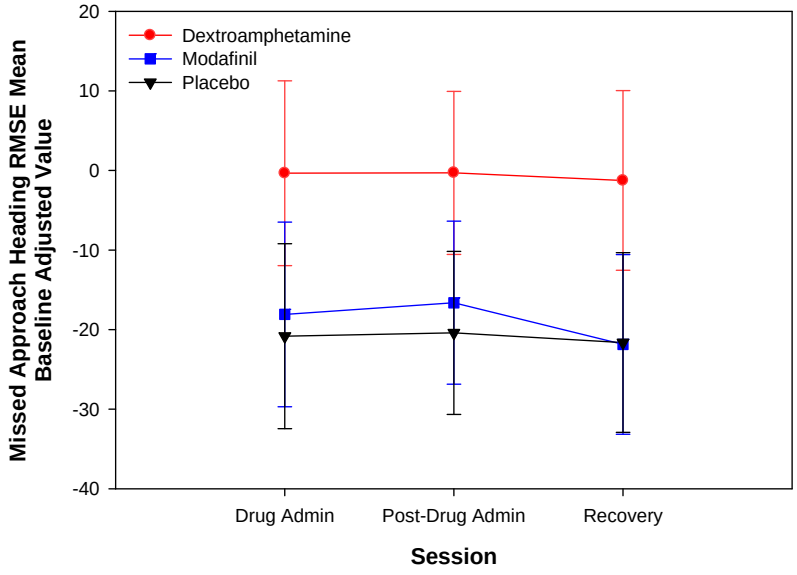

Figure 134. Missed Approach heading RMSE mean comparisons by drug and session (baseline adjusted).

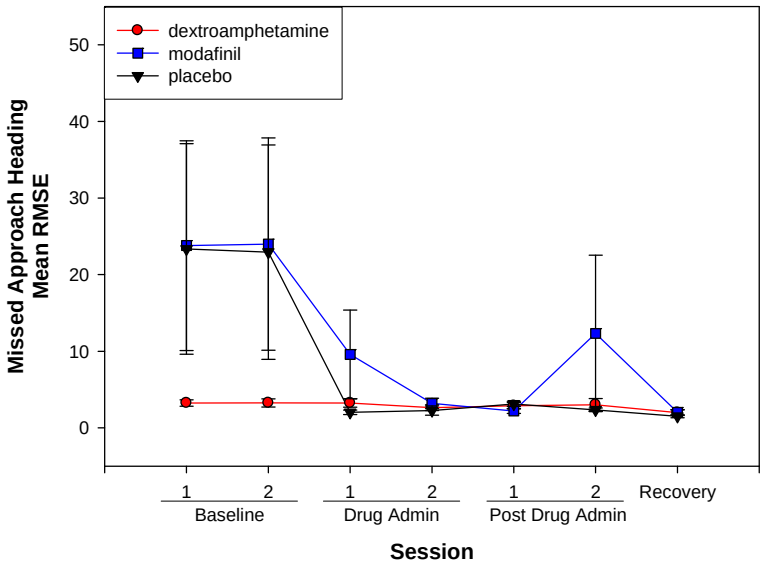

Figure 135. Missed Approach heading RMSE means by drug and session.

For airspeed, a significant main effect existed for session ($F[2, 66] = 6.195$, $p = 0.003$) with significantly more precision in airspeed maintenance during the recovery session than during the drug and post-drug administration sessions. No significant main effects were noted for drug ($F[2, 33] = 0.323$, $p = 0.573$) or the interaction between session and drug ($F[4, 66] = 1.886$, $p = 0.123$) (figure 136). Figure 137 presents the missed approach airspeed RMSE means by drug and session.

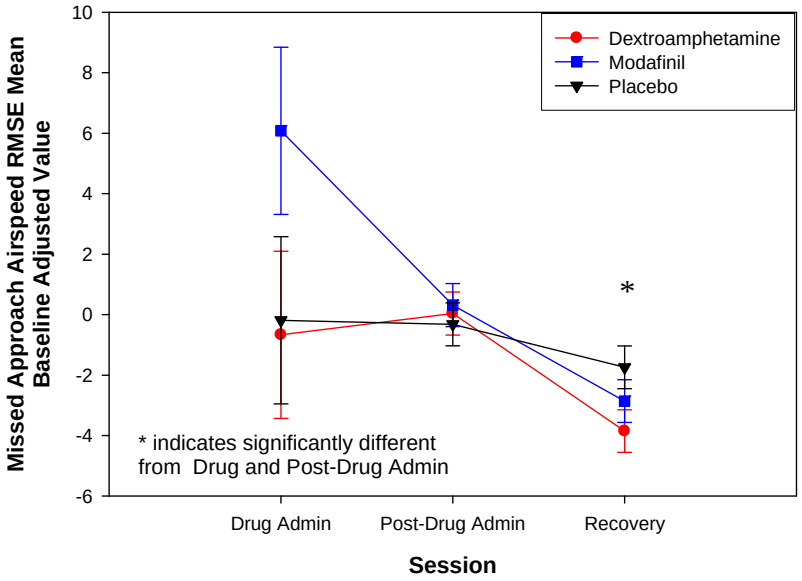

Figure 136. Missed Approach airspeed RMSE mean comparisons by drug and session (baseline adjusted).

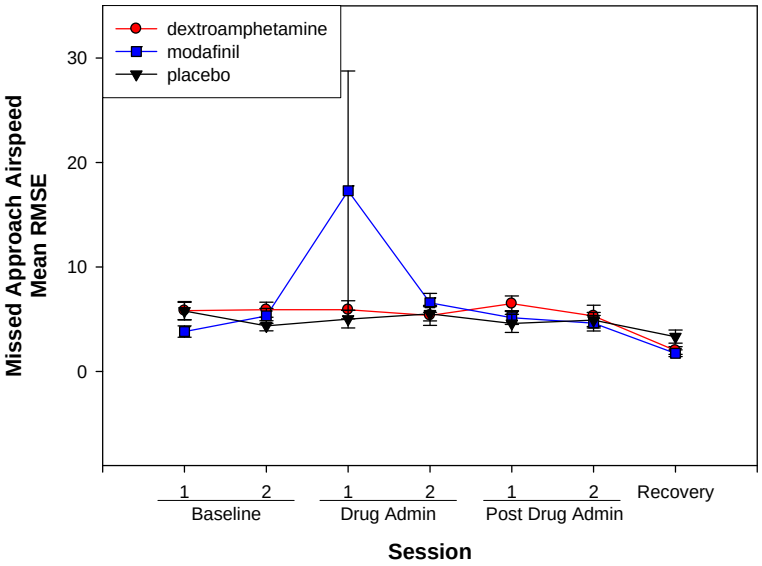

Figure 137. Missed Approach airspeed RMSE means by drug and session.

Discussion

Retrospective comparisons

Leduc et al. (2009) compared their findings with data from earlier studies which used 3 x 10 mg doses of dextroamphetamine (Caldwell, 1999a; 1999b) or 3 x 200 mg doses of modafinil (Caldwell, 2000b). Leduc et al. reported: 1) minimal significant differences in flight performance between data from the earlier Caldwell dextroamphetamine studies and the Leduc data, and 2) no significant differences between modafinil doses on any of the flight maneuvers. POMS data comparisons found no main effects for dose of dextroamphetamine and only one main effect for dose of modafinil with the higher dose (3 x 200 mg) producing more tension in the participants. VAS data comparisons revealed "a significant difference only for reports of irritability between the two doses of dextroamphetamine" with post hoc analyses showing lower irritability with the lower dose. Modafinil VAS data comparisons "showed no significant differences between the two doses on any of the VAS scales."

Although the Leduc et al. (2009) study and the present study are dissimilar in method and design (Leduc et al. also included a caffeine condition), the dosing used for the dextroamphetamine and modafinil conditions (3 x 5 mg doses and 3 x 100 mg doses, respectfully) were the same. Direct comparisons of the data cannot be made due to differences in the extended wakefulness periods between the two studies. Whereas Leduc et al. used 68 hours of continuous wakefulness plus an additional 17 hour period after a 2 hour nap and tested flight performance in flight crews of two subjects, this study employed a 40 hour continuous wakefulness period testing each participant individually. These design differences confound attempts to compare significant main effects. Despite the differences, it may be useful to compare the overall results (particularly significant main effects for drug) for consistency and reliability of the findings (table 27). In addition to comparing significant results, table 27 also serves as a summary of the current study's findings.

Note that Leduc, et al. (2009) used a helicopter simulator exclusively for measuring flight performance and thus, used the Simulator Sickness Questionnaire (SSQ). This study, with most flights conducted in an actual helicopter, employed the more appropriate MSQ. Both instruments ask essentially the same questions and produce the same four output measures.

Vital signs

The Leduc et al. (2009) study found significant session differences for heart rate and blood pressure, whereas the present study did not (only diastolic pressure showed a significant difference). This is likely due to the differences in wakefulness periods: the extreme duration of the Leduc et al. compared to the relatively short wakefulness periods of the present study. As for heart rate, the Leduc et al. study found significant differences for drug condition with the dextroamphetamine and modafinil groups having significantly higher heart rates than the placebo and caffeine groups. The current study recorded generally higher heart rates for the stimulant conditions than for the placebo condition, but not to a significant degree.

Questionnaires

The Symptom Checklist (SC) produced no common findings among the two studies. While both studies found a significant main effect for jitteriness, Leduc et al. (2009) found the effect was produced by higher scores in the caffeine group (not used in this study). The current study found a significant effect of session for jitteriness with the drug and post drug periods differing from the recovery period.

The SSQ/MSQ results of both studies found very similar results in the self-reported symptoms associated with simulator/motion sickness. Each study found significant main effects for drug on all scales except disorientation. The common findings indicate that the placebo group reported higher scores of nausea, oculomotor difficulties, and total symptom severity than the modafinil and dextroamphetamine groups.

Both studies found significant differences in the results of the VAS. Whereas Leduc et al. (2009) found significant main drug effects for talkativeness, sleepiness, and irritability, the current study found such significance only in the sleepiness scale, but for different reasons. The former study reported significantly less sleepiness in the dextroamphetamine group than the placebo group. In contrast, this study's dextroamphetamine group was less sleepy than the placebo group, but not to a significant degree. It was the modafinil group which proved to be significantly less sleepy than the placebo group. On the alertness scale, Leduc et al. found significantly greater alertness in the dextroamphetamine and modafinil groups than in the placebo group. On most tests in the current study, both stimulants consistently outperformed the placebo group, but it was only the modafinil group that achieved statistical significance.

As for the POMS, whereas the Leduc et al. (2009) study's placebo group self-reported to be significantly more fatigued than the dextroamphetamine group, the current study found the stimulant groups to be less fatigued than the placebo group, but not to a statistically significant degree.

Performance tests

In the Leduc et al. (2009) study, the placebo group produced significantly worse CANTAB RVP scores (performance) in hits/hits probability and A' than any of the stimulant groups. This was not the case in the current study during which these measures were not significant for drug effect. However, virtually all performance tests in the current study showed significant session differences with the drug and post-drug sessions almost always producing the best performances on CANTAB tests.

Regarding flight performance, it is impossible to make direct comparisons due to the dissimilarities in the flight profiles and the analytical approach employed by Leduc et al. (2009). Leduc et al. chose to assess composite scores for each flight maneuver, whereby several components of a maneuver (e.g., heading, altitude, airspeed control) is combined to create one maneuver score. The authors of this study sought to assess some of the underlying components of each maneuver in an effort to identify potential aspects of interest. In the Leduc et al. study,

just hover and straight climb were significant for drug condition and there were no main effects for session or the interaction of drug and session. Although this study found no main effects for drug condition during the flight maneuvers, it produced consistent significant main effects for session in which flight performance during the recovery period was consistently superior to the performance during the drug administration and post-drug administration sessions.

Table 27.
Results comparison and summary significance table.

	Measure	Leduc et al. (2009) Drug Analysis			Current Study Drug Analysis		
		Drug(D)	Session(S)	DxS	Drug	Session	DxS
Physiological Tests							
Vital Signs	Heart rate/Pulse	$p<0.001$	$p<0.001$	NS	NS	NS	NS
	Oral temperature	NS	$p<0.001$	$p<0.017$	NS	NS	NS
	Systolic blood pressure	NS	$p<0.007$	NS	NS	NS	NS
	Diastolic blood pressure	NS	NS	$p<0.078$	NS	$p<0.001$	NS
Questionnaires							
SC	Nausea	$p<0.001$	NS	NS	NS	NS	NS
	Jitteriness	$p<0.024$	NS	NS	NS	$p=0.011$	NS
	Nervousness	$p<0.005$	NS	NS	NS	NS	NS
	Excitation	NS	NS	NS	NS	NS	NS
	Anger	NS	NS	NS	NS	NS	NS
	Headache	NS	NS	NS	NS	NS	NS
	Happiness	NS	NS	NS	NS	NS	NS
	Stomach pain	NS	NS	NS	NS	NS	NS
	Dry mouth	NS	NS	NS	NS	$p=0.031$	NS
	Pounding heart	NS	NS	NS	NS	NS	NS
	Racing heartbeat	NS	NS	NS	NS	NS	NS
	Aggression	NR	NR	NR	NS	NS	NS
SSQ/MSQ	Nausea	$p<0.034$	$p<0.024$	NS	$p<0.001$	$p<0.001$	$p=0.003$
	Visuomotor/Oculomotor	$p<0.018$	$p<0.001$	NS	$p=0.006$	$p<0.001$	$p=0.003$
	Disorientation	NS	$p<0.001$	NS	NS	$p<0.001$	$p=0.021$
	Total symptom severity	$p<0.026$	$p<0.001$	NS	$p=0.004$	$p<0.001$	$p=0.006$
EVAR	Control	NS	NR	NR	NS	$p=0.032$	NS
	Confidence	NS	NR	NR	NS	$p=0.004$	NS
	Risk	NS	NR	NR	NS	$p=0.009$	NS
	Total	NR	NR	NR	NS	$p=0.002$	NS
VAS	Talkativeness	$p<0.011$	NS	NS	NS	$p<0.001$	$p=0.039$
	Sleepiness	$p<0.033$	$p<0.001$	$p<0.002$	$p=0.036$	$p<0.001$	$p=0.010$
	Jitteriness/Nervous	NS	$p<0.029$	NS	NS	$p<0.001$	NS
	Irritability	$p<0.045$	NS	NS	NS	NS	NS
	Confidence	NS	$p<0.001$	NS	NS	$p<0.001$	NS
	Energy	NS	$p<0.001$	NS	NS	$p<0.001$	NS
	Anxiousness	NS	NS	NS	NS	NS	NS
	Alertness	$p<0.009$	$p<0.001$	NS	NS	$p<0.001$	$p=0.001$
POMS	Fatigue	$p<0.013$	$p<0.001$	NS	NS	$p<0.001$	$p=0.025$
	Confusion	NS	$p<0.001$	NS	NS	$p=0.041$	$p=0.011$
	Tension	NS	$p<0.013$	NS	NS	$p<0.001$	$p=0.007$
	Depression	NS	$p<0.028$	NS	$p=0.043$	$p=0.001$	NS
	Anger	NS	NS	NS	NS	NS	NS
	Vigor	NS	$p<0.001$	NS	NS	$p<0.001$	$p=0.012$

NS = not significant; NR = not reported

Table 27(continued).
Results comparison and summary significance table.

	Measure	Leduc et al. (2009) Drug Analysis			Current Study Drug Analysis		
		Drug(D)	Session(S)	DxS	Drug	Session	DxS
Performance Tests							
PVT	Reaction time	NS	p<0.003	NS	NS	*p*=0.026	*p*=0.029
	Major lapses	NR	NR	NR	NS	*p*=0.024	NS
	Minor lapses	NR	NR	NR	NS	*p*<0.001	*p*=0.017
BART	Average pump counts				NS	*p*=0.003	*p*=0.025
IGT	Ratio of good/bad cards				NS	NS	NS
CANTAB-RVP	Hits/Hit probability	p<0.001	p<0.001	NS	NS	*p*=0.016	*p*=0.045
	False alarm probability				NS	NS	NS
	A'	p<0.001	p<0.001	NS	NS	*p*=0.019	NS
CANTAB-SOC	Thinking reaction time				NS	*p*<0.001	NS
	Mean moves to solve				NS	NS	NS
CANTAB-SWM	Total errors				NS	*p*<0.001	NS
	Strategy use				NS	*p*=0.018	NS
	Reaction time to 1st move				NS	NS	NS
EST2000-M16 (prone supported)	Accuracy				NS	NS	NS
	Reaction time				NS	NS	NS
	Shot distance				NS	NS	NS
EST2000-M16 (prone unsupported)	Accuracy				NS	NS	NS
	Reaction time				NS	*p*=0.049	NS
	Shot distance				NS	NS	NS
EST2000-M16 (kneeling)	Accuracy				NS	NS	NS
	Reaction time				NS	NS	NS
	Shot distance				NS	NS	NS
EST2000-9mm	Accuracy				NS	NS	NS
	Reaction time				NS	NS	NS
	Shot distance				NS	NS	NS

NS = not significant; NR = not reported; shaded = not tested

Table 27(continued).
Results comparison and summary significance table.

	Measure	Leduc et al. (2009) Drug Analysis			Current Study Drug Analysis		
		Drug(D)	Session(S)	DxS	Drug	Session	DxS
Performance Tests							
Flt Performance	Hover (altitude)	p<0.011*	NS*	NS*	NS	*p*<0.001	NS
	Hover (heading)	p<0.011*	NS*	NS*	NS	NS	NS
	Instrument takeoff (heading)				NS	NS	NS
	Instrument takeoff (climb rate)				NS	*p*<0.001	NS
	Straight & level (heading)	NS*	NS*	NS*	NS	NS	NS
	Straight & level (airspeed)				NS	*p*<0.001	NS
	Straight & level (altitude)				NS	*p*<0.001	NS
	Standard rate turn (turn rate)				NS	*p*<0.001	NS
	Standard rate turn (airspeed)				NS	*p*<0.001	NS
	Standard rate turn (altitude)				NS	*p*<0.001	NS
	Climbing right turn (climb rate)	NS*	NS*	NS*	NS	NS	NS
	Climbing right turn (airspeed)				NS	*p*=0.037	NS
	Straight Climb - VMC	p<0.018*	NS*	NS*			
	Climbing right turn - IMC	NS*	NS*	NS			
	DME Arc (altitude)				NS	*p*<0.001	NS
	DME Arc (airspeed)				NS	*p*<0.001	NS
	ILS (level segment)(altitude)	NS*	NS*	NS*	NS	*p*<0.001	NS
	ILS (apprch segment)(airspeed)				NS	*p*<0.001	NS
	ILS (apprch segment)(course)				NS	*p*<0.001	NS
	Missed approach (heading)				NS	NS	NS
	Missed approach (airspeed)				NS	*p*=0.003	NS

NS = not significant; NR = not reported; shaded = not tested; VMC = visual meteorological conditions; IMC = instrument meteorological conditions; * = used composite scores for flight maneuvers

Current Study

In this study, 18 helicopter pilots each completed 15 UH-60 flights. Twelve out of the 15 flights were conducted in an actual helicopter unless inclement weather caused the flight to be conducted in a full-motion flight simulator. In addition, a variety of subjective and objective evaluations were conducted during the two 40 hr periods of continuous wakefulness. It is important to recall that this study was commissioned (and jointly funded with the USAMRMC) by the U.S. Special Operations Command Biomedical Initiative Steering Committee (SOCOM BISC) in order to establish the efficacy and safety of modafinil for use during actual flying operations. The SOCOM BISC's overarching goal was to establish the face or operational validity needed to approve the use of modafinil for actual military flight operations and field conditions. Since dextroamphetamine is currently approved for use by U.S. Army Aviation forces (U.S. Army Flight Surgeon's Aeromedical Checklists, 2008), establishing modafinil as a well tolerated stimulant (few adverse side effects and purportedly reduced potential for addiction and abuse [Warot et al., 1993]) which demonstrates the same or similar benefits as

dextroamphetamine (Caldwell, 2001) would go far in securing its approval by the U.S. Army Aeromedical Consultant Advisory Panel (ACAP).

As mentioned above, one rationale for approving modafinil versus dextroamphetamine is the latter's reputation for addiction and abuse. Until very recently, it appeared that modafinil had less abuse potential than stimulants that target dopamine transporters (Wesensten, 2006; Phend, 2009, Warot et al., 1993). It is instructive to note that a recent study by Volkow et al. (2009) found evidence that modafinil does increase dopamine in the nucleus accumbens and their report recommends heightened awareness for abuse potential in vulnerable populations.

Vital signs

At the dosages used in this study, both dextroamphetamine and modafinil increased heart rate slightly above placebo, but not to a significant level. Other modafinil research, especially when using higher dosages, have reported significant increases in heart rate (Volkow et al., 2009; Leduc et al., 2009; Eddy et al, 2004, Muller et al, 2004). Not surprisingly, self reports of a pounding or racing heart via the SC questionnaire were slightly, although not significantly, higher under the stimulant conditions than under the placebo condition.

Modafinil has been shown to increase blood pressure (usually systolic) in humans (Volkow et al., 2009; Leduc et al., 2009; Turner et al., 2003; Rush et al., 2002). In this study, it was not systolic, but diastolic blood pressure that showed a significant increase for session with the greatest increases by both stimulant groups occurring five hours after the final doses (figure 14). Turner et al. suggested that these increases in blood pressure may "complement a possible indirect involvement of the noradrenergic system." They added that although these cardiovascular effects may be statistically significant, they are not clinically significant (Rush et al. quoted by Turner et al.).

Side effects

Sleep

According to Wesensten, Killgore, and Balkin (2005), an important consideration when assessing the alerting properties and side effects of stimulants is the effect they may have on the ability to obtain restorative recovery sleep. Analysis of the actigraphy data confirms that participants were in fact inactive (asleep) during rest periods and active (awake) during wake periods. Results showed significant differences between the sleep periods of the placebo group and the modafinil group. Of the eight hours (480 min) allowed for sleep, the placebo group recorded a longer inactivity (recovery sleep) than the modafinil group (453.91 min versus 438.91 min, respectively). Significant differences were also detected for mean sleep efficiency (the percentage of time in bed actually sleeping) with the placebo group recording significantly greater sleep efficiency than the modafinil group (94.58 percent versus 91.55 percent). These significant differences may suggest one of two hypotheses. One, that participants required a longer period of rest to recover from the placebo condition and also slept more efficiently than in the recovery from the modafinil condition. Two, that modafinil interferes with the amount of

time to go to sleep. This second hypothesis is supported by the level of estimated serum concentration that remained at bedtime (figure 6). This potentially suggests that sleep deprivation differentially impacted the body's required amount of recovery rest between the placebo group and modafinil group. A review of the mood and performance assessment results showed that the sleep effects identified had no detectable impact on recovery session performance with nearly all measures returning to general baseline levels following the eight hours provided for recovery sleep.

Mood and symptoms questionnaires

Naturally, when considering the use of drugs for aviation applications, knowledge of the side effect profiles is critically important. Among the most important considerations for aviation is the potential for nausea. Data from the subjective MSQ and SC showed that nausea under all drug conditions increased beyond baseline during the study and returned to baseline levels at recovery (figures 22 and Appendix G, respectively). However, self reports of nausea were significantly lower under the stimulant conditions than under placebo (figure 21). The post-drug administration period saw a significant peak in overall nausea scores that dissipated thereafter. Just as in the Leduc et al. study (figures 1 and 2), it appears that both dextroamphetamine and modafinil may have protected against the increase in nausea. For modafinil, the findings of this study, like those of Leduc et al., support the use of the lower dose regimen (3 x 100 mg) compared to the higher dose regimen (3 x 200 mg) employed by Caldwell et al. (1999a). As in the Leduc et al. (2009) study, none of the serious modafinil-related side effects (vertigo, dizziness, and nausea; table 1) reported by Caldwell et al. were observed in the modafinil group in this study. As highlighted by Leduc et al., several recent studies have suggested that symptoms such as nausea, vertigo and jitteriness seen with modafinil may have been dose dependent (Buguet et al., 2003; Eddy et al., 2005; Wesensten et al, 2002).

Other results of the MSQ showed that oculomotor difficulties and total motion sickness symptoms were significantly higher under placebo than under either of the stimulant conditions (figures 23 and 25). In addition, greater disorientation was reported by those under placebo than those in the dextroamphetamine group during the post drug administration period (figure 27). Session differences and drug-by-session differences existed for these measures due to the placebo group’s significantly greater adverse feelings. In summary, participants who were administered dextroamphetamine or modafinil experienced fewer motion sickness effects than those on placebo.

Most SC measures resulted in non-significant differences with most self-reports ranging from no symptoms to only mild severity. This is consistent with other similar research (Leduc et al. 2009; Killgore et al., 2008). Only two measures showed significant session differences (dry mouth and jitteriness, figures 16 and 18, respectively). Self-reports of dry mouth were greater (by those under the stimulant conditions) during the drug and post-drug administration periods than during the recovery period. The relatively higher scores (although not significantly) for jitteriness reported by the modafinil group during the post-drug administration period did not appear to have a deleterious effect on the group’s overall comportment.

Of notable importance was the significant finding from the VAS questionnaire showing that the modafinil group felt significantly less sleepy (table 17) and more alert (figure 51) during the sleep-deprived drug and post-drug administration periods than the placebo group. In addition, the ratings by both stimulant groups indicated that they felt somewhat more confident and energetic (albeit, non-significantly; figures 45 and 47) than the placebo group during the drug and post-drug administration periods. Other studies report similar findings (Baranski et al., 2002; Pigeau et al., 1995). Consistent with Leduc et al. (2009), the data revealed that modafinil tended to preserve talkativeness at or around baseline levels throughout the entire period of wakefulness (figures 37), unlike dextroamphetamine and placebo which seemed to suppress talkativeness.

Regarding the POMS data, feelings of depression were significantly higher in the placebo group than either stimulant group (figure 59). With only minor variations, the depression scores of the stimulant groups remained at their baseline levels throughout the testing period (figure 60). All POMS measures except anger, which was without effect (figure 61), showed significant main effects for session and drug-by-session. Not unexpectedly, there was greater overall fatigue, confusion, tension, and depression, and less vigor reported during the drug and post-drug administration periods than during recovery period (following eight hours of sleep). The drug-by-session interaction was due to the self-reports of higher overall fatigue, confusion, tension, and depression, and less vigor by those in the placebo group (figures 53, 55, 57, 59, and 63). This is consistent with other research which tested for mood states (Caldwell, 2001; Pigeau et al., 1995).

As reported, not all data collected via the subjective questionnaires resulted in statistical significance. However, these results are in general agreement with others who have conducted similar research on stimulant compounds used to mitigate fatigue-induced mood declines (Caldwell et al., 1999a; 2004; Turner et al., 2003; Baranski et al., 2004; Killgore et al., 2008; Leduc et al., 2009).

Reportable event

One male participant reported evidence of a rash on the back of his legs and over his abdomen following what turned out to be (after un-blinding by the study physician and medical monitor) his third and final 100 mg dose of modafinil. The participant was examined and his condition monitored closely throughout the day with serial observations and vital signs. The symptoms were not severe enough to warrant additional treatment. The rash remained essentially unchanged throughout the day and the participant's condition was never characterized as serious by the medical staff. The following morning the rash had improved significantly with a small area remaining on the back of his right leg indicating no manifestations of serious modafinil-related sequelae. The medical assessment was that the rash probably represented a simple drug eruption. The participant completed the study and was released per the study schedule. Four days following release, the participant, contacted by the study principal investigator, informed that all signs of the rash were completely resolved. In summary, the adverse event was expected (i.e., briefed in the consent process), was likely related to the research, but did not suggest any greater risk of harm than was previously recognized.

Tests of risk propensity

An important faculty for any pilot is the ability to make sound judgments based on the weighing of potential risks. As such, measures which assess the drug effects on risk propensity are important to any comprehensive assessment of stimulants intended for aviation applications. This study employed three such tests: the EVAR (subjective), and the BART and IGT (both objective). It is important to understand that these instruments test different facets of risk propensity. Whereas the EVAR examines feelings of control and the confidence to take risks, the BART measures the ability to judge the probability of risk. The IGT, on the other hand, measures one's ability to assess reward/punishment contingencies.

On all EVAR measures (control, confidence, judgment of risk, and total score), results showed no significant differences among drug conditions and very small variations from baseline by the modafinil group (figures 29, 31, 33, and 35). In other words, the modafinil group's EVAR scores did not vary to any great extent throughout the entire testing periods. These findings are in contrast to those of Gurtman, Broadbear, and Redman (2008) who conducted a simulator driving study of sleep-deprived individuals on a single 300 mg dose. Pre- and post-drive self-assessments of driving performance indicated that modafinil "may induce overconfidence." In the current study, for session, significant differences were found for each of the EVAR measures. Essentially, notable increases in control, confidence, risk propensity, and total scores of the dextroamphetamine and placebo groups in the recovery session caused the recovery session to be significantly different than the drug and post-drug administration sessions. In contrast to the steady results of the modafinil group, it appears that the stress of the sleep deprivation periods (drug and post-drug administration sessions) may have weakened the feelings of control, confidence, and risk propensity of the dextroamphetamine and placebo groups which were then restored at recovery, consistent with Killgore (2007).

BART results indicated a significantly greater risk aversion during the post-drug administration session than during the recovery period with the placebo group most averse to risk, especially compared to the dextroamphetamine group. It is logical for the placebo group to feel the least capable of the groups to make judgments regarding the probability of risks considering that the post-drug administration period was the most stressful in terms of sleep deprivation.

The IGT results indicated no significant differences in risk taking among the drug conditions or sessions. These findings imply that one night of sleep deprivation may not be sufficiently stressful to impair one's ability to make cost/benefit analyses and adjustments of risk.

Performance tests

PVT

As in the Leduc et al. (2009) study, none of the PVT measures (reaction time, major lapses, and minor lapses) were significantly influenced by drug condition (figures 65, 67, and 69); however, all showed significant main effects for session, indicating that they were capturing

fatigue-induced increases in reaction time. Significant drug-by-session findings for reaction time and minor lapses were due to the placebo group's generally slower reaction times and more minor lapses than the stimulant conditions during the drug and post-drug administration sessions, the periods characterized by sleep deprivation. Several studies examining the effects of modafinil and dextroamphetamine have shown drug effects on measures of psychomotor function. Producing the same non-significant results for drug condition as the Leduc et al. study, the results of the current study may indicate that the use of lower doses of modafinil and dextroamphetamine may produce enough stimulation to perform at satisfactory levels while at the same time not enough to discriminate from placebo. In addition, one study by Park et al. (2007) found that the PVT measures of mean reaction time and the number of lapses were the least sensitive measure of sleepiness (thus, alertness) of the three psychomotor instruments they used. Research involving various higher dosing regimens (generally greater than 200 mg) of modafinil has shown it to maintain psychomotor speed at levels significantly better than placebo (Lundorff, Jønsson, & Sjøgren, 2009; Theunissen et al., 2009, Killgore et al., 2008). Other studies suggest that modafinil's effects on reaction time may be dose dependent (Baranski et al., 1998; Wesensten, 2002), although even at low doses (100 mg or less), performance is maintained at acceptable, near baseline levels across time while at the same time not demonstrating statistical superiority to placebo.

CANTAB

Eight elements of the CANTAB were used to test cognitive performance (e.g., sustained attention, spatial reasoning, and procedural strategy). None of the CANTAB tests were significant for drug condition across all sessions due to the convergence of performance levels of all three test conditions at the non-sleep-deprived recovery period. This is despite studies and reviews of studies that have reported cognitive improvements from modafinil and dextroamphetamine when compared to placebo (Saletu et al., 2009; Lundorff, Jønsson, & Sjøgren, 2009; Gerrard and Malcolm, 2007; Turner et al., 2003; Pigeau et al., 1995). As for session, five of the eight measures were significant. Results of the RVP Hit Probability test indicated that both modafinil and dextroamphetamine similarly improved detection of stimuli better than placebo during the drug and post-drug administration periods (figure 75). The RVP A' test (the ability to detect sequences) found that the post-drug administration period was very nearly significantly different than the recovery session due to the relatively poor performance of the placebo group during the post-drug administration period (figure 79). The SOC Thinking Reaction Time and SWM Total Errors (figures 81 and 85, respectively) also showed the recovery period to be significantly different than the drug and post-drug administration periods. Again, the difference was due primarily to the lower performing placebo condition during the post-drug administration period relative to the stimulant conditions.

The results of the cognitive tests demonstrate that during the sessions in which sleep-deprivation was a factor (drug and post-drug administration sessions), the performance effects of modafinil and dextroamphetamine were quite similar and generally superior to placebo, at times significantly better. It is worth noting Wesensten (2006), who in her detailed review of modafinil research, summarizes by writing that "overall the bulk of studies indicate that

modafinil improves psychomotor and cognitive performance during sleep deprivation, most notably during the circadian nadir in performance."

EST2000

Analyses of the EST2000 marksmanship tasks, comprised of M16 rifle and 9mm pistol firing performance by accuracy (# of hits), reaction time, and shot distance from the center of target (radius), produced few significant findings of questionable importance.

The results of the M16 rifle prone unsupported position yielded significantly faster reaction times during the drug administration period than during the post-drug administration and recovery periods (figure 91). It is suspected that the level of arousal associated with this task being conducted during the drug administration period (and before significant sleep deprivation) may have contributed to this effect. A similar situation exists regarding the in-flight data discussed later. In addition, there was a significant session-by-range difference with the furthest targets (at 250 and 300 meters) being engaged more swiftly (adjusted from baseline) during the drug administration period than the other periods (figure 92). It is suspected that closer targets are perceived easier to hit and are more patiently engaged. Further targets, being more difficult to sight, seem to provoke a faster response.

The kneeling position produced a significant result for shooting radius. The participants' baseline corrected shooting from the kneeling position was significantly less precise for the 150 meter targets than for the 50 meter targets, a result that is expected given the higher level of difficulty in shooting targets that are more distant.

The 9mm data, a friend/foe detection task, revealed no significant differences between any conditions (drug, session, or interactions) on any of the dependent measures: accuracy (# of hits), reaction time, and shot distance from the center of target (radius). It is suspected that the level of arousal associated with this shooting task mitigated any potential differences between the drug or session conditions.

In brief, the EST2000 results are disappointing and suggest that the weapons simulator is not a sensitive measure for studies of this kind. (Ongoing research at USAARL is investigating techniques to improve the sensitivity, validity, and reliability of the EST2000 as a research tool.) On the other hand, it is possible that the drug and session conditions truly did not yield any changes in performance, however, the data to support this claim is weak and requires further investigation.

Flight performance

Of the 19 component measures of flight performance analyzed within the 10 flight maneuvers conducted, there were no main effects for drug or drug-by-session. There were, however, significant session effects observed in 13 of the 19 components, all (except takeoff climb rate) due to significantly fewer control errors (adjusted from baseline) during the recovery period than during the drug and post-drug administration periods. None of the significant

findings, however, involved heading performance which, considering the aircraft's automatic heading hold feature, may have been too easy a task and therefore, lacking the challenge to be a discriminating variable. The significant main effects for the recovery session (for the flights between 1130 and 1300 hrs) indicate better control of altitude, airspeed, and turn rate (baseline adjusted) over the other test periods. This is very likely because of practice effects and that all recovery flights were conducted in the simulator where environmental conditions remain constant (no winds, no turbulence, etc.). Also, all were conducted when participants were well rested.

Analogous to the cognitive arousal described by DeValck, Cluydts, & Pirrera (2004) and supported by comments in Caldwell, Roberts, & Jones (1999), the absence of significantly different performance between the stimulant drugs and placebo during the sleep-deprivation periods may be due to the stimulating nature of flying an actual aircraft at night when limited visibility of the ground and surrounding airspace can produce, in many aviators, a heightened state of arousal, apprehension, anxiety, and awareness. A similar concept emerged during a study by Ramsey et al. (2008) during which the effects of dextroamphetamine, modafinil, methylphenidate, and placebo were assessed on fatigued participants undergoing the stress of rapid onset centrifuge runs. According to the authors, they were not able to draw conclusions about the impact of fatigue or of the pharmacological countermeasures due to suspicions that subject anticipation of the centrifuge ride provided cognitive arousal.

Limitations and recommendations

The lack of significant drug effects for flight performance may have been due to the relatively short duration of the flights. Economic constraints resulted in the helicopter flights being limited to approximately 35-40 min each. When possible, future studies should employ flights (in aircraft or simulators) of greater duration (2-3 hours) which may provide a much better opportunity to provoke more fatigue-related differences in flight performance. (See Caldwell, Roberts, & Jones, 1999c, for related discussion.) Finally, consideration should be given to testing under greater periods of wakefulness. Although more likely to be operationally relevant, one night of wakefulness may not be sufficient to produce significantly different effects in flight performance, especially considering the cognitively arousing nature of short-duration flights.

Summary and conclusions

Generally stated, the goals of this study were to determine the degree to which three doses of 100 mg of modafinil and three doses of 5 mg of dextroamphetamine sustained mood and performance. In addition, this study was to identify operationally significant side effects, evaluate the recovery from the sustained wakefulness after one full night of sleep, and perform retrospective study comparisons.

The results of this study showed that, in most instances, dextroamphetamine and modafinil provided the same or similar positive effects (quite similar in efficacy) over placebo during the study's sleep-deprived drug administration and post-drug administration periods. Overall, these drugs maintained alertness, feelings of well-being, cognitive function, judgment, risk perception,

and situation awareness of sleep-deprived normals at levels consistently better than placebo. A retrospective study comparison with Leduc et al. (2009) yielded very similar findings, especially for mood, symptoms, vital signs, and flight performance.

Analyses of vital signs showed no issues of clinical significance for any of the test conditions. Recovery sleep, although significantly different between the modafinil and placebo conditions, had no detectable impact on performance during the recovery session. At the study dosages, neither modafinil nor dextroamphetamine demonstrated clear flight performance benefits over placebo during one night of sleep deprivation. Just as importantly, however, neither drug produced any side effects that would be of an aeromedical concern. In light of the results reported by Caldwell et al. (1999a) during which participants on 3 doses of 200 mg of modafinil reported serious symptoms of vertigo, nausea, and dizziness, it is fair to say that there is a greater expectation for adverse side effects at higher dosages than at the dosages used in this effort.

This study, like many others before it, strongly suggest that stimulant medications can assist the Warfighter in maintaining acceptable levels of mood and performance when combat requirements dictate long periods of sleep deprivation. Regarding modafinil, the authors, based on the results of this study, agree with the conclusions of Pigeau et al. (1995), Leduc et al. (2009), and Chua et al. (2010) that modafinil, at multiple doses of 100 mg and 200 mg, is well tolerated. The evidence suggests that modafinil is a good alternative to dextroamphetamine for countering the debilitating mood and cognitive effects of sleep loss during sustained operations.

In summation, while the results of this study did not show dramatic flight performance enhancements by either modafinil or dextroamphetamine at the study dosages, they do reveal the unambiguous benefits of modafinil and dextroamphetamine over placebo and substantiate the findings of previous research. Just as importantly, the results of this study provide additional evidence that neither drug impaired or adversely affected the mood and performance of sleep-deprived aviators.

The results of this study were presented on 22 March 2010 to the U.S. Army Aeromedical Activity's (USAAMA) Aeromedical Consultant Advisory Panel (ACAP) to support a policy regarding the use of modafinil by U.S. Army aviation forces. According to the USAAMA Director, the ACAP recommended that modafinil be authorized for use by Army aircrew. A follow-on USAARL report is in preparation to detail for the user modafinil dosages, side effects, and expected performance effects.

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Appendix A
Product monographs

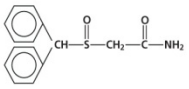
PROVIGIL®

(modafinil) Tablets [C-IV]
Rx Only

DESCRIPTION

PROVIGIL (modafinil) is a wakefulness-promoting agent for oral administration. Modafinil is a racemic compound. The chemical name for modafinil is 2-[(diphenylmethyl)sulfinyl]acetamide. The molecular formula is $C_{15}H_{15}N0_2S$ and the molecular weight is 273.35.

The chemical structure is:



Modafinil is a white to off-white, crystalline powder that is practically insoluble in water and cyclohexane. It is sparingly to slightly soluble in methanol and acetone. PROVIGIL tablets contain 100 mg or 200 mg of modafinil and the following inactive ingredients: lactose, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, povidone, and magnesium stearate.

CLINICAL PHARMACOLOGY

Mechanism of Action and Pharmacology

The precise mechanism(s) through which modafinil promotes wakefulness is unknown. Modafinil has wake-promoting actions similar to sympathomimetic agents like amphetamine and methylphenidate, although the pharmacologic profile is not identical to that of sympathomimetic amines.

Modafinil has weak to negligible interactions with receptors for norepinephrine, serotonin, dopamine, GABA, adenosine, histamine-3, melatonin, and benzodiazepines. Modafinil also does not inhibit the activities of MAO-B or phosphodiesterases II-V.

Modafinil-induced wakefulness can be attenuated by the α_1-adrenergic receptor antagonist prazosin; however, modafinil is inactive in other in vitro assay systems known to be responsive to α-adrenergic agonists, such as the rat vas deferens preparation.

Modafinil is not a direct- or indirect-acting dopamine receptor agonist. However, in vitro, modafinil binds to the dopamine transporter and inhibits dopamine reuptake. This activity has been associated in vivo with increased extracellular dopamine levels in some brain regions of animals. In genetically engineered mice lacking the dopamine transporter (DAT), modafinil lacked wake-promoting activity, suggesting that this activity was DAT-dependent. However, the wake-promoting effects of modafinil, unlike those of amphetamine, were not antagonized by the dopamine receptor antagonist haloperidol in rats. In addition, alpha-methyl-p-tyrosine, a dopamine synthesis inhibitor, blocks the action of amphetamine, but does not block locomotor activity induced by modafinil.

In the cat, equal wakefulness-promoting doses of methylphenidate and amphetamine increased neuronal activation throughout the brain. Modafinil at an equivalent wakefulness-promoting dose selectively and prominently increased neuronal activation in more discrete regions of the brain. The relationship of this finding in cats to the effects of modafinil in humans is unknown.

In addition to its wake-promoting effects and ability to increase locomotor activity in animals, modafinil produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants in humans. Modafinil has reinforcing properties, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine. Modafinil was also partially discriminated as stimulant-like.

The optical enantiomers of modafinil have similar pharmacological actions in animals. Two major metabolites of modafinil, modafinil acid and modafinil sulfone, do not appear to contribute to the CNS-activating properties of modafinil.

Pharmacokinetics

Modafinil is a racemic compound, whose enantiomers have different pharmacokinetics (e.g., the half-life of the *l*-isomer is approximately three times that of the *d*-isomer in adult humans). The enantiomers do not interconvert. At steady state, total exposure to the *l*-isomer is approximately three times that for the *d*-isomer. The trough concentration (C_{minss}) of circulating modafinil after once daily dosing consists of 90% of the *l*-isomer and 10% of the *d*-isomer. The effective elimination half-life of modafinil after multiple doses is about 15 hours. The enantiomers of modafinil exhibit linear kinetics upon multiple dosing of 200-600 mg/day once daily in healthy volunteers. Apparent steady states of total modafinil and *l*-(-)-modafinil are reached after 2-4 days of dosing.

Absorption

Absorption of PROVIGIL tablets is rapid, with peak plasma concentrations occurring at 2-4 hours. The bioavailability of PROVIGIL tablets is approximately equal to that of an aqueous suspension. The absolute oral bioavailability was not determined due to the aqueous insolubility (<1 mg/mL) of modafinil, which precluded intravenous administration. Food has no effect on overall PROVIGIL bioavailability; however, its absorption (t_{max}) may be delayed by approximately one hour if taken with food.

Distribution

Modafinil is well distributed in body tissue with an apparent volume of distribution (~0.9 L/kg) larger than the volume of total body water (0.6 L/kg). In human plasma, in vitro, modafinil is moderately bound to plasma protein (~60%, mainly to albumin). At serum concentrations obtained at steady state after doses of 200 mg/day, modafinil exhibits no displacement of protein binding of warfarin, diazepam or propranolol. Even at much larger concentrations (1000μM; >25 times the C_{max} of 40μM at steady state at 400 mg/day), modafinil has no effect on warfarin binding. Modafinil acid at concentrations >500μM decreases the extent of warfarin binding, but these concentrations are >35 times those achieved therapeutically.

Metabolism and Elimination

The major route of elimination is metabolism (~90%), primarily by the liver, with subsequent renal elimination of the metabolites. Urine alkalinization has no effect on the elimination of modafinil.

Metabolism occurs through hydrolytic deamidation, S-oxidation, aromatic ring hydroxylation, and glucuronide conjugation. Less than 10% of an administered dose is excreted as the parent compound. In a clinical study using radiolabeled modafinil, a total of 81% of the administered radioactivity was recovered in 11 days post-dose, predominantly in the urine (80% vs. 1.0% in the feces). The largest fraction of the drug in urine was modafinil acid, but at least six other metabolites were present in lower concentrations. Only two metabolites reach appreciable concentrations in plasma, i.e., modafinil acid and modafinil sulfone. In preclinical models, modafinil acid, modafinil sulfone, 2-[(diphenylmethyl)sulfonyl]acetic acid and 4-hydroxy modafinil, were inactive or did not appear to mediate the arousal effects of modafinil.

In adults, decreases in trough levels of modafinil have sometimes been observed after multiple weeks of dosing, suggesting auto-induction, but the magnitude of the decreases and the inconsistency of their occurrence suggest that their clinical significance is minimal. Significant accumulation of modafinil sulfone has been observed after multiple doses due to its long elimination half-life of 40 hours. Induction of metabolizing enzymes, most importantly cytochrome P-450 (CYP) 3A4, has also been observed in vitro after incubation of primary cultures of human hepatocytes with modafinil and in vivo after extended administration of modafinil at 400 mg/day. (For further discussion of the effects of modafinil on CYP enzyme activities, see **PRECAUTIONS, Drug Interactions**.)

Drug-Drug Interactions: Based on in vitro data, modafinil is metabolized partially by the 3A isoform subfamily of hepatic cytochrome P450 (CYP3A4). In addition, modafinil has the potential to inhibit CYP2C19, suppress CYP2C9, and induce CYP3A4, CYP2B6, and CYP1A2. Because modafinil and modafinil sulfone are reversible inhibitors of the drug-metabolizing enzyme CYP2C19, co-administration of modafinil with drugs such as diazepam, phenytoin and propranolol, which are largely eliminated via that pathway, may increase the circulating levels of those compounds. In addition, in individuals deficient in the enzyme CYP2D6 (i.e., 7-10% of the Caucasian population; similar or lower in other populations), the levels of CYP2D6 substrates such as tricyclic antidepressants and selective serotonin reuptake inhibitors, which have ancillary routes of elimination through CYP2C19, may be increased by co-administration of modafinil. Dose adjustments may be necessary for patients being treated with these and similar medications (See **PRECAUTIONS, Drug Interactions**). An in vitro study demonstrated that armodafinil (one of the enantiomers of modafinil) is a substrate of P-glycoprotein.

Coadministration of modafinil with other CNS active drugs such as methylphenidate and dextroamphetamine did not significantly alter the pharmacokinetics of either drug.

Chronic administration of modafinil 400 mg was found to decrease the systemic exposure to two CYP3A4 substrates, ethinyl estradiol and triazolam, after oral administration suggesting that CYP3A4 had been induced. Chronic administration of modafinil can increase the elimination of substrates of CYP3A4. Dose adjustments may be necessary for patients being treated with these and similar medications (See **PRECAUTIONS, Drug Interactions**).

An apparent concentration-related suppression of CYP2C9 activity was observed in human hepatocytes after exposure to modafinil in vitro suggesting that there is a potential for a metabolic interaction between modafinil and the substrates of this enzyme (e.g., S-warfarin, phenytoin). However, in an interaction study in healthy volunteers, chronic modafinil treatment did not show a significant effect on the pharmacokinetics of warfarin when compared to placebo. (See **PRECAUTIONS, Drug Interactions,** *Other Drugs*, Warfarin).

Special Populations

Gender Effect: The pharmacokinetics of modafinil are not affected by gender.

Age Effect: A slight decrease (~20%) in the oral clearance (CL/F) of modafinil was observed in a single dose study at 200 mg in 12 subjects with a mean age of 63 years (range 53 - 72 years), but the change was considered not likely to be clinically significant. In a multiple dose study (300 mg/day) in 12 patients with a mean age of 82 years (range 67 - 87 years), the mean levels of modafinil in plasma were approximately two times those historically obtained in matched younger subjects. Due to potential effects from the multiple concomitant medications with which most of the patients were being treated, the apparent difference in modafinil pharmacokinetics may not be attributable solely to the effects of aging. However, the results suggest that the clearance of modafinil may be reduced in the elderly (See **DOSAGE AND ADMINISTRATION**).

Race Effect: The influence of race on the pharmacokinetics of modafinil has not been studied.

Renal Impairment: In a single dose 200 mg modafinil study, severe chronic renal failure (creatinine clearance ≤ 20 mL/min) did not significantly influence the pharmacokinetics of modafinil, but exposure to modafinil acid (an inactive metabolite) was increased 9-fold (See **PRECAUTIONS**).

Hepatic Impairment: Pharmacokinetics and metabolism were examined in patients with cirrhosis of the liver (6 males and 3 females). Three patients had stage B or B+ cirrhosis (per the Child criteria) and 6 patients had stage C or C+ cirrhosis. Clinically 8 of 9 patients were icteric and all had ascites. In these patients, the oral clearance of modafinil was decreased by about 60% and the steady state concentration was doubled compared to normal patients. The dose of PROVIGIL should be reduced in patients with severe hepatic impairment (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

CLINICAL TRIALS

The effectiveness of PROVIGIL in reducing excessive sleepiness has been established in the following sleep disorders: narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder (SWSD).

Narcolepsy

The effectiveness of PROVIGIL in reducing the excessive sleepiness (ES) associated with narcolepsy was established in two US 9-week, multicenter, placebo-controlled, two-dose (200 mg per day and 400 mg per day) parallel-group, double-blind studies of outpatients who met the ICD-9 and American Sleep Disorders Association criteria for narcolepsy (which are also consistent with the American Psychiatric Association DSM-IV criteria). These criteria include either 1) recurrent daytime naps or lapses into sleep that occur almost daily for at least three months, plus sudden bilateral loss of postural muscle tone in association with intense emotion (cataplexy) or 2) a complaint of excessive sleepiness or sudden muscle weakness with associated features: sleep paralysis, hypnagogic hallucinations, automatic behaviors, disrupted major sleep episode; and polysomnography demonstrating one of the following: sleep latency less than 10 minutes or rapid eye movement (REM) sleep latency less than 20 minutes. In addition, for entry into these studies, all patients were required to have objectively documented excessive daytime sleepiness, a Multiple Sleep Latency Test (MSLT) with two or more sleep onset REM periods, and the absence of any other clinically significant active medical or psychiatric disorder. The MSLT, an objective daytime polysomnographic assessment of the patient's ability to fall asleep in an unstimulating environment, measures latency (in minutes) to sleep onset averaged over 4 test sessions at 2-hour intervals following nocturnal polysomnography. For each test session, the subject was told to lie quietly and attempt to sleep. Each test session was terminated after 20 minutes if no sleep occurred or 15 minutes after sleep onset.

In both studies, the primary measures of effectiveness were 1) sleep latency, as assessed by the Maintenance of Wakefulness Test (MWT) and 2) the change in the patient's overall disease status, as measured by the Clinical Global Impression of Change (CGI-C). For a successful trial, both measures had to show significant improvement.

The MWT measures latency (in minutes) to sleep onset averaged over 4 test sessions at 2 hour intervals following nocturnal polysomnography. For each test session, the subject was asked to attempt to remain awake without using extraordinary measures. Each test session was terminated after 20 minutes if no sleep occurred or 10 minutes after sleep onset. The CGI-C is a 7-point scale, centered at *No Change*, and ranging from *Very Much Worse* to *Very Much Improved*. Patients were rated by evaluators who had no access to any data about the patients other than a measure of their baseline severity. Evaluators were not given any specific guidance about the criteria they were to apply when rating patients.

Other assessments of effect included the Multiple Sleep Latency Test (MSLT), Epworth Sleepiness Scale (ESS; a series of questions designed to assess the degree of sleepiness in everyday situations) the Steer Clear Performance Test (SCPT; a computer-based evaluation of a patient's ability to avoid hitting obstacles in a simulated driving situation), standard nocturnal polysomnography, and patient's daily sleep log. Patients were also assessed with the Quality of Life in Narcolepsy (QOLIN) scale, which contains the validated SF-36 health questionnaire.

Both studies demonstrated improvement in objective and subjective measures of excessive daytime sleepiness for both the 200 mg and 400 mg doses compared to placebo. Patients treated with either dose of PROVIGIL showed a statistically significantly enhanced ability to remain awake on the MWT (all p values <0.001) at weeks 3, 6, 9, and final visit compared to placebo and a statistically significantly greater global improvement, as rated on the CGI-C scale (all p values <0.05).

The average sleep latencies (in minutes) on the MWT at baseline for the 2 controlled trials are shown in Table 1 below, along with the average change from baseline on the MWT at final visit.

The percentages of patients who showed any degree of improvement on the CGI-C in the two clinical trials are shown in Table 2 below.

Similar statistically significant treatment-related improvements were seen on other measures of impairment in narcolepsy, including a patient assessed level of daytime sleepiness on the ESS (p<0.001 for each dose in comparison to placebo).

Nighttime sleep measured with polysomnography was not affected by the use of PROVIGIL.

Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS)

The effectiveness of PROVIGIL in reducing the excessive sleepiness associated with OSAHS was established in two clinical trials. In both studies, patients were enrolled who met the International Classification of Sleep Disorders (ICSD) criteria for OSAHS (which are also consistent with the American Psychiatric Association DSM-IV criteria). These criteria include either, 1) excessive sleepiness or insomnia, plus frequent episodes of impaired breathing during sleep, and associated features such as loud snoring, morning headaches and dry mouth upon awakening; or 2) excessive sleepiness or insomnia and polysomnography demonstrating one of the following: more than five obstructive apneas, each greater than 10 seconds in duration, per hour of sleep and one or more of the following: frequent arousals from sleep associated with the apneas, bradytachycardia, and arterial oxygen desaturation in association with the apneas. In addition, for entry into these studies, all patients were required to have excessive sleepiness as demonstrated by a score ≥10 on the Epworth Sleepiness Scale, despite treatment with continuous positive airway pressure (CPAP). Evidence that CPAP was effective in reducing episodes of apnea/hypopnea was required along with documentation of CPAP use.

In the first study, a 12-week multicenter placebo-controlled trial, a total of 327 patients were randomized to receive PROVIGIL 200 mg/day, PROVIGIL 400 mg/day, or matching placebo. The majority of patients (80%) were fully compliant with CPAP, defined as CPAP use > 4 hours/night on > 70% nights. The remainder were partially CPAP compliant, defined as CPAP use < 4 hours/night on >30% nights. CPAP use continued throughout the study. The primary measures of effectiveness were 1) sleep latency, as assessed by the Maintenance of Wakefulness Test (MWT) and 2) the change in the patient's overall disease status, as measured by the Clinical Global Impression of Change (CGI-C) at week 12 or the final visit. (See **CLINICAL TRIALS**, *Narcolepsy* section above for a description of these tests.)

Patients treated with PROVIGIL showed a statistically significant improvement in the ability to remain awake compared to placebo-treated patients as measured by the MWT (p<0.001) at endpoint [Table 1]. PROVIGIL-treated patients also showed a statistically significant improvement in clinical condition as rated by the CGI-C scale (p<0.001) [Table 2]. The two doses of PROVIGIL performed similarly.

In the second study, a 4-week multicenter placebo-controlled trial, 157 patients were randomized to either PROVIGIL 400 mg/day or placebo. Documentation of regular CPAP use (at least 4 hours/night on 70% of nights) was required for all patients. The primary outcome measure was the change from baseline on the ESS at week 4 or final visit. The baseline ESS scores for the PROVIGIL and placebo groups were 14.2 and 14.4, respectively. At week 4, the ESS was reduced by 4.6 in the PROVIGIL group and by 2.0 in the placebo group, a difference that was statistically significant (p<0.0001).

Nighttime sleep measured with polysomnography was not affected by the use of PROVIGIL.

Shift Work Sleep Disorder (SWSD)

The effectiveness of PROVIGIL for the excessive sleepiness associated with SWSD was demonstrated in a 12-week placebo-controlled clinical trial. A total of 209 patients with chronic SWSD were randomized to receive PROVIGIL 200 mg/day or placebo. All patients met the International Classification of Sleep Disorders (ICSD-10) criteria for chronic SWSD (which are consistent with the American Psychiatric Association DSM-IV criteria for Circadian Rhythm Sleep Disorder: Shift Work Type). These criteria include 1) either: a) a primary complaint of excessive sleepiness or insomnia which is temporally associated with a work period (usually night work) that occurs during the habitual sleep phase, or b) polysomnography and the MSLT demonstrate loss of a normal sleep-wake pattern (i.e., disturbed chronobiological rhythmicity); and 2) no other medical or mental disorder accounts for the symptoms, and 3) the symptoms do not meet criteria for any other sleep disorder producing insomnia or excessive sleepiness (e.g., time zone change [jet lag] syndrome).

It should be noted that not all patients with a complaint of sleepiness who are also engaged in shift work meet the criteria for the diagnosis of SWSD. In the clinical trial, only patients who were symptomatic for at least 3 months were enrolled.

Enrolled patients were also required to work a minimum of 5 night shifts per month, have excessive sleepiness at the time of their night shifts (MSLT score < 6 minutes), and have daytime insomnia documented by a daytime polysomnogram (PSG).

The primary measures of effectiveness were 1) sleep latency, as assessed by the Multiple Sleep Latency Test (MSLT) performed during a simulated night shift at week 12 or the final visit and 2) the change in the patient's overall disease status, as measured by the Clinical Global Impression of Change (CGI-C) at week 12 or the final visit. Patients treated with PROVIGIL showed a statistically significant prolongation in the time to sleep onset compared to placebo-treated patients, as measured by the nighttime MSLT [Table 1] (p<0.05). Improvement on the CGI-C was also observed to be statistically significant (p<0.001). (See **CLINICAL TRIALS**, *Narcolepsy* section above for a description of these tests.)

Daytime sleep measured with polysomnography was not affected by the use of PROVIGIL.

Table 1. Average Baseline Sleep Latency and Change from Baseline at Final Visit in Adults (MWT and MSLT in minutes)

Disorder	Measure	PROVIGIL 200 mg*		PROVIGIL 400 mg*		Placebo	
		Baseline	Change from Baseline	Baseline	Change from Baseline	Baseline	Change from Baseline
Narcolepsy I	MWT	5.8	2.3	6.6	2.3	5.8	-0.7
Narcolepsy II	MWT	6.1	2.2	5.9	2.0	6.0	-0.7
OSAHS	MWT	13.1	1.6	13.6	1.5	13.8	-1.1
SWSD	MSLT	2.1	1.7	–	–	2.0	0.3

*Significantly different than placebo for all trials (p<0.01 for all trials but SWSD, which was p<0.05)

Table 2. Clinical Global Impression of Change (CGI-C) (Percent of Adult Patients Who Improved at Final Visit)

Disorder	PROVIGIL 200 mg*	PROVIGIL 400 mg*	Placebo
Narcolepsy I	64%	72%	37%
Narcolepsy II	58%	60%	38%
OSAHS	61%	68%	37%
SWSD	74%	——	36%

*Significantly different than placebo for all trials (p<0.01)

INDICATIONS AND USAGE

PROVIGIL is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder.

In OSAHS, PROVIGIL is indicated as an adjunct to standard treatment(s) for the underlying obstruction. If continuous positive airway pressure (CPAP) is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating PROVIGIL. If PROVIGIL is used adjunctively with CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary.

In all cases, careful attention to the diagnosis and treatment of the underlying sleep disorder(s) is of utmost importance. Prescribers should be aware that some patients may have more than one sleep disorder contributing to their excessive sleepiness.

The effectiveness of modafinil in long-term use (greater than 9 weeks in Narcolepsy clinical trials and 12 weeks in OSAHS and SWSD clinical trials) has not been systematically evaluated in placebo-controlled trials. The physician who elects to prescribe PROVIGIL for an extended time in patients with Narcolepsy, OSAHS, or SWSD should periodically reevaluate long-term usefulness for the individual patient.

CONTRAINDICATIONS

PROVIGIL is contraindicated in patients with known hypersensitivity to modafinil, armodafinil or its inactive ingredients.

WARNINGS

Serious Rash, including Stevens-Johnson Syndrome

Serious rash requiring hospitalization and discontinuation of treatment has been reported in adults and children in association with the use of modafinil.

Modafinil is not approved for use in pediatric patients for any indication.

In clinical trials of modafinil, the incidence of rash resulting in discontinuation was approximately 0.8% (13 per 1,585) in pediatric patients (age <17 years); these rashes included 1 case of possible Stevens-Johnson Syndrome (SJS) and 1 case of apparent multi-organ hypersensitivity reaction. Several of the cases were associated with fever and other abnormalities (e.g., vomiting, leukopenia). The median time to rash that resulted in discontinuation was 13 days. No such cases were observed among 380 pediatric patients who received placebo. No serious skin rashes have been reported in adult clinical trials (0 per 4,264) of modafinil.

Rare cases of serious or life-threatening rash, including SJS, Toxic Epidermal Necrolysis (TEN), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) have been reported in adults and children in worldwide post-marketing experience. The reporting rate of TEN and SJS associated with modafinil use, which is generally accepted to be an underestimate due to underreporting, exceeds the background incidence rate. Estimates of the background incidence rate for these serious skin reactions in the general population range between 1 to 2 cases per million-person years.

There are no factors that are known to predict the risk of occurrence or the severity of rash associated with modafinil. Nearly all cases of serious rash associated with modafinil occurred within 1 to 5 weeks after treatment initiation. However, isolated cases have been reported after prolonged treatment (e.g., 3 months). Accordingly, duration of therapy cannot be relied upon as a means to predict the potential risk heralded by the first appearance of a rash.

Although benign rashes also occur with modafinil, it is not possible to reliably predict which rashes will prove to be serious. Accordingly, modafinil should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug-related. Discontinuation of treatment may not prevent a rash from becoming life-threatening or permanently disabling or disfiguring.

Angioedema and Anaphylactoid Reactions

One serious case of angioedema and one case of hypersensitivity (with rash, dysphagia, and bronchospasm), were observed among 1,595 patients treated with armodafinil, the R enantiomer of modafinil (which is the racemic mixture). No such cases were observed in modafinil clinical trials. However, angioedema has been reported in postmarketing experience with modafinil. Patients should be advised to discontinue therapy and immediately report to their physician any signs or symptoms suggesting angioedema or anaphylaxis (e.g., swelling of face, eyes, lips, tongue or larynx; difficulty in swallowing or breathing; hoarseness).

Multi-organ Hypersensitivity Reactions

Multi-organ hypersensitivity reactions, including at least one fatality in postmarketing experience, have occurred in close temporal association (median time to detection 13 days: range 4-33) to the initiation of modafinil.

Although there have been a limited number of reports, multi-organ hypersensitivity reactions may result in hospitalization or be life-threatening. There are no factors that are known to predict the risk of occurrence or the severity of multi-organ hypersensitivity reactions associated with modafinil. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations included myocarditis, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, leukopenia, thrombocytopenia), pruritus, and asthenia. Because multi-organ hypersensitivity is variable in its expression, other organ system symptoms and signs, not noted here, may occur.

If a multi-organ hypersensitivity reaction is suspected, PROVIGIL should be discontinued. Although there are no case reports to indicate cross-sensitivity with other drugs that produce this syndrome, the experience with drugs associated with multi-organ hypersensitivity would indicate this to be a possibility.

Persistent Sleepiness

Patients with abnormal levels of sleepiness who take PROVIGIL should be advised that their level of wakefulness may not return to normal. Patients with excessive sleepiness, including those taking PROVIGIL, should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity. Prescribers should also be aware that patients may not acknowledge sleepiness or drowsiness until directly questioned about drowsiness or sleepiness during specific activities.

Psychiatric Symptoms

Psychiatric adverse experiences have been reported in patients treated with modafinil. Postmarketing adverse events associated with the use of modafinil have included mania, delusions, hallucinations, and suicidal ideation, some resulting in hospitalization. Many, but not all, patients had a prior psychiatric history. One healthy male volunteer developed ideas of reference, paranoid delusions, and auditory hallucinations in association with multiple daily 600 mg doses of modafinil and sleep deprivation. There was no evidence of psychosis 36 hours after drug discontinuation.

In the adult modafinil controlled trials database, psychiatric symptoms resulting in treatment discontinuation (at a frequency ≥0.3%) and reported more often in patients treated with modafinil compared to those treated with placebo were anxiety (1%), nervousness (1%), insomnia (<1%), confusion (<1%), agitation (<1%), and depression (<1%). Caution should be exercised when PROVIGIL is given to patients with a history of psychosis, depression, or mania. Consideration should be given to the possible emergence or exacerbation of psychiatric symptoms in patients treated with PROVIGIL. If psychiatric symptoms develop in association with PROVIGIL administration, consider discontinuing PROVIGIL.

PRECAUTIONS

Diagnosis of Sleep Disorders

PROVIGIL should be used only in patients who have had a complete evaluation of their excessive sleepiness, and in whom a diagnosis of either narcolepsy, OSAHS, and/or SWSD has been made in accordance with ICSD or DSM diagnostic criteria (See **CLINICAL TRIALS**). Such an evaluation usually consists of a complete history and physical examination, and it may be supplemented with testing in a laboratory setting. Some patients may have more than one sleep disorder contributing to their excessive sleepiness (e.g., OSAHS and SWSD coincident in the same patient).

General

Although modafinil has not been shown to produce functional impairment, any drug affecting the CNS may alter judgment, thinking or motor skills. Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that PROVIGIL therapy will not adversely affect their ability to engage in such activities.

CPAP Use in Patients with OSAHS

In OSAHS, PROVIGIL is indicated as an adjunct to standard treatment(s) for the underlying obstruction. If continuous positive airway pressure (CPAP) is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating PROVIGIL. If PROVIGIL is used adjunctively with CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary.

Cardiovascular System

Modafinil has not been evaluated in patients with a recent history of myocardial infarction or unstable angina, and such patients should be treated with caution.

In clinical studies of PROVIGIL, signs and symptoms including chest pain, palpitations, dyspnea and transient ischemic T-wave changes on ECG were observed in three subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that PROVIGIL tablets not be used in patients with a history of left ventricular hypertrophy or in patients with mitral valve prolapse who have experienced the mitral valve prolapse syndrome when previously receiving CNS stimulants. Such signs may include but are not limited to ischemic ECG changes, chest pain, or arrhythmia. If new onset of any of these symptoms occurs, consider cardiac evaluation.

Blood pressure monitoring in short-term (<3 months) controlled trials showed no clinically significant changes in mean systolic and diastolic blood pressure in patients receiving PROVIGIL as compared to placebo. However, a retrospective analysis of the use of antihypertensive medication in these studies showed that a greater proportion of patients on PROVIGIL required new or increased use of antihypertensive medications (2.4%) compared to patients on placebo (0.7%). The differential use was slightly larger when only studies in OSAHS were included, with 3.4% of patients on PROVIGIL and 1.1% of patients on placebo requiring such alterations in the use of antihypertensive medication. Increased monitoring of blood pressure may be appropriate in patients on PROVIGIL.

Patients Using Steroidal Contraceptives

The effectiveness of steroidal contraceptives may be reduced when used with PROVIGIL tablets and for one month after discontinuation of therapy (See **PRECAUTIONS, Drug Interactions**). Alternative or concomitant methods of contraception are recommended for patients treated with PROVIGIL tablets, and for one month after discontinuation of PROVIGIL.

Patients Using Cyclosporine

The blood levels of cyclosporine may be reduced when used with PROVIGIL (See **PRECAUTIONS, Drug Interactions**). Monitoring of circulating cyclosporine concentrations and appropriate dosage adjustment for cyclosporine should be considered when these drugs are used concomitantly.

Patients with Severe Hepatic Impairment

In patients with severe hepatic impairment, with or without cirrhosis (See **CLINICAL PHARMACOLOGY**), PROVIGIL should be administered at a reduced dose (See **DOSAGE AND ADMINISTRATION**).

Patients with Severe Renal Impairment

There is inadequate information to determine safety and efficacy of dosing in patients with severe renal impairment. (For pharmacokinetics in renal impairment, see **CLINICAL PHARMACOLOGY**.)

Elderly Patients

In elderly patients, elimination of modafinil and its metabolites may be reduced as a consequence of aging. Therefore, consideration should be given to the use of lower doses in this population. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe PROVIGIL.

PROVIGIL is indicated for patients who have abnormal levels of sleepiness. PROVIGIL has been shown to improve, but not eliminate this abnormal tendency to fall asleep. Therefore, patients should not alter their previous behavior with regard to potentially dangerous activities (e.g., driving, operating machinery) or other activities requiring appropriate levels of wakefulness, until and unless treatment with PROVIGIL has been shown to produce levels of wakefulness that permit such activities. Patients should be advised that PROVIGIL is not a replacement for sleep.

Patients should be informed that it may be critical that they continue to take their previously prescribed treatments (e.g., patients with OSAHS receiving CPAP should continue to do so).

Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking PROVIGIL. See Patient Information at the end of this labeling for the text of the leaflet provided for patients.

Patients should be advised to contact their physician if they experience chest pain, rash, depression, anxiety, or signs of psychosis or mania.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be cautioned regarding the potential increased risk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with PROVIGIL and for one month after discontinuation of therapy (See **Carcinogenesis, Mutagenesis, Impairment of Fertility** and **Pregnancy**).

Nursing

Patients should be advised to notify their physician if they are breast feeding an infant.

Concomitant Medication

Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, because of the potential for interactions between PROVIGIL and other drugs.

Alcohol

Patients should be advised that the use of PROVIGIL in combination with alcohol has not been studied. Patients should be advised that it is prudent to avoid alcohol while taking PROVIGIL.

Allergic Reactions

Patients should be advised to stop taking PROVIGIL and to notify their physician if they develop a rash, hives, mouth sores, blisters, peeling skin, trouble swallowing or breathing or a related allergic phenomenon.

Drug Interactions

CNS Active Drugs

Methylphenidate - In a single-dose study in healthy volunteers, simultaneous administration of modafinil (200 mg) with methylphenidate (40 mg) did not cause any significant alterations in the pharmacokinetics of either drug. However, the absorption of PROVIGIL may be delayed by approximately one hour when coadministered with methylphenidate.

In a multiple-dose, steady-state study in healthy volunteers, modafinil was administered once daily at 200 mg/day for 7 days followed by 400 mg/day for 21 days. Administration of methylphenidate (20 mg/day) during days 22-28 of modafinil treatment 8 hours after the daily dose of modafinil did not cause any significant alterations in the pharmacokinetics of modafinil.

Dextroamphetamine - In a single dose study in healthy volunteers, simultaneous administration of modafinil (200 mg) with dextroamphetamine (10 mg) did not cause any significant alterations in the pharmacokinetics of either drug. However, the absorption of PROVIGIL may be delayed by approximately one hour when coadministered with dextroamphetamine.

In a multiple-dose, steady-state study in healthy volunteers, modafinil was administered once daily at 200 mg/day for 7 days followed by 400 mg/day for 21 days. Administration of dextroamphetamine (20 mg/day) during days 22-28 of modafinil treatment 7 hours after the daily dose of modafinil did not cause any significant alterations in the pharmacokinetics of modafinil.

Clomipramine - The coadministration of a single dose of clomipramine (50 mg) on the first of three days of treatment with modafinil (200 mg/day) in healthy volunteers did not show an effect on the pharmacokinetics of either drug. However, one incident of increased levels of clomipramine and its active metabolite desmethylclomipramine has been reported in a patient with narcolepsy during treatment with modafinil.

Triazolam – In the drug interaction study between PROVIGIL and ethinyl estradiol (EE_2), on the same days as those for the plasma sampling for EE_2 pharmacokinetics, a single dose of triazolam (0.125 mg) was also administered. Mean C_{max} and $AUC_{0-\infty}$ of triazolam were decreased by 42% and 59%, respectively, and its elimination half-life was decreased by approximately an hour after the modafinil treatment.

Monoamine Oxidase (MAO) Inhibitors - Interaction studies with monoamine oxidase inhibitors have not been performed. Therefore, caution should be used when concomitantly administering MAO inhibitors and modafinil.

Other Drugs

Warfarin - There were no significant changes in the pharmacokinetic profiles of R- and S-warfarin in healthy subjects given a single dose of racemic warfarin (5 mg) following chronic administration of modafinil (200 mg/day for 7 days followed by 400 mg/day for 27 days) relative to the profiles in subjects given placebo. However, more frequent monitoring of prothrombin times/INR is advisable whenever PROVIGIL is coadministered with warfarin (See **CLINICAL PHARMACOLOGY, Pharmacokinetics,** Drug-Drug Interactions).

Ethinyl Estradiol - Administration of modafinil to female volunteers once daily at 200 mg/day for 7 days followed by 400 mg/day for 21 days resulted in a mean 11% decrease in C_{max} and 18% decrease in AUC_{0-24} of ethinyl estradiol (EE_2; 0.035 mg; administered orally with norgestimate). There was no apparent change in the elimination rate of ethinyl estradiol.

Cyclosporine - One case of an interaction between modafinil and cyclosporine, a substrate of CYP3A4, has been reported in a 41 year old woman who had undergone an organ transplant. After one month of administration of 200 mg/day of modafinil, cyclosporine blood levels were decreased by 50%. The interaction was postulated to be due to the increased metabolism of cyclosporine, since no other factor expected to affect the disposition of the drug had changed. Dosage adjustment for cyclosporine may be needed.

Potential Interactions with Drugs That Inhibit, Induce, or are Metabolized by Cytochrome P-450 Isoenzymes and Other Hepatic Enzymes

In in vitro studies using primary human hepatocyte cultures, modafinil was shown to slightly induce CYP1A2, CYP2B6 and CYP3A4 in a concentration-dependent manner. Although induction results based on in vitro experiments are not necessarily predictive of response in vivo, caution needs to be exercised when PROVIGIL is coadministered with drugs that depend on these three enzymes for their clearance. Specifically, lower blood levels of such drugs could result (See *Other Drugs*, Cyclosporine above).

The exposure of human hepatocytes to modafinil in vitro produced an apparent concentration-related suppression of expression of CYP2C9 activity suggesting that there is a potential for a metabolic interaction between modafinil and the substrates of this enzyme (e.g., S-warfarin and phenytoin). In a subsequent clinical study in healthy volunteers, chronic modafinil treatment did not show a significant effect on the single-dose pharmacokinetics of warfarin when compared to placebo (See **PRECAUTIONS, Drug Interactions,** Warfarin).

In vitro studies using human liver microsomes showed that modafinil reversibly inhibited CYP2C19 at pharmacologically relevant concentrations of modafinil. CYP2C19 is also reversibly inhibited, with similar potency, by a circulating metabolite, modafinil sulfone. Although the maximum plasma concentrations of modafinil sulfone are much lower than those of parent modafinil, the combined effect of both compounds could produce sustained partial inhibition of the enzyme. Drugs that are largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol, phenytoin (also via CYP2C9) or S-mephenytoin may have prolonged elimination upon coadministration with PROVIGIL and may require dosage reduction and monitoring for toxicity.

Tricyclic antidepressants - CYP2C19 also provides an ancillary pathway for the metabolism of certain tricyclic antidepressants (e.g., clomipramine and desipramine) that are primarily metabolized by CYP2D6. In tricyclic-treated patients deficient in CYP2D6 (i.e., those who are poor metabolizers of debrisoquine; 7-10% of the Caucasian population; similar or lower in other populations), the amount of metabolism by CYP2C19 may be substantially increased. PROVIGIL may cause elevation of the levels of the tricyclics in this subset of patients. Physicians should be aware that a reduction in the dose of tricyclic agents might be needed in these patients.

In addition, due to the partial involvement of CYP3A4 in the metabolic elimination of modafinil, coadministration of potent inducers of CYP3A4 (e.g., carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole) could alter the plasma levels of modafinil.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in which modafinil was administered in the diet to mice for 78 weeks and to rats for 104 weeks at doses of 6, 30, and 60 mg/kg/day. The highest dose studied is 1.5 (mouse) or 3 (rat) times greater than the recommended adult human daily dose of modafinil (200 mg) on a mg/m^2 basis. There was no evidence of tumorigenesis associated with modafinil administration in these studies. However, since the mouse study used an inadequate high dose that was not representative of a maximum tolerated dose, a subsequent carcinogenicity study was conducted in the Tg.AC transgenic mouse. Doses evaluated in the Tg.AC assay were 125, 250, and 500 mg/kg/day, administered dermally. There was no evidence of tumorigenicity associated with modafinil administration; however, this dermal model may not adequately assess the carcinogenic potential of an orally administered drug.

Mutagenesis

Modafinil demonstrated no evidence of mutagenic or clastogenic potential in a series of in vitro (i.e., bacterial reverse mutation assay, mouse lymphoma tk assay, chromosomal aberration assay in human lymphocytes, cell transformation assay in BALB/3T3 mouse embryo cells) assays in the absence or presence of metabolic activation, or in vivo (mouse bone marrow micronucleus) assays. Modafinil was also negative in the unscheduled DNA synthesis assay in rat hepatocytes.

Impairment of Fertility

Oral administration of modafinil (doses of up to 480 mg/kg/day) to male and female rats prior to and throughout mating, and continuing in females through day 7 of gestation produced an increase in the time to mate at the highest dose; no effects were observed on other fertility or reproductive parameters. The no-effect dose of 240 mg/kg/day was associated with a plasma modafinil exposure (AUC) approximately equal to that in humans at the recommended dose of 200 mg.

Pregnancy

Pregnancy Category C: In studies conducted in rats and rabbits, developmental toxicity was observed at clinically relevant exposures.

Modafinil (50, 100, or 200 mg/kg/day) administered orally to pregnant rats throughout the period of organogenesis caused, in the absence of maternal toxicity, an increase in resorptions and an increased incidence of visceral and skeletal variations in the offspring at the highest dose. The higher no-effect dose for rat embryofetal developmental toxicity was associated with a plasma modafinil exposure approximately 0.5 times the AUC in humans at the recommended daily dose (RHD) of 200 mg. However, in a subsequent study of up to 480 mg/kg/day (plasma modafinil exposure approximately 2 times the AUC in humans at the RHD) no adverse effects on embryofetal development were observed.

Modafinil administered orally to pregnant rabbits throughout the period of organogenesis at doses of 45, 90, and 180 mg/kg/day increased the incidences of fetal structural alterations and embryofetal death at the highest dose. The highest no-effect dose for developmental toxicity was associated with a plasma modafinil AUC approximately equal to the AUC in humans at the RHD.

Oral administration of armodafinil (the R-enantiomer of modafinil; 60, 200, or 600 mg/kg/day) to pregnant rats throughout the period of organogenesis resulted in increased incidences of fetal visceral and skeletal variations at the intermediate dose or greater and decreased fetal body weights at the highest dose. The no-effect dose for rat embryofetal developmental toxicity was associated with a plasma armodafinil exposure (AUC) approximately one-tenth times the AUC for armodafinil in humans treated with modafinil at the RHD.

Modafinil administration to rats throughout gestation and lactation at oral doses of up to 200 mg/kg/day resulted in decreased viability in the offspring at doses greater than 20 mg/kg/day (plasma modafinil AUC approximately 0.1 times the AUC in humans at the RHD). No effects on postnatal developmental and neurobehavioral parameters were observed in surviving offspring.

There are no adequate and well-controlled studies in pregnant women. Two cases of intrauterine growth retardation and one case of spontaneous abortion have been reported in association with armodafinil and modafinil. Although the pharmacology of modafinil and armodafinil is not identical to that of the sympathomimetic amines, they do share some pharmacologic properties with this class. Certain of these drugs have been associated with intrauterine growth retardation and spontaneous abortions. Whether the cases reported are drug-related is unknown.

Modafinil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of modafinil on labor and delivery in humans has not been systematically investigated.

Nursing Mothers

It is not known whether modafinil or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PROVIGIL tablets are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients, below age 16, have not been established. Serious skin rashes, including erythema multiforme major (EMM) and Stevens-Johnson Syndrome (SJS) have been associated with modafinil use in pediatric patients (see **WARNINGS, Serious Rash, including Stevens-Johnson Syndrome**).

In a controlled 6-week study, 165 pediatric patients (aged 5-17 years) with narcolepsy were treated with modafinil (n=123), or placebo (n=42). There were no statistically significant differences favoring modafinil over placebo in prolonging sleep latency as measured by MSLT, or in perceptions of sleepiness as determined by the clinical global impression-clinician scale (CGI-C).

In the controlled and open-label clinical studies, treatment emergent adverse events of the psychiatric and nervous system included Tourette's syndrome, insomnia, hostility, increased cataplexy, increased hypnagogic hallucinations and suicidal ideation. Transient leukopenia, which resolved without medical intervention, was also observed. In the controlled clinical study, 3 of 38 girls, ages 12 or older, treated with modafinil experienced dysmenorrhea compared to 0 of 10 girls who received placebo.

Geriatric Use

Safety and effectiveness in individuals above 65 years of age have not been established. Experience in a limited number of patients who were greater than 65 years of age in clinical trials showed an incidence of adverse experiences similar to other age groups.

ADVERSE REACTIONS

Modafinil has been evaluated for safety in over 3500 patients, of whom more than 2000 patients with excessive sleepiness associated with primary disorders of sleep and wakefulness were given at least one dose of modafinil. In clinical trials, modafinil has been found to be generally well tolerated and most adverse experiences were mild to moderate.

The most commonly observed adverse events (≥5%) associated with the use of PROVIGIL more frequently than placebo-treated patients in the placebo-controlled clinical studies in primary disorders of sleep and wakefulness were headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia. The adverse event profile was similar across these studies.

In the placebo-controlled clinical trials, 74 of the 934 patients (8%) who received PROVIGIL discontinued due to an adverse experience compared to 3% of patients that received placebo.

The most frequent reasons for discontinuation that occurred at a higher rate for PROVIGIL than placebo patients were headache (2%), nausea, anxiety, dizziness, insomnia, chest pain and nervousness (each <1%). In a Canadian clinical trial, a 35 year old obese narcoleptic male with a prior history of syncopal episodes experienced a 9-second episode of asystole after 27 days of modafinil treatment (300 mg/day in divided doses).

Incidence in Controlled Trials

The following table (Table 3) presents the adverse experiences that occurred at a rate of 1% or more and were more frequent in adult patients treated with PROVIGIL than in placebo-treated patients in the principal, placebo-controlled clinical trials.

The prescriber should be aware that the figures provided below cannot be used to predict the frequency of adverse experiences in the course of usual medical practice, where patient characteristics and other factors may differ from those occurring during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. Review of these frequencies, however, provides prescribers with a basis to estimate the relative contribution of drug and non-drug factors to the incidence of adverse events in the population studied.

PROVIGIL® (modafinil) Tablets [C-IV]

Table 3. Incidence Of Treatment-Emergent Adverse Experiences In Parallel-Group, Placebo-Controlled Clinical Trials[1] With PROVIGIL In Adults With Narcolepsy, OSAHS, and SWSD (200mg, 300mg and 400mg)*

Body System	Preferred Term	Modafinil (n = 934)	Placebo (n = 567)
Body as a Whole	Headache	34%	23%
	Back Pain	6%	5%
	Flu Syndrome	4%	3%
	Chest Pain	3%	1%
	Chills	1%	0%
	Neck Rigidity	1%	0%
Cardiovascular	Hypertension	3%	1%
	Tachycardia	2%	1%
	Palpitation	2%	1%
	Vasodilatation	2%	0%
Digestive	Nausea	11%	3%
	Diarrhea	6%	5%
	Dyspepsia	5%	4%
	Dry Mouth	4%	2%
	Anorexia	4%	1%
	Constipation	2%	1%
	Abnormal Liver Function[2]	2%	1%
	Flatulence	1%	0%
	Mouth Ulceration	1%	0%
	Thirst	1%	0%
Hemic/Lymphatic	Eosinophilia	1%	0%
Metabolic/Nutritional	Edema	1%	0%
Nervous	Nervousness	7%	3%
	Insomnia	5%	1%
	Anxiety	5%	1%
	Dizziness	5%	4%
	Depression	2%	1%
	Parasthesia	2%	0%
	Somnolence	2%	1%
	Hypertonia	1%	0%
	Dyskinesia[3]	1%	0%
	Hyperkinesia	1%	0%
	Agitation	1%	0%
	Confusion	1%	0%
	Tremor	1%	0%
	Emotional Lability	1%	0%
	Vertigo	1%	0%
Respiratory	Rhinitis	7%	6%
	Pharyngitis	4%	2%
	Lung Disorder	2%	1%
	Epistaxis	1%	0%
	Asthma	1%	0%
Skin/Appendages	Sweating	1%	0%
	Herpes Simplex	1%	0%
Special Senses	Amblyopia	1%	0%
	Abnormal Vision	1%	0%
	Taste Perversion	1%	0%
	Eye Pain	1%	0%
Urogenital	Urine Abnormality	1%	0%
	Hematuria	1%	0%
	Pyuria	1%	0%

*Six double-blind, placebo-controlled clinical studies in narcolepsy, OSAHS, and SWSD.

[1] Events reported by at least 1% of patients treated with PROVIGIL that were more frequent than in the placebo group are included; incidence is rounded to the nearest 1%. The adverse experience terminology is coded using a standard modified COSTART Dictionary.

Events for which the PROVIGIL incidence was at least 1%, but equal to or less than placebo are not listed in the table. These events included the following: infection, pain, accidental injury, abdominal pain, hypothermia, allergic reaction, asthenia, fever, viral infection, neck pain, migraine, abnormal electrocardiogram, hypotension, tooth disorder, vomiting, periodontal abscess, increased appetite, ecchymosis, hyperglycemia, peripheral edema, weight loss, weight gain, myalgia, leg cramps, arthritis, cataplexy, thinking abnormality, sleep disorder, increased cough, sinusitis, dyspnea, bronchitis, rash, conjunctivitis, ear pain, dysmenorrhea[4], urinary tract infection.

[2] Elevated liver enzymes.

[3] Oro-facial dyskinesias.

[4] Incidence adjusted for gender.

Dose Dependency of Adverse Events

In the adult placebo-controlled clinical trials which compared doses of 200, 300, and 400 mg/day of PROVIGIL and placebo, the only adverse events that were clearly dose related were headache and anxiety.

Vital Sign Changes

While there was no consistent change in mean values of heart rate or systolic and diastolic blood pressure, the requirement for antihypertensive medication was slightly greater in patients on PROVIGIL compared to placebo (See **PRECAUTIONS**).

Weight Changes

There were no clinically significant differences in body weight change in patients treated with PROVIGIL compared to placebo-treated patients in the placebo-controlled clinical trials.

Laboratory Changes

Clinical chemistry, hematology, and urinalysis parameters were monitored in Phase 1, 2, and 3 studies. In these studies, mean plasma levels of gamma glutamyltransferase (GGT) and alkaline phosphatase (AP) were found to be higher following administration of PROVIGIL, but not placebo. Few subjects, however, had GGT or AP elevations outside of the normal range. Shifts to higher, but not clinically significantly abnormal, GGT and AP values appeared to increase with time in the population treated with PROVIGIL in the Phase 3 clinical trials. No differences were apparent in alanine aminotransferase, aspartate aminotransferase, total protein, albumin, or total bilirubin.

ECG Changes

No treatment-emergent pattern of ECG abnormalities was found in placebo-controlled clinical trials following administration of PROVIGIL.

Postmarketing Reports

The following adverse reactions have been identified during post-approval use of PROVIGIL. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to

include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of the reporting, or (3) strength of causal connection to PROVIGIL.

Hematologic: agranulocytosis

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Modafinil (PROVIGIL) is listed in Schedule IV of the Controlled Substances Act.

Abuse Potential and Dependence

In addition to its wakefulness-promoting effect and increased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and euphoric effects, alterations in mood, perception, thinking and feelings typical of other CNS stimulants. In in vitro binding studies, modafinil binds to the dopamine reuptake site and causes an increase in extracellular dopamine, but no increase in dopamine release. Modafinil is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine. In some studies, modafinil was also partially discriminated as stimulant-like. Physicians should follow patients closely, especially those with a history of drug and/or stimulant (e.g., methylphenidate, amphetamine, or cocaine) abuse. Patients should be observed for signs of misuse or abuse (e.g., incrementation of doses or drug-seeking behavior).

The abuse potential of modafinil (200, 400, and 800 mg) was assessed relative to methylphenidate (45 and 90 mg) in an inpatient study in individuals experienced with drugs of abuse. Results from this clinical study demonstrated that modafinil produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate).

Withdrawal

The effects of modafinil withdrawal were monitored following 9 weeks of modafinil use in one US Phase 3 controlled clinical trial. No specific symptoms of withdrawal were observed during 14 days of observation, although sleepiness returned in narcoleptic patients.

OVERDOSAGE

Human Experience

In clinical trials, a total of 151 protocol-specified doses ranging from 1000 to 1600 mg/day (5 to 8 times the recommended daily dose of 200 mg) have been administered to 32 subjects, including 13 subjects who received doses of 1000 or 1200 mg/day for 7 to 21 consecutive days. In addition, several intentional acute overdoses occurred; the two largest being 4500 mg and 4000 mg taken by two subjects participating in foreign depression studies. None of these study subjects experienced any unexpected or life-threatening effects. Adverse experiences that were reported at these doses included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. Other observed high-dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea and decreased prothrombin time.

From post-marketing experience, there have been no reports of fatal overdoses involving modafinil alone (doses up to 12 grams). Overdoses involving multiple drugs, including modafinil, have resulted in fatal outcomes. Symptoms most often accompanying modafinil overdose, alone or in combination with other drugs have included: insomnia; central nervous system symptoms such as restlessness, disorientation, confusion, excitation and hallucination; digestive changes such as nausea and diarrhea; and cardiovascular changes such as tachycardia, bradycardia, hypertension and chest pain.

Cases of accidental ingestion/overdose have been reported in children as young as 11 months of age. The highest reported accidental ingestion on a mg/kg basis occurred in a three-year-old boy who ingested 800-1000 mg (50-63 mg/kg) of modafinil. The child remained stable. The symptoms associated with overdose in children were similar to those observed in adults.

Overdose Management

No specific antidote to the toxic effects of modafinil overdose has been identified to date. Such overdoses should be managed with primarily supportive care, including cardiovascular monitoring. If there are no contraindications, induced emesis or gastric lavage should be considered. There are no data to suggest the utility of dialysis or urinary acidification or alkalinization in enhancing drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.

DOSAGE AND ADMINISTRATION

The recommended dose of PROVIGIL is 200 mg given once a day.

For patients with narcolepsy and OSAHS, PROVIGIL should be taken as a single dose in the morning.

For patients with SWSD, PROVIGIL should be taken approximately 1 hour prior to the start of their work shift.

Doses up to 400 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond that of the 200 mg dose (See **CLINICAL PHARMACOLOGY** and **CLINICAL TRIALS**).

General Considerations

Dosage adjustment should be considered for concomitant medications that are substrates for CYP3A4, such as triazolam and cyclosporine (See **PRECAUTIONS, Drug Interactions**).

Drugs that are largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol, phenytoin (also via CYP2C9) or S-mephenytoin may have prolonged elimination upon coadministration with PROVIGIL and may require dosage reduction and monitoring for toxicity.

In patients with severe hepatic impairment, the dose of PROVIGIL should be reduced to one-half of that recommended for patients with normal hepatic function (See **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

There is inadequate information to determine safety and efficacy of dosing in patients with severe renal impairment (See **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

In elderly patients, elimination of PROVIGIL and its metabolites may be reduced as a consequence of aging. Therefore, consideration should be given to the use of lower doses in this population (See **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

HOW SUPPLIED:

PROVIGIL® (modafinil) Tablets

100 mg Each capsule-shaped, white, uncoated tablet is debossed with "PROVIGIL" on one side and "100 MG" on the other. NDC 63459-101-01 – Bottles of 100

200 mg Each capsule-shaped, white, scored, uncoated tablet is debossed with "PROVIGIL" on one side and "200 MG" on the other. NDC 63459-201-01 – Bottles of 100

Store at 20° - 25° C (68° - 77° F).

Manufactured for:
Cephalon, Inc.
Frazer, PA 19355

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PROV-010

PATIENT INFORMATION
PROVIGIL® (pro-vij-el) Tablets [C-IV]
Generic name: modafinil

Read the Patient Information that comes with PROVIGIL before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment.

What is the most important information I should know about PROVIGIL?

1. PROVIGIL may cause you to have a serious rash or a serious allergic reaction. Stop PROVIGIL and call your doctor right away or get emergency treatment if you have any of the following:

- skin rash, hives, sores in your mouth, or your skin blisters and peels
- swelling of your face, eyes, lips, tongue, or throat
- trouble swallowing or breathing
- hoarse voice

2. PROVIGIL is not approved for use in children.

PROVIGIL® (modafinil) Tablets [C-IV]

What is PROVIGIL?

PROVIGIL is a prescription medicine used to improve awakeness in adults who are very sleepy due to one of the following diagnosed sleep problems:

- shift work sleep disorder (SWSD)
- obstructive sleep apnea/hypopnea syndrome (OSAHS). PROVIGIL is used along with other medical treatments for this sleep problem. PROVIGIL is not a replacement for your CPAP machine. It is important that you continue to use your CPAP machine while sleeping.
- narcolepsy

You should be diagnosed with one of these sleep disorders before taking PROVIGIL. Sleepiness can be a symptom of other medical conditions that need to be treated.

- PROVIGIL will not cure the above sleep disorders. PROVIGIL may help the sleepiness caused by these conditions, but it may not stop all your sleepiness.
- PROVIGIL does not take the place of getting enough sleep.
- Follow your doctor's advice about good sleep habits and using other treatments.

PROVIGIL is a federally controlled substance (C-IV) because it can be abused or lead to dependence. Keep PROVIGIL in a safe place to prevent misuse and abuse. Selling or giving away PROVIGIL may harm others, and is against the law. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines or street drugs.

Who should not take PROVIGIL?

Do not take PROVIGIL if you:

- are allergic to any of its ingredients. The active ingredient is modafinil. See the end of this leaflet for a complete list of ingredients.
- have had a rash or allergic reaction to armodafinil, the active ingredient in NUVIGIL™, because these medicines are very similar.

PROVIGIL is not approved for use in children.

What should I tell my doctor before starting PROVIGIL?

Tell your doctor about all of your health conditions including, if you:

- have a history of mental health problems
- have heart problems or had a heart attack
- have high blood pressure
- have liver or kidney problems
- have a history of drug or alcohol abuse or addiction
- have ever had a mental problem called psychosis.
- are pregnant or planning to become pregnant. It is not known if PROVIGIL may harm your unborn baby.
- are breastfeeding. It is not known if PROVIGIL passes into your milk or if it can harm your baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. PROVIGIL and many other medicines can interact with each other, sometimes causing side effects. PROVIGIL may affect the way other medicines work, and other medicines may affect how PROVIGIL works. Especially, tell your doctor if you use a hormonal birth control method. PROVIGIL can affect hormonal birth control methods. Hormonal birth control methods include pills, shots, implants, patches, vaginal rings, and intrauterine devices (IUDs). Women who use hormonal birth control with PROVIGIL may have a higher chance for getting pregnant while taking PROVIGIL, and for one month after stopping PROVIGIL. Talk to your doctor about birth control methods that are right for you while using PROVIGIL.

Keep a list of all the medicines you take. Your doctor or pharmacist will tell you if it is safe to take PROVIGIL and other medicines together. Do not take other medicines with PROVIGIL unless your doctor has told you it is okay.

How should I take PROVIGIL?

- Take PROVIGIL exactly as prescribed by your doctor. Your doctor will prescribe the dose of PROVIGIL that is right for you. Do not change your dose of PROVIGIL without talking to your doctor. Do not take more PROVIGIL than prescribed.
- Your doctor will tell you the right time of day to take PROVIGIL.
  - Patients with narcolepsy or OSAHS usually take one dose of PROVIGIL every day in the morning.
  - Patients with SWSD usually take PROVIGIL about 1 hour before their work shift. Do not change the time of day you take PROVIGIL unless you have talked to your doctor. If you take PROVIGIL too close to your bedtime, you may find it harder to go to sleep.
  - You can take PROVIGIL with or without food.
- If you take more than your prescribed dose or overdose, call your doctor or poison control center right away.

What should I avoid while taking PROVIGIL?

- Do not drive a car or do other dangerous activities until you know how PROVIGIL affects you. People with sleep disorders should always be careful about doing things that could be dangerous. Do not change your daily habits until your doctor tells you it is okay.
- Avoid drinking alcohol.

What are the possible side effects of PROVIGIL?

PROVIGIL may cause serious side effects. Call your doctor or get emergency help if you get any of the following:

- **a serious rash or serious allergic reaction.** (See, "What is the most important information I should know about PROVIGIL.")
- **mental (psychiatric) symptoms.** Symptoms include depression, anxiety, hallucinations, mania, thoughts of suicide or other mental problems.
- **heart problems including chest pain**

The most common side effects of PROVIGIL are headache, nausea, nervousness, stuffy nose, diarrhea, back pain, anxiety, trouble sleeping, dizziness, and upset stomach.

PROVIGIL may cause allergic reactions. If you get a rash, hives or other allergic reaction, stop taking PROVIGIL and call your doctor right away.

If you have either of the problems listed below or any other serious side effects while taking PROVIGIL stop taking PROVIGIL and call your doctor or get emergency help:

- chest pain.
- mental problems.

Some effects of PROVIGIL on the brain are the same as other medicines called "stimulants". These effects may lead to abuse or dependence on PROVIGIL. Before starting PROVIGIL, tell your doctor if you have ever abused drugs, including other stimulant medicines.

Tell your doctor if you get any side effect that bothers you or that does not go away while taking PROVIGIL.

These are not all the side effects of PROVIGIL. For more information, ask your doctor or pharmacist.

How should I store PROVIGIL?

- Store PROVIGIL at room temperature, 68° to 77° F (20° to 25° C).
- Keep PROVIGIL and all medicines out of the reach of children.

General information about PROVIGIL

Medicines are sometimes prescribed for conditions that are not listed in patient information leaflets. Do not use PROVIGIL for a condition for which it was not prescribed. **Do not give PROVIGIL to other people, even if they have the same symptoms you have. It may harm them and it is against the law.**

This leaflet summarizes the most important information about PROVIGIL. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about PROVIGIL that is written for health professionals. For more information, please call 1-800-896-5855, or go to www.PROVIGIL.com.

What are the ingredients in PROVIGIL?

Active Ingredient: modafinil

Inactive Ingredients: croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose, povidone, and pregelatinized starch.

Rx Only

August 2007
Manufactured for:
Cephalon, Inc. Frazer, PA 19355

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Cephalon deliver more.

PRO1046 Aug 2007

PRESCRIBING INFORMATION

DEXEDRINE®

brand of

dextroamphetamine sulfate

Spansule® capsules

brand of sustained release capsules

and Tablets

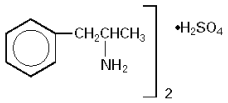
WARNING

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE AND MUST BE AVOIDED. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS, AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

DESCRIPTION

Dexedrine (dextroamphetamine sulfate) is the dextro isomer of the compound *d,l*-amphetamine sulfate, a sympathomimetic amine of the amphetamine group. Chemically, dextroamphetamine is *d*-alpha-methylphenethylamine, and is present in all forms of *Dexedrine* as the neutral sulfate.

Structural Formula:



Spansule® capsules

Each *Spansule* sustained release capsule is so prepared that an initial dose is released promptly and the remaining medication is released gradually over a prolonged period.

Each capsule, with brown cap and clear body, contains dextroamphetamine sulfate. The 5 mg capsule is imprinted 5 mg and 3512 on the brown cap and is imprinted 5 mg and SB on the clear body. The 10 mg capsule is imprinted 10 mg — 3513 — on the brown cap and is imprinted 10 mg — SB — on the clear body. The 15 mg capsule is imprinted 15 mg and 3514 on the brown cap and is imprinted 15 mg and SB on the clear body. A narrow bar appears above and below 15 mg and 3514. Product reformulation in 1996 has caused a minor change in the color of the time-released pellets within each capsule. Inactive ingredients now consist of cetyl alcohol, D&C Yellow No. 10, dibutyl sebacate, ethylcellulose, FD&C Blue No. 1, FD&C Blue No. 1 aluminum lake, FD&C Red No. 40, FD&C Yellow No. 6, gelatin, hydroxypropyl methylcellulose, propylene glycol, povidone, silicon dioxide, sodium lauryl sulfate, sugar spheres and trace amounts of other inactive ingredients.

Tablets

Each triangular, orange, scored tablet is debossed SKF and E19 and contains dextroamphetamine sulfate, 5 mg. Inactive ingredients consist of calcium sulfate, FD&C Yellow No. 5 (tartrazine), FD&C Yellow No. 6, gelatin, lactose, mineral oil, starch, stearic acid, sucrose, talc and trace amounts of other inactive ingredients.

CLINICAL PHARMACOLOGY

Amphetamines are non-catecholamine, sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevations of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action.

There is neither specific evidence which clearly establishes the mechanism whereby amphetamines produce mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

Dexedrine (dextroamphetamine sulfate) *Spansule* capsules are formulated to release the active drug substance *in vivo* in a more gradual fashion than the standard formulation, as demonstrated by blood levels. The formulation has not been shown superior in effectiveness over the same dosage of the standard, noncontrolled-release formulations given in divided doses.

Pharmacokinetics

The pharmacokinetics of the tablet and sustained release capsule were compared in 12 healthy subjects. The extent of bioavailability of the sustained release capsule was similar compared to the immediate release tablet. Following administration of three 5 mg tablets, average maximal dextroamphetamine plasma concentrations (C_{max}) of 36.6 ng/mL were achieved at approximately 3 hours. Following administration of one 15 mg sustained release capsule, maximal dextroamphetamine plasma concentrations were obtained approximately 8 hours after dosing. The average C_{max} was 23.5 ng/mL. The average plasma $T_{1/2}$ was similar for both the tablet and sustained release capsule and was approximately 12 hours.

In 12 healthy subjects, the rate and extent of dextroamphetamine absorption were similar following administration of the sustained released capsule formulation in the fed (58 to 75 gm fat) and fasted state.

INDICATIONS AND USAGE

Dexedrine (dextroamphetamine sulfate) is indicated:

1. **In Narcolepsy.**
2. **In Attention Deficit Disorder with Hyperactivity,** as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in pediatric patients (ages 3 years to 16 years) with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

CONTRAINDICATIONS

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.

Agitated states.

Patients with a history of drug abuse.

During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

PRECAUTIONS

General: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension.

The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

The tablets contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Information for Patients: Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.

Drug Interactions

Acidifying agents—Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, fruit juices, etc.) lower absorption of amphetamines. Urinary acidifying agents (ammonium chloride, sodium acid phosphate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.

Adrenergic blockers—Adrenergic blockers are inhibited by amphetamines.

Alkalinizing agents—Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.

Antidepressants, tricyclic—Amphetamines may enhance the activity of tricyclic or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

MAO inhibitors—MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of neurological toxic effects and malignant hyperpyrexia can occur, sometimes with fatal results.

Antihistamines—Amphetamines may counteract the sedative effect of antihistamines.

Antihypertensives—Amphetamines may antagonize the hypotensive effects of antihypertensives.

Chlorpromazine—Chlorpromazine blocks dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning.

Ethosuximide—Amphetamines may delay intestinal absorption of ethosuximide.

Haloperidol—Haloperidol blocks dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines.

Lithium carbonate—The stimulatory effects of amphetamines may be inhibited by lithium carbonate.

Meperidine—Amphetamines potentiate the analgesic effect of meperidine.

Methenamine therapy—Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy.

Norepinephrine—Amphetamines enhance the adrenergic effect of norepinephrine.

Phenobarbital—Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.

Phenytoin—Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.

Propoxyphene—In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.

Veratrum alkaloids—Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions

- Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening.
- Amphetamines may interfere with urinary steroid determinations.

Carcinogenesis/Mutagenesis: Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of Dexedrine (dextroamphetamine sulfate) have not been performed.

Pregnancy—Teratogenic Effects: Pregnancy Category C. *Dexedrine* has been shown to have embryotoxic and teratogenic effects when administered to A/Jax mice and C57BL mice in doses approximately 41 times the maximum human dose. Embryotoxic effects were not seen in New Zealand white rabbits given the drug in doses 7 times the human dose nor in rats given 12.5 times the maximum human dose. While there are no adequate and well-controlled studies in pregnant women, there has been one report of severe congenital bony deformity, tracheoesophageal fistula, and anal atresia (Vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. *Dexedrine* should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

(continued)

Nursing Mothers: Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

Pediatric Use: Long-term effects of amphetamines in pediatric patients have not been well established.

Amphetamines are not recommended for use in pediatric patients under 3 years of age with Attention Deficit Disorder with Hyperactivity described under INDICATIONS AND USAGE.

Clinical experience suggests that in psychotic children, administration of amphetamines may exacerbate symptoms of behavior disturbance and thought disorder.

Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications.

Data are inadequate to determine whether chronic administration of amphetamines may be associated with growth inhibition; therefore, growth should be monitored during treatment.

Drug treatment is not indicated in all cases of Attention Deficit Disorder with Hyperactivity and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe amphetamines should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with amphetamines is usually not indicated.

ADVERSE REACTIONS

Cardiovascular: Palpitations, tachycardia, elevation of blood pressure. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses (rare), overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome.

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects.

Allergic: Urticaria.

Endocrine: Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE

Dextroamphetamine sulfate is a Schedule II controlled substance.

Amphetamines have been extensively abused. Tolerance, extreme psychological dependence and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG.

Manifestations of chronic intoxication with amphetamines include severe dermatoses, marked insomnia, irritability, hyperactivity and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. This is rare with oral amphetamines.

OVERDOSAGE

Individual patient response to amphetamines varies widely. While toxic symptoms occasionally occur as an idiosyncrasy at doses as low as 2 mg, they are rare with doses of less than 15 mg; 30 mg can produce severe reactions, yet doses of 400 to 500 mg are not necessarily fatal.

In rats, the oral LD_{50} of dextroamphetamine sulfate is 96.8 mg/kg.

Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rhabdomyolysis, rapid respiration, hyperpyrexia, confusion, assaultiveness, hallucinations, panic states.

Fatigue and depression usually follow the central stimulation.

Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

TREATMENT—Consult with a Certified Poison Control Center for up-to-date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic, and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute, severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine (Regitine®, CIBA) has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved.

Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

Since much of the *Spansule* capsule medication is coated for gradual release, therapy directed at reversing the effects of the ingested drug and at supporting the patient should be continued for as long as overdosage symptoms remain. Saline cathartics are useful for hastening the evacuation of pellets that have not already released medication.

DOSAGE AND ADMINISTRATION

Amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening doses—particularly with the *Spansule* capsule form—should be avoided because of the resulting insomnia.

Narcolepsy: Usual dose 5 to 60 mg per day in divided doses, depending on the individual patient response.

Narcolepsy seldom occurs in children under 12 years of age; however, when it does, Dexedrine (dextroamphetamine sulfate) may be used. The suggested initial dose for patients aged 6 to 12 is 5 mg daily; daily dose may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg daily; daily dosage may be raised in increments of 10 mg at weekly intervals until optimal response is obtained. If bothersome adverse reactions appear (e.g., insomnia or anorexia), dosage should be reduced. *Spansule* capsules may be used for once-a-day dosage wherever appropriate. With tablets, give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

Attention Deficit Disorder with Hyperactivity: Not recommended for pediatric patients under 3 years of age.

In pediatric patients from 3 to 5 years of age, start with 2.5 mg daily, by tablet; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained.

In pediatric patients 6 years of age and older, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg per day.

Spansule capsules may be used for once-a-day dosage wherever appropriate.

With tablets, give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

HOW SUPPLIED

***Dexedrine* Spansule capsules:** Each capsule, with brown cap and clear body, contains dextroamphetamine sulfate. The 5 mg capsule is imprinted 5 mg and 3512 on the brown cap and is imprinted 5 mg and SB on the clear body. The 10 mg capsule is imprinted 10 mg — 3513 — on the brown cap and is imprinted 10 mg — SB — on the clear body. The 15 mg capsule is imprinted 15 mg and 3514 on the brown cap and is imprinted 15 mg and SB on the clear body. A narrow bar appears above and below 15 mg and 3514. Available: 5 mg, 10 mg, and 15 mg in bottles of 100.

Store at controlled room temperature between 20° and 25°C (68° and 77°F) [see USP]. Dispense in a tight, light-resistant container.

5 mg 100's: NDC 0007-3512-20

10 mg 100's: NDC 0007-3513-20

15 mg 100's: NDC 0007-3514-20

Dexedrine Spansule capsules are manufactured by **International Processing Corporation**, Winchester, KY 40391.

Dexedrine (dextroamphetamine sulfate) Tablets: Triangular, orange, scored, debossed SKF and E19. Available: 5 mg in bottles of 100.

Store between 15° and 30°C (59° and 86°F). Dispense in a tight, light-resistant container.

5 mg 100's: NDC 0007-3519-20

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℞only

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Appendix B

Inclusion and exclusion criteria.

Inclusion criteria

Volunteers were included if they were members of the U.S. Army active duty, Reserve, National Guard, Department of the Army civilians, or contract UH-60 rated rotary wing pilots. Eligible participants included both men and women (military and civilian) between the ages of 19-50 years. In order to participate in the study, military personnel had to have their Unit Commander's approval. Volunteers were taken on a "first come, first served" basis. No attempt was made to assign equal numbers of males and females to each drug condition.

Exclusion criteria

Potential volunteers were excluded from the study if they were not current in the UH60 Black Hawk helicopter. In addition, they were excluded if they had any history or currently active condition of any of the following: HIV, Hepatitis B or C (acute state), cardiovascular disease (to include mitral valve prolapse: a specific contraindication for modafinil use), cardiac enlargement or heart murmur (other than functional murmur), high blood pressure (to include a resting blood pressure > 140/90 during the screening visit that does not decrease on a second reading taken at least 15 minutes later in the screening visit), gastrointestinal disease, hepatosplenomegaly, abnormalities in kidney or liver function, respiratory disease, asthma, renal disease, history of serious allergic reactions (especially to dextroamphetamine and modafinil or any of their components), hematological disorders, cancer, immunological dysfunction, endocrine or metabolic disorders, serious dermatologic disorders, prostate enlargement, adverse drug reactions, narrow angle glaucoma, any neurological disorder or damage such as a loss of consciousness concurrent with concussion, head injury, history of epilepsy, a history of sleep disorders including narcolepsy, sleep apnea, nocturnal myoclonus, sleep/wake cycle disorders, psychiatric or mental health disorder (to include a history of mental health or in-patient psychiatric therapy), presence or history of depression, anxiety or panic disorder, and use of antidepressants or benzodiazepines. Volunteers were also excluded from the study if they had a history of using the stimulant ephedra or dietary supplements containing ephedra within the past three years or past or current use of licit or illicit psychoactive drugs. The rationale for the preceding exclusionary criteria was based on one or both of the following: (1) the disease or condition is known to alter sleep; and/or (2) the disease or condition puts the subject at additional risk due to study medication administration. For potential volunteers with pre-existing conditions, they could be excluded from the study at the discretion of the examining study physician, depending on the severity of past conditions and possible continuation into the present.

Prior participation in another drug study was not necessarily a criterion for exclusion, presuming that an adequate wash-out phase has occurred between the two studies. Exclusionary criteria also included recent history of caffeine use in excess of 600 mg per day on average, herbal supplements or remedies containing caffeine, or reported use of any drug which, based on its

known pharmacokinetics, would not have been cleared from the body by 48 hours prior to participation (determined on a case-by-case basis depending on type of drug and when used).

Pregnant individuals or those breast feeding were excluded from the study due to potential or unforeseen adverse effects on the fetus or infant from the stimulant medications. Modafinil and dextroamphetamine are classified as Pregnancy Category C. Pharmacologic substances classified as Pregnancy Category C indicate a) that animal studies have shown an adverse effect in the fetus but there are no adequate studies in humans; b) the benefits for the use of the drug in pregnancy may be acceptable (in some cases) despite its potential risks; or c) there are no animal reproduction studies and no adequate studies in humans. Consequently, women who were pregnant or were breast feeding were excluded from participation in the study. It was anticipated that all study medications had cleared from the body prior to release from the study; nonetheless, volunteers were advised to consult with their regular physician before becoming pregnant after participation in the study since the study compounds are known to have effects on the fetus and embryo. During the initial informed consent procedures volunteers were advised that the study compound can reduce the effectiveness of contraceptive drugs, and that to avoid becoming pregnant, they should either abstain from sexual relations or practice a barrier or other non-chemical method of birth control. Volunteers were also be advised that, except for surgical removal of the uterus, birth control methods such as the use of condoms, diaphragm, cervical cap, or IUD in preventing pregnancy was not 100% effective.

Aviators are routinely tested for HIV, Hepatitis B, or Hepatitis C. They are not allowed to remain on flight status with any of these conditions thus, it was unnecessary to test for these conditions in this population. Similarly, a history of illicit drug use disqualifies candidates from flight duty. Additionally, aviators are routinely tested for illicit drug use. They are not allowed to take any medications (prescribed, over the counter, or health food supplements) without explicit, written permission from a flight surgeon to include documentation in their medical records. Thus, drug screenings were not performed for this study.

Appendix C

Symptom Checklist

SUBJECT NUMBER: #_____ DATE: _____/_____/_____ TIME: ____:____

INSTRUCTIONS TO SUBJECTS: "**I am going to ask you if you are CURRENTLY experiencing any of the following symptoms. If you are, I'll ask you to rate its severity, and tell me when you first noticed it**."

TECHNICIANS: Verify that subject's experience is **CURRENT** (i.e., happening RIGHT NOW)! If subject reports that the symptom was experienced PREVIOUSLY, do NOT mark it on this sheet – mark it on EXIT MEDICAL SCREENING sheet.

ITEM	**Y / N (circle one)**	**IF "YES" CIRCLE ONE**			**Time of Onset**
Nervousness	**Y / N**	mild	moderate	severe	
Excitation	**Y / N**	mild	moderate	severe	
Feelings of Aggression	**Y / N**	mild	moderate	severe	
Headache	**Y / N**	mild	moderate	severe	
Feelings of happiness or elation	**Y / N**	mild	moderate	severe	
Pain in abdomen or stomach area	**Y / N**	mild	moderate	severe	
Dry mouth	**Y / N**	mild	moderate	severe	
Pounding heart	**Y / N**	mild	moderate	severe	
Racing heartbeat	**Y / N**	mild	moderate	severe	
Tremor	**Y / N**	mild	moderate	severe	
Nausea	**Y / N**	mild	moderate	severe	
Jitteriness	**Y / N**	mild	moderate	severe	

"**Do you have anything else going on RIGHT NOW that I haven't asked you about**?" - If yes, ask subject to describe symptom or event. Write down their description VERBATIM. Ask subject to rate severity and give time of onset.

ITEM	**Y / N (circle one)**	**IF "YES" CIRCLE ONE**			**Time of Onset**
	Y / N	mild	moderate	severe	
	Y / N	mild	moderate	severe	
	Y / N	mild	moderate	severe	
	Y / N	mild	moderate	severe	

Appendix D

Motion Sickness Questionnaire

For each symptom, please circle the rating that applies to you **RIGHT NOW**.

	1	2	3	4
General discomfort	None	Slight	Moderate	Severe
Fatigue	None	Slight	Moderate	Severe
Boredom	None	Slight	Moderate	Severe
Drowsiness	None	Slight	Moderate	Severe
Headache	None	Slight	Moderate	Severe
Eye Strain	None	Slight	Moderate	Severe
Difficulty focusing	None	Slight	Moderate	Severe
Increased salivation	None	Slight	Moderate	Severe
Decreased salivation	None	Slight	Moderate	Severe
*Sweating	None	Slight	Moderate	Severe
Nausea	None	Slight	Moderate	Severe
Difficulty concentrating	None	Slight	Moderate	Severe

Mental depression…….. No……Yes
"Fullness of the head" ……No……Yes
Blurred vision…….No……Yes
Dizziness with eyes open……No……Yes
Dizziness with eyes closed…….No……Yes
Vertigo……No……Yes
**Visual flashbacks……No……Yes
Faintness…….No……Yes
Aware of breathing…….No……Yes
***Stomach awareness…….. No……Yes
Loss of appetite…….. No……Yes
Increased appetite……...No……Yes
Desire to move bowels……... No……Yes
Confusion……No……Yes
Burping……...No……Yes
Vomiting…….No……Yes
Other: please specify:

_____
_____
_____
_____
_____

* Sweating "Cold sweats" due to discomfort not due to physical exertion.
** Visual flashback – Illusion of movement or false sensation similar to aircraft dynamics when not in the simulator or aircraft.
*** Stomach Awareness – used to indicate a feeling of discomfort just short of nausea.

Appendix E
Evaluation Of Risk Questionnaire

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not at all	I feel like gambling	very much
stopping	I am driving and the light turns yellow. I feel like	accelerating
I don't move	The light goes out in an unfamiliar stairwell	I proceed immediatly
avoiding everyone	I feel like	taking on the world
very high	I feel like diving from a diving board, that is	very low
routine	I like	adventure
the thrill of danger	I seek	tranquility
I take a dangerous short cut	I am in a hurry	I take a safe detour

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negotiation	I am open to	confrontation
direct	I prefer to	be supervised
reason	I give priority to	action
at loud volume	I like to listen to music	very softly
not at all	I am sure of myself	completely
animated	I prefer discussions, which are	calm
weakens me	A hostile situation	reinforces me
I confront it	A menacing dog approaches	I run away

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I take my time	Faced with a potentially dangerous event	I instantly react
dive in	Seeing a person who is drowning, I first	call for help
well planned	I prefer work that is	not planned
all the time	I am right	never
precision	I emphasize	speed
very fast	I like to drive	very slow
very slow	I like to listen to music with a tempo that is	very fast
not at all	I tend to take risks	a lot

Appendix F

Visual Analogue Scale

PLEASE RATE HOW YOU ARE CURRENTLY FEELING (Please mark on the lines below)

Not at all I----------I Extremely
Alert/able to concentrate

Not at all I----------I Extremely
Anxious

Not at all I----------I Extremely
Energetic

Not at all I----------I Extremely
Feel Confident

Not at all I----------I Extremely
Irritable

Not at all I----------I Extremely
Jittery/Nervous

Not at all I----------I Extremely
Sleepy

Not at all I----------I Extremely
Talkative

Appendix G

Profile Of Mood States

"The numbers refer to how you are feeling right now…"

	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. Fatigue	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

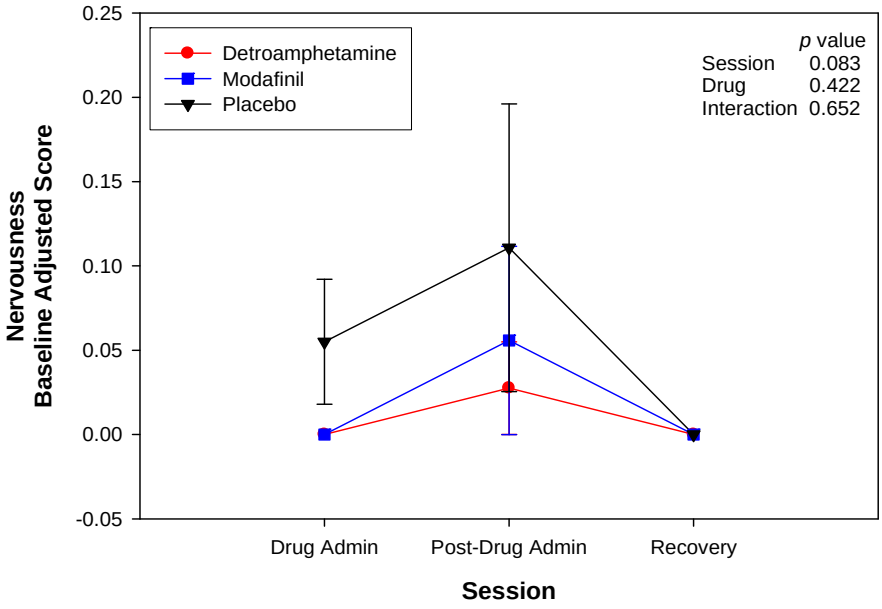
Appendix H

Graphs of non-significant measures

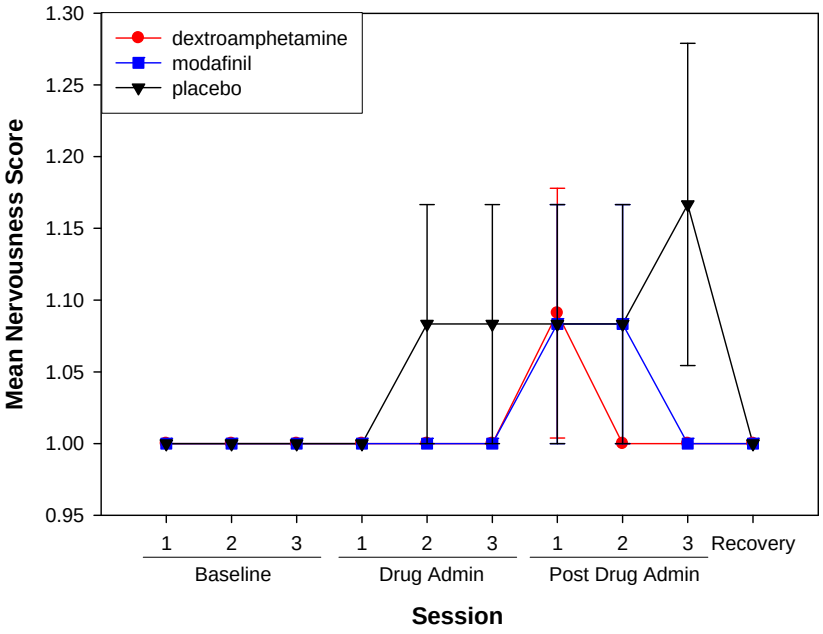
- Symptom Checklist measures

Nervousness

Baseline adjusted:

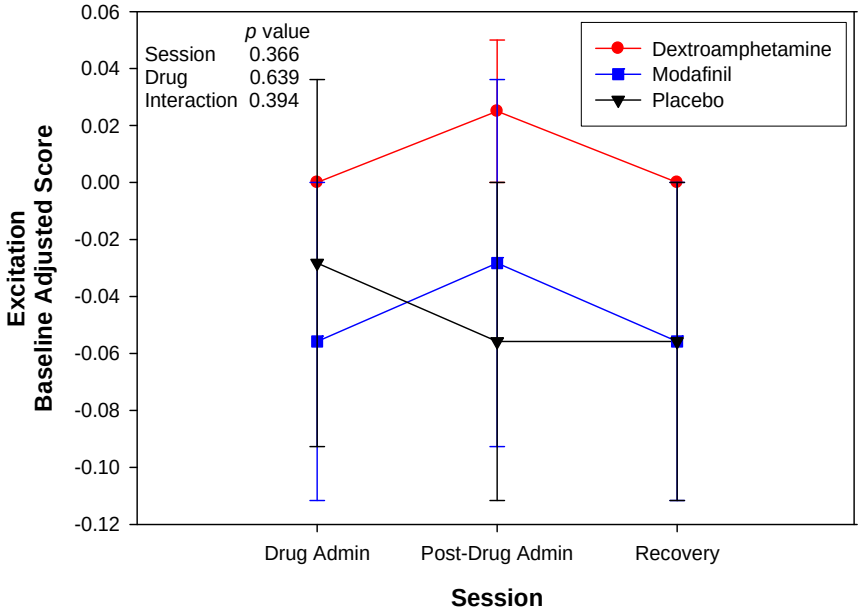


Scores:

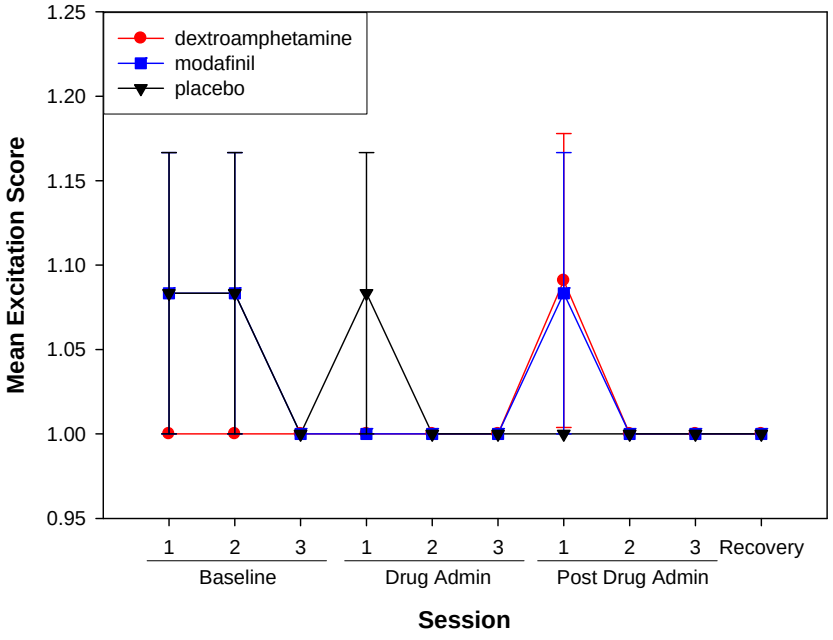


Excitation

Baseline adjusted:

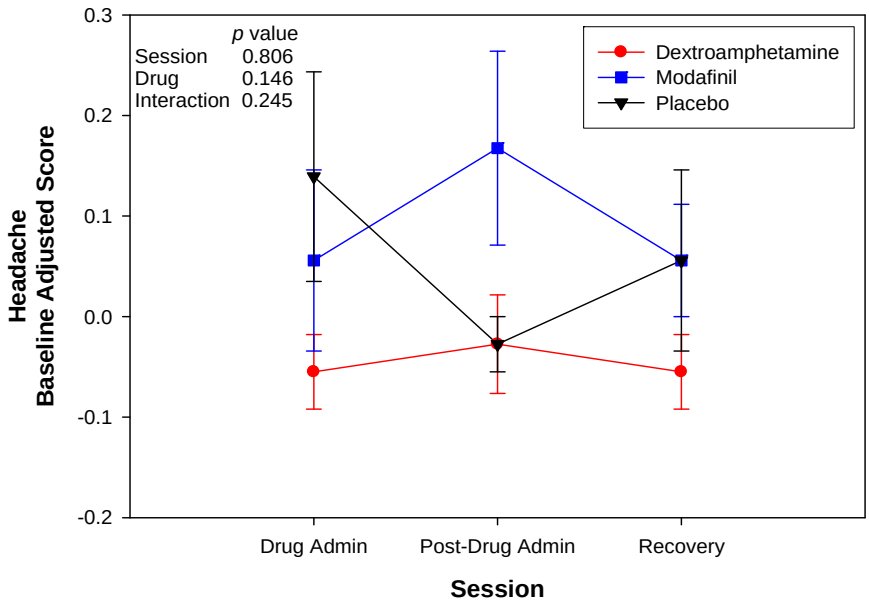


Scores:

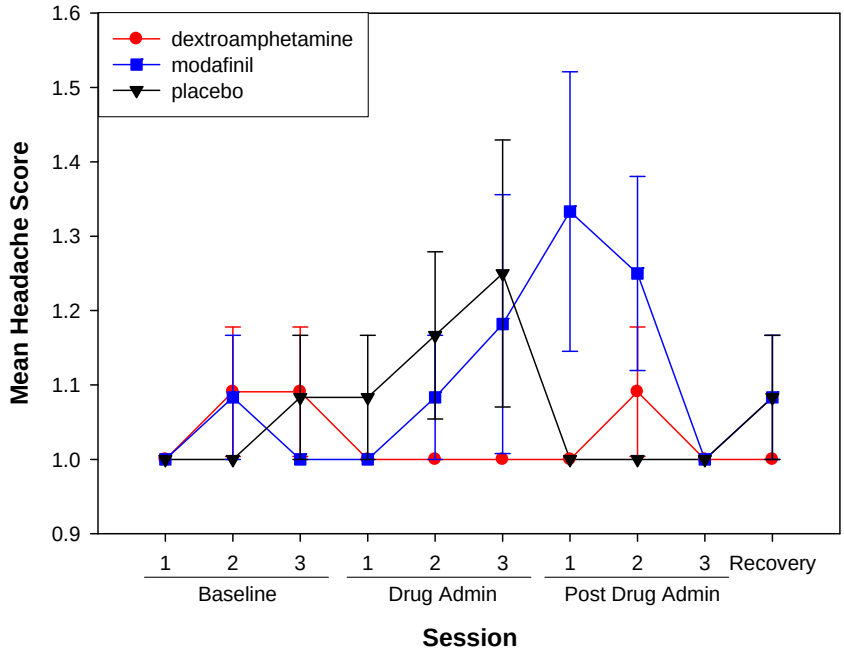


Headache

Baseline adjusted:

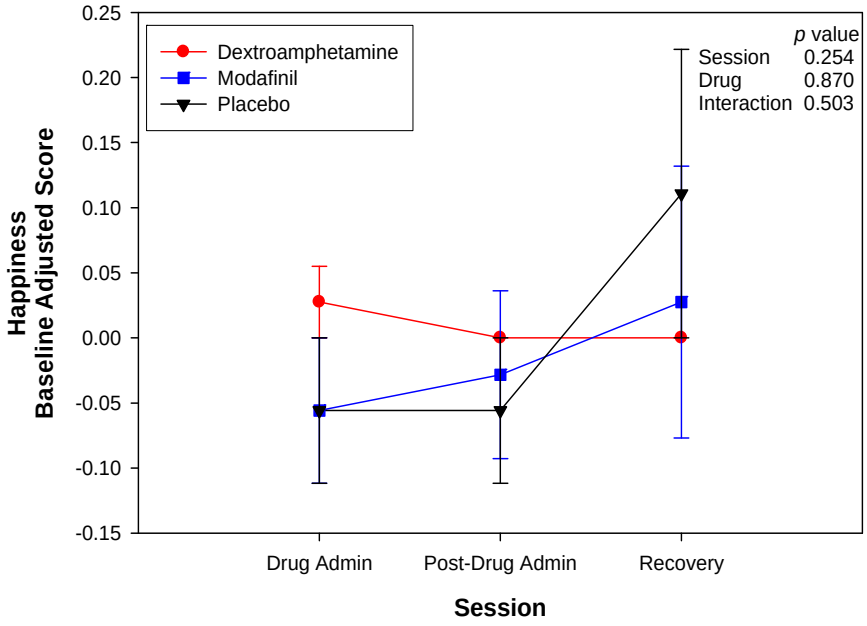


Scores:

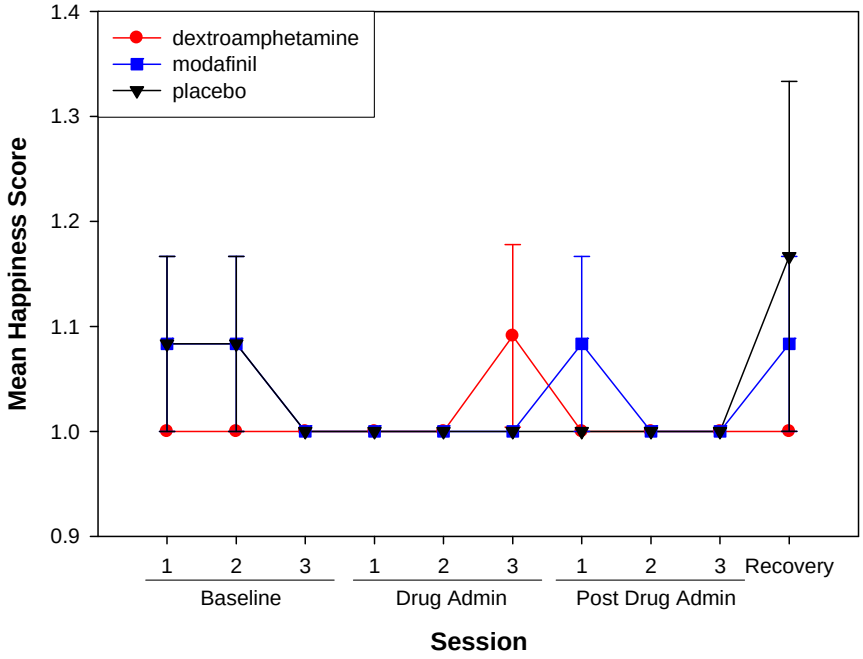


Happiness

Baseline adjusted:

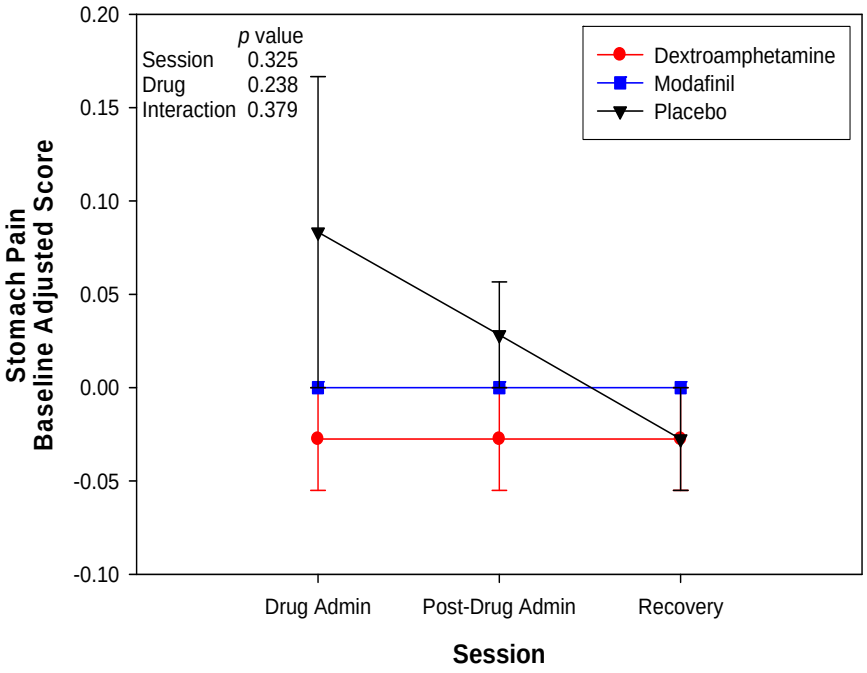


Scores:

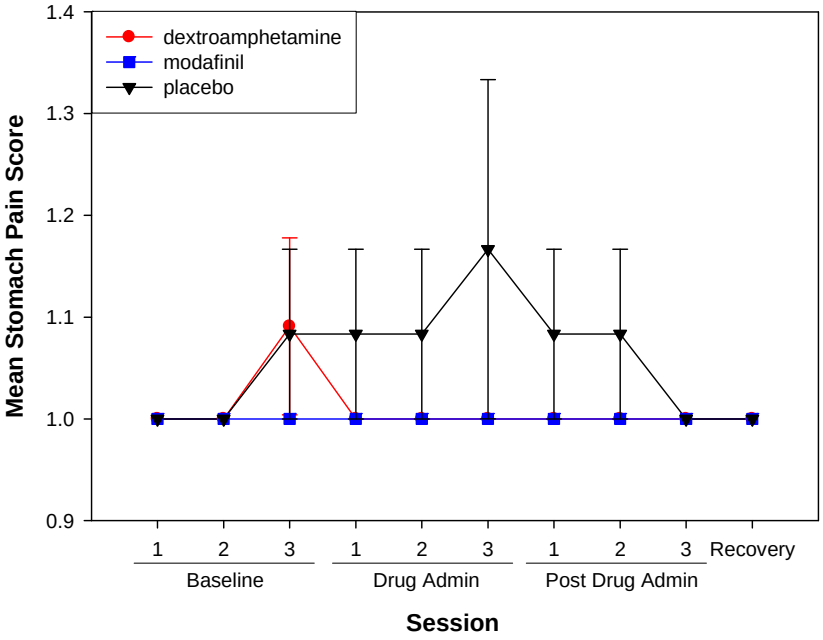


Stomach Pain

Baseline adjusted:

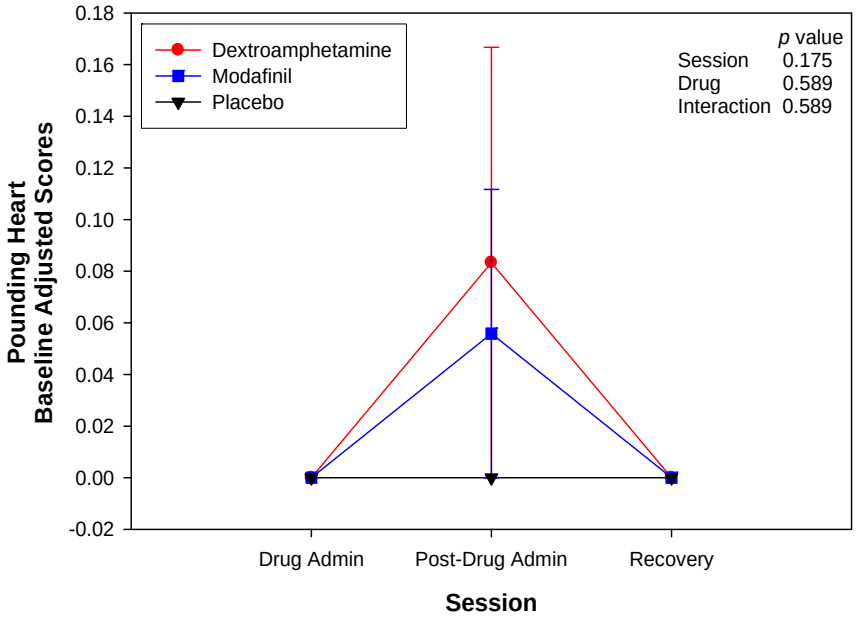


Scores:

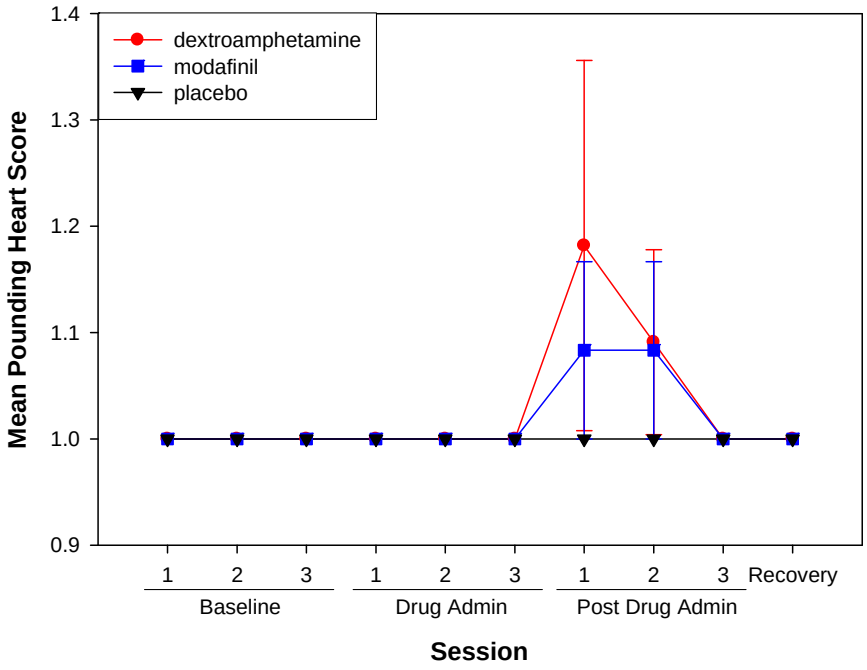


Pounding Heart

Baseline adjusted:

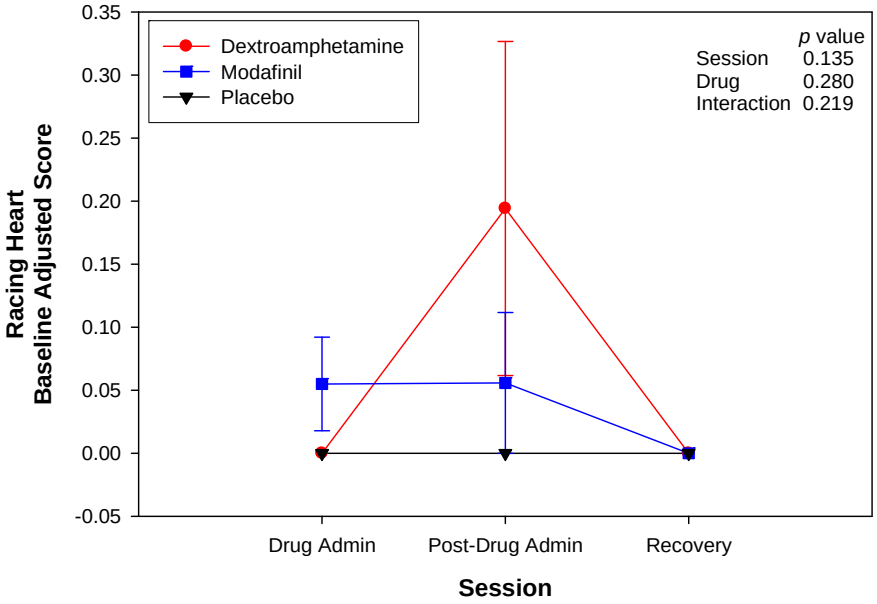


Scores:

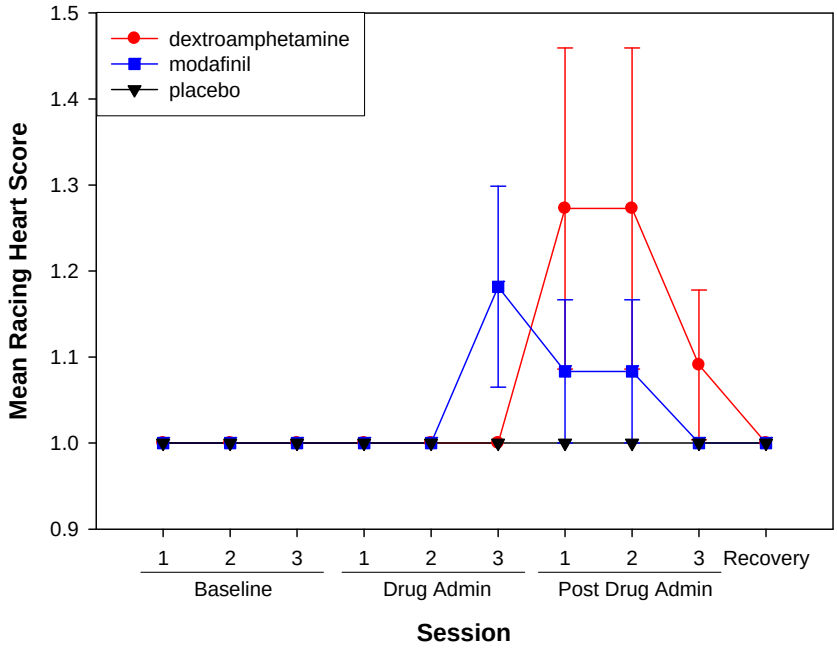


Racing Heart

Baseline adjusted:

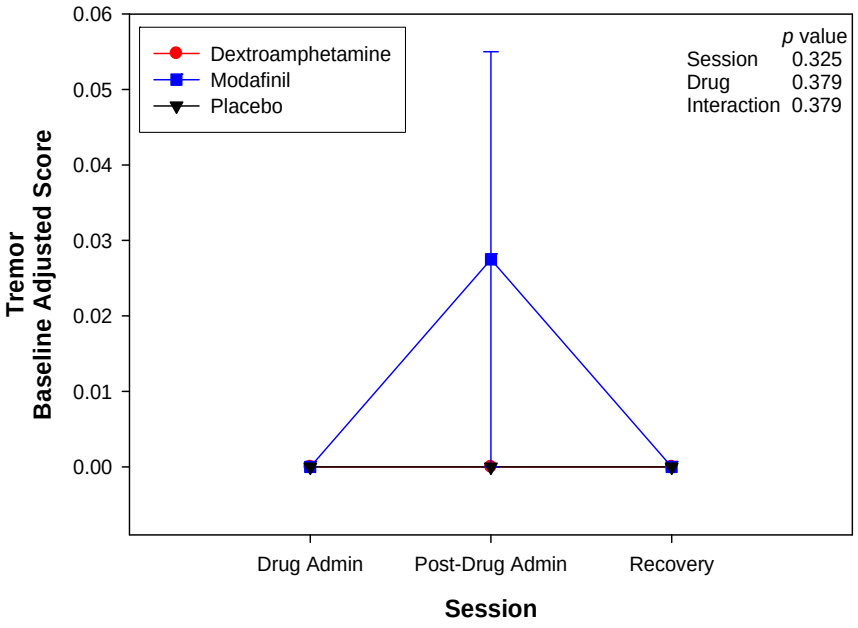


Scores:

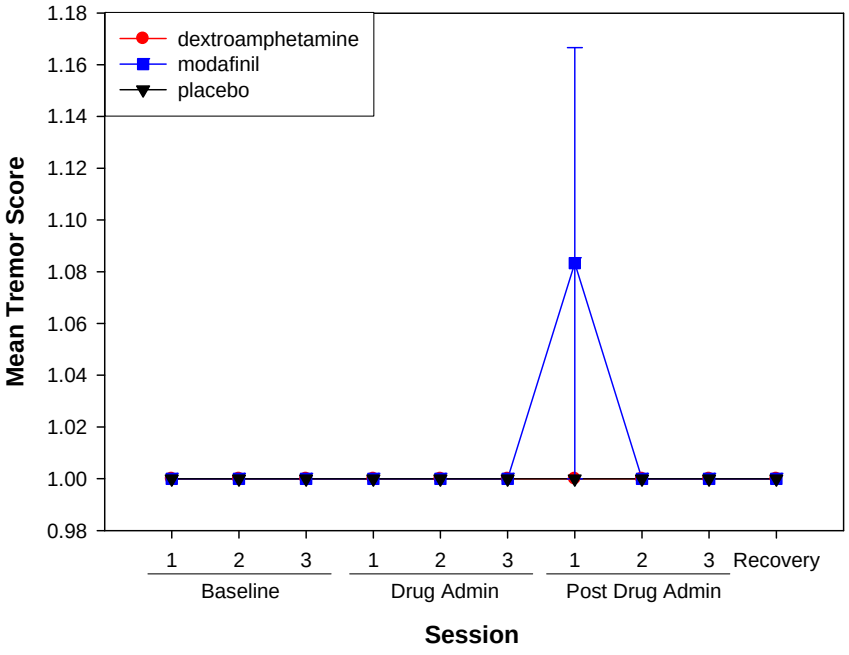


Tremor

Baseline adjusted:

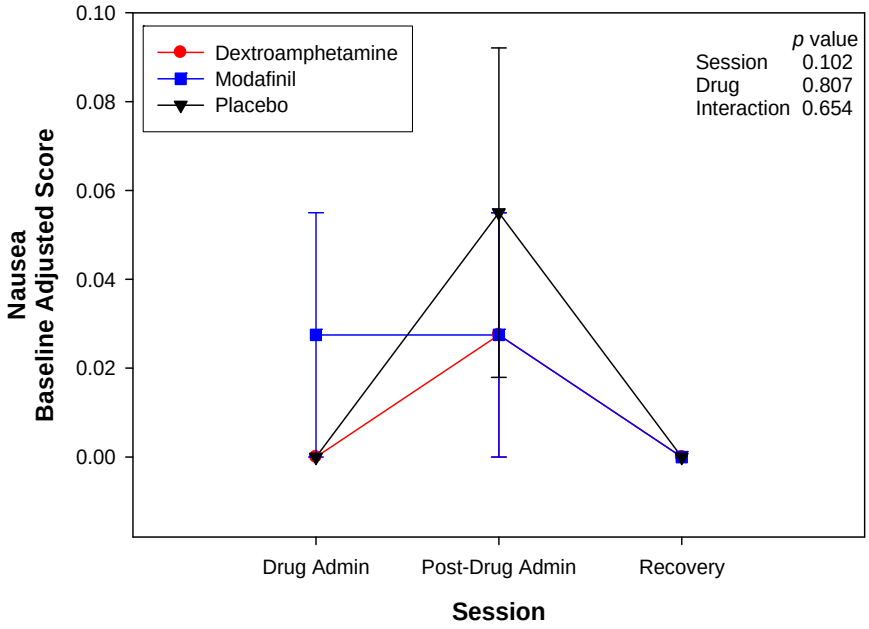


Scores:

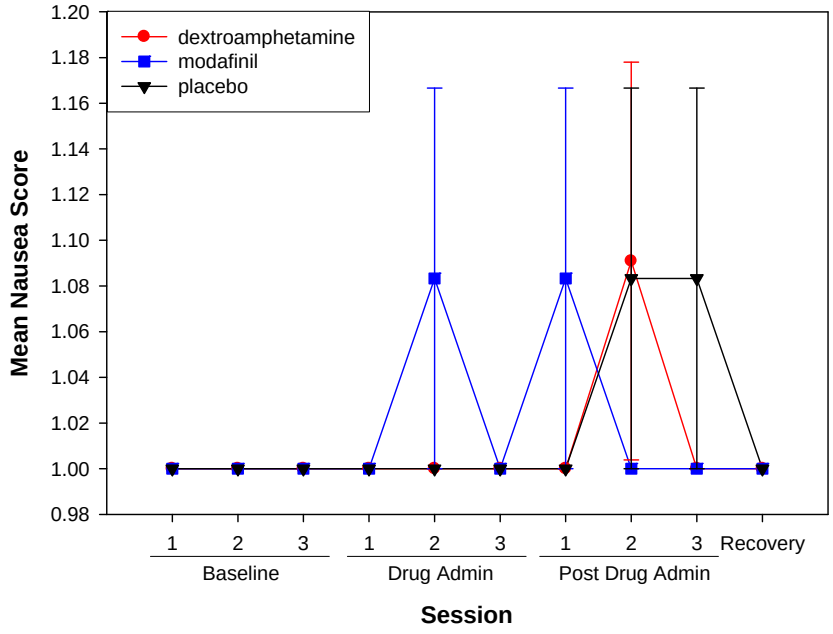


Nausea

Baseline adjusted:

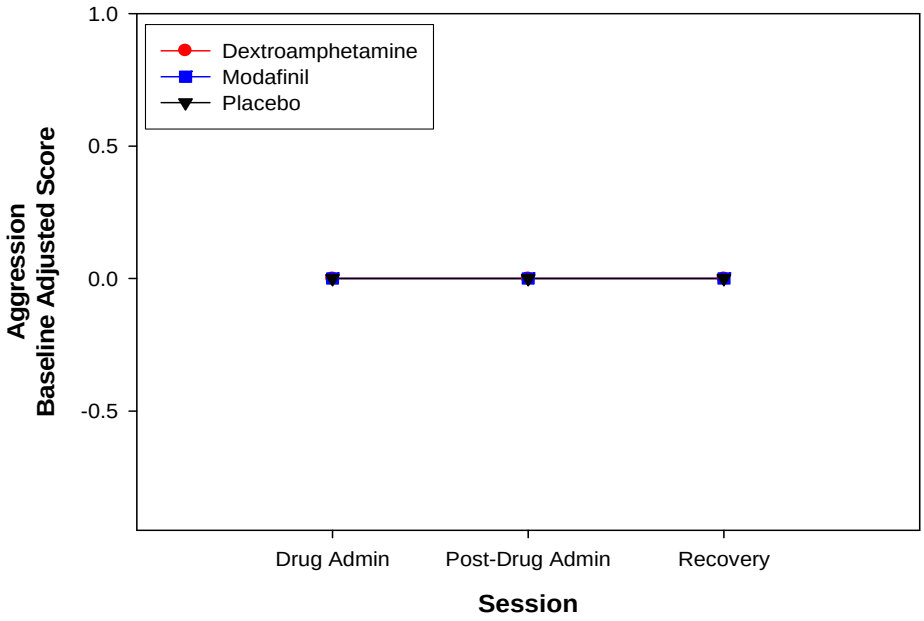


Scores:

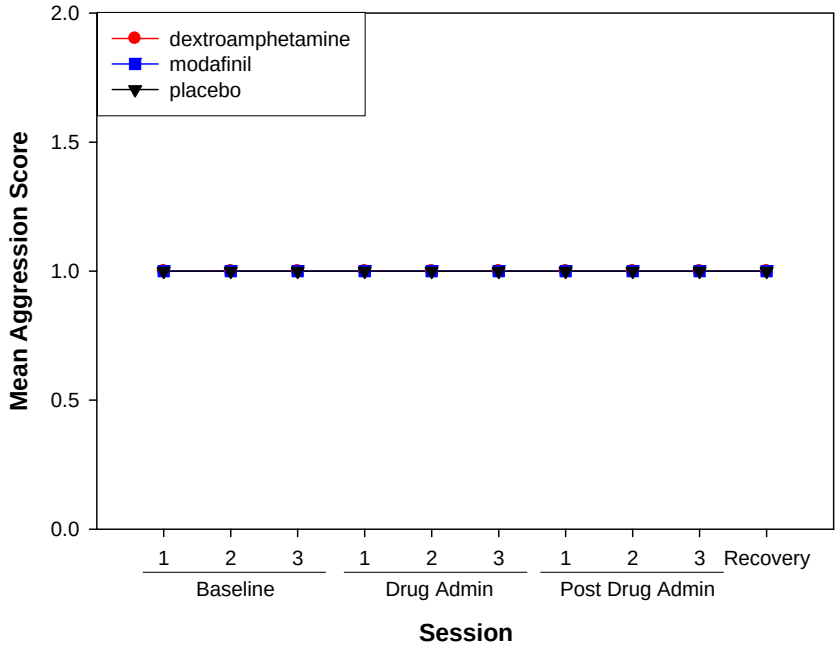


Aggression

Baseline adjusted:



Scores:



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