



NAVAL MEDICAL RESEARCH UNIT DAYTON

Evaluation of suvorexant as an additional sleep aid for military operations

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STATEMENTS

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The views expressed in this technical report are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.

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Human Research/Institutional Review Board (IRB) statement

The study protocol was approved by the Naval Medical Research Unit Dayton Institutional Review Board in compliance with all applicable federal regulations governing the protection of human subjects.

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INTRODUCTION

Sleep is a biological necessity, like food, water, and air. However, unlike consuming food and water, obtaining sufficient sleep requires individuals to engage in behaviors that are affected not only by personal choice, but also by societal expectations regarding productivity. Various factors such as work, home responsibilities, and social activities influence the amount of sleep obtained by individuals, often resulting in insufficient sleep (Grandner, 2017). Sleep experts recommend 7–9 hours of sleep per night for most adults (Hirshkowitz et al., 2015); unfortunately, many adults (in both military and civilian populations) do not obtain adequate sleep. In a summary of military studies, only about 24% of service members report sleeping the recommended 7 to 9 hours of sleep per night with 69%–72% reporting less than 6 hours of sleep per night (Troxel et al., 2015). The reasons for truncated sleep within military members are numerous but can include operational demands that involve long work hours and circadian disruptions.

Truncated sleep leads to adverse effects on performance, including vigilance decrements, increased lapses of attention, cognitive slowing, short-term memory failures, and rapid and involuntary sleep onsets (Banks & Dinges, 2007; Bonnet, 1994; Dinges, 1992; Horne, 1988; Horne, 1993; Koslowsky & Babkoff, 1992; Naitoh, 1975; Thomas, Sing, & Belenky, 1993). Dinges and colleagues (1997) showed that sleep restricted to 4–6 hours per day creates a sleep debt which seriously and rapidly impairs waking performance. Both Belenky et al. (2003) and Van Dongen, Maislin, Mullington, and Dinges (2003) confirmed these results in complementary studies during which participants were restricted to 3–7 hours of sleep per night for several days. Many other experiments have reinforced the fact that 5 hours or less of sleep per night decreases cognitive performance, reduces sleep latency values, increases subjective sleepiness, increases behavioral, mood, and physical complaints, and produces polysomnographic (PSG) indications of elevated sleep pressure (Blagrove, Alexander, & Horne, 1995; Carskadon & Dement, 1981; Frazier, Benignus, Every, & Parker, 1971; Gillberg & Akerstedt, 1994; Hamilton, Wilkinson, & Edwards, 1972; Herscovitch & Broughton, 1981; Herscovitch, Stuss, & Broughton, 1980; Rosenthal, Roehrs, Rosen, & Roth, 1993; Taub & Berger, 1973; Tilley & Wilkinson, 1984; Webb & Agnew, 1965; Wilkinson, 1969). These negative effects are well-known to adversely affect performance and safety in the real world, including military operations (Brown, Berry, & Schmidt, 2013; Drake et al., 2010; Johnson, 2007; Olsen, Pallesen, & Espevik, 2013; Tivaryanas & Thompson, 2006).

Circadian disruptions are problematic from a performance standpoint. The physiological tendency to sleep at night and to be awake during the day is powerful, and thus, difficulties occur when schedule changes cause personnel to work against this tendency (Costa, 2015). Altering the natural sleep/wake cycle affects both the ability to remain alert and the ability to sleep. Shift-lag occurs when non-traditional work hours (night or early morning hours) are required either on a permanent night shift or a rotating schedule, creating a misalignment between the internal clock, the normal activity, and sleep schedule. This results in sleep impairment (often leading to cumulative sleep debt), and will compromise alertness and performance (Costa, 2015). In terms of performance on night shifts, several fatigue and alertness studies have demonstrated that incidents are more related to the time of day as opposed to time spent on task. An increased risk of fatigue-related incidents occurs in the early morning hours, coinciding with the circadian period of peak sleepiness (Lerman et al., 2012). In addition, both shift work and long working

hours demonstrate detrimental effects on safety, including 50%–100% increases in accident rates (Wagstaff & Sigstad Lie, 2011). A description of some of the accidents and errors which occurred in military operations, presented by Johnson (2007), indicated that the problem of inadequate sleep affects the completion and safety of missions.

Taken together, the evidence to date clearly demonstrates that chronically losing even small amounts of sleep each night will seriously degrade alertness, cognition, and vigilance (Balkin et al., 2000; Carskadon & Roth, 1991). When sleep is difficult, prescription sleep aids (hypnotics) may be the only way to prevent deprivation-related performance declines. Generally, sleep aids are intended for short-term use when other options are not adequate. For example, circadian factors such as those encountered with shift lag can lead to short-term insomnia. Numerous prescription options are available, and the decision regarding which one to use can be a challenge. Generally, a hypnotic should be chosen based on the characteristics of the hypnotic and the situation. The timing of the start of the sleep opportunity, the expected length of the sleep period, and whether there is a high probability of unexpected sleep truncation are all factors to be considered. For example, a long-acting hypnotic such as temazepam is useful for maintaining sleep for relatively long periods during the night and/or for optimizing the daytime sleep of night-working personnel (Caldwell et al., 2003; Simons, Koerhuis, Vlak, & Van den Oord, 2006). For short sleep periods or for the initiation of sleep, zolpidem and zaleplon are more suited than the longer acting hypnotics since their shorter half-lives reduce the probability of post-sleep sedation (Caldwell & Caldwell, 1998; Dooley & Plosker, 2000; Whitmore, Fischer, & Storm, 2004). In both situations (increasing length of sleep or initiating sleep), hypnotics can minimize sleep disruptions and, with proper planning, can be used without undue concern about post-sleep hangover effects. A balance between the need to improve sleep with the need to avoid residual effects is needed, considering that sleep may be short and/or disrupted if no hypnotics are used.

Two short-acting hypnotic drugs (zolpidem and zaleplon) are currently approved for controlled use by the U.S. Navy (Performance Maintenance during Continuous Operations, 2000). Operationally, hypnotics may be used to maximize sleep as needed, thus allowing the service member to be as rested as possible and maintain alertness and performance. Zolpidem (5–10mg) must be taken at a minimum of 6 hours prior to reporting for duty to assure clearance and no hangover effects. Zaleplon was approved by the Navy in 2013 (BUMED NOTICE 6410) for the same uses as zolpidem. It replaced temazepam which was removed from the approved list due to concerns about its 12-hour half-life that could impact flight safety. However, zolpidem and zaleplon are short-acting hypnotics that do not address sleep maintenance insomnia; thus, the Navy does not offer a long-acting hypnotic.

Choosing the best hypnotic for each situation requires consideration of a variety of factors. From a strictly pharmacological standpoint, for short sleep periods or help with sleep onset, zolpidem and zaleplon are better suited than the longer acting hypnotics since the shorter half-lives reduce the probability of post-sleep sedation (Caldwell & Caldwell, 1998; Dooley & Plosker, 2000; Whitmore et al., 2004). The arterial times for maximum concentration (T_{max}) for zolpidem is 1.1 hours ($SD = 0.57$), with an elimination half-life of 2.15 hours ($SD = 0.66$). The T_{max} for zaleplon is 1.3 hours ($SD = 0.75$), with an elimination half-life of 1 hour ($SD = 0.16$) (adapted from Drover et al., 2000). Thus, both medications are effective in reducing sleep onset and are useful

when initiation of sleep is a problem. However, when the effects on sleep efficiency and time awake after sleep onset are measured, particularly during a time not conducive to sleep (e.g., biological day), the short-acting hypnotics show less efficacy. In a study by Nicholson and Pascoe (1988), when these medications were administered during the day, total sleep time was only increased in participants administered a 30 mg dose of zolpidem, a dose much higher than the recommended 10 mg (as cited in Walsh, Muehlbach, & Schweitzer, 1995). In healthy participants, Struyk and colleagues (2016) found zolpidem did not affect sleep efficiency and wake after sleep onset as well as a longer-acting hypnotic, suvorexant. Therefore, when addressing sleep maintenance insomnia (which takes place when sleep occurs outside the circadian phase), long-acting hypnotics are useful.

The FDA approved suvorexant (Belsomra®; Merck & Co., Inc., Rahway, NJ) in 2014 for the treatment of insomnia, both sleep onset and sleep maintenance. This hypnotic was the first medication for insomnia which acted on the orexin receptor, blocking orexin which promotes wakefulness, thus inducing sleep, reducing arousal, and improving sleep consolidation (Asnis, Thomas, & Henderson, 2016; Lee-Iannotti & Parish, 2016). The approved dosage range is 5 to 20 mg, with a T_{max} of 3 hours (range from 1 to 6) and a terminal half-life of 9 hours (*SD* of 3.6) in the 10 mg dose (Sun et al., 2013). In a study investigating the effects of this hypnotic on sleep parameters in healthy men, Sun and colleagues (2013) found that a 10 mg dose decreased wake after sleep onset compared to the placebo. Next-day residual effects were tested at 10 hours post-dose; no effects on any objective or subjective evaluations were shown following the 10 mg dose. Adverse effects of suvorexant are dose-related, with higher doses leading to more effects. At the 10 mg dose, Sun et al. (2013) found no serious adverse events in a sample of healthy young men. The most frequent events were somnolence and headache, both in less than 5% of the sample. There were no reports of sleep paralysis, hallucinations, or cataplexy at higher doses. Herring et al. (as cited in Patel, Aspesi, & Evoy, 2015) found similar results. At the 10 mg dose, adverse effects were minor, with only somnolence (1.6%) and abnormal dreams (1.6%) reported.

According to Navy medication protocol, certain medications (including hypnotics) can be used in combat or during exceptional circumstances when operations demonstrate the need. Pilots, Naval Flight Officers (NFOs), and air crew members may use prescription hypnotics. However, before a physician can prescribe a hypnotic to a sailor, a ground test is required which involves administration of the medication and an assessment of its effects and listing of any side effects which may occur. In 2012, the Carrier Air Wing SEVEN conducted an on-board field trial of their fatigue management program during an extended deployment. Two medications were tested, the alertness aid modafinil and the hypnotic zolpidem. An after-action report summarized surveys completed by those who participated in the ground test of these medications. Of the 96 participants, 83 completed the Fatigue Management survey. Of these 83 participants, 81 took at least one dose of zolpidem. Most of those surveyed indicated positive results, with the majority indicating that falling asleep and good quality sleep were the top positive effects. However, truncated sleep was the most reported negative effect, with participants reporting awakening after 6 hours of sleep despite the time available to sleep longer. While not officially tested in a controlled fashion, early awakening has been a consistent complaint over the last three deployments, starting in 2009 (Commander, Naval Air Force Atlantic, 2013).

The question arises whether a longer-acting hypnotic could have extended sleep to 8 hours in situations such as those encountered by military personnel. The possibility of next-day effects from a long-acting hypnotic is a concern, a known effect with temazepam. A non-benzodiazepine hypnotic such as suvorexant may extend sleep to an optimal 8 hours without affecting next-day performance and alertness since its half-life is not as long as temazepam's and does not show evidence of next-day performance effects 10 hours post-dose in the amount to be used in this study (10 mg). The proposed study will address this question in a direct comparison between zolpidem and suvorexant. The hypotheses to be tested are:

1. Suvorexant will improve sleep maintenance compared to zolpidem and placebo by reducing time awake after sleep onset and extending sleep length.
2. Next-day performance and sleepiness will not be affected by suvorexant or zolpidem as compared to placebo.

METHOD

The protocol was a double-blind, repeated measures study in which individuals were tested following administration of three drugs on separate nights: 1) placebo, 2) suvorexant, and 3) zolpidem. The drug conditions were counterbalanced to offset any order effects that may occur. Each condition was separated by a minimum of 7 days, but no more than 21 days ($M_{DaysSeparated} = 7.75$, $SD_{DaysSeparated} = 2.20$). Most participants were tested on consecutive weeks and the same day of the week.

A total of 16 participants enrolled in the study; one was disqualified after the first week due to not meeting sleep requirements, leaving a total of 15 participants who completed the entire study. The Naval Medical Research Unit Dayton Institutional Review Board approved the protocol (NAMRU-D 2019.0016). Participants were paid \$850 for completing the entire study.

Pre-study Screening

Before enrolling in the study, potential participants were screened to ensure they maintained a similar sleep/wake schedule with habitual bedtimes between 2100 and 2400 and wake times between 0500 and 0800. Additional screening certified that potential participants possessed the necessary qualifications (e.g., no tobacco use) to proceed into the study. See Appendix A for the screening questionnaire.

Assessments

The Horne and Östberg Morningness/Eveningness Questionnaire (MEQ)

The Horne and Östberg Morningness/Eveningness Questionnaire (MEQ) (Horne & Östberg, 1976) was used to evaluate each participant's circadian type. This 19-item questionnaire asks the time a person prefers to perform specific activities. Using the answers, the MEQ classifies the timing of peak alertness into morning, evening, or intermediate preference with scores ranging from 16 to 86. This questionnaire was administered on the consent day and scored by a research staff member. Scores of 41 and below indicated "evening types." Scores of 59 and above indicate

"morning types." Scores between 42-58 indicated "intermediate types." Participants answered this questionnaire on a printed copy. The MEQ can be found in Appendix B.

Epworth Sleepiness Scale (ESS)

The Epworth Sleepiness Scale (ESS) was used to assess a participants' sleep propensity during normal daily activities (Johns, 1991). Participants were asked to rate their likelihood of dozing off or falling asleep on a 4-point scale (0 = *would never do* to 4 = *high chance*) while engaged in 8 different life activities. Scores above 10 indicate excessive daytime sleepiness. The participant answered this questionnaire from a printed copy. A research staff member scored the completed questionnaire. This questionnaire was administered on the consent day. This questionnaire can be found in Appendix C.

Profile of Mood States (POMS)

The Profile of Mood States (POMS) is a 65-item questionnaire used to measure affect on six scales: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue inertia, and confusion-bewilderment (McNair, Lorr, & Droppleman, 1981). The questionnaire was digitally administered. Time to complete was less than 5 minutes.

Visual Analogue Scale (VAS)

The Visual Analogue Scale (VAS) 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). At the extremes of each line, "not at all" and "extremely," were printed respectively. Scores (in mm) consisted of the distance of the participant's mark from the left end of the line. The questionnaire was digitally administered immediately after the POMS. Time to complete was less than five minutes. This questionnaire can be found in Appendix D.

Side Effects Questionnaire (SEQ)

The *Side Effects Questionnaire* consists of a list of potential symptoms associated with suvorexant and/or zolpidem use. Participants indicated to what degree they were currently experiencing that side effect. Responses were made on a four-point scale, ranging from 1 (*not at all*) to 4 (*severe*). The questionnaire was digitally administered immediately after the VAS. Time to complete this questionnaire is under five minutes. This questionnaire can be found in Appendix E.

Apparati

Activity/sleep monitor

Participants' activity was measured using a Actiwatch 2™ (Philips Respironics, Murrysville, PA). The Actiwatch 2™ (wrist activity monitor) is a water-resistant, wrist-worn device that measures frequency and intensity of wearer movement using a precision motion sensitive piezoelectric assembly. A 1-minute data capture epoch was used to collect movement data. The movement results were plotted using accompanying software to track participants' sleep patterns. Activity watches were worn 5–7 days before the first study visit. Upon arrival to the lab for each study visit, the watch data were downloaded and reviewed for compliance with the sleep requirement on the first day of the in-house portion of the study. Study volunteers who did not

adhere to the prescribed sleep (between 2100 and 2400) and wake schedules (between 0500 and 0800) were either rescheduled or dismissed from the study.

Vital Signs

Research participants' temperature, blood pressure, and heart rate were measured with a Spot Vitals Signs® Device (Welch Allyn, Skaneateles Falls, NY) during each test session as both a safety measure and to determine any physiological changes which may have incurred under each drug.

Balance Assessment

Balance was assessed using the AMTI AccuSway-Optimized (ACS-0) force plate using Balance Clinic software (Version 1.5.1; Summit Medical & Scientific, Bookham, Surrey, UK). The force plate registers the amount and distribution of downward force and reflects dynamic postural stability and balance when standing upright with no support. Participants stood on the force plate and were instructed to stand with their feet shoulder width apart, knees slightly bent, and with their fingertips touching their thighs while they were fixated on a target positioned approximately six inches away at eye level for four, 30 second trials. Trials alternated eyes open and eyes closed. Data were recorded from the X, Y, and Z planes which allow measures of balance and postural stability. The sampling rate was 50 Hz. Metrics analyzed include the path length of the center of pressure, the standard deviation from the path length in the X plane, and the standard deviation of the path length in the Y plane.

Driving Simulation

The STISIM™ Drive-M100K Driving Simulator (Build 3.15.03; Systems Technology, Inc., Hawthorne, CA) is an interactive computerized driving simulator. It was configured to provide a multi-faceted, but relatively unchallenging, driving simulation which included a curvy, rural drive punctuated with various tasks (e.g., braking tasks and a car following task). During the braking task, a stop sign appeared on the screen. The participant was instructed to bring the car to a complete stop as quickly as possible. During the car following task, a moving car appeared, and the participant was instructed to maintain a constant distance of 2-3 car lengths behind the lead car, which constantly varied its speed according to a sinusoidal pattern. Measures of performance included the standard deviation of lateral position, mean speed (mph), mean distance of lane departures (ft), and mean distance of speed limit exceedances (ft). For the braking task, mean reaction time (ms) to the stop sign stimuli was measured as well as the mean distance to stop. For the car following task, metrics included modulus (a measure of how well the participant matched the speed of the lead vehicle), time delay (the time it took the participant to respond to changes in the lead vehicle's speed), and coherence (how well the driver matched the lead vehicle's actions, 1 being best and 0 being worst – a measure of data reliability). The driving setup utilized a Logitech G29 Driving Force Racing wheel with Logitech foot pedal hardware (Logitech, Newark, CA). The simulation employed an automatic transmission mode, so the participant only manipulated the steering wheel, accelerator, and brake to navigate the driving scenario. The positioning of the braking tasks and the car following task in the overall track was varied across sessions to assure that participants did not memorize the course's sequence of events over the duration of the experiment. This test took approximately 15 minutes to complete. Figure 1 shows one of the scenes from the driving simulation.



Figure 1. An example scene of the driving simulator

Polysomnography

Polysomnographs (PSGs) were recorded during each sleep period according to the American Academy of Sleep Medicine (AASM) standards for routine PSG recordings using a Grass Technologies/Natus AS40-PLUS amplifier system and Twin® sleep acquisition and review software (Version 4.5.3; Natus Medical Incorporated, Middleton, WI). A 60 Hz notch filter was used; the sampling rate was set at 200 Hz. Variables of interest from the sleep recordings were minutes in each stage of sleep, sleep onset time, sleep efficiency, total sleep time, and number of awakenings. PSG were scored according to the AASM standards for sleep scorings (Version 2.5).

Performance Tests

A variety of assessments were administered to determine any next-day effects on cognitive abilities. All tests were run on a Windows 7 (Microsoft Corporation, Redmond, WA) computer with an ASUS monitor (ASUSTek Computer Inc., Taipei, Taisan), resolutions set at 1920 x 1080 and a 60 Hz refresh rate. Participants sat about 30 inches from the monitor and responded with a G203 mouse (Firmware 107.3.15; Logitech International, Newark, CA).

Attention Networking Task - Short

The Attention Networking Task (ANT) - Short software was obtained from the Cognitive Neuroscience Laboratory at Queens College (Version 1; Fan, 2001) and administered to assess attention. E-Prime® (Version 3.0, Build 3.0.3.80; Psychology Software Tools, Pittsburgh, PA) was used to present stimuli. Participants were presented an arrowhead target pointing in a leftward or rightward direction fixated in the center of the screen. Each arrowhead was accompanied by flanked stimuli on either side of the target by two arrows pointing in the same direction (congruent condition) or in the opposite direction (incongruent condition). The task required participants to identify the direction of the central arrow by pressing one key for the left direction and a different key for the right direction whilst avoiding diversion influenced by competing flanked stimuli. The target and flankers were presented; after participants respond, the target and flankers disappeared immediately and a subsequent fixation period was presented based on the duration of the first fixation and RT, completing one trial. Metrics obtained from this test include median reaction times (RTs) for alerting (central cue minus no-cue condition), orienting (central cue minus spatial cue), and conflict or executive (incongruent flanking

conditions minus congruent flanking conditions). In this version of the task, executive control is tapped through the difference between the RT of the congruent target and the RT of the incongruent target ($RT\text{ Congruent} - RT\text{ Incongruent}$). The test consisted of three, 4-minute sections. Figure 2 shows the screen displays of each part of the test.

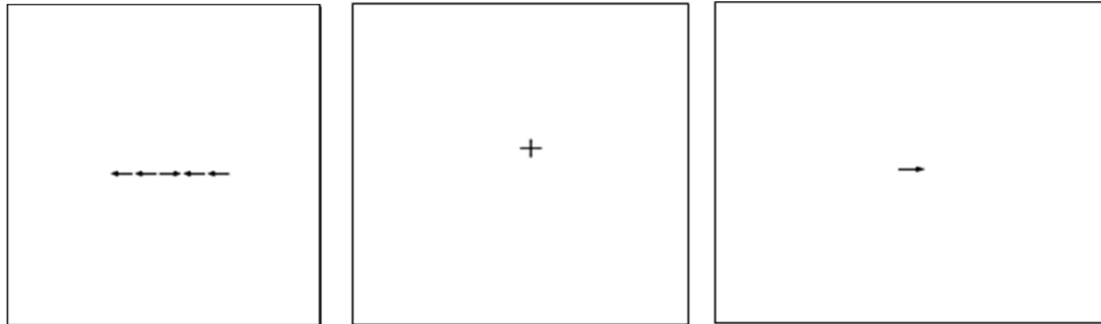


Figure 2. An example of the screens for the ANT

The first (left) panel is an example of a stimulus set, the second panel (middle) is an example of the fixation point, and the third panel (right) shows the correct response for this trial.

The ANAM Running Memory Continuous Performance Task

The Automated Neuropsychological Assessment Metrics (ANAM) Running Memory Continuous Performance Task (CPT; Version 4.5.0.2; Cognitive Science Research Center, Norman, OK), sometimes referred to as the n-back task, indexes the operator's ability to encode and store information in working memory, requiring serial encoding and recall under a changing memory state. In the CPT, a series of single numbers continuously appeared on the display, one after the other, and participants pressed designated buttons to indicate whether the current number matched the number presented two numbers previously. This task took approximately 2 minutes to complete. Figure 3 shows the screen progression of this test.

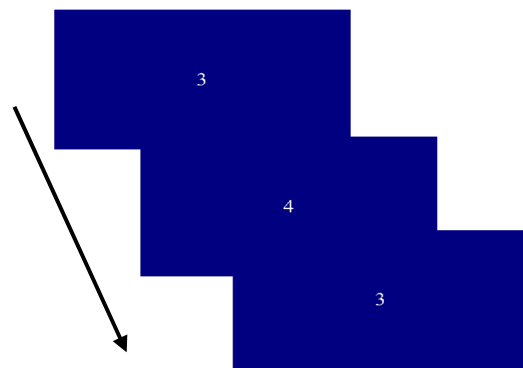


Figure 3. An example of the screens for the Running Memory CPT

Stimuli were presented as white numbers on an all-blue background. Participants stated whether the numeral on the screen matched the numerals they were shown two screens previously.

ANAM Go/No-Go Task

The ANAM Go/No-Go Task (Version 4.5.0.2) assessed response inhibition. The participants were presented with one of two characters, "x" or "o", and the participant was instructed to respond as quickly as possible to the "x" each time it appeared. When the "o" appeared, the participant was instructed to do nothing. This task took approximately 2 minutes to complete. Figure 4 shows the screens for a response versus no response.



Figure 4. An example of the screens for the Go/No-Go Task

Stimuli were presented as white characters ("x" or "o") on an all-blue background. When an "x" appeared, it required a response from the participant, while an "o" did not require a response.

Psychomotor Vigilance Task

The Psychomotor Vigilance Task (PVT) is a simple reaction time test known to be sensitive to sleep loss (Dinges et al., 1997). The PVT requires sustained attention and discrete motor responses. The PC version of the PVT was used to present the test (PC-PVT; Version 2.0; Biotechnology High Performance Computing Software Applications Institute, Ft. Detrick, MD). The stimulus is presented up to 1 minute (60,000 ms), allowing the participant to respond. The participant is asked to press the right mouse button as quickly as possible once the numbers are displayed; reaction time is recorded. The interstimulus interval varies randomly from 2 to 12 seconds. Variables included in the statistical analysis included lapses (reaction time greater than 500 ms), false starts (reaction time less than 100 ms), and reaction time (RT). This task took 10 minutes to complete. Figure 5 shows an example of a display following a response to the stimulus.

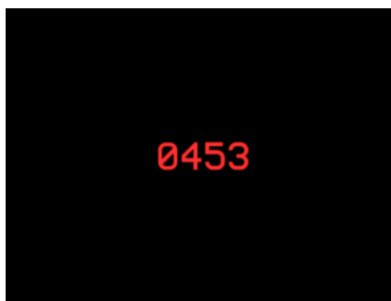


Figure 5. An example of the screen after a PVT response

Reaction times were presented as increasing, red numerals on an all-black screen. Participant responses to the PVT counted from 0 ms until their reaction time was recorded on-screen. A larger on-screen number indicated increased reaction time.

Study Drug

The substances administered during this study were suvorexant (Belsomra[®], 10 mg; Merck, Rahway, NJ), zolpidem (10 mg for men and 5 mg for women), and placebo (inulin fiber). Both suvorexant and zolpidem were placed in gelatin capsules packed with fiber to maintain the double-blind nature of the study. Placebo capsules were packed with only fiber. Drug administration was double-blind; blinding was accomplished by a person not assigned to the research team and occurred prior to the beginning of the study's data collection period. A random numbers table was used to assign participant number to the drug administration order (placebo first, suvorexant second, zolpidem third; suvorexant first, zolpidem second, placebo third; etc.). The treatment (whether active drug or placebo) was placed in small plastic bags with participant number and test period of administration (test period one, test period two, or test period three) written on a label applied to each bag. All drug bags were placed in another bag with the participant number written on a label applied to the bag. All treatment bags were placed in a box in the drug safe located at NAMRU-D. At the dose-administration time, participants received one capsule from their assigned treatment bag containing either suvorexant, zolpidem, or psyllium fiber, depending on the randomly assigned condition.

Participants

Participants consisted of 15 healthy military personnel (6 female) between the ages of 22 and 55, both military and civilian dependents of military personnel. Habitual bedtime was between 2100 and 2400 and wake time between 0500 and 0800 on at least 5 of 7 days of the week with occasional exceptions allowed. Participants were on a day-shift schedule for at least 3 weeks prior to the first data collection period.

Exclusion criteria were used to ensure participants did not have certain characteristics to avoid potential confounding effects. Participants were excluded for any tobacco use during the last 3 months; history of significant neurological, psychiatric, or sleep-related problems based on self-reported answers to screening questions; use of any medications that may impact the validity of the results; and excessive alcohol use during the last 6 months (i.e., more than 14 drinks per week; a drink is 0.6 fluid ounces or 14 grams of alcohol). Obese individuals (i.e., individuals with a body mass index (BMI) of 30 or higher) were excluded due to the higher sensitivity to the drug than in non-obese individuals. Pregnant and nursing women were excluded due unknown risks to fetuses and infants.

Duration of study

The in-lab portion of the study consisted of 7 visits to the laboratory. During the first visit, participants were consented according to the protocol after which they were given at least three training sessions as needed on the cognitive tests until they reach stable performance. Measures of balance and postural sway were also taken during this visit. Afterward, participants were given a wrist monitor with instructions on the required sleep timing and duration. Upon arrival for each of the subsequent visits, the data from the wrist monitor were downloaded and checked for sleep schedule and timing compliance. If the participant met the requirements, they continued the study as scheduled. If the sleep requirements were not met, the participant was given the

opportunity to meet the requirements and scheduled later. Only one individual did not meet the sleep requirements; he withdrew from the study due to inability to change sleep habits to the study protocol.

The follow-on visits consisted of two nights and one day, with the first night of the period scheduled only for overnight sleep and served as the adaptation night prior to each drug night. The sleep time resembled the participant's habitual sleep times, with bedtime at 2200 and wake time at 0600. The second night (experimental night) delayed the habitual sleep time to create sleep maintenance insomnia; bedtime was at 0200 with wake time at 1000. Participants received that night's assigned drug 15 minutes prior to lights out. Familiarity sessions for the cognitive tests were given on the second night prior to electrode connections. Following wake time, participants were allowed approximately 45 minutes to dress and eat breakfast, after which they were tested for approximately 8.5 hours and then released. Participants were instructed to not consume caffeine after 1200 (noon) on both study nights and food 2 hours prior to arrival on the second night.

At least 6 days, but not more than 21 days after completion of the first test period, participants returned to the laboratory to complete the second and third test periods, with 6 to 21 days between the second and third test periods. The second and third test periods were exactly like the first period (adaptation night followed by experimental night) except for the medication that was administered during the experimental night. Sleep/wake times were monitored at least 5 days prior to each visit, with required habitual bedtimes at home between 2100 and 2400 and wake times between 0500 and 0800. Participants were required to maintain the requisite sleep times at least 5 of the 7 days monitored, including at least 2 weekend nights (Friday night/Saturday morning through Sunday night/Monday morning). The schedule is shown in Appendix F.

Data Collection

Consent Day

All participants were tested in the NAMRU-D Fatigue Assessment and Countermeasures lab. Participants arrived at the lab on the first visit for informed consent. Three training sessions on the cognitive tests, questionnaires, and balance measures were completed. Before departure, they were provided a wrist monitor and instructions regarding sleep requirements, caffeine and alcohol restrictions, and other information concerning the return visits to the lab. In approximately 7 days, participants returned to the lab for the data collection periods. Two participants had 14 days between two of the conditions.

Test Periods

Three test periods were completed, each consisting of two nights of monitoring and one day of testing. On the first night of each test period, participants arrived around 2000. Electrodes were applied and lights out for bedtime was at 2200; wake time was at 0600 (similar to habitual sleep times). This night served as the adaptation night. A polysomnogram consisting of EEG, EMG, and EOG was recorded throughout the night. Upon awakening, electrodes were removed, and participants were allowed time to shower and eat breakfast as desired and depart the lab with instructions to remain awake throughout the day. They continued to wear their wrist activity monitor to record compliance with this requirement. Prior to the experimental night, food intake

was restricted to no later than 2 hours prior to arrival at the lab due to the delayed peak drug concentration when food is consumed near dose administration. In addition, due to the potential interaction with alcohol, all participants were restricted from any alcohol intake 12 hours prior to reporting to the lab. Caffeine intake was not allowed after noon. A compliance questionnaire was completed to assure these restrictions were met (Appendix G). If they were not, the participant was not allowed to continue. For this second night in the lab, sleep time was phase-delayed relative to habitual sleep time, imposing sleep maintenance insomnia. Participants were required to stay awake until they arrived at the lab around 2100. A familiarity test session was administered prior to electrode application. Electrodes were applied and drug administration was at 0145. Lights out occurred 0200 and polysomnography was recorded throughout the sleep period. After a wake time of 1000, a balance measure was taken within 5 minutes of rising. Afterward, electrodes were removed, and participants were allowed approximately 45 minutes to shower, dress and eat breakfast, after which they completed approximately 8.5 hours of cognitive testing with the first session beginning at 1100 and the last session ending about 1815, for a total of 4 sessions. No caffeine was allowed during the testing period to prevent the alerting effects that may mask potential somnolence from the hypnotic. At the end of the fourth testing session, participants were debriefed and dismissed. The testing schedule for the 2-day test periods is outlined in Table 2.

RESULTS

The SPSS statistical software package (Version 25; International Business Machines Corporation®, Armonk, NY) was used to analyze all data. The analysis was a repeated measures design, with condition (placebo, suvorexant, and zolpidem) and session (sessions 1–4) as the repeated measures. Performance on the tasks, subjective mood, and sleep architecture were analyzed to determine whether the treatment conditions affected any of the measures. Analyses were conducted to directly test the stated hypotheses:

1. Suvorexant will improve sleep maintenance compared to zolpidem and placebo by reducing time awake after sleep onset and extending sleep length.
2. Next-day performance and sleepiness will not be affected by suvorexant or zolpidem as compared to placebo.

A sample of 16 individuals were enrolled in the protocol, with 15 successfully completing all data collection periods. One was dismissed from the study prior to data collection due to not meeting sleep requirements. One participant was excluded due to having a possible sleep disorder. The final sample of 14 participants were between the ages of 22 and 36 ($M = 29.71$; $SD = 5.13$; 6 female). Two male participants were above the BMI criteria of 30 but were allowed to stay in the study. Based on the results of the Horne and Östberg Morningness/Eveningness Questionnaire (MEQ), 2 individuals were definite morning types, 7 were moderate morning types, and 5 were intermediate types. The demographic characteristics of the 14 volunteers are shown in Table 1.

Table 1. Study Demographics

Age	BMI	MEQ	ESS
<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>
29.71 (5.13)	26.92 (3.95)	61.14 (8.82)	5.79 (2.21)

Note. $n = 14$. BMI = Body mass index. MEQ = Morningness/Eveningness Questionnaire. ESS = Epworth Sleepiness Scale.

Data Analysis

The design of the study yielded three drug conditions (placebo, suvorexant, and zolpidem) and four test sessions to investigate the effects of these substances on sleep metrics and next day performance. For most metrics, a two-way repeated-measures analysis of variance (ANOVA) was conducted with condition (placebo, suvorexant, and zolpidem) and session (four time points) as the repeated factors. Some tests had an additional factor analyzed (e.g., balance assessment, ANT). Each analysis yielded three F -tests: a main effect for condition, a main effect for session, and a condition by session interaction (and appropriate interactions for tests with additional factors).

For each sleep metric, a one-way repeated-measures ANOVA was conducted with condition (placebo, suvorexant, and zolpidem) as the repeated factor. Mauchly's Test of Sphericity was used to test the assumption of sphericity. When the sphericity assumption was violated, the Huynh-Feldt correction was used. For all the metrics, statistically significant interactions were followed with an analysis of simple effects and Fisher's Least Significant Difference (LSD) test as appropriate. Statistically significant main effects were followed with the LSD test. Missing data were estimated using the mean of the session within the condition from all participants.

Balance Assessment

The balance assessment data included metrics for path length (in inches), Y standard deviation from center ($Y\ SD$), and X standard deviation from center ($X\ SD$). The data were analyzed with a three-way repeated measures ANOVA with condition (placebo, suvorexant, and zolpidem), session (sessions 1 through 4), and eyes (open and closed) as the repeated measures factors. F -statistics, p -values, and effect sizes (η_p^2) can be found in Table 2. The means and standard errors for the main effect factors of each metric are shown in Tables 3-5.

Table 2. ANOVA Statistics for Balance Assessment Metrics

Metric	Effect	$F(df)$	p	η_p^2
<i>Path Length</i>	Condition Main Effect	$F(2, 26) = 1.805$	.184	.122
	Session Main Effect	$F(2.579, 33.530) = 8.852$	<.001	.405
	Eyes Main Effect	$F(1, 13) = 22.346$	<.001	.632
	Condition $\times$ Session Interaction	$F(5.538, 71.995) = 0.656$	.673	.048
	Condition $\times$ Eyes Interaction	$F(2, 26) = 2.020$	.153	.135
	Session $\times$ Eyes Interaction	$F(4, 52) = 0.289$	.884	.022
	Condition $\times$ Session $\times$ Eyes Interaction	$F(5.410, 70.333) = 1.523$	.189	.105
<i>X SD</i>	Condition Main Effect	$F(2, 26) = 2.464$	.105	.159
	Session Main Effect	$F(2.674, 34.763) = 0.643$	.575	.047
	Eyes Main Effect	$F(1, 13) = 6.357$	.026	.328
	Condition $\times$ Session Interaction	$F(3.381, 43.948) = 1.087$	.369	.077
	Condition $\times$ Eyes Interaction	$F(2, 26) = 0.494$	.616	.037
	Session $\times$ Eyes Interaction	$F(4, 52) = 1.636$	.179	.112
	Condition $\times$ Session $\times$ Eyes Interaction	$F(8, 104) = 1.255$	.275	.088
<i>Y SD</i>	Condition Main Effect	$F(2, 26) = 1.986$	.157	.133
	Session Main Effect	$F(3.014, 39.180) = 2.542$	.070	.164
	Eyes Main Effect	$F(1, 13) = 7.910$	.015	.378
	Condition $\times$ Session Interaction	$F(8, 104) = 1.191$	.311	.084
	Condition $\times$ Eyes Interaction	$F(2, 26) = 7.781$	.002	.374
	Session $\times$ Eyes Interaction	$F(4, 52) = 0.259$	.903	.020
	Condition $\times$ Session $\times$ Eyes Interaction	$F(4.171, 54.227) = 1.232$	.308	.087

Note. Significant results are bolded. Path length was in inches. ANOVA = analysis of variance. X SD = X standard deviation from center. Y SD = Y standard deviation from center.

Table 3. Descriptive Statistics for Main Effect of Condition

Metric	Placebo	Suvorexant	Zolpidem
	$M (SE)$	$M (SE)$	$M (SE)$
Path Length	14.393 (0.732)	14.586 (0.889)	15.353 (0.828)
X SD	0.097 (0.007)	0.110 (0.011)	0.093 (0.013)
Y SD	0.191 (0.010)	0.194 (0.013)	0.209 (0.013)

Note. Path length was in inches. X SD = X standard deviation from center. Y SD = Y standard deviation from center.

Table 4. Descriptive Statistics for Main Effect of Session

Metric	ASAP	T1 (1100)	T2 (1300)	T3 (1500)	T4 (1700)
	$M (SE)$	$M (SE)$	$M (SE)$	$M (SE)$	$M (SE)$
Path Length	16.844 (1.214)	14.357 (0.641)	14.229 (0.872)	14.109 (0.634)	14.348 (0.662)
X SD	0.109 (0.016)	0.097 (0.008)	0.103 (0.012)	0.096 (0.007)	0.096 (0.011)
Y SD	0.217 (0.019)	0.173 (0.011)	0.199 (0.011)	0.209 (0.017)	0.193 (0.012)

Note. Path length was in inches. X SD = X standard deviation from center. Y SD = Y standard deviation from center.

Table 5. Descriptive Statistics for Main Effect of Eyes

Metric	Open	Closed
	<i>M (SE)</i>	<i>M (SE)</i>
Path Length	12.953 (0.626)	16.601 (1.028)
X SD	0.092 (0.007)	0.108 (0.012)
Y SD	0.179 (0.010)	0.218 (0.015)

Note. Path length was in inches. X SD = X standard deviation from center. Y SD = Y standard deviation from center.

Path Length. The assumption of sphericity for the three-way interaction among condition, session, and eyes was violated ($\chi^2(35) = 56.943, p = .018, \varepsilon = .676$). The ANOVA for the interaction was not significant; these results are displayed in Figure 6.

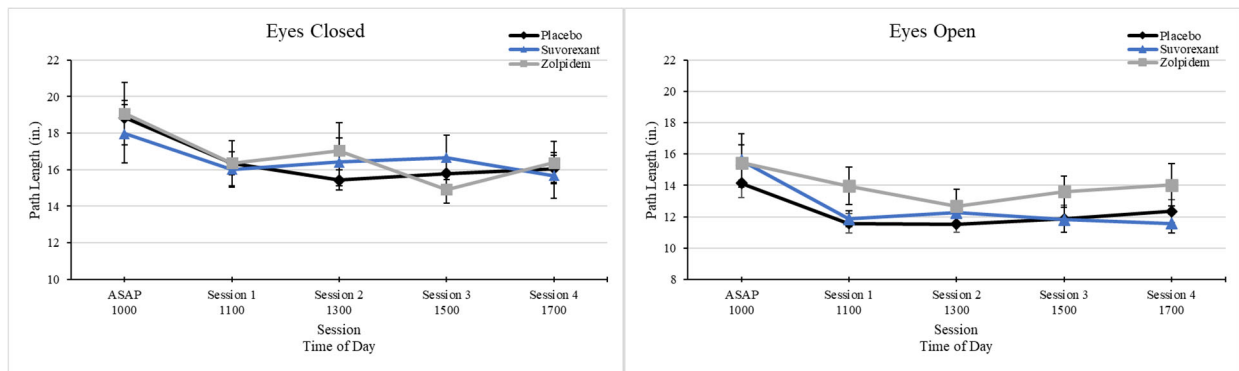


Figure 6. Balance Assessment Path Length Condition $\times$ Session $\times$ Eyes Interaction
Error bars represent standard errors.

The assumption of sphericity was violated for the interaction between condition and session ($\chi^2(35) = 58.137, p = .014, \varepsilon = .692$). The ANOVA for the condition and session interaction was not significant. These results are illustrated in Figure 7.

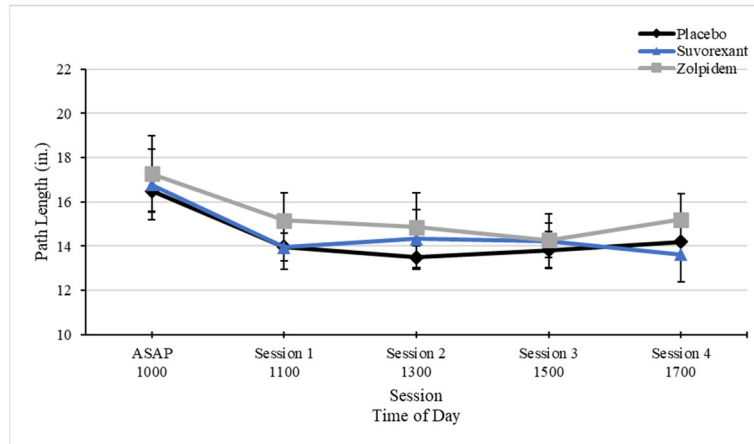


Figure 7. Balance Assessment Path Length Condition $\times$ Session Interaction
Error bars represent standard errors.

The interaction between condition and eyes was not significant. The results of this interaction are illustrated in Figure 8.

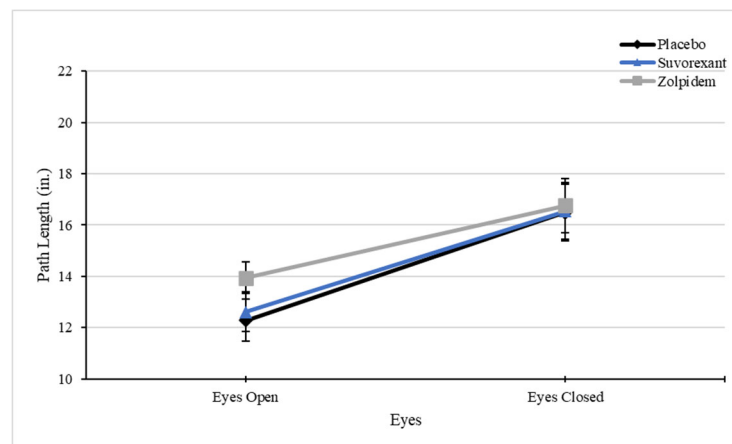


Figure 8. Balance Assessment Path Length Condition $\times$ Eyes Interaction
Error bars represent standard errors.

The ANOVA for the two-way interaction between session and eyes was not significant. These results are illustrated in Figure 9.

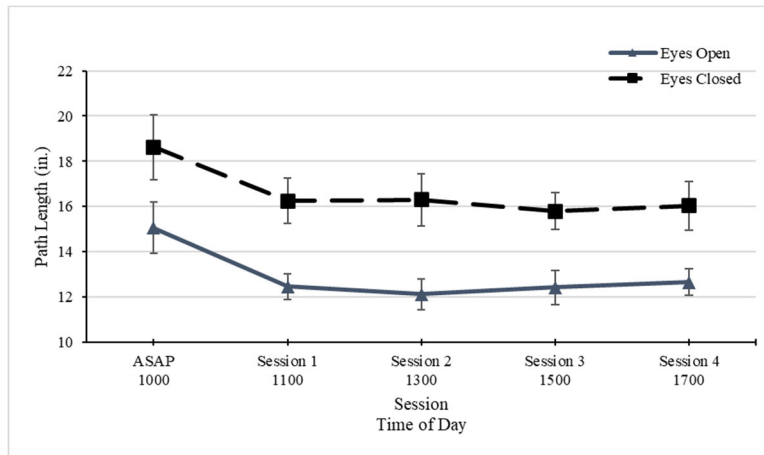


Figure 9. Balance Assessment Path Length Session $\times$ Eyes Interaction
Error bars represent standard errors.

The ANOVA did not reveal a significant main effect of condition. These means and standard errors for this effect can be found in Table 3.

The main effect of session violated the assumption of sphericity ($\chi^2(9) = 21.717, p = .011, \varepsilon = .645$). The ANOVA revealed a significant main effect of session. Post hoc comparisons revealed a significant difference between ASAP and session 1 ($t(134) = 3.298, p = .006$), session 2 ($t(134) = 4.493, p = .001$), session 3 ($t(134) = 3.462, p = .004$), and session 4 ($t(134) = 3.586, p = .003$). The path length for the ASAP session was significantly longer than session 1, session 2, session 3, and session 4. These means and standard errors can be found in Table 4.

The ANOVA revealed a significant main effect of eyes. The path length was significantly shorter during the eyes open assessment than during the eyes closed assessment. The means (*SE*) are 12.953 (0.626) for eyes open and 16.601 (1.028) for eyes closed.

Y Standard Deviation. The assumption of sphericity for the interaction among condition, session, and eyes was violated ($\chi^2(35) = 58.959, p = .011, \varepsilon = .423$). The ANOVA for the condition by session by eyes interaction was not significant. The results are displayed in Figure 10.

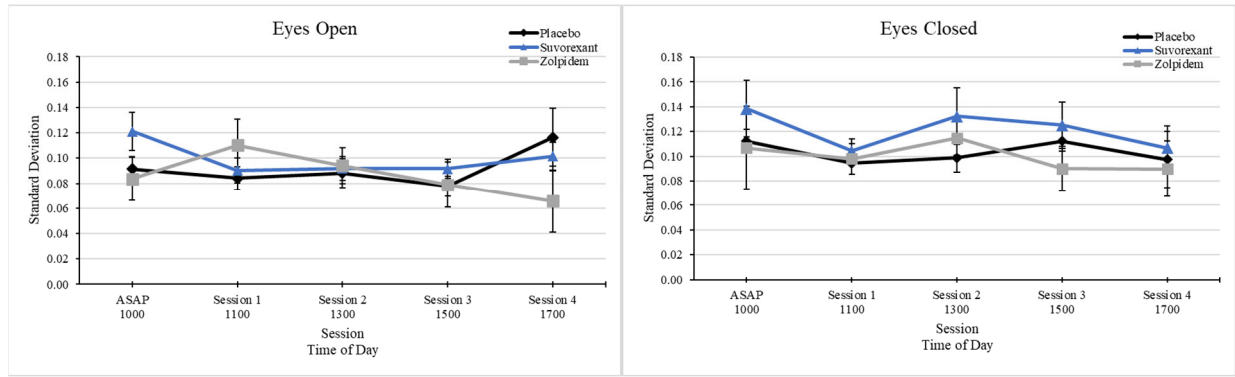


Figure 10. Balance Assessment Y Standard Deviation Condition $\times$ Session $\times$ Eyes Interaction
Error bars represent standard errors.

The ANOVA for the condition and session interaction was not significant. These results are illustrated in Figure 11.

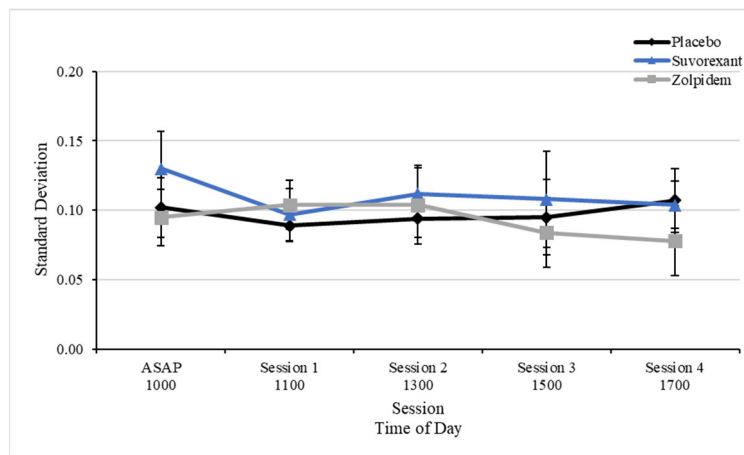


Figure 11. Balance Assessment Y Standard Deviation Condition $\times$ Session Interaction
Error bars represent standard errors.

The ANOVA revealed a significant interaction between condition and eyes. Post hoc analyses indicated significantly lower y-plane deviations when eyes were open than when eyes were closed during the placebo condition ($t(132) = 3.313, p = .006$) and during the suvorexant condition ($t(132) = 4.000, p = .001$). When the eyes were open, path deviations were significantly lower during the placebo ($t(132) = 3.500, p = .003$) and suvorexant conditions ($t(132) = 6.143, p = .007$) compared to the zolpidem condition. The results of this interaction are illustrated in Figure 12.

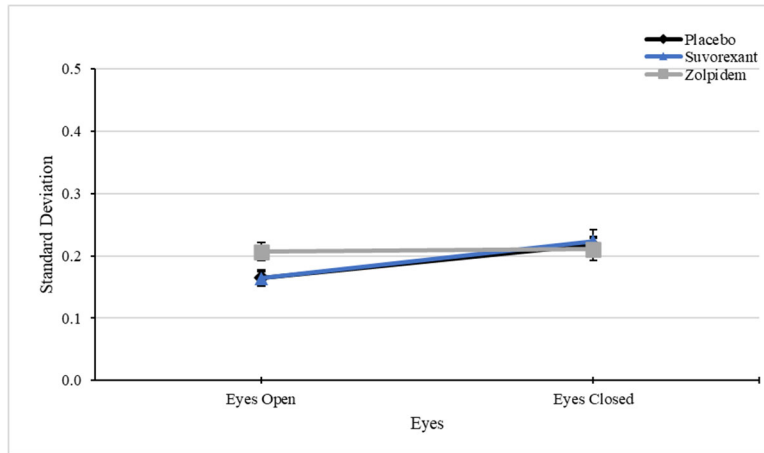


Figure 12. Balance Assessment Y Standard Deviation Condition × Eyes Interaction
Error bars represent standard errors.

The ANOVA for the two-way interaction between session and eyes was not significant. The results are illustrated in Figure 13.

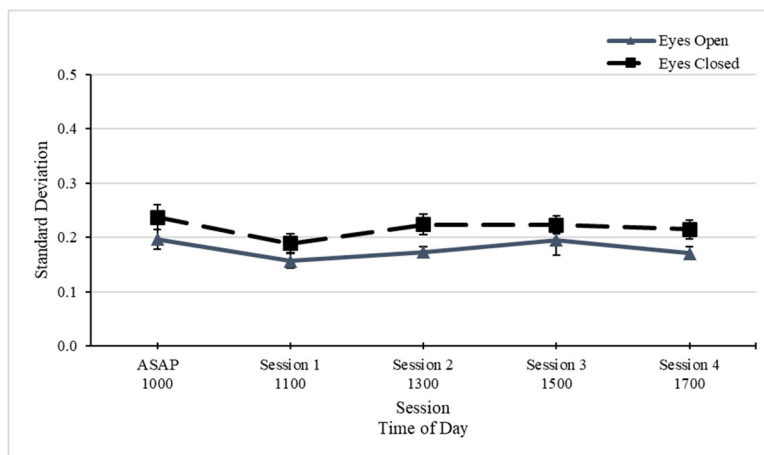


Figure 13. Balance Assessment Y Standard Deviation Session × Eyes Interaction
Error bars represent standard errors.

The ANOVA did not reveal a significant main effect of condition. These means and standard errors for this effect can be found in Table 3.

The main effect of session violated the assumption of sphericity ($\chi^2(9) = 21.204, p = .013, \varepsilon = .605$). The ANOVA revealed a significant main effect of session. Post hoc analyses indicated lower y-plane deviations during session 2 compared to session 1 ($t(13) = 2.316, p = .038$), session 3 ($t(13) = 2.364, p = .030$), and session 4 ($t(13) = 2.250, p = .038$). The results of this analysis can be found in Table #. The ANOVA revealed a significant main effect of eyes. The y-

plane deviation was significantly lower during the eyes open assessment than during the eyes closed assessment ($t(13) = 2.786, p = .015$). The means (SE) are 0.179 (0.010) for eyes open and 0.218 (0.015) for eyes closed.

X Standard Deviation. The ANOVA for the condition by session by eyes interaction was not significant. The results are displayed in Figure 14.

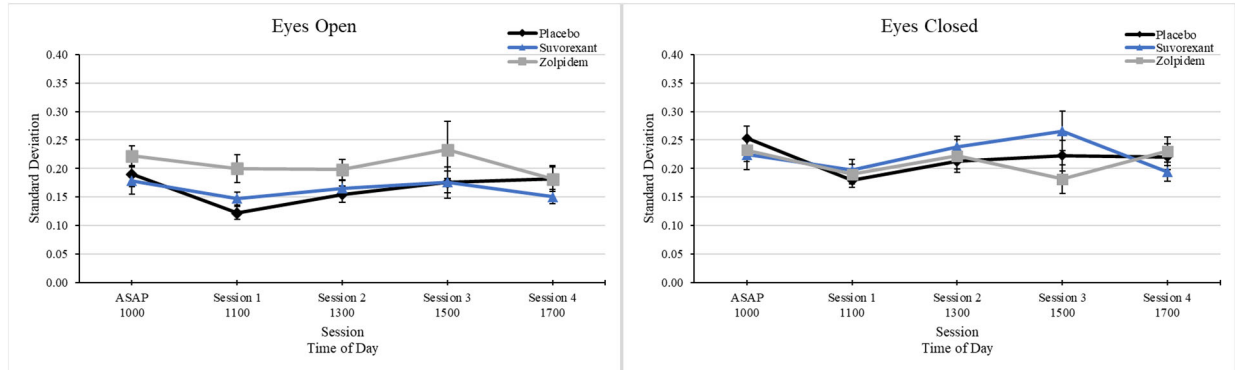


Figure 14. Balance Assessment X Standard Deviation Condition $\times$ Session $\times$ Eyes Interaction Error bars represent standard errors.

The assumption of sphericity for the interaction between condition and session was violated ($\chi^2(35) = 71.436, p = .001, \epsilon = .423$). The ANOVA for the condition and session interaction was not significant. These results are illustrated in Figure 15.

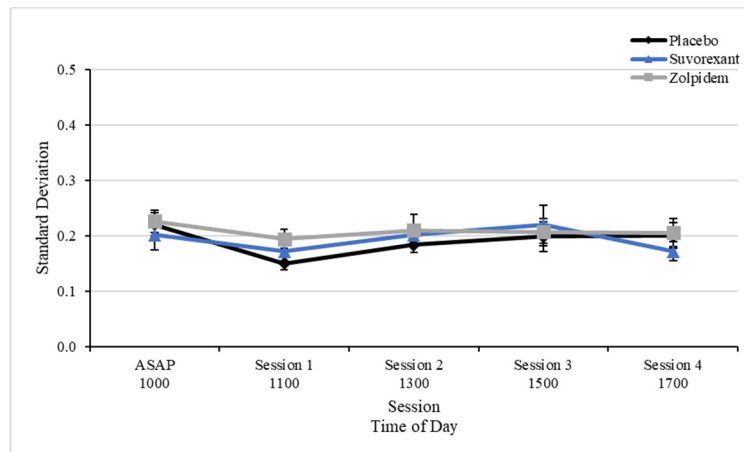


Figure 15. Balance Assessment X Standard Deviation Condition $\times$ Session Interaction Error bars represent standard errors.

The interaction between condition and eyes was not significant. The result of this interaction is illustrated in Figure 16.

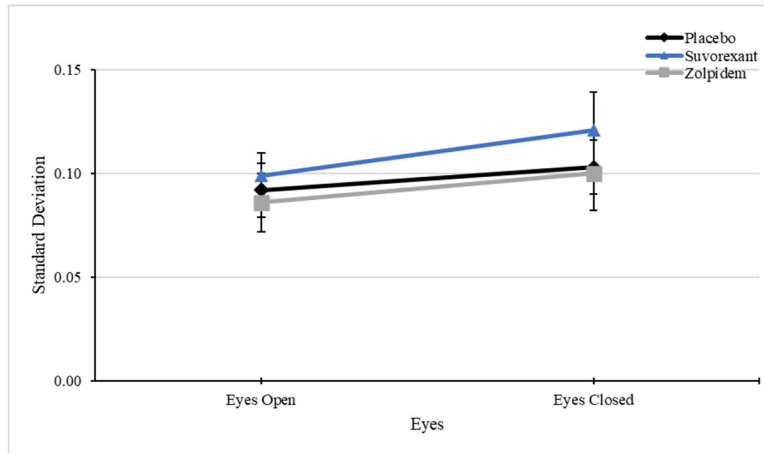


Figure 16. Balance Assessment X Standard Deviation Condition $\times$ Eyes Interaction
Error bars represent standard errors.

The ANOVA for the two-way interaction between session and eyes was not significant. The results are illustrated in Figure 17.

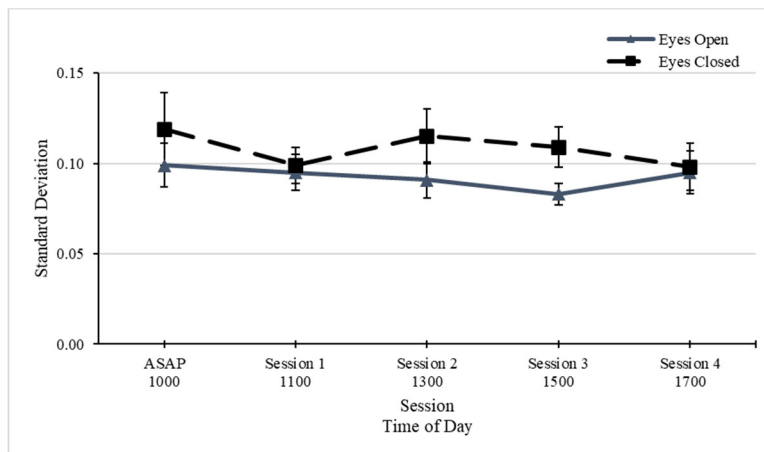


Figure 17. Balance Assessment X Standard Deviation Session $\times$ Eyes Interaction
Errors bars represent standard errors.

The ANOVA did not reveal a significant main effect of condition. These means and standard errors for this effect can be found in Table 3.

The main effect of session violated the assumption of sphericity ($\chi^2(9) = 19.196, p = .025, \epsilon = .669$). The ANOVA did not reveal a significant main effect of session. The results of this analysis can be found in Table 4.

The ANOVA revealed a significant main effect of eyes. The x -plane deviation was significantly lower during the eyes open assessment than during the eyes closed assessment. The means (SE) are 0.092 (0.007) for eyes open and 0.108 (0.012) for eyes closed.

Performance Assessments

Driving Simulation. The driving simulator included metrics for the number of center line crosses (center cross), road edge excursions (road edge), speed exceedances, distance spent outside of lane, time spent outside of lane, time spent over the speed limit, distance spent over the speed limit, brake reaction times (brake RT), modulus, coherence, and delay. F -statistics, p -values, and effect sizes (η_p^2) can be found in Table 6. The means and standard errors for the main effect factors of each metric are shown in Tables 7-8.

Table 6. ANOVA Statistics for Driving Simulator Metrics

<i>Metric</i>	<i>Effect</i>	<i>F(df)</i>	<i>p</i>	η_p^2
<i>Center Cross</i>	Condition Main Effect	$F(2, 26) = 1.221$	.311	.086
	Session Main Effect	$F(3, 39) = 1.388$	.261	.096
	Condition $\times$ Session Interaction	$F(3.973, 51.647) = 0.327$	.857	.025
<i>Road Edge</i>	Condition Main Effect	$F(1.271, 16.522) = 1.440$	.256	.100
	Session Main Effect	$F(1.954, 25.404) = 0.071$	.928	.005
	Condition $\times$ Session Interaction	$F(1.974, 25.668) = 0.887$	.423	.064
<i>Speed Exceedances</i>	Condition Main Effect	$F(2, 26) = 2.593$	.094	.166
	Session Main Effect	$F(3, 39) = 6.574$	.001	.336
	Condition $\times$ Session Interaction	$F(6, 78) = 1.131$	.352	.080
<i>Distance Outside Lane</i>	Condition Main Effect	$F(1.418, 18.431) = 0.782$	.431	.057
	Session Main Effect	$F(1.193, 15.511) = 1.080$	.328	.077
	Condition $\times$ Session Interaction	$F(4.506, 58.581) = 1.052$	.393	.075
<i>Time Spent Outside Lane</i>	Condition Main Effect	$F(1.355, 17.610) = 0.751$	.437	.055
	Session Main Effect	$F(1.204, 15.651) = 0.991$	.351	.071
	Condition $\times$ Session Interaction	$F(5.236, 68.068) = 1.077$	.382	.076
<i>Time Spent Over the Speed Limit</i>	Condition Main Effect	$F(2, 26) = 2.563$	.096	.466
	Session Main Effect	$F(2.112, 27.450) = 1.788$	.185	.350
	Condition $\times$ Session Interaction	$F(4.506, 58.581) = 1.052$	.393	.075
<i>Distance Spent Over the Speed Limit</i>	Condition Main Effect	$F(2, 26) = 1.823$	.182	.123
	Session Main Effect	$F(2.005, 26.068) = 2.063$	.147	.137
	Condition $\times$ Session Interaction	$F(3.487, 45.335) = 0.292$	.859	.022
<i>Brake RT</i>	Condition Main Effect	$F(2, 26) = 4.059$	.029	.238
	Session Main Effect	$F(3, 39) = 5.255$	.004	.288
	Brake Main Effect	$F(1, 13) = 0.433$	.522	.032
	Condition $\times$ Brake Interaction	$F(2, 26) = 0.007$	.993	.001
	Session $\times$ Brake Interaction	$F(3, 39) = 1.171$	.333	.083
	Condition $\times$ Session Interaction	$F(2.895, 37.636) = 1.262$	.301	.088
	Condition $\times$ Session $\times$ Brake Interaction	$F(6, 78) = 0.446$	.846	.033
<i>Modulus</i>	Condition Main Effect	$F(2, 26) = 1.344$	.278	.094
	Session Main Effect	$F(3, 39) = 1.932$	.140	.129
	Condition $\times$ Session Interaction	$F(6, 78) = 2.045$	.069	.136
<i>Coherence</i>	Condition Main Effect	$F(2, 26) = 0.804$	.459	.058
	Session Main Effect	$F(2.108, 27.410) = 2.777$	.077	.176
	Condition $\times$ Session Interaction	$F(6, 78) = 1.118$	.360	.079
<i>Delay</i>	Condition Main Effect	$F(2, 26) = 0.146$	.865	.011
	Session Main Effect	$F(3, 39) = 1.267$	.299	.089
	Condition $\times$ Session Interaction	$F(6, 78) = 0.912$	.491	.066

Note. Significant results are bolded. Metrics evaluating time were recorded in seconds. Metrics evaluating distance were recorded in feet. ANOVA = analysis of variance. Center cross = center line crosses. Road edge = road edge excursions. Brake RT = brake reaction time.

Table 7. Descriptive Statistics for Driving Simulator Metrics by Condition

Metric	Placebo	Suvorexant	Zolpidem
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>
Center Cross	8.661 (3.016)	7.143 (2.641)	6.854 (1.958)
Road Edge	1.108 (0.269)	2.054 (0.655)	2.809 (1.392)
Speed Exceedances	16.982 (0.778)	16.929 (0.741)	18.071 (0.812)
Distance Outside Lane	4.192 (2.368)	3.299 (1.976)	3.283 (1.483)
Time Spent Outside Lane	4.504 (2.534)	3.676 (2.127)	3.422 (1.526)
Time Spent Over Speed Limit	12.151 (0.364)	11.969 (0.273)	12.508 (0.339)
Distance Spent Over Speed Limit	14.711 (0.413)	14.605 (0.321)	15.112 (0.373)
Brake RT	786.491 (16.954)	794.402 (19.774)	770.892 (12.846)
Modulus	0.999 (0.022)	1.021 (0.023)	1.015 (0.023)
Coherence	0.866 (0.018)	0.875 (0.011)	0.865 (0.016)
Delay	1.439 (0.147)	1.457 (0.142)	1.485 (0.149)

Note. Metrics evaluating time were recorded in seconds. Metrics evaluating distance were recorded in feet. Center cross = center line crosses. Road edge = road edge excursions. Brake RT = brake reaction time.

Table 8. Descriptive Statistics for Driving Simulator Metrics by Session

Metric	T1 (1100)	T2 (1300)	T3 (1500)	T4 (1700)
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>
Center Cross	6.810 (1.976)	8.592 (2.913)	7.619 (2.566)	7.190 (2.605)
Road Edge	2.024 (0.600)	2.031 (0.694)	1.881 (0.732)	1.905 (0.797)
Speed Exceedances	16.429 (0.676)	16.714 (0.542)	18.333 (0.983)	17.833 (0.804)
Distance Outside Lane	2.900 (1.308)	4.288 (2.300)	3.324 (1.635)	3.854 (2.457)
Time Spent Outside Lane	3.170 (1.384)	4.556 (2.418)	3.615 (1.774)	4.128 (2.599)
Time Spent Over Speed Limit	11.861 (0.183)	12.080 (0.311)	12.439 (0.411)	12.457 (0.440)
Distance Spent Over Speed Limit	14.353 (0.195)	14.674 (0.351)	15.115 (0.461)	15.095 (0.517)
Brake RT	800.393 (18.308)	785.416 (18.593)	782.000 (16.613)	767.905 (13.239)
Modulus	1.006 (0.020)	1.027 (0.022)	1.009 (0.024)	1.004 (0.023)
Coherence	0.875 (0.010)	0.876 (0.014)	0.850 (0.023)	0.875 (0.014)
Delay	1.487 (0.125)	1.422 (0.133)	1.538 (0.177)	1.395 (0.143)

Note. Metrics evaluating time were recorded in seconds. Metrics evaluating distance were recorded in feet. Center cross = center line crosses. Road edge = road edge excursions. Brake RT = brake reaction time.

Center Cross. Machley's test of sphericity revealed a violation for the condition and session interaction ($\chi^2(20) = 52.090, p < .001, \varepsilon = .662$). The ANOVA did not show a significant interaction between condition and session. The effect is shown in Figure 18.

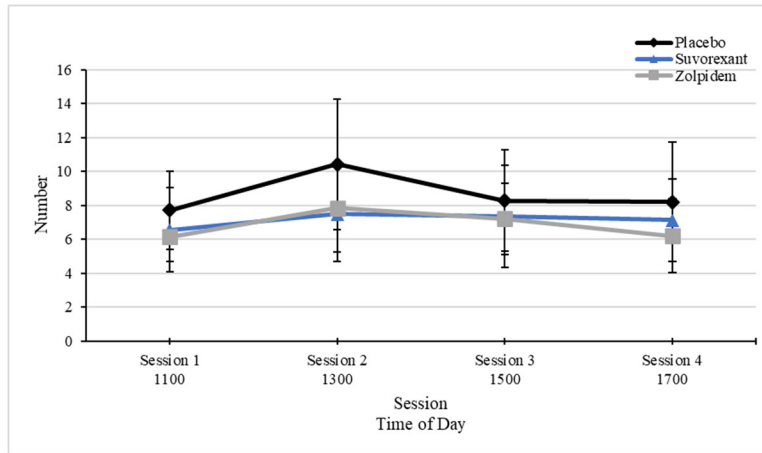


Figure 18. Driving Simulation Center Cross Condition x Session Interaction
Error bars represent standard errors.

The ANOVA did not show a significant main effect of condition or session. The means and standard errors can be found in Tables 7-8.

Road edge. The assumption of sphericity was violated for the interaction between condition and session ($\chi^2(20) = 77.415, p < .001, \varepsilon = .329$). The ANOVA did not show a significant interaction and is displayed in Figure 19.

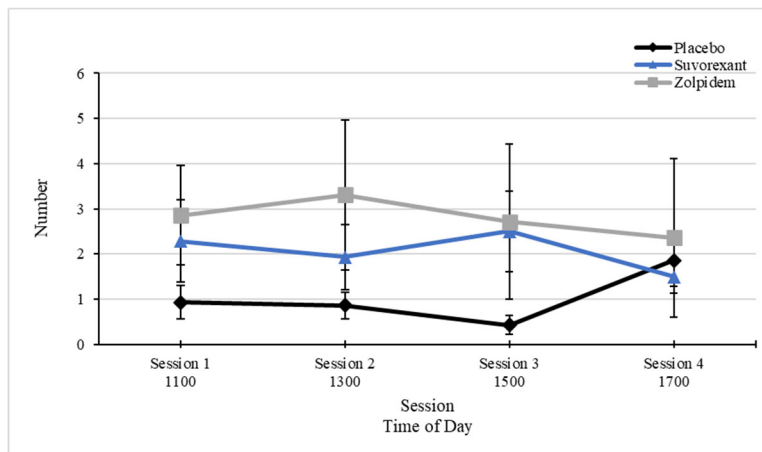


Figure 19. Driving Simulation Road Edge Condition $\times$ Session Interaction
Error bars represent standard errors.

The assumption of sphericity was violated for the main effect of condition ($\chi^2(2) = 12.562, p = .002, \varepsilon = .635$). The ANOVA did not show a significant main effect of condition. The assumption of sphericity was violated for the main effect of session ($\chi^2(5) = 14.116, p = .015, \varepsilon =$

.651). The ANOVA did not show a significant main effect of session. These results are displayed in Table 6.

Speed Exceedances. The repeated measures ANOVA did not reveal a significant interaction between condition and session. The interaction is displayed in Figure 20.

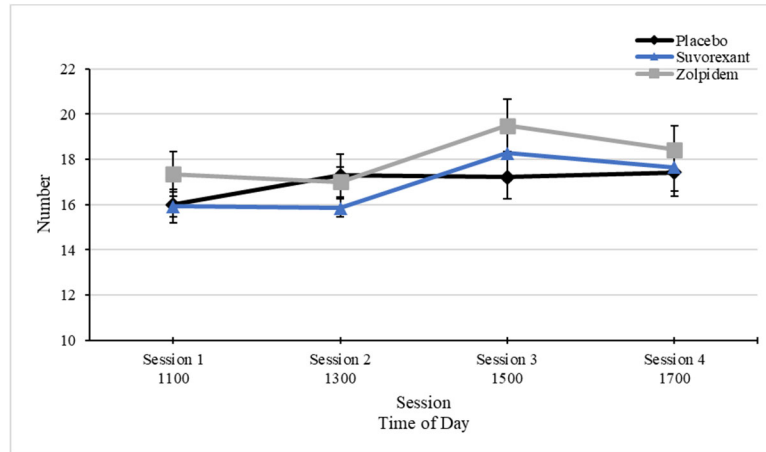


Figure 20. Driving Simulation Speed Exceedances Condition × Session Interaction
Error bars represent standard errors.

The ANOVA did not show a significant main effect of condition. However, it revealed a significant main effect of session. Pairwise comparisons showed a significant difference between sessions 1 and 3 ($t(13) = 3.502, p = .004$), sessions 2 and 3 ($t(13) = 2.676, p = .019$), sessions 1 and 4 ($t(13) = 3.06, p = .009$), and sessions 2 and 4 ($t(13) = 2.465, p = .028$). The trend across comparisons shows later sessions (3 and 4) exhibited significantly more speed exceedances than the early sessions (1 and 2). The means and standard errors are shown in Tables 7-8.

Distance Outside Lane. Machley's test of sphericity revealed a violation for the condition and session interaction ($\chi^2(20) = 8.542, p = .014, \epsilon = .709$). The ANOVA did not show a significant interaction between condition and session. The effect is shown in Figure 21.

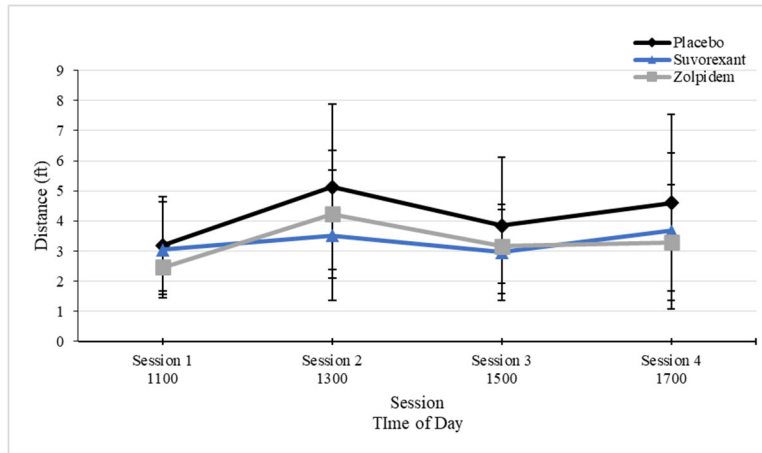


Figure 21. Driving Simulation Distance Outside Lane Condition $\times$ Session Interaction
Error bars represent standard errors.

Machley's test of sphericity revealed a violation for the condition main effect ($\chi^2(2) = 8.542, p = .014, \varepsilon = .709$). The ANOVA did not show a significant main effect of condition. Machley's test of sphericity revealed a violation for the session main effect ($\chi^2(5) = 44.355, p < .001, \varepsilon = .398$). The ANOVA did not show a significant main effect of session. The means and standard errors can be found in Tables 7-8.

Time Spent Over the Speed Limit. Machley's test of sphericity revealed a violation for the condition and session interaction ($\chi^2(20) = 46.556, p = .001, \varepsilon = .567$). The ANOVA did not show a significant interaction between condition and session. The effect is shown in Figure 22.

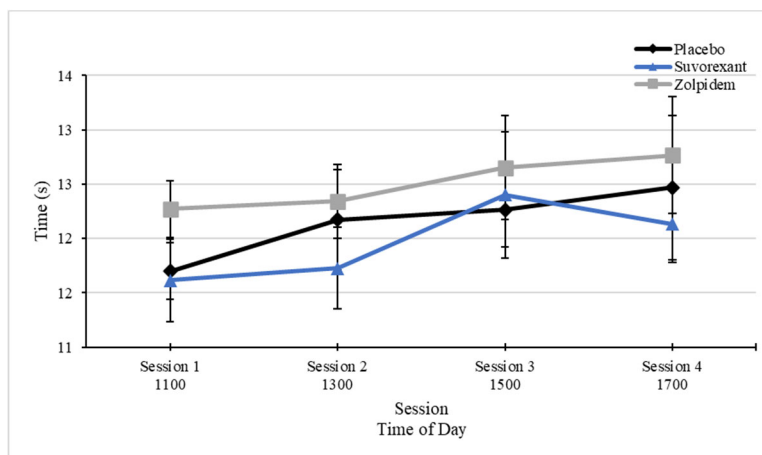


Figure 22. Driving Simulation Time Spent Over the Speed Limit Condition $\times$ Session Interaction
Error bars represent standard errors.

The ANOVA did not show a significant main effect of condition. Machley's test of sphericity revealed a violation for the session main effect ($\chi^2(5) = 18.940, p = .002, \varepsilon = .704$). The ANOVA did not show a significant main effect of session. The means and standard errors can be found in Tables 7-8.

Distance Spent Over the Speed Limit. Machley's test of sphericity revealed a violation for the condition and session interaction ($\chi^2(20) = 42.860, p = .003, \varepsilon = .581$). The ANOVA did not show a significant interaction between condition and session. The effect is shown in Figure 23.

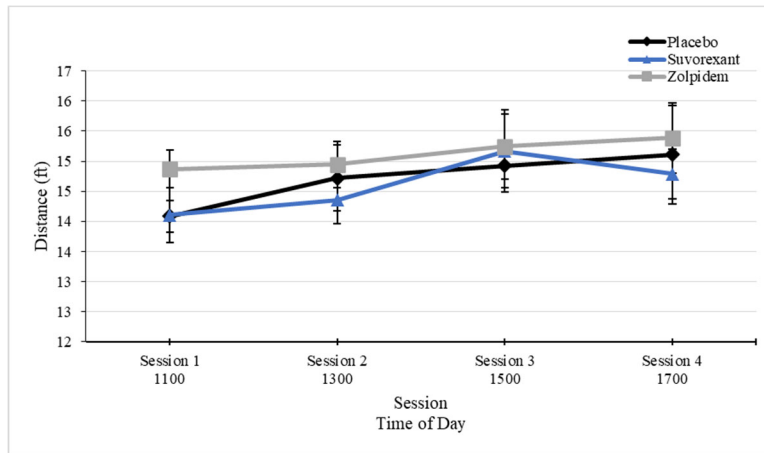


Figure 23. Driving Simulation Distance Spent Over the Speed Limit Condition $\times$ Session Interaction

Error bars represent standard errors.

The ANOVA did not show a significant main effect of condition. Machley's test of sphericity revealed a violation for the session main effect ($\chi^2(5) = 19.230, p = .002, \varepsilon = .668$). The ANOVA did not show a significant main effect of session. The means and standard errors can be found in Tables 7-8.

Brake Reaction Time. The braking task had two incidences in which the participant was required to stop, therefore the three-way repeated measures ANOVA investigated the effects among condition, session, and brake. The assumption of sphericity was violated for the interaction among condition, session, and brake ($\chi^2(20) = 33.019, p = .040, \varepsilon = .755$). The ANOVA did not reveal a significant interaction among condition, session, and brake. The interaction is portrayed in Figure 24.

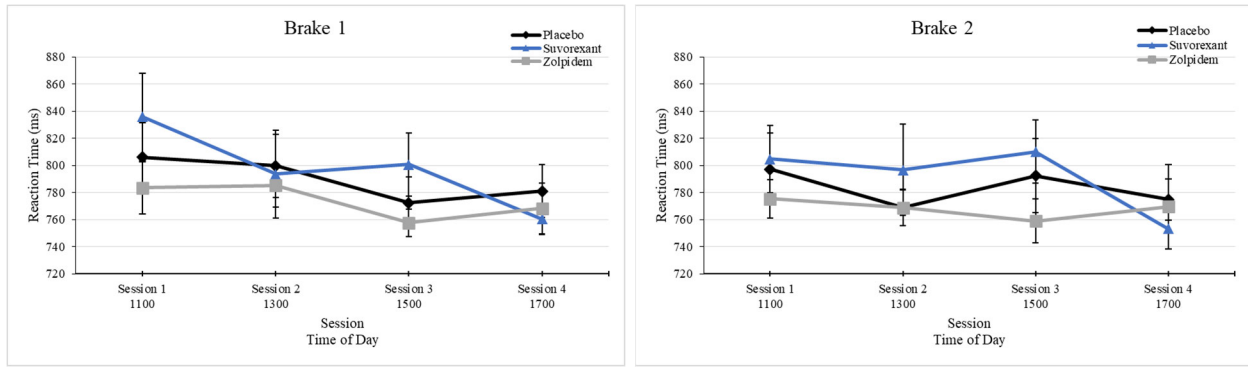


Figure 24. Driving Simulation Brake Reaction Time Condition $\times$ Session $\times$ Brake Interaction Error bars represent standard errors.

The assumption of sphericity was violated for the interaction between condition and session ($\chi^2(20) = 41.903, p = .004, \epsilon = .483$). The ANOVA did not reveal a significant interaction. The interaction is portrayed in Figure 25.

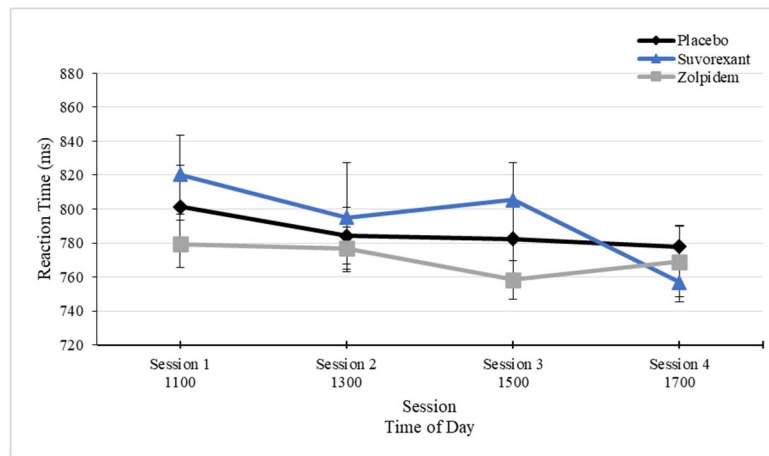


Figure 25. Driving Simulation Brake Reaction Time Condition $\times$ Session Interaction Error bars represent standard errors.

The ANOVA did not reveal a significant interaction between condition and brake. The interaction is portrayed in Figure 26.

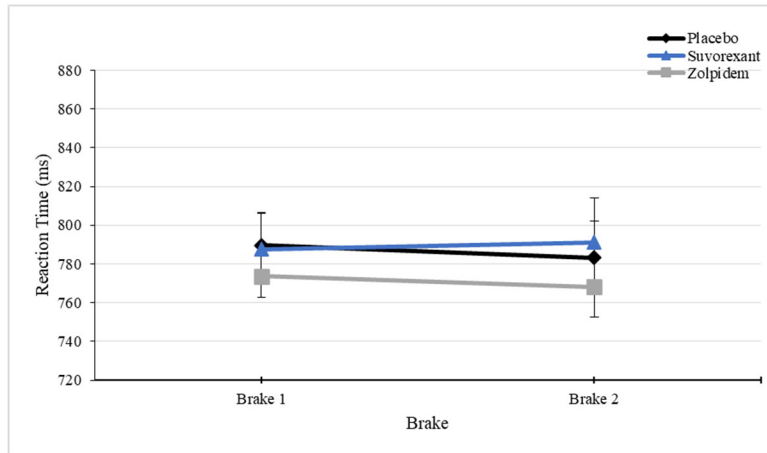


Figure 26. Driving Simulation Brake Reaction Time Condition × Brake Interaction
Error bars represent standard errors.

The ANOVA did not reveal a significant interaction between session and brake. The interaction is portrayed in Figure 27.

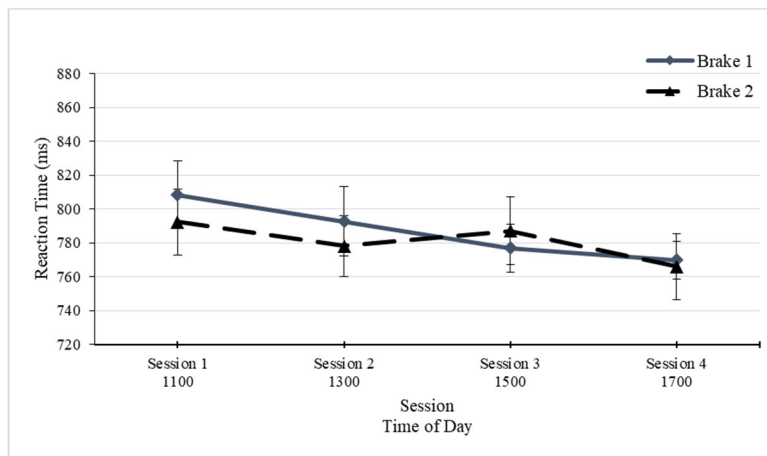


Figure 27. Driving Simulation Brake Reaction Time Session X Brake Interaction
Error bars represent standard errors.

The ANOVA showed a significant main effect of condition with pairwise comparisons revealing a significant difference between suvorexant and zolpidem ($t(13) = 2.487, p = .027$); breaking reaction times were significantly faster in the zolpidem group than in the suvorexant group. These means and standard errors are displayed in Table 7.

The ANOVA revealed a significant main effect of session. Follow-up pairwise comparisons revealed a significant difference between session 1 and session 4 ($t(13) = 2.68, p = .019$) and

between session 2 and 4 ($t(13) = 2.54, p = .0259$); reaction times during sessions 1 and 2 were slower than during session 4. Means and standard errors are displayed in Table 8.

The ANOVA did not reveal a significant main effect of brake. The means and standard errors for the first and second brake tasks are 786.959 (14.753) and 780.897 (18.441), respectively.

Modulus. A repeated measures ANOVA did not reveal a significant interaction between condition and session. The effect is shown in Figure 28.

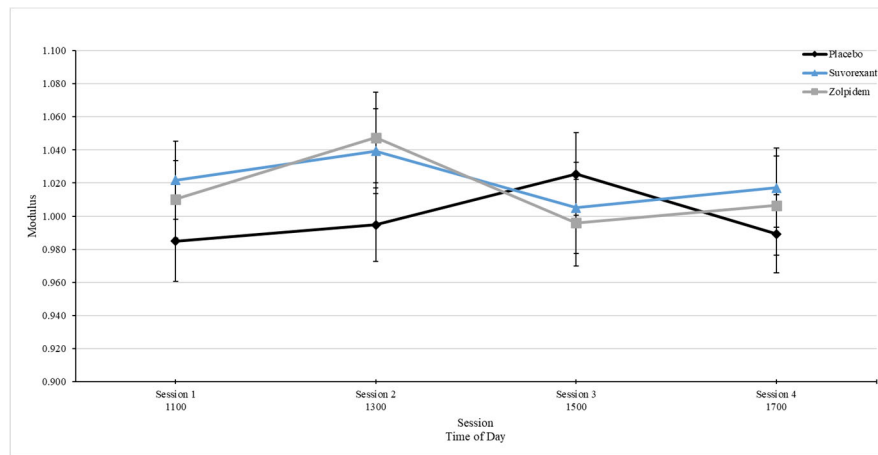


Figure 28. Driving Simulation Modulus Condition X Session Interaction
Error bars represent standard errors.

The repeated measures ANOVA produced two non-significant main effects of condition and session. The means and standard errors are displayed in Tables 7-8.

Coherence. The repeated measures did not reveal a significant interaction between condition and session. The effect is shown in Figure 29.

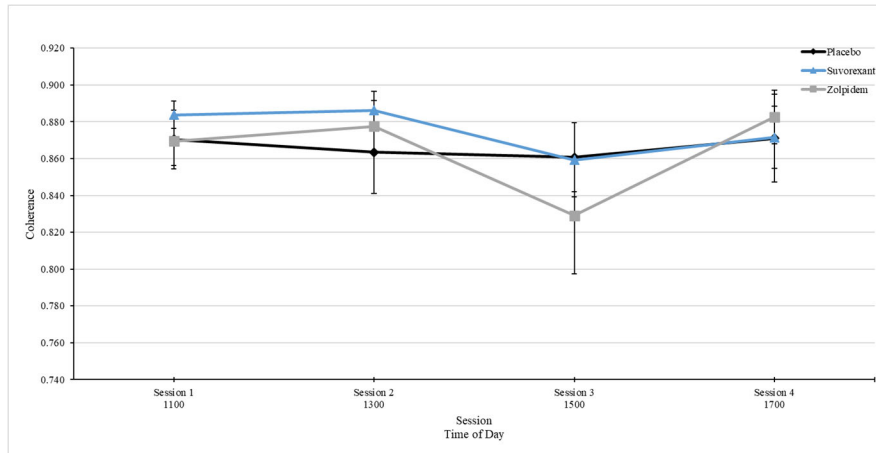


Figure 29. Driving Simulation Coherence Condition X Session Interaction
Error bars represent standard errors.

The ANOVA revealed both main effects of condition and session were not significant. The means and standard errors are displayed in Tables 7-8.

Delay. The repeated measures ANOVA revealed the interaction between condition and session was not significant. The effect is displayed in Figure 30.

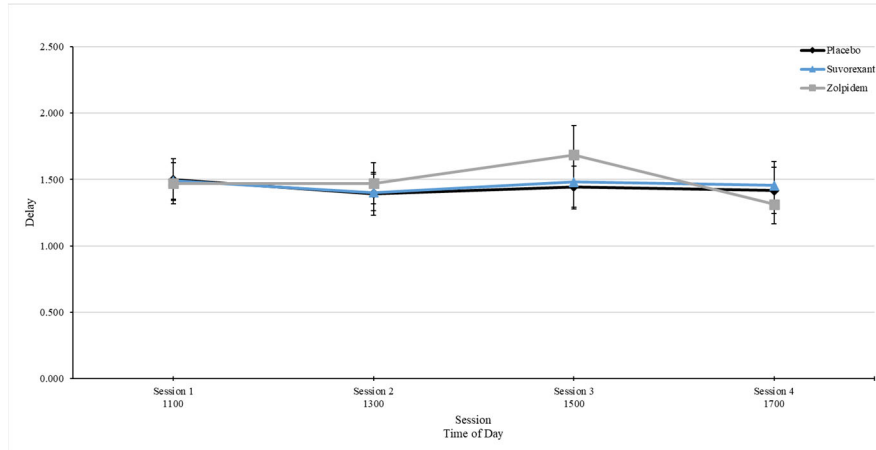


Figure 30. Driving Simulation Delay Condition X Session Interaction
Error bars represent standard errors.

The Attention Network Test (ANT). Metrics for the ANT included calculated values for the alerting response ($RT_{no\ cue} - RT_{central}$), the orienting response ($RT_{central} - RT_{spatial}$), and the executive control ($RT_{incongruent} - RT_{congruent}$) as used by Vilaverde, Correia, and Lima (2020). The data were analyzed with a three-way repeated measures ANOVA with condition (placebo, suvorexant, and zolpidem), session (sessions 1 through 4), and flanker type (congruent and incongruent) as the repeated measures factors. F -statistics, p -values, and effect sizes (η_p^2) can be

found in Table 9. The means and standard errors for the main effect factors of each metric are shown in Tables 10-11.

Table 9. ANOVA Statistics for the ANT

<i>Metric</i>	<i>Effect</i>	<i>F(df)</i>	<i>p</i>	<i>η_p^2</i>
<i>Alerting Response</i>	Condition Main Effect	$F(2, 26) = 0.286$	.754	.021
	Session Main Effect	$F(3, 39) = 1.717$	.179	.117
	Condition $\times$ Session Interaction	$F(6, 78) = 0.998$	.433	.071
<i>Orienting Response</i>	Condition Main Effect	$F(2, 26) = 2.060$	.148	.137
	Session Main Effect	$F(3, 29) = 3.179$	.034	.197
	Condition $\times$ Session Interaction	$F(4.600, 59.805) = 0.953$	.449	.068
<i>Executive Control</i>	Condition Main Effect	$F(2, 26) = 0.044$	.957	.003
	Session Main Effect	$F(3, 39) = 0.361$	.716	.027
	Condition $\times$ Session Interaction	$F(6, 78) = 0.751$	.610	.055

Note. Significant results are bolded. Metrics were recorded in milliseconds.

Table 10. Descriptive Statistics for the ANT by Condition

<i>Metric</i>	<i>Placebo</i>	<i>Suvorexant</i>	<i>Zolpidem</i>
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>
Alerting Response	39.320 (3.629)	43.036 (4.257)	42.638 (5.208)
Orienting Response	48.931 (6.514)	42.931 (4.755)	50.789 (6.834)
Executive Control	70.069 (4.362)	71.719 (5.580)	70.809 (5.237)

Note. Metrics were recorded in milliseconds.

Table 11. Descriptive Statistics for the ANT by Session

<i>Metric</i>	<i>T1 (1100)</i>	<i>T2 (1300)</i>	<i>T3 (1500)</i>	<i>T4 (1700)</i>
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>
Alerting Response	34.414 (4.770)	45.908 (3.062)	42.873 (5.226)	43.463 (4.836)
Orienting Response	45.907 (5.438)	42.290 (5.464)	48.437 (7.068)	53.568 (6.243)
Executive Control	69.467 (4.773)	72.601 (6.106)	72.545 (4.200)	68.849 (4.119)

Note. Metrics were recorded in milliseconds.

Alerting Response. The ANOVA for the condition by session interaction was not significant. These results can be found in Figure 31.

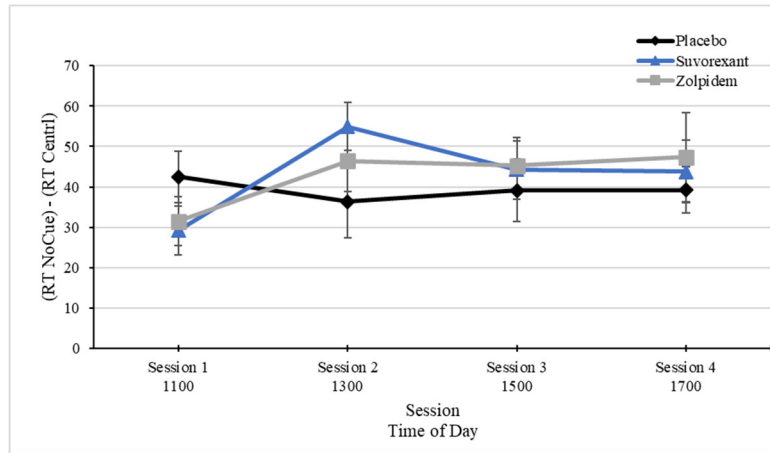


Figure 31. ANT Alerting Response Condition × Session Interaction
Error bars represent standard errors.

The ANOVA for neither the condition main effect nor the session main effect was significant. The means and standard errors can be found in Tables 10-11.

Orienting Response. The assumption of sphericity was violated for the interaction between condition and session ($\chi^2(20) = 38.022, p = .011, \varepsilon = .767$). The ANOVA for the condition by session interaction was not significant. These results can be found in Figure 32.

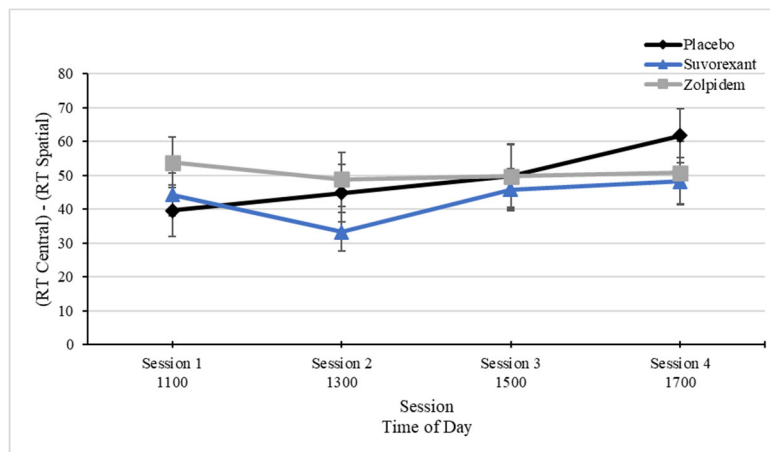


Figure 32. ANT Orienting Response Condition × Session Interaction
Error bars represent standard errors.

The ANOVA for the condition main effect was not significant. The ANOVA revealed a significant main effect of session. Post hoc analyses indicated a lower orienting response during sessions 1 and 2 compared to session 4 ($t(13) = 2.215, p = .045$; $t(13) = 3.856, p = .002$, respectively). Descriptive statistics can be found in Tables 10-11.

Executive Control. The ANOVA for the condition by session interaction was not significant. These results can be found in Figure 33.

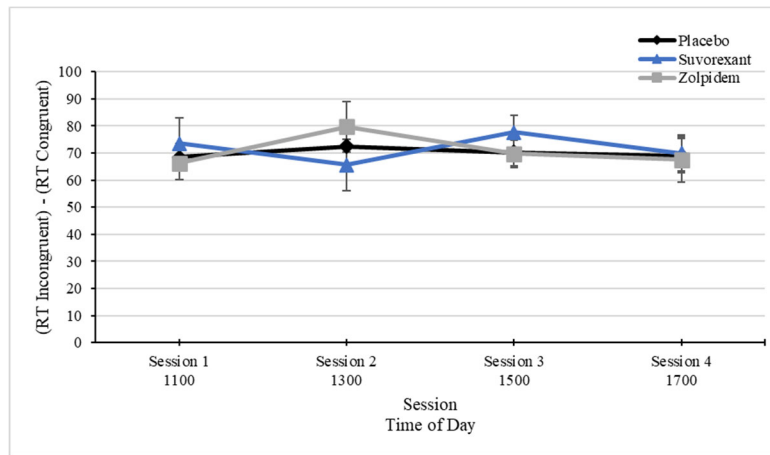


Figure 33. ANT Executive Control Condition $\times$ Session Interaction
Error bars represent standard errors.

The ANOVA did not reveal a significant main effect of condition nor session. The means and standard errors can be found in Tables 10-11.

The ANAM Running Memory Continuous Performance Task. The ANAM CPT data included metrics for mean reaction time (MeanRT), mean reaction time of the correct answers (MeanRTCorr), percentage correct (PercCorr), and throughput (the number of correct responses per minute). F -statistics, p -values, and effect sizes (η_p^2) can be found in Table 12. The means and standard errors for the main effect factors of each metric are shown in Tables 13-14.

Table 12. ANOVA Statistics for the ANAM CPT

<i>Metric</i>	<i>Effect</i>	<i>F (df)</i>	<i>p</i>	η_p^2
<i>Mean RT</i>	Condition Main Effect	$F(2, 26) = 2.408$	.110	.156
	Session Main Effect	$F(2.351, 30.568) = 11.918$	<.001	.478
	Condition $\times$ Session Interaction	$F(6, 78) = 2.452$	.032	.159
<i>Percentage Correct</i>	Condition Main Effect	$F(2, 26) = 1.958$	.161	.131
	Session Main Effect	$F(1.365, 17.743) = 1.349$	.274	.094
	Condition $\times$ Session Interaction	$F(1.969, 25.593) = 1.014$	.376	.072
<i>Mean RT Correct</i>	Condition Main Effect	$F(2, 26) = 2.369$	.113	.154
	Session Main Effect	$F(2.249, 29.236) = 11.363$	<.001	.466
	Condition $\times$ Session Interaction	$F(6, 78) = 2.243$	.048	.147
<i>Throughput</i>	Condition Main Effect	$F(2, 26) = 1.378$	.270	.096
	Session Main Effect	$F(3, 39) = 9.051$	<.001	.410
	Condition $\times$ Session Interaction	$F(6, 78) = .888$	.508	.064

Note. Significant results are bolded. Reaction time (RT) metrics were recorded in milliseconds. ANOVA = analysis of variance.

Table 13. Descriptive Statistics for the ANAM CPT by Condition

Metric	Placebo	Suvorexant	Zolpidem
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>
Mean RT	816.100 (4.140)	812.300 (43.760)	752.670 (42.400)
Percentage Correct	93.988 (1.077)	94.816 (1.008)	93.079 (1.564)
Mean RT Correct	808.756 (43.664)	805.866 (42.894)	747.222 (42.982)
Throughput	72.775 (4.616)	73.652 (4.514)	77.771 (4.668)

Note. Reaction time (RT) metrics were recorded in milliseconds.

Table 14. Descriptive Statistics for the ANAM CPT by Session

Metric	T1 (1100)	T2 (1300)	T3 (1500)	T4 (1700)
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>
Mean RT	858.068 (35.324)	781.081 (42.185)	778.560 (44.901)	757.056 (39.942)
Percentage Correct	93.816 (1.255)	94.786 (0.919)	92.496 (2.004)	94.745 (1.125)
Mean RT Correct	848.985 (35.253)	776.084 (41.685)	772.697 (44.563)	751.359 (40.171)
Throughput	68.177 (3.634)	76.928 (4.488)	75.159 (5.093)	78.667 (4.312)

Note. Reaction time (RT) metrics were recorded in milliseconds.

Mean RT. The ANOVA revealed a statistically significant interaction between condition and session. Post hoc analyses indicated a significant difference in the placebo condition between session 1 and session 2 ($t(13) = 3.90, p = .002$), session 1 and session 3 ($t(13) = 5.88, p < .000$), session 1 and session 4 ($t(13) = 5.37, p < .000$), and session 2 and session 4 ($t(13) = 2.63, p = 0.21$). Within the suvorexant condition, there was a significant difference between session 1 and session 2 ($t(13) = 2.44, p = .030$.) Within the zolpidem condition, there was a significant difference between session 1 and session 2 ($t(13) = 2.78, p = 0.16$). Comparing the condition conditions within each session, the zolpidem condition had significantly faster RTs during

session 1 than the placebo and suvorexant conditions during session 1, but there were no other significant differences in any other session. This effect is displayed in Figure 34.

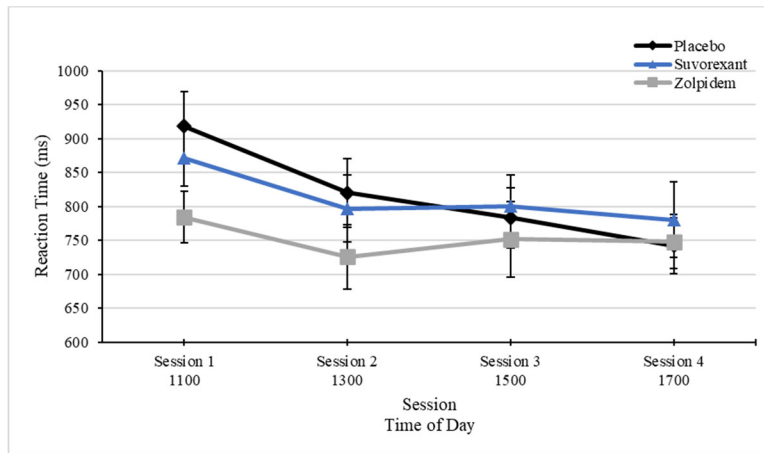


Figure 34. ANAM CPT Mean RT Condition $\times$ Session Interaction
Error bars represent standard errors.

The ANOVA did not indicate a significant main effect of condition. The assumption of sphericity was violated for the main effect of session ($\chi^2(5) = 11.33, p = .046, \varepsilon = .784$). The ANOVA showed a significant main effect of session. Post hoc analyses revealed significantly slower reaction times at session 1 than session 2 ($t(13) = 4.44, p = .001$), session 3 ($t(13) = 3.54, p = .004$), and session 4 ($t(13) = 4.22, p = .001$). The means and standard errors are shown in Tables 13-14.

Mean RT_{Corr}. The repeated measure ANOVA revealed a significant interaction between condition and session ($F(6, 78) = 2.24, p = .048, \eta_p^2 = .147$). Within the placebo condition, post hoc analyses revealed significantly slower RTs at session 1 than at session 2 ($t(13) = 4.03, p = .001$), session 3 ($t(13) = 5.54, p < .001$), and session 4 ($t(13) = 5.53, p = .001$), as well as significantly slower RTs at session 2 than session 4 ($t(13) = 2.61, p = .021$). Within the suvorexant condition, post hoc analyses revealed significantly slower RTs at session 1 than session 2 ($t(13) = 2.27, p = .041$). Within the zolpidem condition, post hoc analyses revealed significantly slower RTs at session 1 than session 2 ($t(13) = 2.47, p = .022$). Post hoc analyses also indicated significantly slower RTs for placebo and suvorexant compared to zolpidem at session 1 ($t(13) = 3.10, p = .009$; $t(13) = 2.20, p = .046$, respectively). These effects are illustrated in Figure 35.

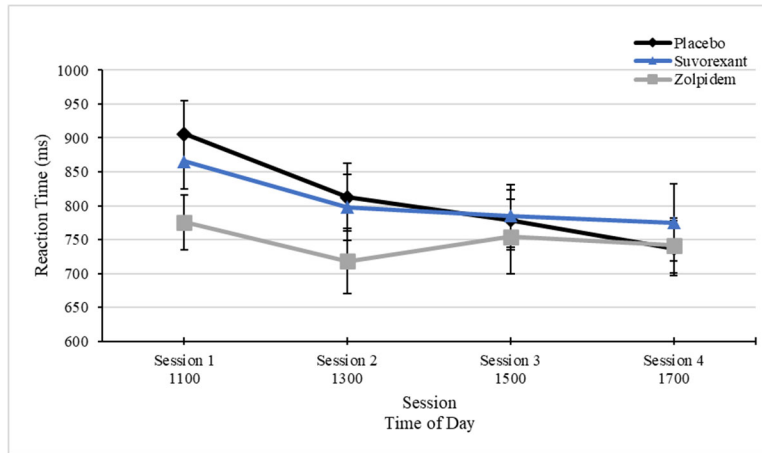


Figure 35. ANAM CPT Reaction Time Correct Answers Condition $\times$ Session Interaction. Error bars represent standard errors.

The assumption of sphericity was violated for the main effect of session ($\chi^2(5) = 12.66, p = .027, \varepsilon = .750$). The ANOVA showed a significant main effect of session ($F(2.25, 29.24) = 11.36, p < .000, \eta_p^2 = .466$) with pairwise comparisons revealing significantly slower RTs at session 1 compared to session 2 ($t(13) = 4.42, p = .001$), session 3 ($t(13) = 3.52, p = .004$), and session 4 ($t(13) = 4.02, p = .001$). The means and standard errors are shown in Tables 13-14.

The main effect of condition was not significant ($F(2, 26) = 2.37, p = .113, \eta_p^2 = .154$). Means and standard errors are shown in Tables 13-14.

PercCorr. The assumption of sphericity was violated for the interaction between condition and session ($\chi^2(20) = 66.69, p < .000, \varepsilon = .33$); the interaction was not significant ($F(1.97, 25.59) = 1.01, p = .422, \eta_p^2 = .072$). These results are displayed in Figure 36.

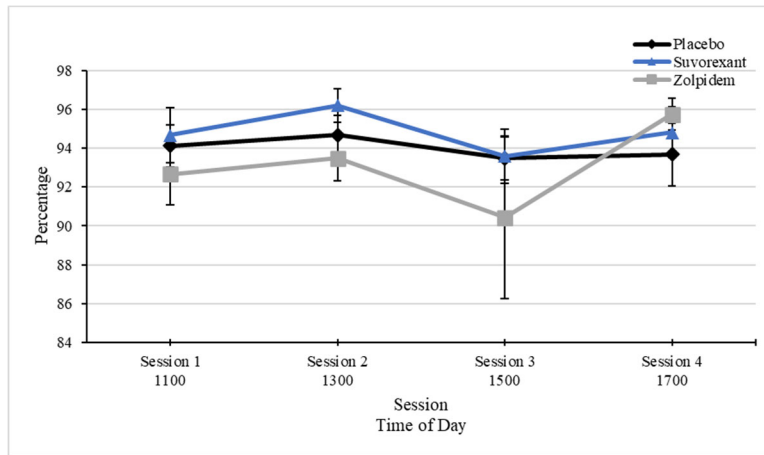


Figure 36. ANAM CPT Percentage of Correct Answers Condition $\times$ Session Interaction
Error bars represent standard errors.

The main effect of condition was not significant. The assumption of sphericity was violated for the main effect of session ($\chi^2(5) = 30.205, p < .000, \epsilon = .43$). The means and standard errors are shown in Tables 13-14.

Throughput. An ANOVA revealed a non-significant interaction between condition and session. The effect is illustrated in Figure 37.

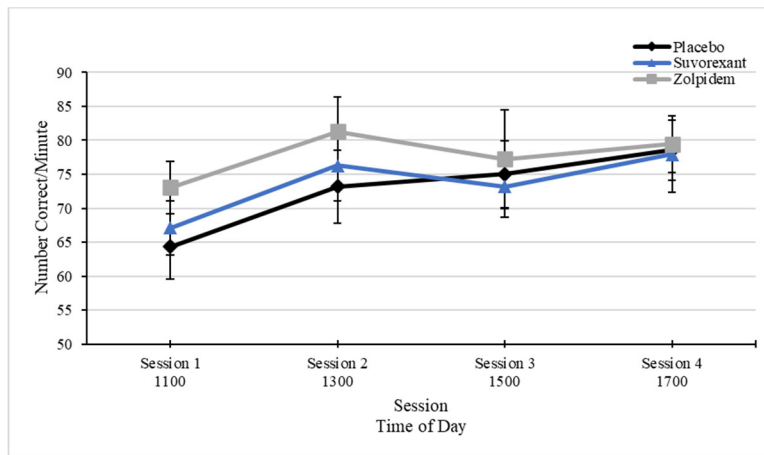


Figure 37. ANAM CPT Throughput Condition $\times$ Session Interaction
Error bars represent standard errors.

The main effect of condition was not significant. The ANOVA revealed a significant main effect of session. Pairwise comparisons revealed a significant difference between session 2 and session 1 ($t(13) = 4.715, p < .001$), session 3 and session 1 ($t(13) = 2.54, p = .025$), and between session

4 and session 1 ($t(13) = 4.29, p = .001$); with sessions 2, 3, and 4 having significantly higher throughput values than session 1. The means and standard errors are shown in Tables 13-14.

The ANAM Go/No-Go Task. Measures for the ANAM Go/No-Go task include number correct responses (NumCorr), number incorrect responses (NumIncorr), mean RT (RT), number missed (NumMissed), percentage correct (PercCorr), and D prime (D'; separation between the means of the signal and the noise distributions), reported in standard deviation units. F -statistics, p -values, and effect sizes (η_p^2) can be found in Table 15. The means and standard errors for the main effect factors of each metric are shown in Tables 16-17.

Table 15. ANOVA Statistics for the ANAM Go/No-Go Task

Metric	Effect	$F(df)$	p	η_p^2
Number Correct Responses	Condition Main Effect	$F(2, 26) = 1.043$	.367	.074
	Session Main Effect	$F(3, 39) = 0.768$	.519	.056
	Condition $\times$ Session Interaction	$F(6, 78) = 0.949$	.465	.068
Number Incorrect Responses	Condition Main Effect	$F(2, 26) = 1.055$	.363	.075
	Session Main Effect	$F(3, 39) = 0.326$	.806	.024
	Condition $\times$ Session Interaction	$F(6, 78) = 1.094$	.373	.078
Mean RT	Condition Main Effect	$F(2, 26) = 0.091$	.913	.007
	Session Main Effect	$F(3, 39) = 2.480$	.075	.160
	Condition $\times$ Session Interaction	$F(6, 78) = 0.383$	.888	.029
Number Missed	Condition Main Effect	$F(2, 26) = 0.687$	.512	.050
	Session Main Effect	$F(3, 39) = 0.893$	.453	.064
	Condition $\times$ Session Interaction	$F(3.473, 45.146) = 1.131$	.351	.080
Percent Correct	Condition Main Effect	$F(2, 26) = 0.395$	.678	.029
	Session Main Effect	$F(3, 39) = 0.254$	.858	.019
	Condition $\times$ Session Interaction	$F(6, 78) = 0.614$	.719	.045
D'	Condition Main Effect	$F(2, 26) = 0.534$	.593	.039
	Session Main Effect	$F(3, 39) = 0.570$	.638	.042
	Condition $\times$ Session Interaction	$F(6, 78) = 0.583$	.743	.043

Note. Mean RT was recorded in milliseconds. ANOVA = analysis of variance.

Table 16. Descriptive Statistics for the ANAM Go/No-Go Task by Condition

Metric	Placebo	Suvorexant	Zolpidem
	$M (SE)$	$M (SE)$	$M (SE)$
Number Correct Responses	95.482 (0.132)	95.393 (0.208)	95.018 (0.406)
Number Incorrect Responses	5.214 (0.584)	4.714 (0.523)	4.893 (0.612)
Mean RT	322.789 (9.415)	325.722 (9.751)	324.766 (7.941)
Number Missed	0.339 (0.110)	0.482 (0.179)	0.661 (0.296)
Percentage Correct	95.364 (0.519)	95.660 (0.535)	95.620 (0.604)
D'	4.462 (0.235)	4.541 (0.298)	4.313 (0.295)

Note. Mean RT was recorded in milliseconds. ANOVA = analysis of variance.

Table 17. Descriptive Statistics for the ANAM Go/No-Go Task by Session

Metric	T1 (1100)	T2 (1300)	T3 (1500)	T4 (1700)
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>
Number Correct Responses	95.548 (0.166)	95.333 (0.195)	95.119 (0.359)	95.190 (0.300)
Number Incorrect Responses	4.881 (0.566)	4.667 (0.466)	5.143 (0.742)	5.071 (0.698)
Mean RT	320.360 (7.711)	328.612 (8.325)	328.375 (8.874)	320.357 (9.095)
Number Missed	0.286 (0.125)	0.524 (0.147)	0.667 (0.288)	0.500 (0.194)
Percentage Correct	95.689 (0.484)	95.664 (0.489)	95.505 (0.643)	95.335 (0.696)
D'	4.589 (0.212)	4.443 (0.307)	4.450 (0.270)	4.272 (0.342)

Note. Mean RT was recorded in milliseconds.

NumCorr. The assumption of sphericity was violated for the interaction effect of condition and session ($\chi^2(20) = 50.789, p < .000, \varepsilon = .581$). An ANOVA revealed the interaction term was not significant. These results can be found in Figure 38.

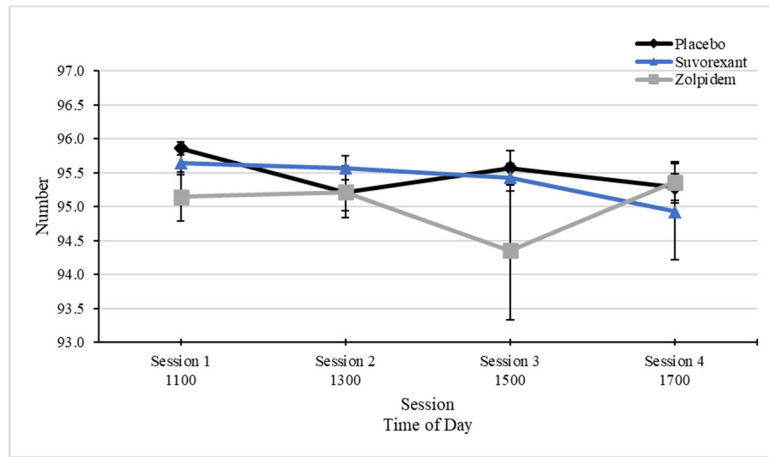


Figure 38. ANAM Go/No-Go Number of Correct Responses Condition $\times$ Session Interaction
Error bars represent standard errors.

The assumption of sphericity was violated for the main effect of condition ($\chi^2(2) = 9.198, p = .010, \varepsilon = .694$). The ANOVA did not reveal a significant main effect for condition or session. These means and standard errors can be found in Tables 16-17.

NumIncorr. The ANOVA did not reveal a significant interaction between condition and session. These results can be found in Figure 39.

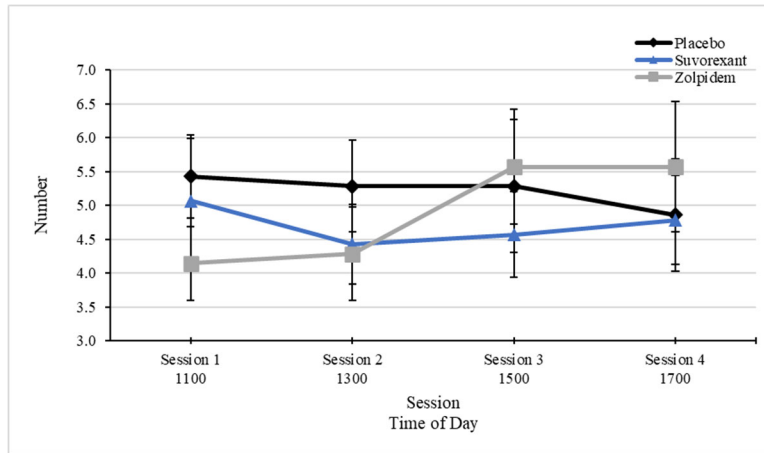


Figure 39. ANAM Go/No-Go Number of Incorrect Responses Condition × Session Interaction
Error bars represent standard errors.

The ANOVA did not reveal a significant main effect of condition or session. The means and standard errors can be found in Tables 16-17.

Reaction Time. The ANOVA did not reveal a significant interaction between condition and session. These results can be found in Figure 40.

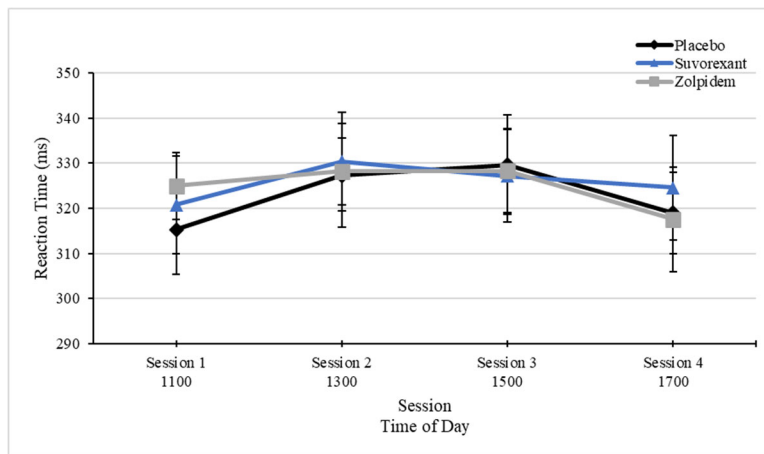


Figure 40. ANAM Go/No-Go Reaction Time Condition × Session Interaction
Error bars represent standard errors.

The ANOVA did not reveal a significant main effect of condition or session. Means and standard errors can be found in Tables 16-17.

Number Missed. The assumption of sphericity was violated for the interaction between condition and session ($\chi^2(20) = 45.038, p = .002, \epsilon = .579$). The ANOVA did not reveal a significant interaction between these factors. The effect is illustrated in Figure 41.

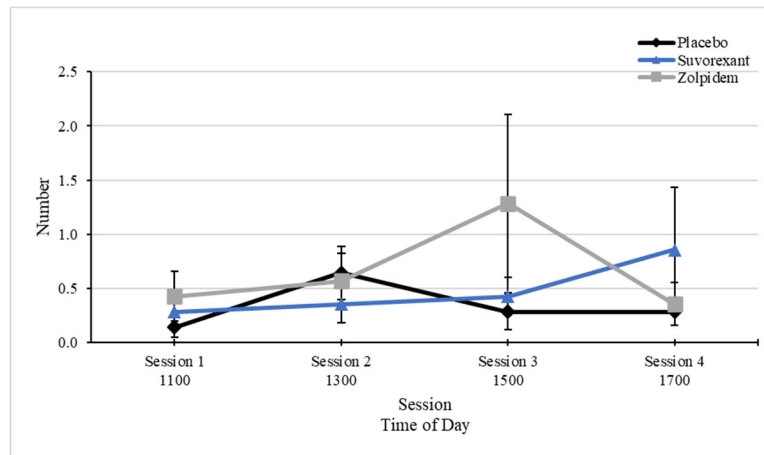


Figure 41. ANAM Go/No-Go Number of Missed Responses Condition $\times$ Session Interaction Error bars represent standard errors.

The ANOVA did not reveal a significant main effect of condition or session. These means and standard errors can be found in Table 16-17.

Correct Responses. The ANOVA did not reveal a significant interaction between condition and session. The results are showcased in Figure 42.

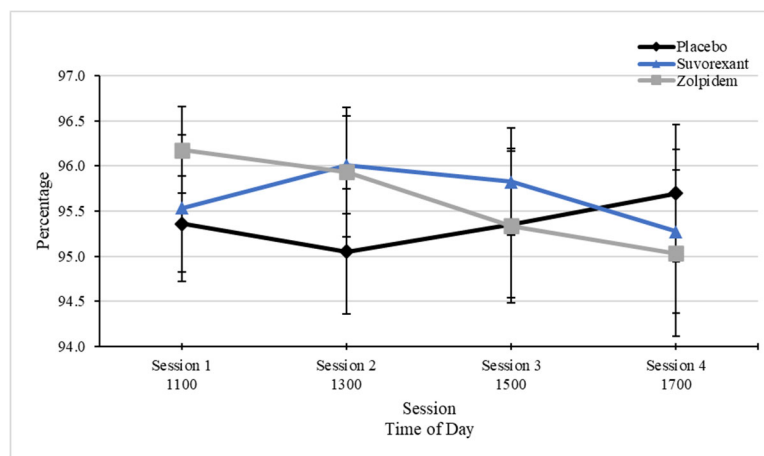


Figure 42. ANAM Go/No-Go Percentage of Correct Responses Condition $\times$ Session Interaction Error bars represent standard errors.

The ANOVA did not indicate a significant main effect of condition or session. The results can be found in Tables 16-17.

D'. The interaction between condition and session, investigated with a repeated measures ANOVA, was not significant. These results can be found in Figure 43.

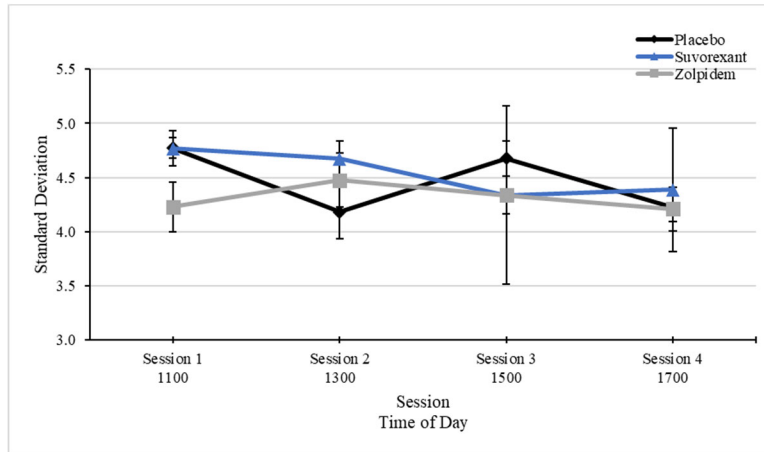


Figure 43. ANAM Go/No-Go *D'* Condition × Session Interaction
Error bars represent standard errors.

The ANOVA did not reveal a significant main effect of condition or session. The means and standard errors can be found in Tables 16-17.

Psychomotor Vigilance Test. The measures analyzed for the PVT include mean reciprocal reaction time (RRT), mean fastest reciprocal reaction time (FRRT), mean slowest reciprocal reaction time (SRRT), lapses, and false starts (FS). *F*-statistics, *p*-values, and effect sizes (η_p^2) can be found in Table 18. The means and standard errors for the main effect factors of each metric are shown in Tables 19-20.

Table 18. ANOVA Statistics for the PVT

<i>Metric</i>	<i>Effect</i>	<i>F(df)</i>	<i>p</i>	η_p^2
<i>Mean RRT</i>	Condition Main Effect	$F(2, 26) = 0.155$	.857	.012
	Session Main Effect	$F(3, 39) = 3.727$	.019	.223
	Condition $\times$ Session Interaction	$F(6, 78) = 1.882$	.094	.126
<i>Mean FRRT</i>	Condition Main Effect	$F(2, 26) = 0.255$	.777	.019
	Session Main Effect	$F(3, 39) = 0.536$	.660	.040
	Condition $\times$ Session Interaction	$F(6, 78) = 1.692$	.134	.115
<i>Mean SRRT</i>	Condition Main Effect	$F(2, 26) = 1.384$	.268	.096
	Session Main Effect	$F(3, 39) = 5.367$	.003	.292
	Condition $\times$ Session Interaction	$F(6, 78) = 0.672$	.672	.049
<i>Lapses</i>	Condition Main Effect	$F(2, 26) = 0.880$	.427	.063
	Session Main Effect	$F(3, 39) = 1.668$	.190	.114
	Condition $\times$ Session Interaction	$F(2.046, 26.596) = 1.863$	.174	.125
<i>False Starts</i>	Condition Main Effect	$F(1.428, 18.562) = 2.794$	.100	.177
	Session Main Effect	$F(1.327, 17.246) = 0.979$	.362	.070
	Condition $\times$ Session Interaction	$F(6, 78) = 0.533$	.782	.039

Note. Significant results are bolded. Reaction time (RT) metrics were recorded in milliseconds. ANOVA = analysis of variance. RRT = reciprocal reaction time. FRRT = fastest reciprocal reaction time. SRRT = slowest reciprocal reaction time.

Table 19. Descriptive Statistics for the PVT by Condition

<i>Metric</i>	<i>Placebo</i>	<i>Suvorexant</i>	<i>Zolpidem</i>
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>
Mean RRT	3.543 (0.109)	3.548 (0.152)	3.503 (0.168)
Mean FRRT	4.807 (0.080)	4.751 (0.143)	4.817 (0.146)
Mean SRRT	2.265 (0.128)	2.301 (0.157)	2.175 (0.187)
Lapses	3.607 (1.152)	5.078 (2.570)	5.750 (2.015)
False Starts	0.071 (0.071)	0.198 (0.144)	0.196 (0.126)

Note. Reaction time (RT) metrics were recorded in milliseconds. RRT = reciprocal reaction time. FRRT = fastest reciprocal reaction time. SRRT = slowest reciprocal reaction time.

Table 20. Descriptive Statistics for the PVT by Session

<i>Metric</i>	<i>T1 (1100)</i>	<i>T2 (1300)</i>	<i>T3 (1500)</i>	<i>T4 (1700)</i>
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>
Mean RRT	3.639 (0.136)	3.475 (0.145)	3.465 (0.132)	3.545 (0.148)
Mean FRRT	4.821 (0.110)	4.755 (0.127)	4.781 (0.109)	4.809 (0.124)
Mean SRRT	2.390 (0.141)	2.153 (0.160)	2.145 (0.151)	2.301 (0.181)
Lapses	3.319 (1.306)	5.405 (2.373)	5.667 (2.092)	4.857 (1.619)
False Starts	0.073 (0.051)	0.214 (0.190)	0.214 (0.147)	0.119 (0.075)

Note. Reaction time (RT) metrics were recorded in milliseconds. RRT = reciprocal reaction time. FRRT = fastest reciprocal reaction time. SRRT = slowest reciprocal reaction time.

Reciprocal Reaction Time. A repeated measures ANOVA was employed to analyze the interaction between condition and session. The ANOVA revealed that the interaction was not significant. These results can be found in Figure 44.

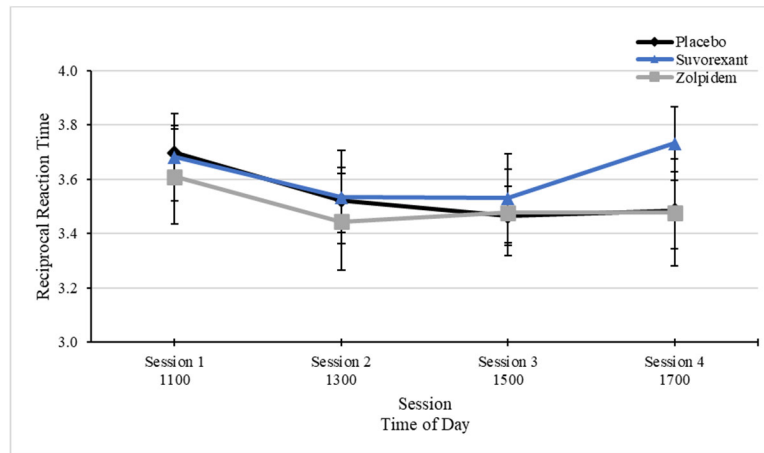


Figure 44. PVT Reciprocal Reaction Time Condition $\times$ Session Interaction
Error bars represent standard errors

The ANOVA did not show a significant main effect of condition but did show a significant main effect of session. Pairwise comparisons revealed a significant difference between session 1 and session 2 ($t(13) = 3.417, p = .005$) and session 1 and session 3 ($t(13) = 2.852, p = .013$). Sessions 2 and 3 were significantly faster than session 1. These results can be found in Table 18.

Fastest Reciprocal Reaction Time. The ANOVA did not show a significant interaction between condition and session. The results can be found in Figure 45.

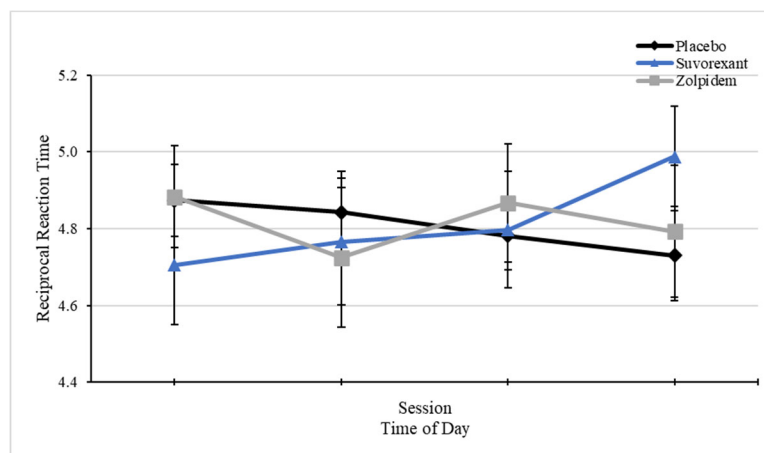


Figure 45. PVT Fastest Reciprocal Reaction Time Condition $\times$ Session Interaction
Error bars represent standard errors.

The ANOVA did not show a significant main effect of condition or session. The means and standard errors can be found in Tables 19-20.

Slowest Reciprocal Reaction Time. The ANOVA did not show a significant interaction between condition and session. These results are depicted in Figure 46.

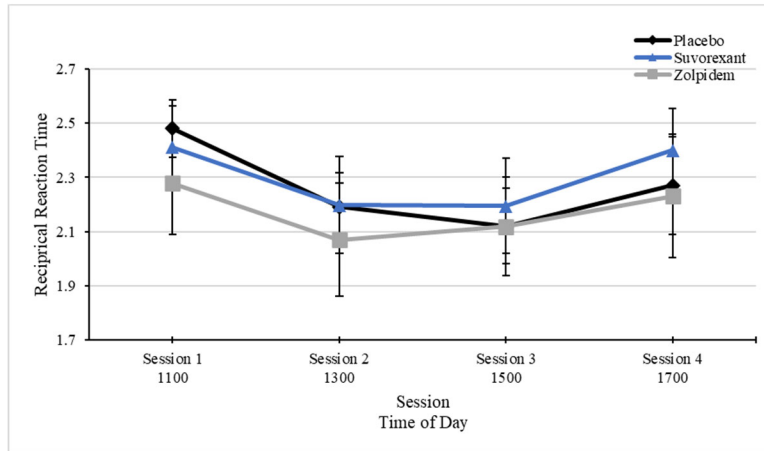


Figure 46. PVT Slowest Reciprocal Reaction Time Condition $\times$ Session Interaction
Error bars represent standard errors.

The ANOVA did not show a significant main effect of condition but did reveal a significant main effect of session. Pairwise comparisons showed a significant difference between session 1 and session 2 ($t(13) = 4.232, p = .001$) and between session 1 and session 3 ($t(13) = 5.00, p < .001$). The reaction times for session 1 ($M = 2.390, SE = 0.141$) were significantly slower than those at session 2 ($M = 2.153, SE = 0.160$) and session 3 ($M = 2.301, SE = 0.181$). These means and standard errors can be found in Tables 19-20.

Lapses. The assumption of sphericity was violated for the interaction between condition and session ($\chi^2(20) = 68.021, p < .001, \epsilon = .341$). The ANOVA did not show a significant interaction between condition and session. These results can be found in Figure 47.

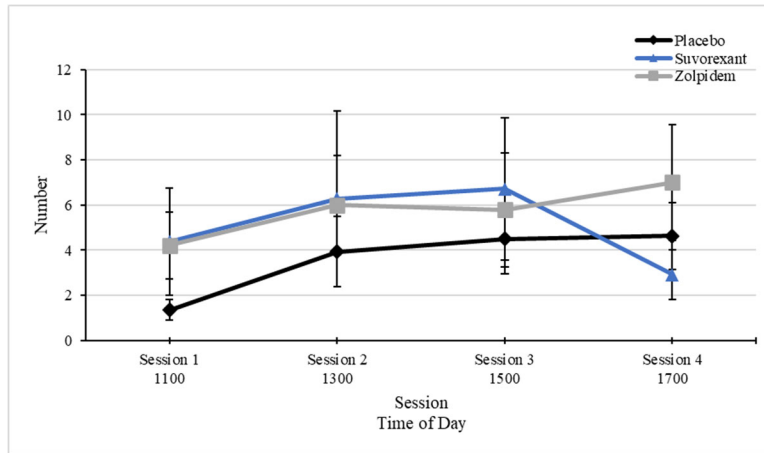


Figure 47. PVT Number of Lapses Condition × Session Interaction
Error bars represent standard errors.

The ANOVA did not reveal a significant main effect of condition or session. The means and standard errors can be found in Tables 19-20.

False Starts. The ANOVA did not show a significant interaction between condition and session. The results can be found in Figure 48.

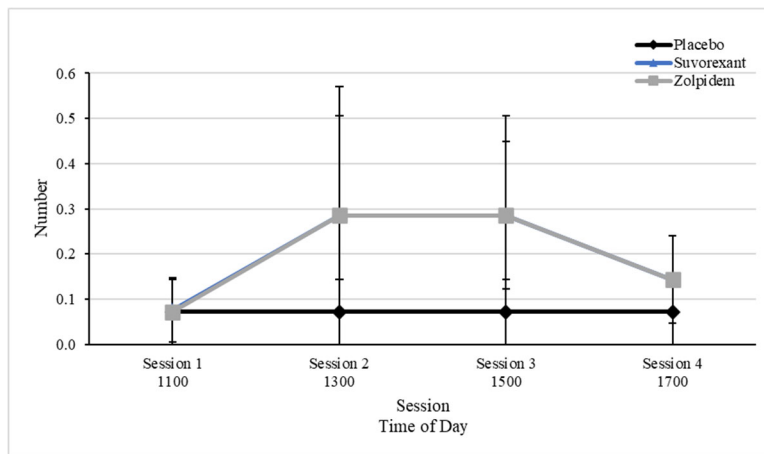


Figure 48. PVT Number of False Starts Condition × Session Interaction
Error bars represent standard errors.

The assumption of sphericity was violated for the main effect of condition ($\chi^2(2) = 8.332, p = .016, \epsilon = .714$) and for the main effect of session ($\chi^2(5) = 31.733, p < .001, \epsilon = .442$). The ANOVA did not show a significant main effect for either factor. The mean and standard errors can be found in Tables 19-20.

Mood Assessments

Mood was measured with the Profile of Mood States (POMS) and the Visual Analogue Scale (VAS). Scores from each condition were analyzed with a repeated measures ANOVA and results are reported below.

Profile of Mood States (POMS). All six factors from the POMS (Tension, Depression, Anger, Vigor, Fatigue, Confusion, and the Total Mood Disturbance scores) were calculated. F -statistics, p -values, and effect sizes (η_p^2) can be found in Table 21. The means and standard errors for the main effect factors of each metric are shown in Tables 22-23.

Table 21. ANOVA Statistics for the POMS

<i>Metric</i>	<i>Effect</i>	<i>F(df)</i>	<i>p</i>	<i>η_p^2</i>
<i>Tension</i>	Condition Main Effect	$F(2, 26) = 1.055$	.363	.075
	Session Main Effect	$F(3, 39) = 1.307$	.286	.091
	Condition $\times$ Session Interaction	$F(4.391, 57.088) = 0.651$	.643	.048
<i>Depression</i>	Condition Main Effect	$F(2, 26) = 0.230$	.796	.017
	Session Main Effect	$F(2.403, 31.236) = 0.454$	.675	.034
	Condition $\times$ Session Interaction	$F(6, 78) = 0.842$	.453	.061
<i>Anger</i>	Condition Main Effect	$F(1.353, 17.589) = 0.946$	.373	.068
	Session Main Effect	$F(1.473, 19.149) = 0.382$	.624	.029
	Condition $\times$ Session Interaction	$F(6, 78) = 0.943$	.470	.068
<i>Vigor</i>	Condition Main Effect	$F(2, 26) = 0.141$	.870	.011
	Session Main Effect	$F(1.767, 22.965) = 10.909$	< .001	.456
	Condition $\times$ Session Interaction	$F(6, 78) = 0.424$	.861	.032
<i>Fatigue</i>	Condition Main Effect	$F(2, 26) = 0.674$	.518	.049
	Session Main Effect	$F(3, 39) = 7.692$	<.001	.372
	Condition $\times$ Session Interaction	$F(6, 78) = 0.248$	.959	.019
<i>Confusion</i>	Condition Main Effect	$F(2, 26) = 0.975$	.390	.070
	Session Main Effect	$F(3, 39) = 3.703$	.019	.222
	Condition $\times$ Session Interaction	$F(6, 78) = 0.149$	.989	.011
<i>TMD Score</i>	Condition Main Effect	$F(2, 26) = 0.315$	.732	.024
	Session Main Effect	$F(3, 39) = 9.086$	< .001	.411
	Condition $\times$ Session Interaction	$F(6, 78) = 0.136$	.991	.010

Note. Significant results are bolded. TMD Score = Total Mood Disturbance score.

Table 22. Descriptive Statistics for the POMS by Condition

Metric	Placebo	Suvorexant	Zolpidem
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>
Tension	11.107 (0.171)	10.786 (0.241)	10.911 (0.249)
Depression	15.214 (0.148)	15.214 (0.146)	15.107 (0.063)
Anger	12.464 (0.358)	12.732 (0.462)	12.625 (0.426)
Vigor	18.536 (1.435)	18.054 (1.785)	18.000 (1.660)
Fatigue	9.411 (0.513)	10.161 (0.741)	9.929 (0.694)
Confusion	9.196 (0.278)	9.607 (0.398)	9.304 (0.427)
TMD Score	38.857 (1.633)	40.446 (2.527)	39.875 (2.233)

Note. TMD Score = Total Mood Disturbance score.

Table 23. Descriptive Statistics for the POMS by Session

Metric	T1 (1100)	T2 (1300)	T3 (1500)	T4 (1700)
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>
Tension	11.143 (0.190)	10.929 (0.219)	10.762 (0.176)	10.905 (0.274)
Depression	15.262 (0.127)	15.143 (0.084)	15.167 (0.097)	15.143 (0.084)
Anger	12.643 (0.438)	12.571 (0.371)	12.595 (0.368)	12.619 (0.433)
Vigor	20.762 (1.541)	18.690 (1.508)	16.833 (1.689)	16.500 (1.604)
Fatigue	8.524 (0.407)	9.881 (0.635)	10.643 (0.717)	10.286 (0.626)
Confusion	9.476 (0.292)	9.262 (0.362)	9.762 (0.459)	8.976 (0.310)
TMD Score	36.286 (1.841)	39.095 (1.954)	42.143 (2.305)	41.381 (1.736)

Note. TMD Score = Total Mood Disturbance score.

Tension. The assumption of sphericity was violated for the condition and session interaction ($\chi^2(20) = 38.875, p = .009, \varepsilon = .167$). The ANOVA did not reveal a significant interaction between condition and session. The results are illustrated in Figure 49.

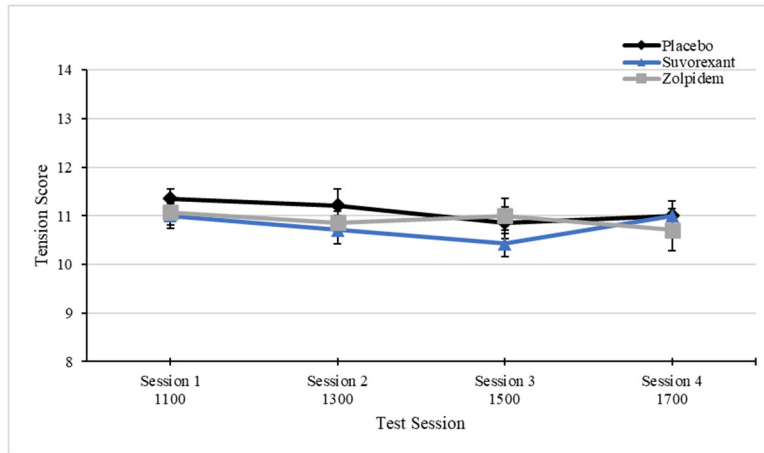


Figure 49. POMS Tension Score Condition $\times$ Session Interaction
Error bars represent standard errors.

The ANOVA did not show a significant main effect of condition or session. The means and standard errors for these results can be found in Tables 22-23.

Depression. The assumption of sphericity was violated for the interaction between condition and session ($\chi^2(20) = 70.832, p < .001, \epsilon = .377$). The ANOVA did not show a significant interaction; these results can be found in Figure 50.

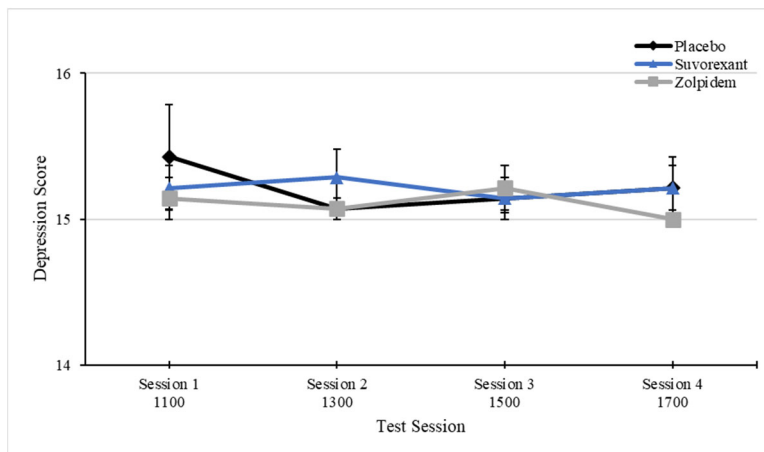


Figure 50. POMS Depression Score Condition $\times$ Session Interaction
Error bars represent standard errors.

The ANOVA did not reveal a significant main effect of condition. The assumption of sphericity was violated for the main effect of session ($\chi^2(5) = 13.204, p = .022, \epsilon = .801$). The ANOVA did not show a significant main effect of session; the means and standard errors can be found in Tables 22-23.

Anger. The ANOVA did not show a significant interaction between condition and session. These results can be found in Figure 51.

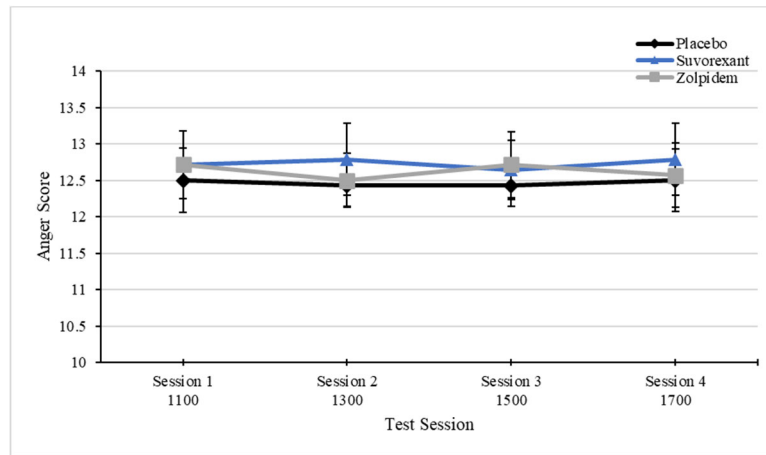


Figure 51. POMS Anger Score Condition $\times$ Session Interaction
Error bars represent standard errors.

The assumption of sphericity was violated for the main effect of session ($\chi^2(5) = 31.536, p < .001, \varepsilon = .491$) and the main effect of Condition ($\chi^2(2) = 31.536, p = .007, \varepsilon = .677$). The ANOVA did not show a significant main effect of either factor. The means and standard errors can be found in Tables 22-23.

Vigor. The ANOVA did not reveal a significant interaction between condition and session. These results are portrayed in Figure 52.

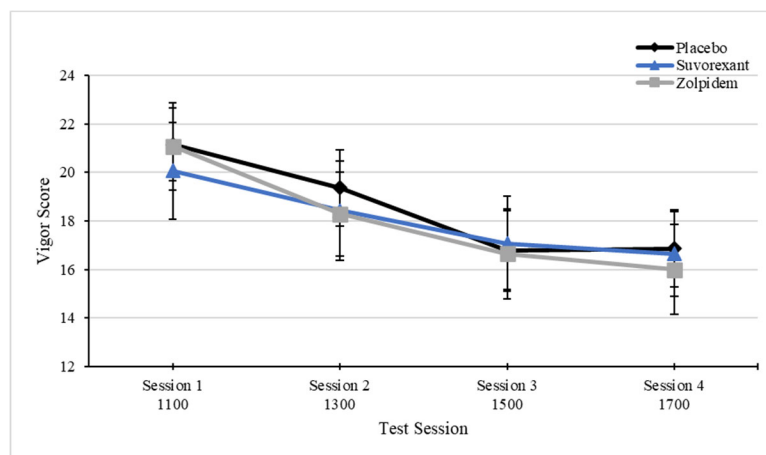


Figure 52. POMS Vigor Score Condition $\times$ Session Interaction
Error bars represent standard errors.

The ANOVA did not reveal a main effect of condition. The main effect of session violated the assumption of sphericity ($\chi^2(5) = 16.360, p = .006, \epsilon = .589$). The ANOVA revealed a significant session main effect; post hoc analyses showed that session 1 reported significantly greater vigor scores than session 2 ($t(13) = 3.378, p = .005$), session 3 ($t(13) = 5.239, p < .001$), and session 4 ($t(13) = 3.385, p = .005$). Session 2 had significantly greater vigor scores compared to Session 3 ($t(13) = 3.909, p = .002$) and Session 4 ($t(13) = 2.335, p = .036$). The means and standard errors can be found in Tables 22-23.

Fatigue. The ANOVA did not indicate a significant interaction between condition and session. These results can be found in Figure 53.

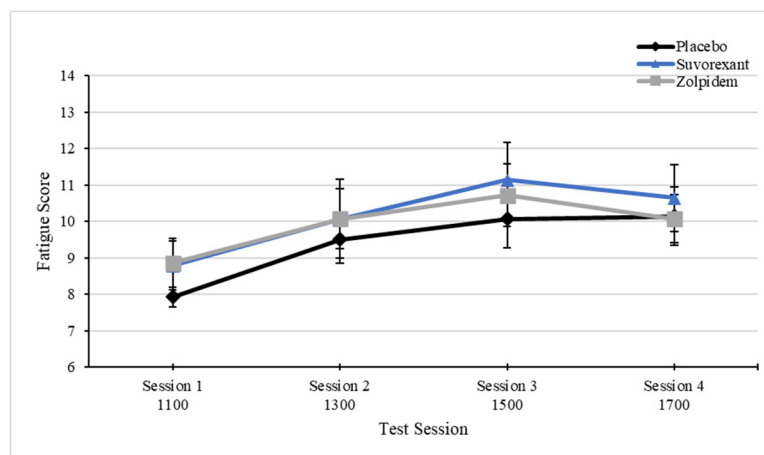


Figure 53. POMS Fatigue Score Condition $\times$ Session Interaction
Error bars represent standard errors.

The ANOVA did not reveal a significant main effect of condition, however there was a significant main effect of session. Post hoc comparisons revealed that session 1 showed lower subjective fatigue scores than sessions 2, 3, and 4 ($t(13) = 2.666, p = .019$; ($t(13) = 3.744, p = .002$; $t(13) = 3.350, p = .005$, respectively). The means and standard errors for these results can be found in Tables 22-23.

Confusion. The ANOVA did not show a significant interaction between condition and session. These results can be found in Figure 54.

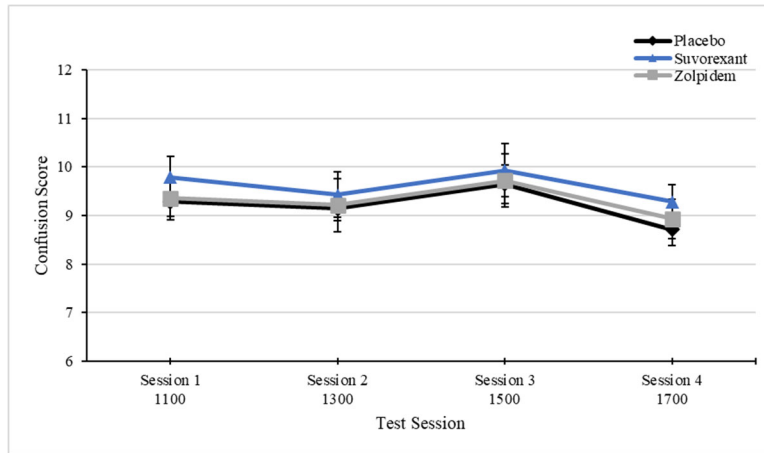


Figure 54. POMS Confusion Score Condition $\times$ Session Interaction
Error bars represent standard errors.

The ANOVA did not show a significant main effect of condition but did reveal a significant main effect of session. Post hoc comparisons revealed session 1 had significantly lower confusion scores compared to session 3 ($t(13) = 2.472, p = .028$) and session 4 ($t(13) = 2.185, p = .047$). The means and standard error for the main effect of session can be found in Tables 22-23.

Total Mood Disturbance Score. The ANOVA did not indicate a significant interaction between condition and session. These results can be found in Figure 55.

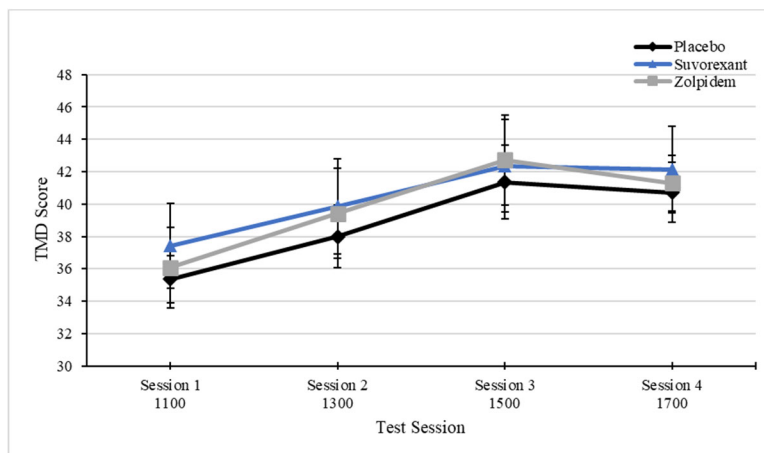


Figure 55. POMS Total Mood Disturbance Score Condition $\times$ Session Interaction
Error bars represent standard errors.

The ANOVA did not show a significant main effect of condition but did reveal a significant main effect of session. Post hoc analyses indicated significantly lower TMD scores during

session 1 compared to session 2 ($t(13) = 3.386, p = .005$), session 3 ($t(13) = 5.014, p < .001$), and session 4 ($t(13) = 3.621, p = .003$). Session 2 had significantly lower scores than session 3 ($t(13) = 2.776, p = .016$). The means and standard errors can be found in Tables 22-23.

Visual Analogue Scale. All eight adjectives from the VAS (alert/able to concentrate, anxious, energetic, confident, irritable, jittery/nervous, sleepy, and talkative) were analyzed with a two-way repeated measures ANOVA, with condition and session as the repeated factors. The results from these analyses are presented below. F -statistics, p -values, and effect sizes (η_p^2) can be found in Table 24. The means and standard errors for the main effect factors of each metric are shown in Tables 25-26.

Table 24. ANOVA Statistics for the VAS

<i>Metric</i>	<i>Effect</i>	<i>F(df)</i>	<i>p</i>	<i>η_p^2</i>
<i>Alert/Able to Concentrate</i>	Condition Main Effect	$F(2, 26) = 0.091$	.913	.007
	Session Main Effect	$F(3, 39) = 11.953$	<.001	.479
	Condition $\times$ Session Interaction	$F(6, 78) = 0.607$	.724	.045
<i>Anxious</i>	Condition Main Effect	$F(1.570, 20.407) = 1.556$	.234	.107
	Session Main Effect	$F(1.889, 24.552) = 1.093$	.348	.078
	Condition $\times$ Session Interaction	$F(2.784, 36.193) = 1.495$	.243	.103
<i>Energetic</i>	Condition Main Effect	$F(2, 26) = 0.318$	.731	.024
	Session Main Effect	$F(3, 39) = 6.881$	<.001	.346
	Condition $\times$ Session Interaction	$F(4.360, 56.685) = 0.600$	.678	.044
<i>Confident</i>	Condition Main Effect	$F(2, 26) = 0.019$	.981	.001
	Session Main Effect	$F(3, 39) = 5.744$	.002	.306
	Condition $\times$ Session Interaction	$F(6, 78) = 0.401$	.877	.030
<i>Irritable</i>	Condition Main Effect	$F(2, 26) = 0.418$	.663	.031
	Session Main Effect	$F(1.924, 25.006) = 1.374$	.271	.096
	Condition $\times$ Session Interaction	$F(2.177, 28.304) = 1.732$	.193	.118
<i>Jittery</i>	Condition Main Effect	$F(1.147, 14.911) = 1.107$	.320	.078
	Session Main Effect	$F(1.443, 18.761) = 1.247$	.297	.088
	Condition $\times$ Session Interaction	$F(2.621, 34.077) = 0.367$	.751	.027
<i>Sleepy</i>	Condition Main Effect	$F(2, 26) = 0.058$	.944	.004
	Session Main Effect	$F(3, 39) = 15.612$	<.001	.546
	Condition $\times$ Session Interaction	$F(6, 78) = 0.728$	.628	.053
<i>Talkative</i>	Condition Main Effect	$F(2, 26) = 0.745$	.484	.054
	Session Main Effect	$F(2.521, 32.772) = 5.178$	.007	.285
	Condition $\times$ Session Interaction	$F(3.853, 50.089) = 0.569$	.680	.042

Note. Significant results are bolded.

Table 25. Descriptive Statistics for the VAS by Condition

Metric	Placebo	Suvorexant	Zolpidem
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>
Alert/Able to Concentrate	53.768 (5.564)	55.679 (5.101)	53.268 (5.300)
Anxious	9.125 (2.716)	5.571 (2.139)	5.304 (2.282)
Energetic	53.482 (4.506)	49.696 (4.687)	49.268 (5.913)
Confident	64.375 (4.327)	63.661 (4.734)	63.518 (5.234)
Irritable	6.571 (2.880)	8.875 (4.994)	7.393 (4.124)
Jittery	6.929 (2.304)	4.250 (1.810)	8.732 (4.054)
Sleepy	43.732 (5.517)	44.232 (6.485)	42.232 (6.380)
Talkative	48.661 (5.203)	44.036 (5.398)	44.232 (5.531)

Table 26. Descriptive Statistics for the VAS by Session

Metrics	T1 (1100)	T2 (1300)	T3 (1500)	T4 (1700)
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>
Alert/Able to Concentrate	68.762 (4.259)	56.262 (4.676)	42.476 (5.937)	49.542 (4.735)
Anxious	7.167 (1.859)	4.810 (1.559)	8.238 (3.132)	6.452 (2.252)
Energetic	63.310 (4.554)	51.286 (4.739)	40.976 (5.800)	47.690 (4.380)
Confident	69.571 (3.779)	62.714 (4.648)	58.357 (4.643)	64.762 (3.963)
Irritable	7.119 (3.079)	6.810 (3.258)	9.786 (5.112)	6.738 (4.085)
Jittery	6.786 (2.400)	6.048 (1.985)	5.333 (2.202)	8.381 (3.265)
Sleepy	27.333 (5.511)	43.786 (5.865)	52.476 (6.286)	50.000 (4.602)
Talkative	51.286 (5.213)	45.429 (5.005)	38.952 (5.468)	46.905 (4.925)

Alert/Able to Concentrate. The ANOVA did not show a significant interaction between condition and session. The results can be found in Figure 56.

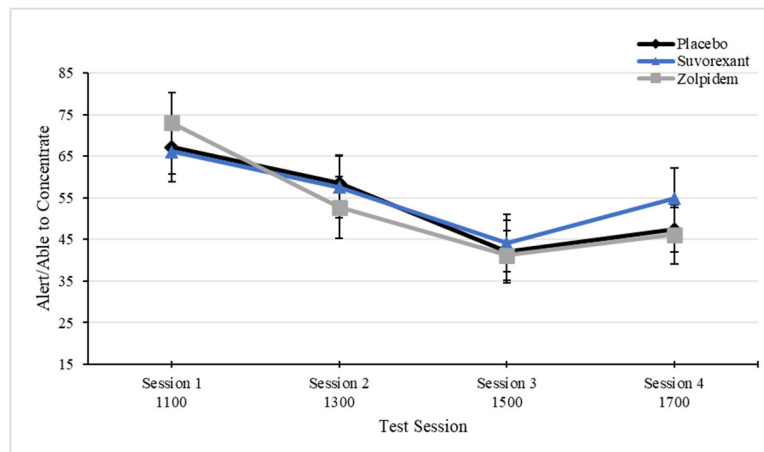


Figure 56. VAS Alert/Able to Concentrate Score Condition × Session Interaction
Error bars represent standard errors.

The ANOVA did not show a significant main effect of condition was not significant, however, the main effect of session was significant. Post hoc comparisons revealed a significant difference between session 1 and session 2 ($t(13) = 3.813, p = .002$), session 3 ($t(13) = 6.883, p < .001$), and session 4 ($t(13) = 3.618, p = .003$) and between sessions 2 and 3 ($t(13) = 4.661, p < .001$). These results demonstrated that session 1 reflected significantly higher alertness scores than all other sessions; session 2 yielded significantly higher alertness than session 3. These means and standard errors for the sessions can be found in Tables 25-26.

Anxious. The assumption of sphericity was violated for the interaction between condition and session ($\chi^2(20) = 84.605, p < .001, \varepsilon = .464$). The ANOVA did not show a significant interaction. The results can be found in Figure 57.

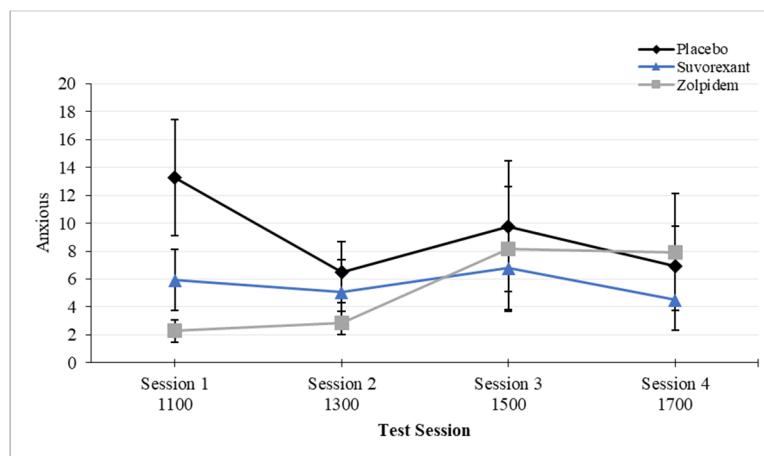


Figure 57. VAS Anxious Score Condition × Session Interaction
Error bars represent standard errors.

The ANOVA did not show a significant main effect of condition. The assumption of sphericity was violated for the main effect of session ($\chi^2(5) = 21.098, p = .001, \varepsilon = .630$). The ANOVA did not show a significant main effect of session; the results can be found in Table 24.

Energetic. The assumption of sphericity was violated for the interaction between condition and session ($\chi^2(20) = 35.400, p = .022, \varepsilon = .727$). The ANOVA did not reveal a significant interaction. The results can be found in Figure 58.

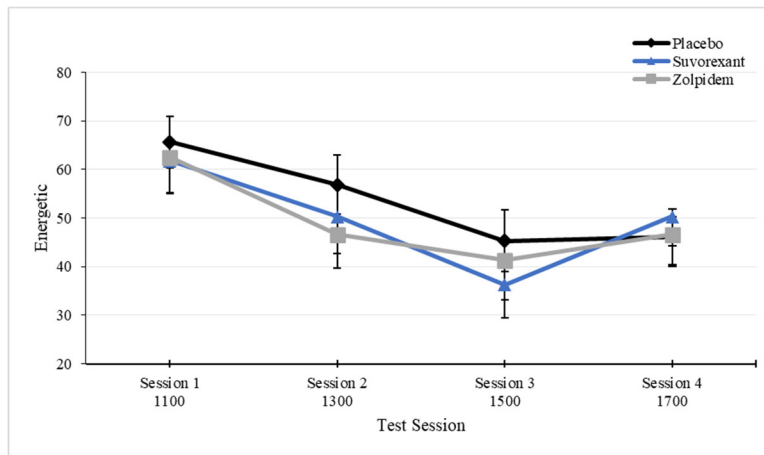


Figure 58. VAS Energetic Score Condition × Session Interaction
Error bars represent standard errors.

The ANOVA did not reveal a significant main effect of condition but did reveal a significant main effect of session. Post hoc comparisons showed a significant difference between session 1 and sessions 2 ($t(13) = 3.254, p = .006$), 3 ($t(13) = 4.743, p < .001$), and 4 ($t(13) = 2.655, p = .020$). These differences demonstrate that session 1 had greater energetic scores than all other sessions. The means and standard errors can be found in Table 25-26.

Confident. The ANOVA did not show a significant interaction between condition and session was not significant. The results can be found in Figure 59.

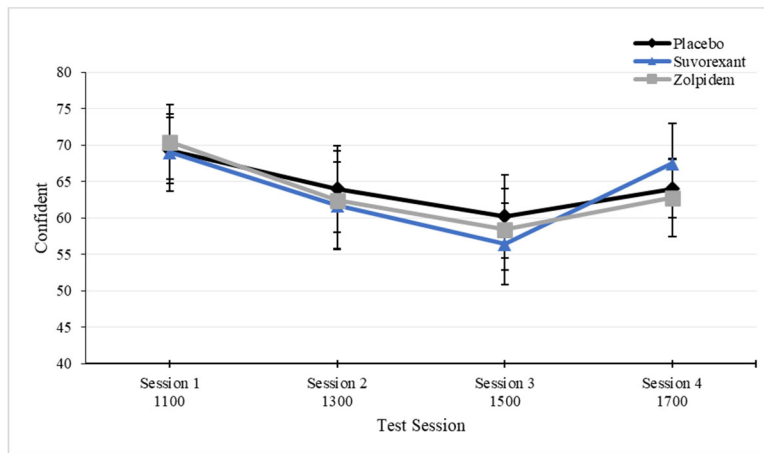


Figure 59. VAS Confident Score Condition × Session Interaction
Error bars represent standard errors.

The ANOVA did not show a significant main effect of condition but did reveal a significant main effect of session. Pairwise comparisons demonstrated that session 1 had higher confusion scores than session 2 ($t(13) = 3.502, p = .004$) and session 3 ($t(13) = 3.750, p = .002$). The means and standard errors can be found in Table 25-26.

Irritable. The assumption of sphericity was violated for the interaction between condition and session ($\chi^2(20) = 119.023, p < .001, \varepsilon = .363$). The ANOVA demonstrated that the interaction was not significant. The effect is illustrated in Figure 60.

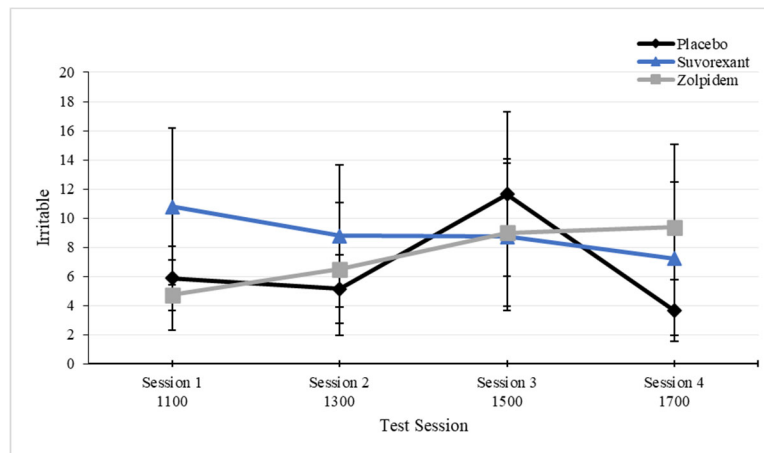


Figure 60. VAS Irritable Score Condition $\times$ Session Interaction
Error bars represent standard errors.

The ANOVA did not show a significant main effect of condition. The assumption of sphericity was violated for the main effect of session ($\chi^2(5) = 16.358, p = .006, \varepsilon = .641$). The ANOVA did not show a significant main effect of session. The means and standard errors for these results can be found in Tables 25-26.

Jittery. The assumption of sphericity was violated for the interaction term between condition and session ($\chi^2(20) = 90.441, p < .001, \varepsilon = .437$). The ANOVA revealed the interaction was not significant. These results can be found in Figure 61.

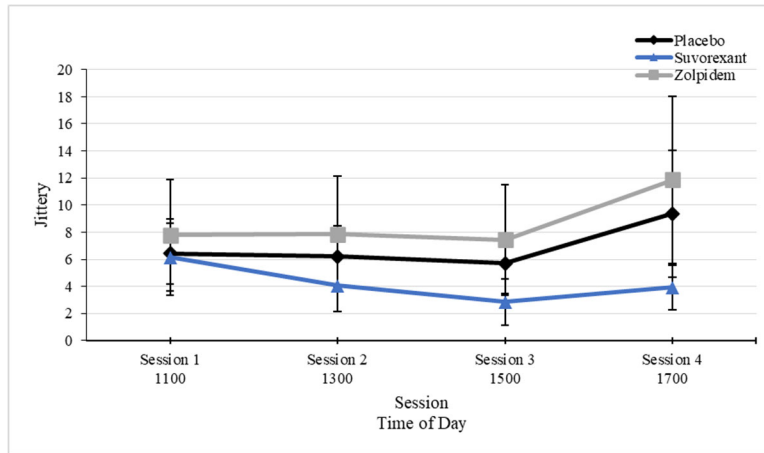


Figure 61. VAS Jittery Score Condition $\times$ Session Interaction
Error bars represent standard errors.

The assumption of sphericity was violated for the main effect of condition ($\chi^2(2) = 18.809, p < .001, \epsilon = .573$) and the main effect of session ($\chi^2(5) = 26.534, p < .001, \epsilon = .481$). The ANOVA did not show a significant main effect of either of these factors. The results can be found in Table 24.

Sleepy. The ANOVA revealed the interaction between condition and session was not significant. These results can be found in Figure 62.

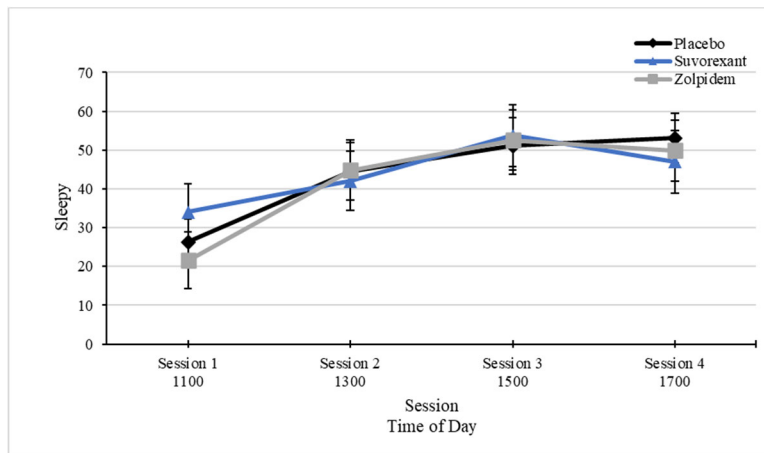


Figure 62. VAS Sleepy Score Condition $\times$ Session Interaction
Error bars represent standard errors.

The ANOVA did not show a significant main effect of condition but did reveal a significant main effect of session. Pairwise comparisons demonstrated that session 1 reported significantly lower sleepiness scores than session 2 ($t(13) = 4.354, p = .001$), session 3 ($t(13) = 6.300, p <$

.001), and session 4 scores ($t(13) = 6.083, p < .001$). Session 2 sleepiness scores were significantly lower than session 3 scores ($t(13) = 3.064, p = .009$). The means and standard errors can be found in Tables 25-26.

Talkative. The assumption of sphericity was violated for the interaction between condition and session ($\chi^2(20) = 40.364, p = .006, \varepsilon = .642$). The ANOVA did not reveal a significant interaction. These results are portrayed in Figure 63.

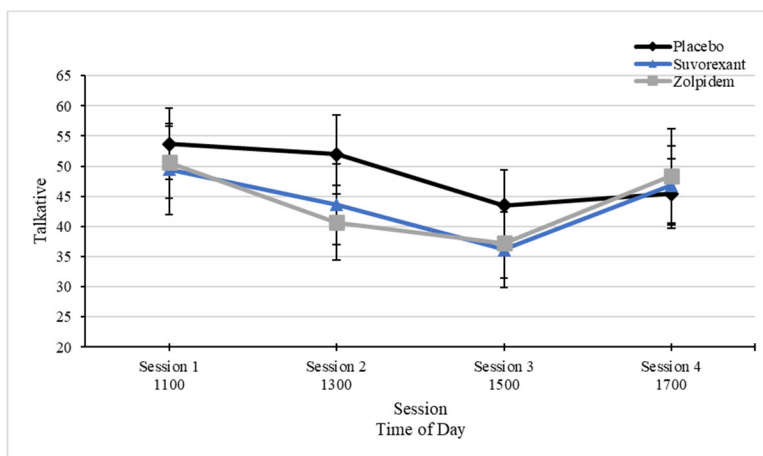


Figure 63. VAS Talkative Score Condition × Session Interaction
Error bars represent standard errors

The ANOVA did not reveal a significant main effect of condition. The assumption of sphericity was violated for the main effect of session ($\chi^2(5) = 16.560, p = .006, \varepsilon = .840$). The ANOVA revealed a significant main effect of session. Post hoc analyses indicated greater talkative scores for session 1 compared with session 2 ($t(13) = 2.199, p = .047$) and session 3 ($t(13) = 3.229, p = .007$). Session 2 exhibited greater talkative scores than session 3 ($t(13) = 3.251, p = .006$). Means and standard errors can be found in Tables 25-26.

Side Effects Questionnaire (SEQ). Side effect endorsements are presented in Appendix H. A Friedman test (the non-parametric alternative to a repeated measures ANOVA) was utilized to analyze these data. Only side effects with an endorsement greater than none were included in the analyses (marked as “not quantifiable” in the table). For those questions with a significant Friedman χ^2 , post hoc Wilcoxon signed-rank tests were used for post hoc analyses. Due to the number of possible comparisons with this analysis, only comparisons between condition conditions within each session were explored. The summary statistics are presented in Appendix I.

The Friedman test revealed three significant effects: “Difficulty concentrating,” “Fatigue,” and “Headache,” all during session 1. For “Fatigue,” the Wilcoxon signed-rank post hoc test indicated significant differences between placebo and suvorexant ($Z = -2.236, p = .025$) and between placebo and zolpidem ($Z = -2.333, p = .020$), with the placebo condition having lower

scores than suvorexant and zolpidem. Post hoc analyses did not reveal differences between condition conditions for the other two questions.

Vital Signs. Vital signs were collected at the end of every test session and included temperature, pulse rate, and blood pressure. *F*-statistics, *p*-values, and effect sizes (η_p^2) can be found in Table 27. The means and standard errors for the main effect factors of each metric are shown in Tables 28-29.

Table 27 ANOVA Statistics for Vital Signs

<i>Metric</i>	<i>Effect</i>	<i>F(df)</i>	<i>p</i>	η_p^2
<i>Temperature</i>	Condition Main Effect	$F(2, 26) = 1.945$	.163	.366
	Session Main Effect	$F(3, 39) = 2.597$	.066	.593
	Condition $\times$ Session Interaction	$F(6, 78) = 0.602$	.728	.227
<i>Pulse Rate</i>	Condition Main Effect	$F(1.570, 20.407) = 1.556$	.234	.107
	Session Main Effect	$F(1.889, 24.552) = 1.093$	.348	.078
	Condition $\times$ Session Interaction	$F(2.784, 36.193) = 1.495$	.243	.103
<i>Diastolic Blood Pressure</i>	Condition Main Effect	$F(2, 26) = 0.318$	.731	.024
	Session Main Effect	$F(3, 39) = 6.881$	<.001	.346
	Condition $\times$ Session Interaction	$F(4.360, 56.685) = 0.600$	.678	.044
<i>Systolic Blood Pressure</i>	Condition Main Effect	$F(2, 26) = 0.019$	.981	.001
	Session Main Effect	$F(3, 39) = 5.744$	.002	.306
	Condition $\times$ Session Interaction	$F(6, 78) = 0.401$	.877	.030

Note. Significant results are bolded. Temperature was measured in degrees Fahrenheit. Pulse was measured in beats per minute (bpm). Blood pressure metrics were measured in millimeters of mercury (mmHg).

Table 28. Descriptive Statistics for Vital Signs by Condition

<i>Metric</i>	<i>Placebo</i>	<i>Suvorexant</i>	<i>Zolpidem</i>
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>
Temperature	97.582 (0.094)	97.527 (0.130)	97.746 (0.128)
Pulse Rate	68.179 (2.188)	71.857 (2.161)	71.800 (1.942)
Diastolic Blood Pressure	73.107 (2.248)	73.446 (2.380)	73.304 (2.471)
Systolic Blood Pressure	116.946 (3.509)	117.000 (3.912)	119.321 (4.202)

Note. Temperature was measured in degrees Fahrenheit. Pulse was measured in beats per minute (bpm). Blood pressure metrics were measured in millimeters of mercury (mmHg).

Table 29. Descriptive Statistics for Vital Signs by Session

<i>Metric</i>	<i>T1 (1100)</i>	<i>T2 (1300)</i>	<i>T3 (1500)</i>	<i>T4 (1700)</i>
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>
Temperature	97.752 (0.088)	97.571 (0.108)	97.498 (0.106)	97.652 (0.146)
Pulse Rate	72.811 (2.738)	71.017 (1.525)	69.762 (2.171)	68.857 (2.000)
Diastolic Blood Pressure	72.476 (2.381)	72.952 (2.116)	72.286 (2.406)	75.429 (2.575)
Systolic Blood Pressure	115.786 (3.946)	117.119 (3.774)	118.048 (3.524)	120.071 (3.933)

Note. Temperature was measured in degrees Fahrenheit. Pulse was measured in beats per minute (bpm). Blood pressure metrics were measured in millimeters of mercury (mmHg).

Temperature. The ANOVA did not reveal a significant interaction between condition and session. The results can be found in Figure 64.

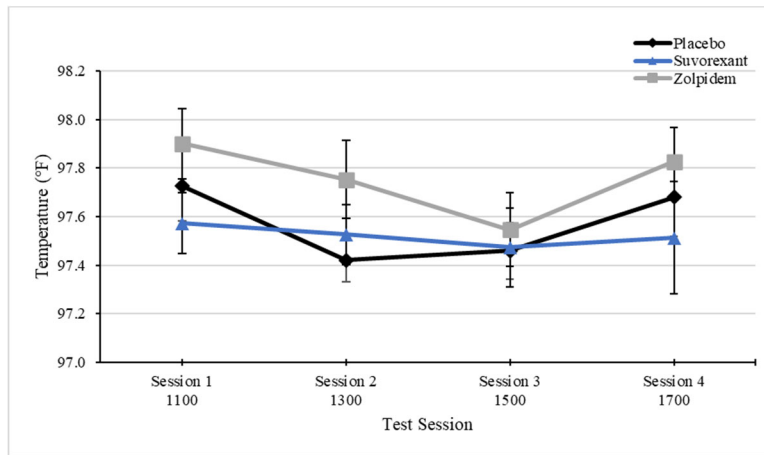


Figure 64. Temperature Condition $\times$ Session Interaction
Error bars represent standard errors.

The ANOVA did not reveal a significant main effect of condition or session. The means and standard errors are highlighted in Tables 28-29.

Pulse Rate. The assumption of sphericity was violated for the interaction between condition and session ($\chi^2(20) = 35.488, p = .022, \epsilon = .742$). A repeated measures ANOVA did not show a significant interaction. These results can be found in Figure 65.

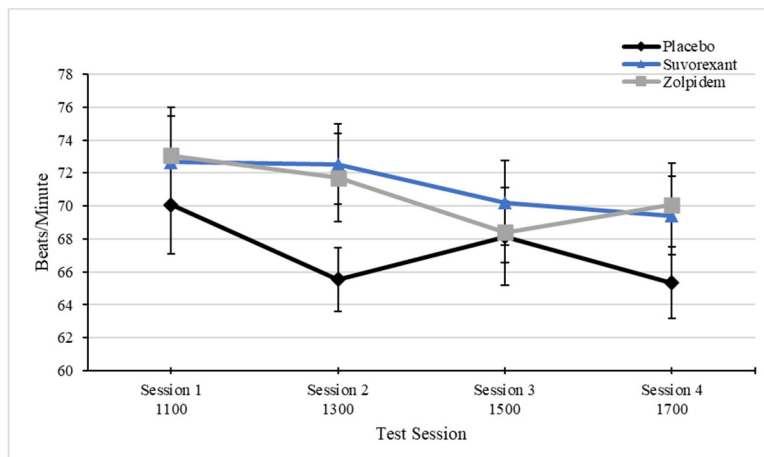


Figure 65. Pulse Rate Condition $\times$ Session Interaction
Error bars represent standard errors.

The ANOVA did not reveal a significant main effect of condition or session. The means and standard errors can be found in Tables 28-29.

Diastolic Blood Pressure. The ANOVA did not reveal a significant interaction between condition and session. These results can be found in Figure 66.

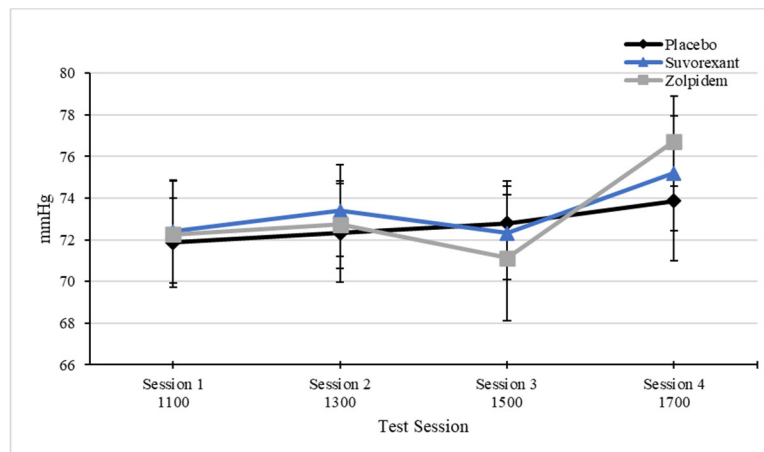


Figure 66. Diastolic Blood Pressure Condition $\times$ Session Interaction
Error bars represent standard errors.

The ANOVA did not reveal a significant main effect of condition but did reveal a significant main effect of session. Post hoc comparisons revealed a higher systolic diastolic blood pressure during session 4 than during session 1 ($t(13) = 2.495, p = .027$), session 2 ($t(13) = 2.853, p = .014$), and session 3 ($t(13) = 2.814, p = .015$). The means and standard errors can be found in Tables 28-29.

Systolic Blood Pressure. The ANOVA did not reveal a significant interaction between condition and session. These results can be found in Figure 67.

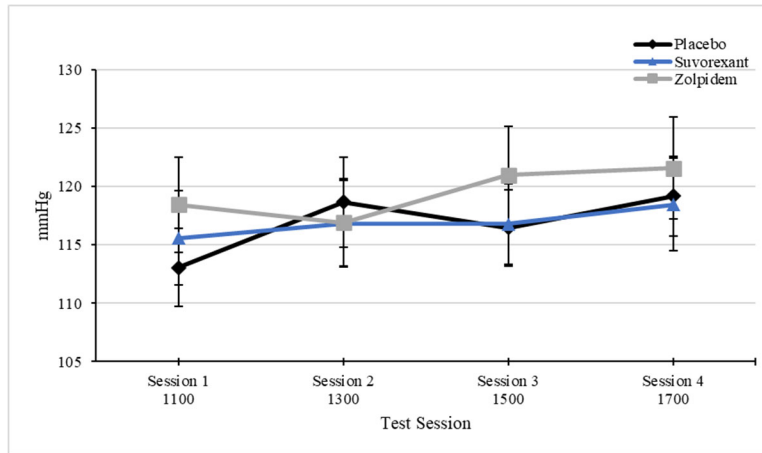


Figure 67. Systolic Blood Pressure Condition $\times$ Session Interaction
Error bars represent standard errors.

The ANOVA did not reveal a significant main effect of condition but did reveal a significant main effect of session. Pairwise comparisons showed that Session 3 had significantly higher diastolic blood pressure compared to session 1 ($t(13) = 2.186, p = .048$). Session 4 had significantly higher systolic blood pressure compared to session 1 ($t(13) = 4.669, p < .001$), session 2 ($t(13) = 4.000, p = .002$), and session 3 ($t(13) = 2.284, p = .040$). The means and standard errors can be found in Tables 28-29.

Polysomnography (PSG)

The data from each night were analyzed with a one-way repeated measures ANOVA with condition (placebo, suvorexant, and zolpidem) as the repeated factor. The variables analyzed consisted of minutes to sleep onset (time from lights out to the first full minute of stage N2 sleep – SO), the percent of time spent in each of the four stages of sleep (stage N1, stage N2, stage N3, and stage REM), the number of minutes awake after sleep onset (WASO), sleep efficiency (total number of minutes spent in stages N2, N3, N4, and REM divided by the total time in bed – SE), REM latency (the time from sleep onset to the first epoch scored as REM), and number of awakenings lasting at least 15 seconds. If a participant went to the bathroom during the sleep period, the time was scored as awake. If a technical problem occurred during the sleep period (e.g., an electrode became loose), the time until it was corrected was tagged as "not scored" and was not included in the sleep metrics.

Full Experimental Night. The data from each participant's 8-hour sleep period for each condition was analyzed to determine whether the condition affected sleep architecture. F -statistics, p -values, and effect sizes (η_p^2) can be found in Table 30. The means and standard errors are shown in Table 31. The percentage of time in each sleep stage is illustrated in Figure 68.

Table 30. ANOVA Statistics for PSG Full Experimental Night

<i>Metric</i>	<i>Effect</i>	<i>F(df)</i>	<i>p</i>	<i>η_p^2</i>
<i>N1 PCT</i>	Condition Main Effect	<i>F</i>(2, 26) = 3.703	.038	.222
<i>N2 PCT</i>	Condition Main Effect	<i>F</i>(2, 26) = 3.526	.044	.213
<i>N3 PCT</i>	Condition Main Effect	<i>F</i> (2, 26) = 1.471	.248	.102
<i>REM PCT</i>	Condition Main Effect	<i>F</i>(2, 26) = 5.903	.008	.312
<i>Latency to Sleep Onset</i>	Condition Main Effect	<i>F</i> (2, 26) = 0.915	.413	.066
<i>REM Latency</i>	Condition Main Effect	<i>F</i> (1.499, 19.493) = 0.218	.742	.017
<i>Total Wake Time</i>	Condition Main Effect	<i>F</i> (2, 26) = 0.795	.462	.058
<i>Total Sleep Time</i>	Condition Main Effect	<i>F</i> (2, 26) = 1.602	.221	.110
<i>Sleep Efficiency</i>	Condition Main Effect	<i>F</i> (2, 26) = 1.553	.231	.107
<i>WASO</i>	Condition Main Effect	<i>F</i> (2, 26) = 1.133	.337	.080
<i>Number of Awakenings</i>	Condition Main Effect	<i>F</i> (1.372, 17.837) = .513	.540	.038

Note. Significant results are bolded. Time metrics are measured in minutes. WASO = wake after sleep onset. N1 PCT = percentage of time spent in stage N1 sleep. N2 PCT = percentage of time spent in stage N2 sleep. N3 PCT = percentage of time spent in stage N3 sleep. REM PCT = percentage of time spent in stage REM sleep.

Table 31. Descriptive Statistics for PSG Full Experimental Night by Condition

<i>Metric</i>	<i>Placebo</i>	<i>Suvorexant</i>	<i>Zolpidem</i>
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>
N1 PCT	14.070 (1.964)	10.891 (1.095)	11.545 (1.300)
N2 PCT	57.202 (2.247)	54.881 (2.309)	58.965 (2.475)
N3 PCT	18.413 (2.421)	18.471 (2.259)	20.150 (2.115)
REM PCT	24.385 (1.592)	26.648 (1.284)	20.885 (1.611)
Latency to Sleep Onset	7.893 (0.996)	8.500 (1.806)	9.808 (2.195)
REM Latency	71.500 (7.236)	70.286 (5.167)	74.846 (8.684)
Total Wake Time	33.621 (7.247)	29.550 (7.515)	23.946 (6.457)
Total Sleep Time	391.586 (10.423)	407.257 (8.816)	402.554 (7.642)
Sleep Efficiency	81.589 (2.176)	84.792 (1.839)	83.859 (1.602)
WASO	25.729 (7.332)	21.050 (7.348)	14.138 (5.220)
Number of Awakenings	10.786 (2.128)	8.357 (1.640)	9.308 (2.538)

Note. Time metrics are measured in minutes. WASO = wake after sleep onset. N1 PCT = percentage of time spent in stage N1 sleep. N2 PCT = percentage of time spent in stage N2 sleep. N3 PCT = percentage of time spent in stage N3 sleep. REM PCT = percentage of time spent in stage REM sleep.

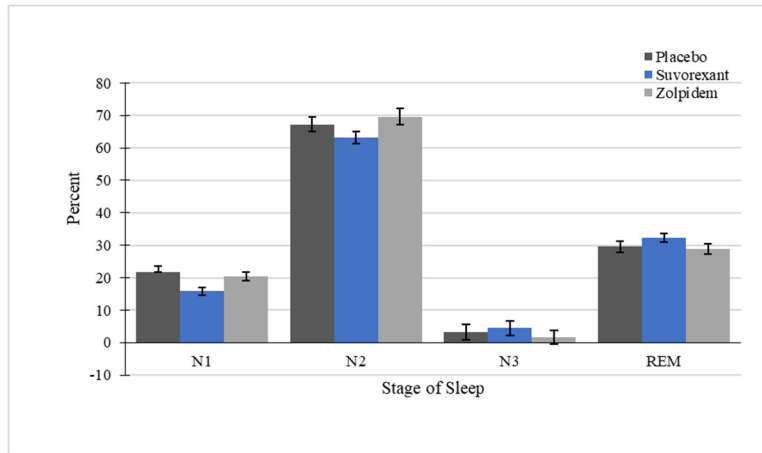


Figure 68. Percentages of Time Spent in Sleep Stages: Full Experimental Night. Error bars represent standard errors.

Percentage of Time in Stage N1. The ANOVA revealed a significant effect of condition for the percentage of time in stage N1. Pairwise comparisons showed that the percentage of time in stage N1 was higher in the placebo condition than in the suvorexant condition ($t(13) = 2.145, p = .051$). The means and standard errors are shown in Table 31.

Percentage of Time in Stage N2. The ANOVA revealed a significant effect of condition for the percentage of time in stage N2. Pairwise comparisons showed that the percentage of time in stage N2 was higher in the zolpidem condition than in the suvorexant condition ($t(13) = -2.298, p = .039$). The means and standard errors are shown in Table 31.

Percentage of Time in Stage N3. The ANOVA did not show a significant effect of condition for the percentage of time in stage N3. The means and standard errors are shown in Table 31.

Percentage of Time in Stage REM. The ANOVA revealed a significant effect of condition for the percentage of time in stage REM. Pairwise comparisons showed that the percentage of time in stage REM was lower in the zolpidem condition than in the placebo condition ($t(13) = 2.198, p = .047$) and lower in the suvorexant condition than in the placebo condition ($t(13) = 3.288, p = .006$). The means and standard errors are shown in Table 31.

Latency to Sleep Onset (SO). The ANOVA did not reveal any differences among the conditions for the time to sleep onset ($F(2, 26) = 0.915, p = .413, \eta_p^2 = .191$). The means and standard errors are shown in Table 31.

REM Latency. The assumption of sphericity was violated for the condition factor ($\chi^2(2) = 7.007, p = .030, \varepsilon = .750$). The ANOVA did not reveal a significant effect of condition for latency to REM onset. The means and standard errors are shown in Table 31.

Total Wake Time. The ANOVA did not reveal a significant effect of condition for total wake time. The means and standard errors are shown in Table 31.

Total Sleep Time. The ANOVA did not reveal a significant effect of condition for total sleep time. The means and standard errors are shown in Table 31.

Sleep Efficiency. The ANOVA did not reveal a significant effect of condition for sleep efficiency (SE). The means and standard errors are shown in Table 31.

Wake After Sleep Onset. The ANOVA did not reveal a significant effect of condition for the time awake after sleep onset (WASO). The means and standard errors are shown in Table 31.

Number of Awakenings. The assumption of sphericity was violated for the condition factor ($\chi^2(2) = 9.577, p = .008, \varepsilon = .686$). The ANOVA did not reveal a significant effect of condition for the number of awakenings. The means and standard errors are shown in Table 31.

Second Half of Experimental Night. To address the hypothesis that early awakening would be reduced following the suvorexant condition, the data from each participant's 8-hour sleep period were halved and the sleep architecture from the second 4 hours of sleep was analyzed. The F -statistics, p -values, and effect sizes (η_p^2) are summarized in Table 32. The means and standard errors of each metric are shown in Table 33. The percentage of time in each sleep stage during the second half of the night is illustrated in Figure 69.

Table 32. ANOVA Statistics for PSG Second Half of Full Experimental Night

<i>Metric</i>	<i>Effect</i>	<i>F (df)</i>	<i>p</i>	<i>η_p^2</i>
<i>N1 PCT</i>	Condition Main Effect	$F(2, 26) = 2.818$	.078	.178
<i>N2 PCT</i>	Condition Main Effect	$F(2, 26) = 3.383$	.049	.206
<i>N3 PCT</i>	Condition Main Effect	$F(1.392, 18.099) = 5.205$	.025	.286
<i>REM PCT</i>	Condition Main Effect	$F(2, 26) = 0.879$	.427	.063
<i>Total Wake Time</i>	Condition Main Effect	$F(2, 26) = 0.843$	.442	.061
<i>Total Sleep Time</i>	Condition Main Effect	$F(2, 26) = 0.976$	.390	.070
<i>Sleep Efficiency</i>	Condition Main Effect	$F(2, 26) = 0.975$	.390	.070
<i>Number of Awakenings</i>	Condition Main Effect	$F(1.329, 17.275) = 0.567$	.509	.042

Note. Time metrics are measured in minutes. N1 PCT = percentage of time spent in stage N1 sleep. N2 PCT = percentage of time spent in stage N2 sleep. N3 PCT = percentage of time spent in stage N3 sleep. REM PCT = percentage of time spent in stage REM sleep.

Table 33. Descriptive Statistics for PSG Second Half of Experimental Night by Drug

Metric	Placebo	Suvorexant	Zolpidem
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>
N1 PCT	13.394 (3.580)	15.800 (1.821)	20.332 (2.740)
N2 PCT	67.205 (1.785)	63.286 (2.165)	69.605 (2.472)
N3 PCT	3.273 (0.754)	4.491 (1.153)	1.525 (0.584)
REM PCT	29.521 (1.686)	32.223 (1.938)	28.870 (2.361)
Total Wake Time	24.336 (7.313)	19.907 (7.395)	14.254 (5.101)
Total Sleep Time	178.729 (8.869)	190.400 (7.729)	184.008 (6.577)
Sleep Efficiency	74.770 (3.634)	79.585 (3.246)	76.931 (2.685)
WASO	24.336 (7.313)	19.836 (7.409)	14.214 (5.107)
Number of Awakenings	7.714 (1.724)	5.857 (1.244)	8.077 (2.366)

Note. Time metrics are measured in minutes. N1 PCT = percentage of time spent in stage N1 sleep. N2 PCT = percentage of time spent in stage N2 sleep. N3 PCT = percentage of time spent in stage N3 sleep. REM PCT = percentage of time spent in stage REM sleep.

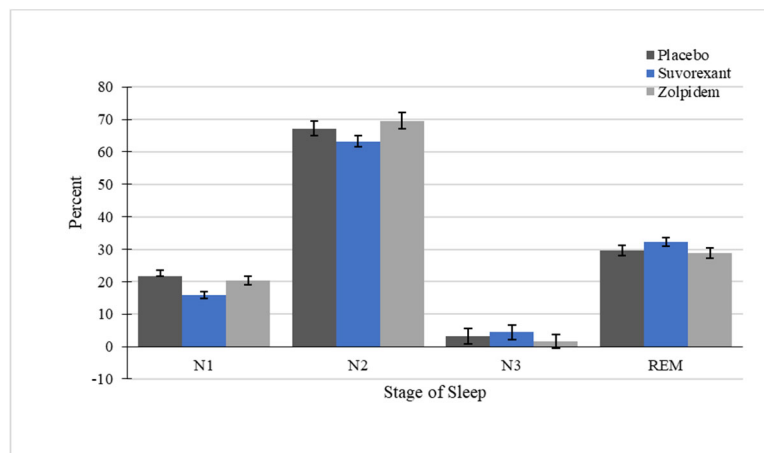


Figure 69. Percentages of Time Spent in Sleep Stages: Second Half of Experimental Night. Error bars represent standard errors.

Percentage of Time in Stage N1. The ANOVA did not reveal a significant effect of condition for the percentage of time in stage N1. The means and standard errors are shown in Table 33.

Percentage of Time in Stage N2. The ANOVA revealed a significant effect of condition for the percentage of time in stage N2. Pairwise comparisons showed that the percentage of time in stage N2 was higher in the zolpidem condition than in the suvorexant condition ($t(13) = 2.544, p = .024$). The means and standard errors are shown in Table 33.

Percentage of Time in Stage N3. The assumption of sphericity was violated for the condition factor ($\chi^2(2) = 9.101, p = .011, \varepsilon = .696$). The ANOVA revealed a significant effect of condition for the percentage of time in stage N3. Pairwise comparisons showed that the percentage of time in stage N3 was lower in the zolpidem condition than in the placebo condition ($t(13) = 2.913, p =$

.013) and the suvorexant condition ($t(13) = 2.476, p = .028$). The means and standard errors are shown in Table 33.

Percentage of Time in Stage REM. The ANOVA did not reveal a significant effect of condition for the percentage of time in stage REM. The means and standard errors are shown in Table 33.

Total Wake Time. The ANOVA did not reveal a significant effect of condition for total wake time. The means and standard errors are shown in Table 33.

Total Sleep Time. The ANOVA did not reveal a significant effect of condition for total sleep time. The means and standard errors are shown in Table 33.

Sleep Efficiency. The ANOVA did not reveal a significant effect of condition for sleep efficiency (SE). The means and standard errors are shown in Table 33.

Number of Awakenings. The assumption of sphericity was violated for the condition factor ($\chi^2(2) = 10.714, p = .005, \epsilon = .664$). The ANOVA did not reveal a significant effect of condition for the number of awakenings. The means and standard errors are shown in Table 33.

DISCUSSION AND CONCLUSIONS

The present study addressed the question of whether suvorexant would be a viable alternative to zolpidem as an operational sleep aid by extending sleep length without affecting next-day performance. Participants were tested over three separate periods during which they received either suvorexant (10 mg), zolpidem (10 mg in males, 5 mg in females), or placebo, counterbalanced among the visits. Sleep architecture during the overnight sleep period and next-day performance were measured to determine the effects of the three conditions.

The results of the study did not find clinically relevant differences in sleep architecture between suvorexant and zolpidem. When the sleep period was scheduled from 0200 until 1000 to mimic a jet lag situation in which sleep is phase-delayed, suvorexant was expected to maintain sleep better than either zolpidem or placebo. However, the time awake was not different among the conditions, nor was sleep efficiency. Sleep architecture following administration of zolpidem showed a higher percentage of time spent in N2 sleep compared to suvorexant, whereas a higher percentage of time occurred in REM sleep following administration of suvorexant compared to zolpidem. All conditions showed restful sleep with slightly lighter sleep following administration of placebo than the active medications.

To evaluate whether suvorexant extended sleep longer than zolpidem, the second half of the sleep period was assessed since early wakeups or lighter sleep may have occurred during the last part of the sleep period. The results indicated that on average, sleep was lighter in the zolpidem condition compared to both suvorexant and placebo, with more time in N2 and less time in N3 during the zolpidem nights.

Performance was assessed to determine if the longer-acting suvorexant would lead to next-day effects on performance and mood. Several cognitive functions were assessed, included memory,

reaction time, attention, and impulsivity. A driving simulator was presented as an operationally-relevant task. Balance was assessed immediately upon rising from sleep and throughout the day to determine possible lingering stability effects of the medications. Mood was also assessed through questionnaires. Next-day performance was not affected by any of the conditions in any consistent manner. Time of day tended to affect performance in that the earlier sessions tended to be worse than the later sessions, particularly in response times. This may have been due to sleep inertia rather than drug since this effect occurred regardless of condition.

Limitations and Future Directions

The lack of either medication affecting sleep architecture could be due to the study sample being good sleepers, therefore, a ceiling effect occurred. Volunteers' habitual bedtime was no later than midnight with rise times no later than 0800. The sleep period in the present study was delayed until 0200; this delay may have been too short to tap into the natural circadian wake-up time. Had the sleep period been delayed another 2–3 hours, the longer-acting suvorexant may have affected sleep efficiency as hypothesized. In addition, a higher dosage of suvorexant may have improved sleep better than the starting dose of 10 mg which is the FDA's recommended dose. Several clinical studies indicated 15 mg of suvorexant improved sleep consistently. However, a higher dosage may lead to next-day performance effects; therefore, the need for improved sleep would need to offset potential performance effects.

Conclusions

The current study potentially supports the addition of 10 mg suvorexant to the Navy's approved medication list for aircrew. The results did not indicate any significant differences in sleep quality following administration of suvorexant versus zolpidem; further, suvorexant did not affect next day performance. Therefore, suvorexant appears to perform similarly to zolpidem and may serve as an alternative hypnotic to those who do not respond well to zolpidem, therefore, offering this hypnotic as an alternative for those who do not respond well to zolpidem. While zolpidem is an effective hypnotic for Navy operations, it may not be a good choice for everyone. Including another medication as an option for those who do not respond well to zolpidem would address the needs of Navy personnel who need medication to improve sleep in operational settings. More research involving a higher dosage of suvorexant with a delayed sleep period is needed before a final decision is made regarding this medication.

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Appendix A

Screening Questionnaire

“You have shown an interest in participating in the research study titled “Evaluation of Suvorexant as an Additional Sleep Aid for Military Operations.” The purpose of this study is to test the efficacy of a medium acting hypnotic sleep aid (suvorexant) against an established short-acting sleep aid (zolpidem). In order to be eligible for this study you must be screened to ensure you meet all the qualifications. There is no risk in participating in this screening. The screening consists of some personal, including medical, questions and will take approximately 5 minutes. Your answers will be kept confidential; only the research team will have access to them. After you have answered the screening questions and you are deemed eligible to participate in the study, you will be given an informed consent document. If you are not eligible to participate in the study, we will remove your name from the screening questionnaire and only keep the questionnaire for record purposes. Would you be interested in being screened for eligibility?”

Consent obtained by _____ Date _____

Participant Initials _____ Age _____ Height _____ Weight _____

Are you a Department of Defense beneficiary (e.g., active duty military, military spouse, or dependent) and covered by DoD insurance? Yes / No

Do you have any drug allergies or reaction? Yes / No

Does your medical history include any of the following:

Allergic reaction to medical tape? Yes / No

Emotional or mental illness including depression? Yes / No

Drug abuse (including alcohol and prescriptions meds)? Yes / No

Seizures or a neurological disease? Yes / No

Head injury? What/when: _____ Yes / No

Excessive daytime sleepiness? (Complete Epworth SS) Yes / No

Any sleep disorders (apnea, narcolepsy, insomnia, etc.)? _____ Yes / No

Have you recently taken any medications, prescription or over the counter? Yes / No

What, when, why: _____

How many alcoholic beverages do you consume in a week? (max = 14/wk) _____

Have you used any tobacco products in the last 6 months? Yes / No

What, amount, frequency: _____

How much caffeine do you regularly consume in any beverage (coffee, tea, cola, energy drinks)?

What, amount, frequency: _____

Have you been on a day-shift schedule for the past 3 weeks? Yes / No

What is your habitual bedtime and rise time, both on work days on off-work days?

Work days: _____ Off-work days: _____

Appendix B

Horne and Östberg Morningness/Eveningness Questionnaire

Instructions:

1. Please read each question very carefully before answering.
2. Answer **ALL** questions.
3. Answer questions in numerical order.
4. Each question should be answered independently of others. Do **NOT** go back and check your answers.
5. All questions have a selection of answers. For each question, place a cross alongside **ONE** answer only. Some questions have a scale instead of a selection of answers. Place a cross at the appropriate point along the scale.
6. Please answer each question as honestly as possible. Both your answers and the results will be kept **in strict confidence**.
7. Please feel free to make any comments in the section provided below each question.

1. Considering only your own "feeling best" rhythm, at what time would you get up if you were entirely free to plan your day?		
05000600070008000900100011001200		
2. Considering only your own "feeling best" rhythm, at what time would you go to bed if you were entirely free to plan your evening?		
20002100220023002400010002000300		
3. If there is a specific time at which you have to get up in the morning, to what extent are you dependent on being woken up by an alarm clock?	Not at all dependent.	
	Slightly dependent.	
	Fairly dependent.	
	Very dependent.	
4. Assuming adequate environmental conditions, how easy do you find getting up in the mornings?	Not at all easy.	
	Not very easy.	
	Fairly easy.	
	Very easy.	
5. How alert do you feel during the first half hour after having woken in the mornings?	Not at all alert.	
	Slightly alert.	
	Fairly alert.	
	Very alert.	
6. How is your appetite during the first half-hour after having woken in the mornings?	Very poor.	
	Fairly poor.	
	Fairly good.	
	Very good.	
7. During the first half-hour after having woken in the morning, how tired do you feel?	Very tired.	
	Fairly tired.	
	Fairly refreshed.	
	Very refreshed.	
8. When you have no commitments the next day, at what time do you go to bed compared to your usual bedtime?	Seldom or never later.	
	Less than one hour later.	
	1 - 2 hours later.	
	More than two hours later.	
9. You have decided to engage in some physical exercise. A friend suggests that you do this one hour twice a week, and the best time for him is between 0700 and 0800. Bearing in mind nothing else but your own "feeling best" rhythm, how do you think you would perform?	Would be in good form.	
	Would be in reasonable form.	
	Would find it difficult.	
	Would find it very difficult.	
10. At what time in the evening do you feel tired and as a result, in need of sleep?		
20002100220023002400010002000300		

11. You wish to be at your peak performance for a test, which you know, is going to be mentally exhausting and lasting for two hours. You are entirely free to plan your day and, considering only your own "feeling best" rhythm, which ONE of the four testing times would you choose?	0800 - 1000. 1100 - 1300. 1500 - 1700. 1900 - 2100.	☐ ☐ ☐ ☐
12. If you went to bed at 2300, at what level of tiredness would you be?	Not at all tired. A little tired. Fairly tired. Very tired.	☐ ☐ ☐ ☐
13. For some reason, you have gone to bed several hours later than usual, but there is no need to get up at any particular time the next morning. Which ONE of the following events are you most likely to experience?	Will wake up at usual time and will NOT fall asleep. Will wake up at usual time and will doze thereafter. Will wake up at usual time but will fall asleep again. Will NOT wake up until later than usual. . .	☐ ☐ ☐ ☐
14. One night you have to remain awake between 0400 - 0600 in order to carry out a night watch. You have no commitments the next day. Which ONE of the following alternatives will suit you best?	Would NOT go to bed until watch was over. Would take a nap before and sleep after. . Would take a good sleep before and nap after. Would take ALL sleep before watch.	☐ ☐ ☐ ☐
15. You have to do two hours of hard physical work. You are entirely free to plan your day and, considering only your own "feeling best" rhythm, which ONE of the following times would you choose?	0800 - 1000. 1100 - 1300. 1500 - 1700. 1900 - 2100.	☐ ☐ ☐ ☐
16. You have decided to engage in hard physical exercise. A friend suggests that you do this for one hour twice a week, and the best time for him is between 2200 - 2300. Bearing in mind nothing else but your own "feeling best" rhythm, how well do you think you would perform?	Would be in good form. Would be in reasonable form. Would find it difficult. Would find it very difficult.	☐ ☐ ☐ ☐
17. Suppose that you can choose your own work hours. Assume that you worked a FIVE hour day (including breaks) and that your job was interesting and paid by results. Which FIVE CONSECUTIVE HOURS would you select?		
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 24 AM 123456789101112131415161718192021222324 PM		
18. At what time of the day do you think that you reach your "feeling best" peak?		
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 24 AM 123456789101112131415161718192021222324 PM		
19. One hears about "morning" and "evening" types of people. Which ONE of these types do you consider yourself to be?	Definitely a "morning" type. More a "morning" than an "evening" type. More an "evening" type than a "morning" type. Definitely an "evening" type.	☐ ☐ ☐ ☐

Appendix C

Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times.

Please check one box per line.

	Would never doze	Slight chance	Moderate chance	High chance
Sitting and reading	0 ☐	1 ☐	2 ☐	3 ☐
Watching TV	0 ☐	1 ☐	2 ☐	3 ☐
Sitting inactive in a public place (e.g. theatre, meeting)	0 ☐	1 ☐	2 ☐	3 ☐
As a passenger in a car for an hour without a break	0 ☐	1 ☐	2 ☐	3 ☐
Lying down in the afternoon when circumstances permit	0 ☐	1 ☐	2 ☐	3 ☐
Sitting and talking to someone	0 ☐	1 ☐	2 ☐	3 ☐
Sitting quietly after a lunch <u>without</u> alcohol	0 ☐	1 ☐	2 ☐	3 ☐
In a car, while stopped for a few minutes in traffic	0 ☐	1 ☐	2 ☐	3 ☐

Total Score _____

Volunteer's Initials _____

Date administered _____

Appendix D

Visual Analogue Scale (VAS)

Below is a series of words that describe feelings that people have. Please read each word carefully. Mark an “X” on the line in the directions toward whichever adjective describes how you are feeling *right now*.

Not At All _____ | _____ Extremely
Alert / Able to Concentrate

Not At All _____ | _____ Extremely
Anxious

Not At All _____ | _____ Extremely
Energetic

Not At All _____ | _____ Extremely
Feel Confident

Not At All _____ | _____ Extremely
Irritable

Not At All _____ | _____ Extremely
Jittery/Nervous

Not At All _____ | _____ Extremely
Sleepy

Not At All _____ | _____ Extremely

Appendix E

Side Effects Questionnaire

Participant Number: _____ Date: _____ Time: _____

Please circle the appropriate rating to each of the symptoms listed below that you have experienced since the last time you answered the questionnaire.

1	Trouble Staying Awake	None	Slight	Moderate	Severe
2	Chills	None	Slight	Moderate	Severe
3	Loss of Balance	None	Slight	Moderate	Severe
4	Numbness	None	Slight	Moderate	Severe
5	Dry Mouth	None	Slight	Moderate	Severe
6	Nervousness	None	Slight	Moderate	Severe
7	Anxiety	None	Slight	Moderate	Severe
8	Stomach Cramps	None	Slight	Moderate	Severe
9	Muscle Cramps	None	Slight	Moderate	Severe
10	Visual Illusions	None	Slight	Moderate	Severe
11	“Drugged” Feeling (“out of it”, “woozy”)	None	Slight	Moderate	Severe
12	Light Headed	None	Slight	Moderate	Severe
13	Excessive Thirst	None	Slight	Moderate	Severe
14	Irritability	None	Slight	Moderate	Severe
15	Loss of Coordination	None	Slight	Moderate	Severe
16	Irregular Heartbeat	None	Slight	Moderate	Severe
17	Tremor	None	Slight	Moderate	Severe
18	General Discomfort	None	Slight	Moderate	Severe
19	Fatigue	None	Slight	Moderate	Severe
20	Boredom	None	Slight	Moderate	Severe
21	Drowsiness	None	Slight	Moderate	Severe
22	Headache	None	Slight	Moderate	Severe
23	Nausea	None	Slight	Moderate	Severe
24	Difficulty Concentrating	None	Slight	Moderate	Severe
25	Mental Depression	None	Slight	Moderate	Severe
26	Dizziness with Eyes Open	None	Slight	Moderate	Severe
27	Confusion	None	Slight	Moderate	Severe
28	Vomiting	None	Slight	Moderate	Severe
29	Rapid Heart Beats	None	Slight	Moderate	Severe
30	Dyspnea (labored breathing)	None	Slight	Moderate	Severe

Appendix F

Study Schedule

Time	Break	Consent/Training day	Habituation night	Experimental night	Test day
0:00	5-9 days of sleep monitoring with the Actiwatch				
1:00					
1:45					Drug dose
2:00					Lights out
3:00					
4:00					
5:00					
6:00				Wake-up	
6:30				Dismiss	
7:00					
8:00		Consent; MEQ; ESS; Actiwatch™ instructions	Watch Check for Sleep Compliance; Dismiss		
9:00		Training session 1			
					Wake-up; balance plate; remove electrodes; shower/dress/ breakfast
10:00					
11:00		Training session 2			Test session 1
12:00					
12:30					Break
13:00		Training Session 3			Test session 2
14:00		Dismiss			
14:30					Break
15:00					Test session 3
16:00					
16:30					Break
17:00					Test session 4
18:00					
18:30					Debrief; dismiss
19:00					
20:00			Participant Arrival; check watch for naps		
20:30			Electrode hook-up		
21:00					
				Participant Arrival; electrode hook-up; Familiarity session	
22:00			Lights out		
23:00					
0:00					

Appendix G

Compliance Questionnaire

Participant #: _____ Date: _____ Visit #: _____

- | | | |
|--|-----|----|
| 1. Have you consumed any food products in the last 2 hours? | YES | NO |
| a. If yes, what time did you eat? _____ | | |
| 2. Have you used tobacco products since your last visit? | YES | NO |
| 3. Have you consumed any caffeine since your last visit? | YES | NO |
| a. If yes, how much? _____ | | |
| b. Is this your normal amount? _____ | | |
| c. Did you consume any caffeine prior to coming in today? If yes, How when and much? | | |
| _____ | | |
| 4. Have you consumed any alcohol within the past 24 hours? | YES | NO |
| a. If yes, how many drinks? _____ | | |
| 6. Have you taken any supplements or multivitamins since your last visit? | YES | NO |
| a. If yes, please list _____ | | |
| 7. Have you taken any over-the-counter medications since your last visit? | YES | NO |
| a. If yes, please list _____ | | |
| 8. Have you taken any prescription medication since your last visit? | YES | NO |
| a. If yes, please list _____ | | |
| 9. Have you been on a day-shift schedule since your last visit? | YES | NO |

Appendix H

Side Effects Questionnaire Endorsements

	Placebo				Suvorexant				Zolpidem			
Trouble staying awake	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	13	10	8	10	10	7	6	9	11	7	9	6
Slight	1	4	5	3	3	5	6	4	3	5	2	6
Moderate	0	0	0	1	1	1	0	1	0	1	1	1
Severe	0	0	1	0	0	1	2	0	0	1	2	1

	Placebo				Suvorexant				Zolpidem			
Chills	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	14	14	14	14	14	14	14	14
Slight	0	0	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Loss of balance	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	13	14	14	13	14	14	14	14
Slight	0	0	0	0	1	0	0	1	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Numbness	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	14	14	14	14	14	14	14	14
Slight	0	0	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Dry mouth	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	14	14	14	14	13	14	14	14
Slight	0	0	0	0	0	0	0	0	1	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Nervousness	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	14	14	14	14	14	14	14	13
Slight	0	0	0	0	0	0	0	0	0	0	0	1
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Anxiety	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	14	14	14	14	14	13	14	14
Slight	0	0	0	0	0	0	0	0	0	1	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Stomach cramps	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	13	14	14	14	14	14	14	14	14	13	13	14
Slight	1	0	0	0	0	0	0	0	0	1	1	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Muscle cramps	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	13	14	14	14	14	14	14	14	14	13	13	14
Slight	1	0	0	0	0	0	0	0	0	1	1	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Visual illusions	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	14	14	14	14	14	14	14	14
Slight	0	0	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Drugged feeling	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	13	12	12	13	13	13	13	14
Slight	0	0	0	0	1	2	1	0	1	1	1	0
Moderate	0	0	0	0	0	0	1	1	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Light headed	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	13	14	13	14	14	14	14	14
Slight	0	0	0	0	1	0	1	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Excessive thirst	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	13	14	14	14	14	14	14	14
Slight	0	0	0	0	1	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Irritability	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	13	13	14	14	13	13	13	13	14	14	14	14
Slight	1	1	0	0	1	1	1	1	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Loss of coordination	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	13	13	12	13	13	14	14	14
Slight	0	0	0	0	1	1	2	1	1	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Irregular heartbeat	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	14	14	14	14	14	13	13	14
Slight	0	0	0	0	0	0	0	0	0	1	1	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Tremor	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	14	14	14	14	14	14	14	14
Slight	0	0	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
General discomfort	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	13	13	14	14	14	14	14	14
Slight	0	0	0	0	1	1	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Fatigue	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	13	10	7	9	9	6	7	6	7	9	6	6
Slight	1	3	5	3	4	6	5	5	6	4	5	7
Moderate	0	1	2	2	1	2	2	3	1	1	3	1
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Boredom	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	10	8	7	8	8	8	7	7	9	8	6	8
Slight	3	5	5	4	5	3	5	5	4	4	4	4
Moderate	1	0	1	2	1	1	1	2	1	1	2	1
Severe	0	1	1	0	0	2	1	0	0	1	2	1

	Placebo				Suvorexant				Zolpidem			
Drowsiness	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	12	11	12	11	10	12	9	11	11	10	9	9
Slight	2	3	1	2	3	1	4	2	3	3	3	3
Moderate	0	0	1	1	1	1	1	1	0	1	2	2
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Headache	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	7	9	9	11	13	13	12	11	10	12	11	12
Slight	7	5	5	3	1	1	2	3	4	2	3	1
Moderate	0	0	0	0	0	0	0	0	0	0	0	1
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Nausea	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	14	14	14	14	14	14	14	14
Slight	0	0	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Difficulty concentrating	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	11	10	11	10	8	9	11	12	12	9	9
Slight	0	3	4	2	2	5	3	1	1	0	3	4
Moderate	0	0	0	1	2	0	0	2	1	2	0	1
Severe	0	0	0	0	0	1	2	0	0	0	2	0

	Placebo				Suvorexant				Zolpidem			
Mental depression	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	14	14	14	14	14	13	14	14
Slight	0	0	0	0	0	0	0	0	0	1	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Dizziness with Eyes Open	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	13	14	13	14	14	14	14	14
Slight	0	0	0	0	1	0	1	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Confusion	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	13	13	13	13	14	14	14	14
Slight	0	0	0	0	1	1	1	1	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Vomiting	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	14	14	14	14	14	14	14	14
Slight	0	0	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Rapid heart beats	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	13	14	14	14	14	13	13	14
Slight	0	0	0	0	1	0	0	0	0	1	1	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo				Suvorexant				Zolpidem			
Dyspnea	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
None	14	14	14	14	14	14	14	14	14	14	14	14
Slight	0	0	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0

Appendix I

Friedman χ^2 Statistics for Side Effects Questionnaire

<i>Metric</i>	<i>Effect</i>	$\chi^2(df)$	<i>P</i>
<i>Anxiety</i>	Drugs at Session 1	Not quantifiable	--
	Conditions at Session 2	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 3	Not quantifiable	--
	Conditions at Session 4	Not quantifiable	--
<i>Boredom</i>	Conditions at Session 1	$\chi^2(2) = 1.50$	0.472
	Conditions at Session 2	$\chi^2(2) = 0.85$	0.651
	Conditions at Session 3	$\chi^2(2) = 2.80$	0.247
	Conditions at Session 4	$\chi^2(2) = 0.10$	0.949
<i>Confusion</i>	Conditions at Session 1	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 2	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 3	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 4	$\chi^2(2) = 2.00$	0.368
<i>Difficulty Concentrating</i>	Conditions at Session 1	$\chi^2(2) = 6.61$	0.037
	Conditions at Session 2	$\chi^2(2) = 2.57$	0.276
	Conditions at Session 3	$\chi^2(2) = 0.88$	0.641
	Conditions at Session 4	$\chi^2(2) = 0.88$	0.641
<i>Drugged Feeling</i>	Conditions at Session 1	$\chi^2(2) = 1.00$	0.607
	Conditions at Session 2	$\chi^2(2) = 3.00$	0.223
	Conditions at Session 3	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 4	$\chi^2(2) = 2.00$	0.368
<i>Dry Mouth</i>	Conditions at Session 1	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 2	Not quantifiable	--
	Conditions at Session 3	Not quantifiable	--
	Conditions at Session 4	Not quantifiable	--
<i>Dizziness with Eyes Open</i>	Conditions at Session 1	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 2	Not quantifiable	--
	Conditions at Session 3	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 4	Not quantifiable	--
<i>Drowsiness</i>	Conditions at Session 1	$\chi^2(2) = 3.50$	0.174
	Conditions at Session 2	$\chi^2(2) = 1.62$	0.444
	Conditions at Session 3	$\chi^2(2) = 3.71$	0.156
	Conditions at Session 4	$\chi^2(2) = 1.65$	0.438
<i>Excessive Thirst</i>	Conditions at Session 1	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 2	Not quantifiable	--
	Conditions at Session 3	Not quantifiable	--
	Conditions at Session 4	Not quantifiable	--
<i>Fatigue</i>	Conditions at Session 1	$\chi^2(2) = 6.88$	0.032
	Conditions at Session 2	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 3	$\chi^2(2) = 1.35$	0.507
	Conditions at Session 4	$\chi^2(2) = 2.66$	0.264
<i>General Discomfort</i>	Conditions at Session 1	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 2	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 3	Not quantifiable	--
	Conditions at Session 4	Not quantifiable	--

<i>Headache</i>	Conditions at Session 1	$\chi^2(2) = 6.00$	0.050
	Conditions at Session 2	$\chi^2(2) = 4.33$	0.115
	Conditions at Session 3	$\chi^2(2) = 2.80$	0.247
	Conditions at Session 4	$\chi^2(2) = 0.10$	0.949
<i>Irritability</i>	Conditions at Session 1	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 2	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 3	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 4	$\chi^2(2) = 2.00$	0.368
<i>Loss of Balance</i>	Conditions at Session 1	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 2	Not quantifiable	--
	Conditions at Session 3	Not quantifiable	--
	Conditions at Session 4	$\chi^2(2) = 2.00$	0.368
<i>Loss of Coordination</i>	Conditions at Session 1	$\chi^2(2) = 1.00$	0.607
	Conditions at Session 2	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 3	$\chi^2(2) = 4.00$	0.135
	Conditions at Session 4	$\chi^2(2) = 2.00$	0.368
<i>Lightheaded</i>	Conditions at Session 1	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 2	Not quantifiable	--
	Conditions at Session 3	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 4	Not quantifiable	--
<i>Irregular Heartbeats</i>	Conditions at Session 1	Not quantifiable	--
	Conditions at Session 2	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 3	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 4	Not quantifiable	--
<i>Muscle Cramps</i>	Conditions at Session 1	Not quantifiable	--
	Conditions at Session 2	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 3	Not quantifiable	--
	Conditions at Session 4	Not quantifiable	--
<i>Mental Depression</i>	Conditions at Session 1	Not quantifiable	--
	Conditions at Session 2	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 3	Not quantifiable	--
	Conditions at Session 4	Not quantifiable	--
<i>Rapid Heartbeats</i>	Conditions at Session 1	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 2	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 3	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 4	Not quantifiable	--
<i>Stomach Cramps</i>	Conditions at Session 1	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 2	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 3	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 4	Not quantifiable	--
<i>Trouble Staying Awake</i>	Conditions at Session 1	$\chi^2(2) = 2.00$	0.368
	Conditions at Session 2	$\chi^2(2) = 4.35$	0.113
	Conditions at Session 3	$\chi^2(2) = 1.40$	0.497
	Conditions at Session 4	$\chi^2(2) = 7.75$	0.021