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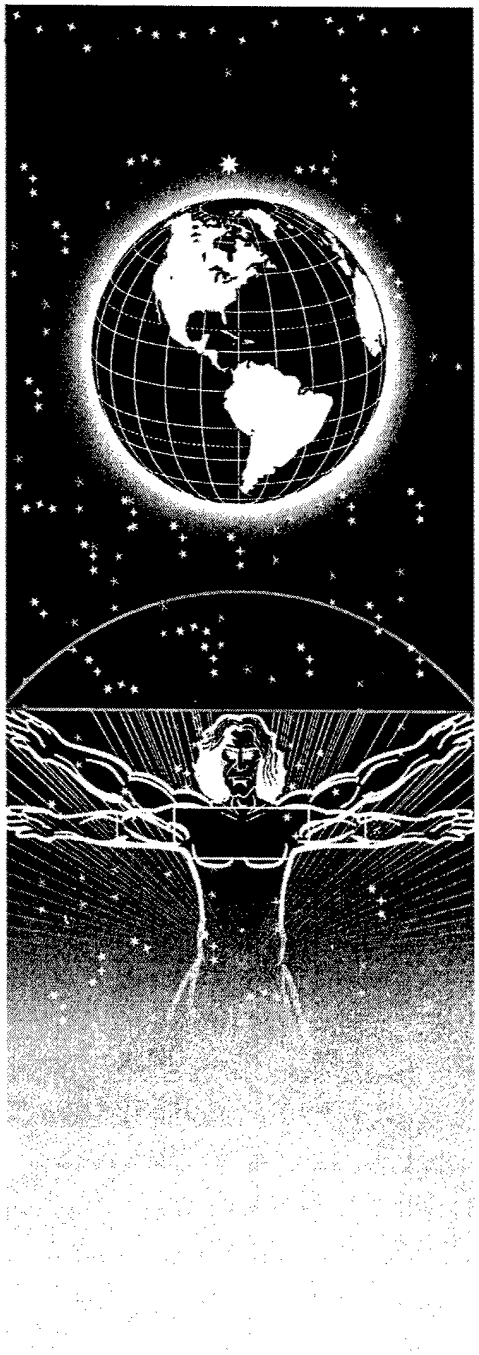

UNITED STATES AIR FORCE RESEARCH LABORATORY

A LABORATORY EVALUATION OF PERFORMANCE FOLLOWING A DAYTIME NAP UNDER ZALEPLON AND PLACEBO CONDITIONS

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This report has been reviewed and is approved for publication.

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14. ABSTRACT
Primary objective was to determine if zaleplon (10-mg) negatively impacted human performance, compared to placebo, after a sudden awakening from a short period (1 hour) of daytime sleep. 16 volunteers, 8 males and 8 females, were formed into 4 groups of 4 participants each. The study used a repeated measures design with 2 within-subject factors: drug and trial. Each participant experienced both drug conditions. Drug administration was counterbalanced and double-blinded. Performance measures (cognition and memory, balance, strength) and subjective reports were collected during every waking hour. Performance was significantly negatively impacted in the zaleplon condition up to 3-hrs post-dose. A few measures remained significantly below baseline at 3-hrs post-awakening. All measures returned to baseline by 4-hrs post-awakening. Caution is advised regarding daytime zaleplon use in operational settings involving extreme environments or emergency procedures that include higher cognitive tasks. Findings support insertion of a minimum of 10-min recovery time prior to any work activities following a daytime nap.

15. SUBJECT TERMS
Performance measures, EEG, zaleplon, placebo, nap

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ABSTRACT

The primary objective of this study was to determine whether zaleplon (10-mg) negatively impacted human performance, compared to placebo, after a sudden awakening from a short period (1 hour) of daytime sleep. Sixteen participants, eight males and eight females, volunteered to participate in this study. Participants were formed into four groups of four participants each. The study was conducted using a repeated measures design with two within-subject factors: drug and trial. Each participant experienced both drug conditions and the two experimental sessions were separated by one week. Drug administration was counterbalanced and double-blinded. One participant was removed from analyses due to poor and unstable performance. Performance measures (cognition and memory, balance, and strength) and subjective reports were collected during every waking hour of each session. Generally, performance was significantly negatively impacted in the zaleplon condition up to 2-hours post-awakening (3-hrs post-dose). A few measures remained significantly below baseline at 3-hrs post-awakening. All measures returned to baseline by 4-hrs post-awakening.

CONCLUSIONS AND RECOMMENDATIONS

Performance was generally affected for up to 3-hrs following a 10-mg dose of zaleplon. Caution is advised regarding daytime zaleplon usage in operational settings involving extreme environments or emergency procedures that include higher cognitive tasks. Unlike higher performance, basic performance does not appear affected.

Sleep inertia was short-lived following a daytime nap (< 1-hr). The findings from this study support the insertion of a minimum of 10-min recovery time prior to any work activities which may follow a daytime nap.

INTRODUCTION

There has been a need within operational communities for a short-acting sleep aid to assist individuals or teams in obtaining rest in demanding environments where brief daytime periods are available for sleep. (e.g. military special operation teams deploying to an action area, teams transitioning from daytime to night-time operations). Until recently there did not exist an appropriate substance to fulfill this role. The substance of choice would effectively promote sleep and would not have long-lasting effects (< 6 hrs). With the advent of zaleplon it is possible that the operational requirements may be met. The employment of a successful daytime sleep aid will have many potential benefits such as allowing teams which are rapidly transitioning to night work or responding to critical situations to be better rested for night operations. An important requirement for a daytime sleep aid in any sort of extreme environment is minimal, negative effects on the user when sudden, unplanned awakening is required.

Zaleplon is a short-duration sleep aid which has been shown to reduce sleep latency in insomniacs at the 10-mg dose level (Elie, Ruther, Farr, Emilien, & Salinas, 1999). Maximum plasma concentrations occur at approximately 1-hr post-dose with a half-life of about 1-hr (Beer, Ieni, Wu, Clody, Amorusi, Rose, Mant, Gaudreault, Cato, and Stern, 1994). Zaleplon is marketed in the United States by Wyeth-Ayers Pharmaceuticals under the name Sonata®. Sonata® is commonly administered in 10-mg oral doses, but is also given in 20-mg doses to people more resistant to its effects, for the treatment of insomnia. The most common side effects include: headache, dizziness and somnolence. Outside of somnolence, in short-term clinical studies, the subjective side effects for zaleplon are not significantly different from placebo (Elie et al.). Thus it appears that zaleplon may be suited for situations where a rest break of 4-8 hours duration is available. However, the performance effects of a rapid-awakening from daytime sleep are unknown.

There are several critical performance concerns when considering the use of a sleep aid while airborne, or in any extreme environment (i.e. a ship's pilot on break). First, in the event of an emergency, will individuals be able to perform emergency procedures? Second, are there any cognitive performance decrements (e.g. anterograde amnesia) induced by the medication which might impair job performance? Third, are there any symptoms produced which might impact the mission. These issues relate not only to the safety of the individual but also to the safety of the entire crew if the individual happens to be one of those responsible for its safe conduct. These issues also address the operational question of, "How soon after taking zaleplon may a person be expected to perform their duties reasonably well?"

Danjou, Paty, Fruncillo, Worthington, Unruh, Cevallos, & Martion (1999), found no adverse performance effects with a 10-mg zaleplon dose during a morning awakening study when waking participants 2-hours post dose, and performance benefits when waking individuals 5-hours post dose. In a similar study, Hindmarch, Patat, Stanley, Paty & Rigney (2001) woke participants 1-hr after a 10-mg nighttime dose and found only one statistically significant cognitive performance decrement in the zaleplon group. Additionally, Troy, Lucki, Unruh, Cevallos, Leister, Martin, Furlan, and Mangano (2000) showed no significant performance differences between placebo and 10-mg zaleplon 1.25 hours post-dose. However, Vermeeren, Danjou, & O'Hanlon (1998) found a significantly degraded memory effect at 6.5 hours after a

single dose administration of both 10-mg and 20-mg zaleplon. Allen, Curran, & Lader (1993), tested normal participants after a 20-mg dose of zaleplon and found most performance at 3-hrs post-dose to be "generally similar to performance on placebo." Similarly, Beer et al., examined differing levels of zaleplon in small samples of normal individuals during the day, with no sleep period and found significant changes in performance up to 2.5-hrs post-dose. The United States Air Force's School of Aerospace Medicine conducted a review of zaleplon as a candidate drug to be used for in-flight sleep which would potentially result in performance enhancement. Some of the results from this review were that the working group did not find any reason to remove zaleplon from consideration for ground-based operations. Additionally, this group determined that zaleplon may be a candidate for in-flight consideration.

Like some of the studies mentioned in the previous paragraph, this study is focused on the effects of zaleplon upon human performance rather than the hypnotic efficacy of the sleep aid. This study utilized normally entrained, well-rested, healthy individuals as participants, and required them to sleep briefly during the day, then to awaken and begin an array of performance tests. This approach was taken because, often in extreme environments during protracted operations (characterized by several days of near-continuous operations), workers are given a chance to sleep during the day. The potential risks associated with sudden awakening in such situations need to be identified and understood.

The primary objective of this study was to determine whether zaleplon negatively impacted human performance, compared to placebo, after a sudden awakening from a short period (1 hour) of daytime sleep. As a by-product of the design we also examined performance immediately following awakening in the placebo condition to determine whether there were simple sleep inertia effects.

METHODS

Participants

Sixteen participants, eight males and eight females, volunteered to participate in this study. Six of these participants were active duty USAF. The mean age of the group was 25.88 years (range18 – 42 yrs). The mean weight for males was 166.75 lbs. (range 140 – 190 lbs) and the mean weight for females was 132.50 lbs (range 98 – 162 lbs). Based upon a participant demographic survey, participants were normally entrained individuals (i.e., no night-shift workers), who were not heavy caffeine users. Participants were screened medically (blood chemistry and liver function) the week prior to their first experimental session. The study required a total of 22 hours of time per individual. Participants were paid for their participation. Because of facility accommodation limitations, participants were formed into four groups of four participants each. Each group of participants experienced one experimental session per week (10-hours duration) for two successive weeks. In addition a 2-hour training session was conducted the week prior to the first experimental session. The research protocol for this experiment was reviewed by the Brooks Air Force Base Institutional Review Board and approved by the Air Force Surgeon General (#F-BR-2002-0022-H).

Design

The study was conducted using a repeated measures design with two within-subject factors: drug (zaleplon or placebo), and trial (eight data collection time points; Table 1). Each participant experienced both drug conditions and the two experimental sessions were separated by one week. Drug administration was counterbalanced and double-blinded. Participants were asked not to consume alcohol the night before an experimental session and to drink one or less caffeinated beverages on the morning of an experimental session. They were told to get a good (normal) night's sleep the night before each session.

Time	Activity
1045	Arrive - Practice
1100	Eat
1200	TEST, GS
1300	Dose / Sleep
1400	Awaken / TEST, GS, WM
1500	TEST, GS - snack
1600	TEST
1700	TEST, GS, WM
1800	TEST – snack
1900	TEST
2000	TEST, GS
2100	Session Complete
TEST = ANAM, PVT, POMS, Symptom Survey, Force Platform GS = Grip Strength WM = Word Memory	

Table 1 Experimental session schedule.

Facility and Materials

The study was conducted at the Chronobiology and Sleep Laboratory (CASL) located at Brooks Air Force Base. Each participant was assigned a number under which his or her data was recorded to maintain anonymity. The lab layout consisted of four bedrooms and bathrooms, and one additional room containing equipment for measuring postural sway. Participants completed cognitive tasks at computer workstations within their bedrooms. The workstations were located next to the beds so that participants could sit down at their desks immediately upon waking. Participants completed all cognitive tasks

with their bedroom door closed to limit distractions. Audio-visual equipment was used to monitor the testing areas for safety purposes.

The zaleplon doses used in this study were, originally, 10-mg Sonata® capsules obtained in an unopened manufacturers bottle. These capsules were individually packaged inside a gelatin capsule. Gelatin capsules of identical appearance, but containing granular fiber, were constructed as the placebos. The capsules were prepared and randomized by the pharmacy at Wilford Hall Medical Center, Lackland AFB, TX.

Tests and Measures

ANAM – A selection of tests from the Automated Neuropsychological Assessment Metrics, a cognitive performance assessment battery (Perez, Masline, Ramsey, & Urban, 1987), was administered at each of the eight test trials (see Table 1), each test day. The entire ANAM test battery took 13 to 15 minutes to complete. All tests are listed below in the order of presentation. Table 2 shows the individual test start times and durations during the first test block after awakening.

Stanford Sleepiness Scale (SSS) – Participants chose one of seven Likert-scale descriptors, ranging from 1, "Feeling active and vital; alert; wide awake," to 7, "Almost in reverie; sleep onset soon; lost struggle to remain awake." (Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973)

Code Substitution Learning Test – This test provided a reference row with pairs of numbers and associated symbols at the top of the screen. During the test, individual stimulus items containing one pair, number and symbol, were presented below the reference row. Participants used the reference row to determine whether or not a number and symbol were associated with each other. A total of 72 items were presented during this test.

Code Substitution Immediate Memory Test – This test presented 18 number and symbol items, without providing the reference row of numbers and symbols. Participants were to recall the Learning Test associations to make their determination.

Simple Reaction Time Test (SRT) – This test required participants to respond as quickly as possible with a mouse click to an asterisk stimulus appearing on the screen. A total of 20 stimuli were presented.

Mathematical Processing Test – This test called for participants to perform addition and subtraction problems by responding to whether or not the answer was greater or less than 5 with the answer never being 5. Each problem consisted of three single-digit numbers and two operands. The test lasted for 3 minutes.

Matching to Sample Test – This test displayed a sample matrix box containing a pattern of red and blue squares. After the sample matrix was presented, it was replaced with two matrix boxes. Participants had to decide which of the two matrix

boxes matched the sample stimulus using a left or right mouse click. The test lasted for 3 minutes.

Symbolic Logical Reasoning Test – In this test, participants answered whether a single statement accurately described the relational order of two symbols (# and &). The test lasted 3 minutes.

Code Substitution Delayed Memory Test – This test was similar to the Immediate Memory Test, but contained 36 items. Again, participants had to respond to whether the number and symbol stimulus were associated based upon the reference row provided only during the Code Substitution Learning Test.

In general, for these ANAM tests, the following outcome measures were recorded for analysis: accuracy, mean reaction time to correct responses (MRTC), standard deviation of reaction time to correct responses (SDRTC), throughput ((60,000/RT_{All}) * % Correct), and omissions. The exceptions to this rule were the SSS and SRT. The SSS returned a single rating value. Mean reaction time and standard deviation for reaction time were the only two measures used from the SRT.

Word Memory Test – This test provided an assessment of short-term memory. In this study it was used to test for anterograde amnesia effects. Approximately 30 minutes after awakening, the participants were aurally presented a 15-word list. They wrote down the words on a piece of paper. The word lists were selected from the Williams Word Memory Test (Williams & Williams, 1966). After a one-minute memorization period, participants handed in their papers. Fifteen minutes later they were asked to recall the list on paper. After an additional three hours, participants were asked once more to recall and write down as much of the list as possible. The number correct was the single outcome measure derived from this test.

Test Start Time (min)	Test Duration*	Activity
0	.5	Stanford Sleepiness Scale
.5	1.5	Code Substitution - Learning
2.0	.5	Code Substitution - Immediate
2.5	.5	Simple Reaction Time
3.0	3.0	Math Processing
6.0	3.0	Matching to Sample
9.0	3.0	Logical Reasoning
12.0	1.0	Code Substitution – Delayed
13.0	1.5	Word Memory Memorization
14.5	10.0	Psychomotor Vigilance Test
24.5	2.0	Profile of Moods States
26.5	1.5	Grip Strength
28.0	2.5	Force Platform
30.5	1.0	Word Memory Recall
* includes transition times between tests		

Table 2 Test order and duration upon awakening.

Psychomotor Vigilance Task – The PVT required sustained attention and discrete motor responses (Dinges, 1992). The 8" x 4.5" x 2.4" portable battery-operated device presented a continuous simple reaction time test for 10-minutes. Training required only one ten-minute practice session. The PVT was self-administered at all trials. The outcome measures from this test were mean reciprocal reaction time (RRT), standard deviation of RRT (SDRRT), and number of lapses. RRT was used here instead of RT because of the nature of the PVT, which tends to exacerbate the usual problems with RT data (e.g. skewness).

Profile of Mood States (POMS) – This paper-and-pencil survey was used to assess affect (McNair, Lorr, & Droppleman, 1971). The POMS consisted of sixty-five adjectives describing feeling and mood to which the participant responded according to a five-point scale ranging from "Not at all" to "Extremely." There were six subscales derived from the questions: Depression, Tension, Vigor, Fatigue, Anger and Confusion. The POMS was administered at all trials.

Sleep Aid Symptom Questionnaire - To assess sleep aid subjective effects, participants were asked to rate a list of 56 symptoms on a scale from 0-7, where 0 was "none" and 7 was "severe". Participants were to note whether or not they thought that the drug administration caused the symptom and also to what extent they thought the symptom would interfere with daily activities. The questionnaire also called for participants to indicate whether or not they thought they received the placebo or Sonata. Participants completed this questionnaire every trial.

Grip Strength – Strength was assessed with a Sammons Preston JAMAR hand dynamometer (Mawdsley, Girio, Desmet, Bull, Petrick & Hartman, 1999) five times each test day. Each of the five trials consisted of two 5-sec squeezes that were separated by one minute's rest. Two values were recorded for each trial of which the highest was used as the outcome measure for this test.

Force Platform Test – Postural stability was assessed by requiring the participant to stand upon a platform that measures changes in the body's center of pressure over time (Platform

model OR6-5-1, strain-gage amplifier model SGA6-4, a-to-d converter model DT2801; AMTI, Watertown MA). This test had been used previously to analyze postural stability after benzodiazepine administration (Patat & Foulhoux, 1985). The participants' posture was heels together, feet open at a 30-deg angle, and hands at sides, much like a relaxed version of the military position of attention. One minute of data was collected for both eyes open and eyes closed conditions, at a sampling rate of 10 Hz. The Force Platform Test was completed every trial. An area measurement that accounted for 95% (A95) of the variation in the center of pressure changes was used as the outcome measure.

EEG – Sleep onset and quality during the experiment were assessed with ambulatory electrophysiological equipment. Brain electrical signals were acquired from the O4, C2, A1 and A2 scalp leads of the International 10-20 system (Jasper, 1958) with an Oxford Medilog ambulatory recorder system and digitized on an Oxford data system (Oxford Instruments Ltd., Abingdon, Oxon, England). The EEG signal was digitized at 128 samples/sec. EOG signals were also acquired to support sleep scoring by a polysomnographic technologist. In total, six electrodes were used (2 scalp, 2 mastoid, 2 outer canthi). Participants wore the electrodes for a total of two hours during each session. Sleep latency, total sleep time, time spent in each stage of sleep, and stage of sleep upon awakening were assessed.

Actigraphs - SleepWatch-L model actigraphs were issued to each participant (Ambulatory Monitoring, Inc., Ardsley, NY). The actigraph resembled a wristwatch and was worn in a similar manner. A small accelerometer systematically recorded the individual's movement over time, both while awake and asleep, allowing for the objective identification of sleep/wake patterns (Brown, Smolensky, D'Alonzo, & Redman, 1990). Each participant wore an actigraph for three days prior to each test day. Actigraphy was used to confirm activity log results.

Activity Log – Participants recorded their sleep intervals as they occurred for three days prior to each experimental session. Subjective rating scales were also provided to periodically register sleepiness ratings. This form (developed by Jonathan French at the Air Force Research Laboratory) allowed us to assess the number of hours slept each night for the three days prior to each session (Whitmore & Fisher, 1996).

Procedures

A training session was conducted the week prior to data collection. During training, participants completed 6 trials of the ANAM battery to assure asymptotic performance on each test. Training on the other tests required only a single trial. It was conducted on the morning of the first experimental session.

For each experimental session, participants arrived at 1045 and completed one ANAM training test trial to become re-familiarized with the tests. Participants were also introduced to the remaining tests at that time. Lunch was served after these familiarization trials. EEG electrodes were then installed and data recording begun. Prior to sleep, participants completed their first testing trial at 1200 hrs (baseline). Drug administration occurred at 1300 hrs and participants slept from 1300 to 1400 hrs. Participants were awakened at 1400 hrs and were told to remain in bed until a proctor could help them into their chairs at the

computer workstations. Testing began once everyone was seated (1400 hrs/1-hr post-dose). Testing continued on the hour every hour until 2100 hrs. Participants were given half hour breaks each hour. At the conclusion of the test day, participants were given actigraphs and activity logs for the intermediary week. Participants returned the following week for the second experimental session. The experimental session schedule is presented in Table1.

Statistical Analyses

Our power analysis was based on the post-hoc comparison (paired t-test) of the pre-to-immediate awakening change in performance between the two drug conditions. Our proposed sample of 16 participants provided a 96% chance (power) of detecting a standardized effect size (ES) = 1.0 when comparing the change under Sonata with the change under Placebo (i.e., a difference that is about one standard deviation of the difference in magnitude). Using mean reaction time from the PVT as an example, data collected in our laboratory showed the standard deviation of the difference to be about 25 msec. Thus, we had a 96% chance of detecting about a 25 msec difference in the changes of the two conditions, which represents about a 10% change from baseline. In this manuscript any mention of statistical significance refers to an alpha level of 0.05.

Zalepon vs. Placebo

For continuous variables (e.g., mean reaction time correct, throughput, etc), repeated measures analyses of variance were used to test for significant interactions between drug condition and time. A Huyhn-Feldt adjustment was made to the ANOVA for variables that failed Mauchly's Test of Sphericity. When significant interactions were detected, post-hoc analyses (Student's t-tests) were performed to compare the change from baseline to post-awakening while under zaleplon to the change from baseline to post-awakening while under placebo. This was done for the first four post-dose trials. For discrete variables and variables where non-normality was suspected (e.g., symptoms, number of lapses, etc), Wilcoxon signed-rank tests were used to compare the drug and placebo conditions for differences in the change from baseline to the first four post-dose trials. Because the goal of this study was to identify potential problems and symptoms associated with the use of zaleplon, and all post-hoc comparisons where planned a priori, no conservative adjustments were made for the multiple post-hoc comparisons.

Sleep Inertia

Only data from the first three trials of the placebo condition (baseline, 1-hr post-dose, 2-hr post-dose) were examined to determine sleep inertia effects. Any additional effect upon sleep inertia from zaleplon would be captured in the zaleplon versus placebo comparisons. A repeated measures ANOVA with one within-subjects factor (time) was performed on each dependent measure. When a significant effect was observed, post-hoc comparisons between baseline and each of the post-awakening time periods were performed using Student's t-tests.

RESULTS

One of the 16 participants was dropped from the analyses due to poor and highly variable performance for periods where performance should have been stable. The participant appeared to lack the motivation required to perform the tests with any regularity. Measures for which any interaction test resulted in a significant finding are graphed in Figures 1-30. Note that the 1-hr post-dose trial is the trial performed immediately upon awakening, and contains data from 60 to 100 min post-dose. Similarly, the other post-dose trials began at the time indicated post-dose and had a duration of 25-40 min. The results have been broken into two sections. The first section details the results of the drug comparisons. For variables where non-parametric tests were performed, means were graphed to provide trend information. The second section examines only the placebo data for sleep inertia effects.

Zaleplon vs. Placebo Results

Sleep and Activity

Results from the Activity Log indicated that the participants averaged 7.0 hrs of sleep per night during the week and 7.9 hrs of sleep per night during the weekend prior to participating in an experimental session. Overall, the average sleep start time was 23:54 with an average intra-individual standard deviation of 42-min. Participants averaged 7.6 hrs of sleep the night prior to an experimental session, with an average sleep start time of 23:45.

EEG

No significant differences were found between drug conditions for any EEG measures. Comparisons were made for sleep latency, time spent in sleep stages, and total sleep time. The average sleep latency across conditions was 14.93-min. Thus, on average, participants had approximately 45-min available for sleep of which they actually slept 42.02-min. The mean times spent in each stage of sleep across conditions were: Stage-I 10.77-min, Stage-II 26.87-min, Stage-III 1.77-min, and Stage-IV 2.62-min. Participants were generally awakened from either Stage-I or Stage-II sleep (69% in both placebo and zaleplon conditions – see Figure 1).

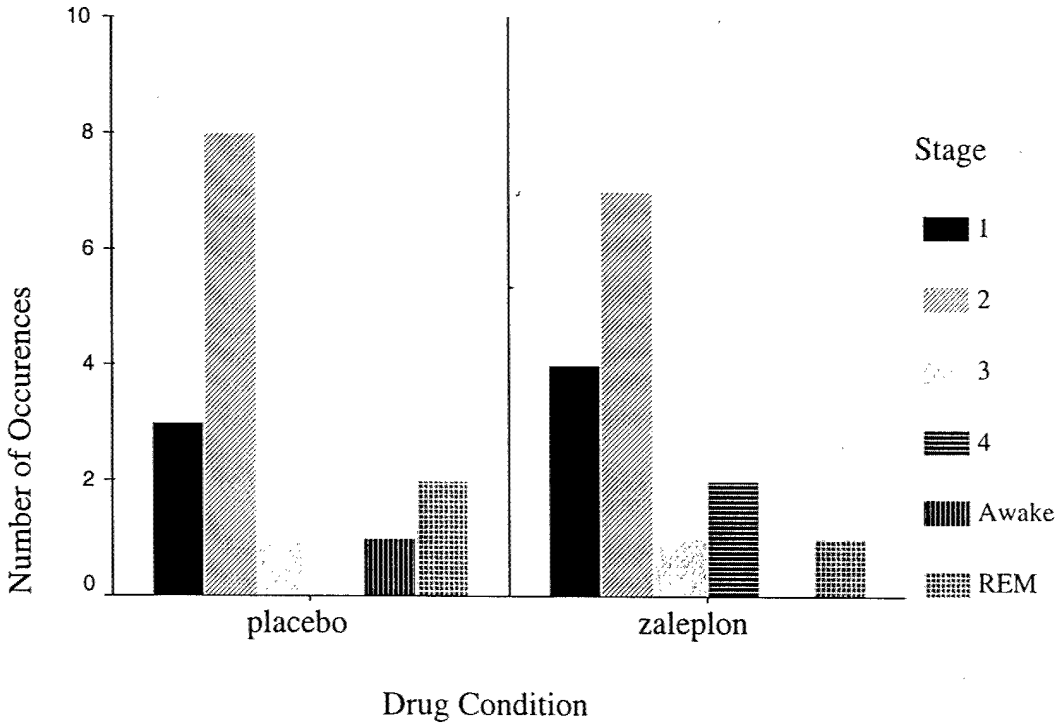

Figure 1 Stage of sleep upon awakening by condition.

Cognitive Performance and Memory

Code Substitution Test-Learning– Significant drug by trial interactions were detected for MRTC (Huyhn-Feldt $F(2.1,29.5)=3.32$, $MSE=39331.6$) and throughput ($F(7,98)=3.80$, $MSE=23.1$). Under zaleplon, MRTC significantly increased from baseline at the 2-hr ($t(14)=4.21$) post-dose trial when compared to placebo (see Fig 2). Under zaleplon, throughput significantly decreased from baseline values at both the 1-hr ($t(14)=2.22$) and 2-hr ($t(14)=4.28$) post-dose trials when compared to placebo (see Fig 3).

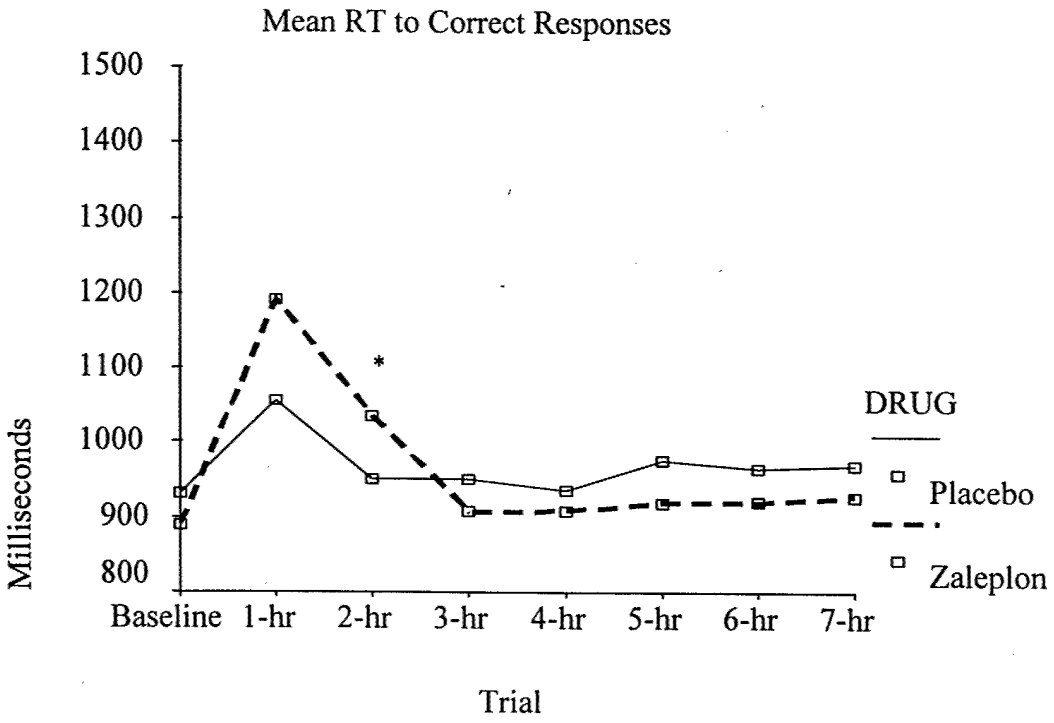

Figure 2 Codes Substitution Test-Learning
* sig. difference between drugs in the change from baseline

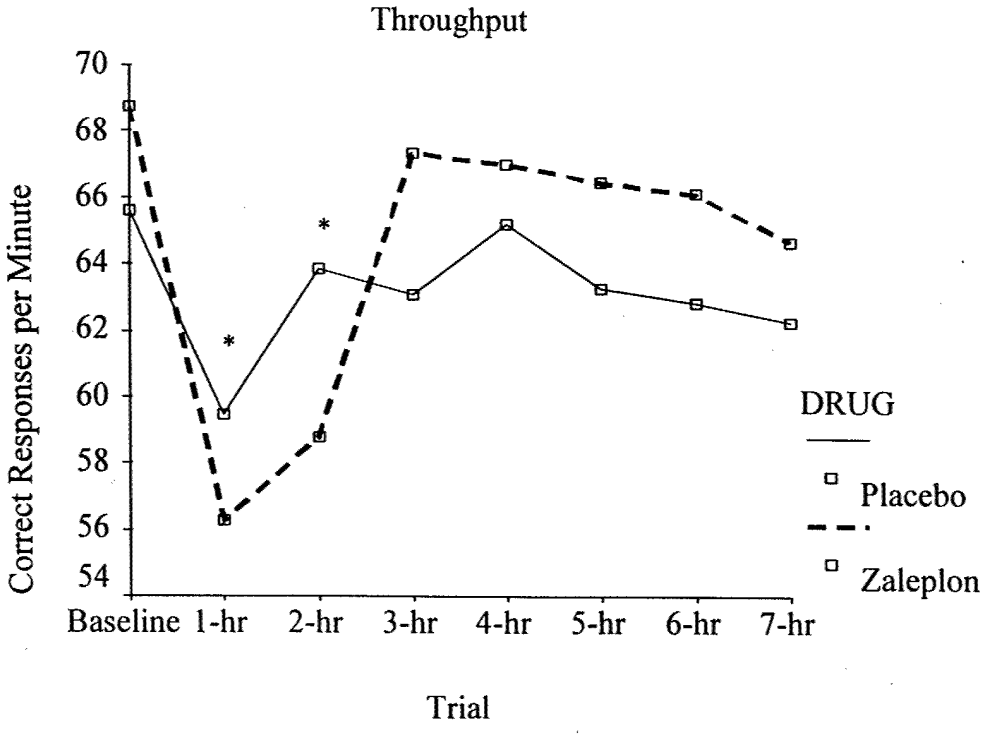

Figure 3 Code Substitution Test-Learning
* sig. difference between drugs in the change from baseline

Code Substitution Test-Immediate– No significant drug by trial interactions were detected for any of the four outcome measures.

Code Substitution Test-Delayed– Significant drug by trial interactions were detected for MRTC (Huyhn-Feldt F(4.1,56.8)=7.59, MSE=51934.0), SDRTC (Huyhn-Feldt F(3.8,53.1)=6.70, MSE=60494.7) and throughput (F(7,98)=4.36, MSE=86.1). Under zaleplon, MRTC significantly increased from baseline values at both the 1-hr (t(14)=3.07) and 2-hr (t(14)=3.06) post-dose trials when compared to placebo (see Fig 4). Under zaleplon, SDRTC significantly decreased from baseline values at both the 1-hr (t(14)=2.98) and 2-hr (t(14)=4.24) post-dose trials when compared to placebo (see Fig 5). Under zaleplon, throughput significantly decreased from baseline values at both the 1-hr (t(14)=3.77) and 2-hr (t(14)=4.08) post-dose trials when compared to placebo (see Fig 6).

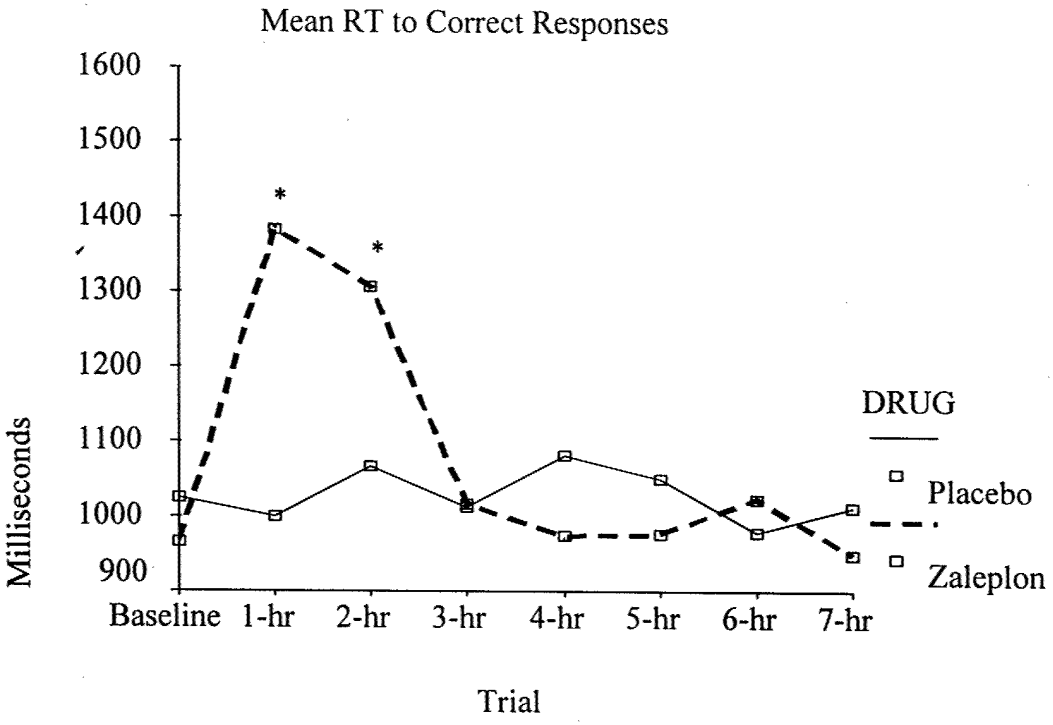

Figure 4 Code Substitution Test-Delayed Recall
* sig. difference between drugs in the change from baseline

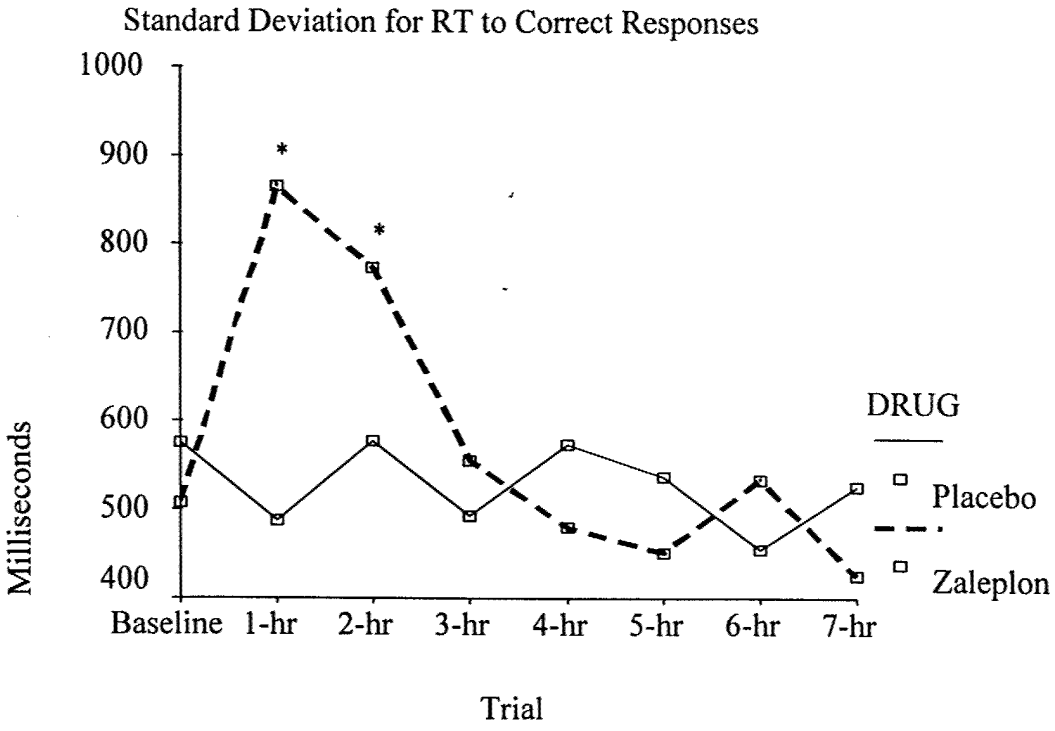

Figure 5 Code Substitution Test-Delayed Recall
* sig. difference between drugs in the change from baseline

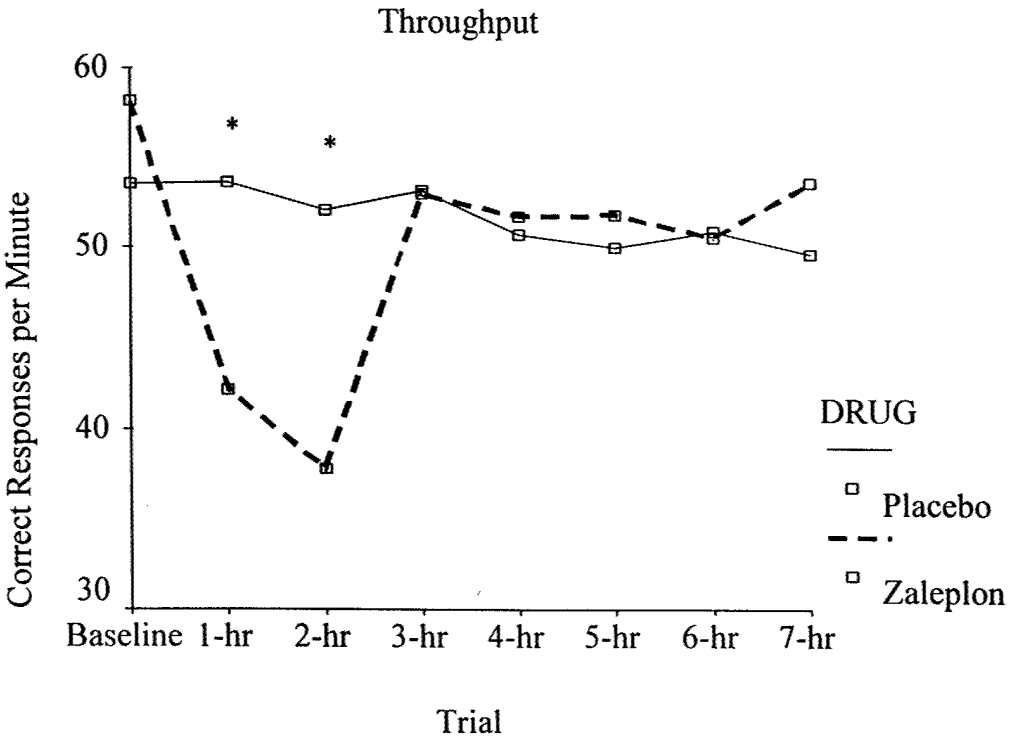

Figure 6 Code Substitution Test-Delayed Recall
* sig. difference between drugs in the change from baseline

Math Processing Test– Significant drug by trial interactions were detected for accuracy (Huyhn-Feldt F(2.5,35.5)=3.19, MSE=38.6), MRTC (Huyhn-Feldt F(2.4,33)=4.48, MSE=75303.3), and throughput (Huyhn-Feldt F(3.5,48.5)=4.47, MSE=28.3). Under zaleplon, accuracy decreased from baseline at the 1-hr post-dose trial when compared to placebo; however the change was not significant (see Fig 7). Under zaleplon, MRTC significantly increased from baseline values at the 1-hr (t(14)=2.25), 2-hr (t(14)=3.26), and 3-hr (t(14)=2.50) post-dose trials when compared to placebo (see Fig 8). Under zaleplon, throughput significantly decreased from baseline at the 2-hr (t(14)=3.29) post-dose trial when compared to placebo (see Fig 9). Under zaleplon, omissions significantly increased from baseline at the 1-hr (Wilcoxon z=2.04) post-dose trial when compared to placebo (see Fig 10).

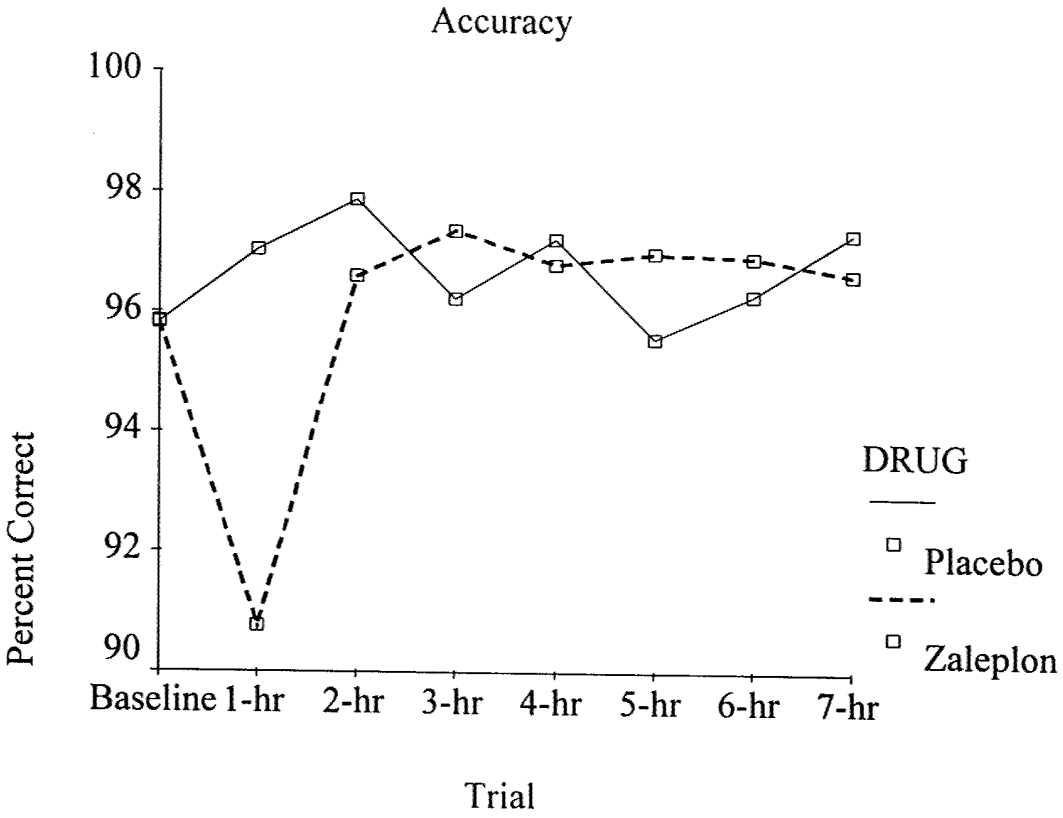

Figure 7 Math Processing Test
There were no significant post-hoc comparisons.

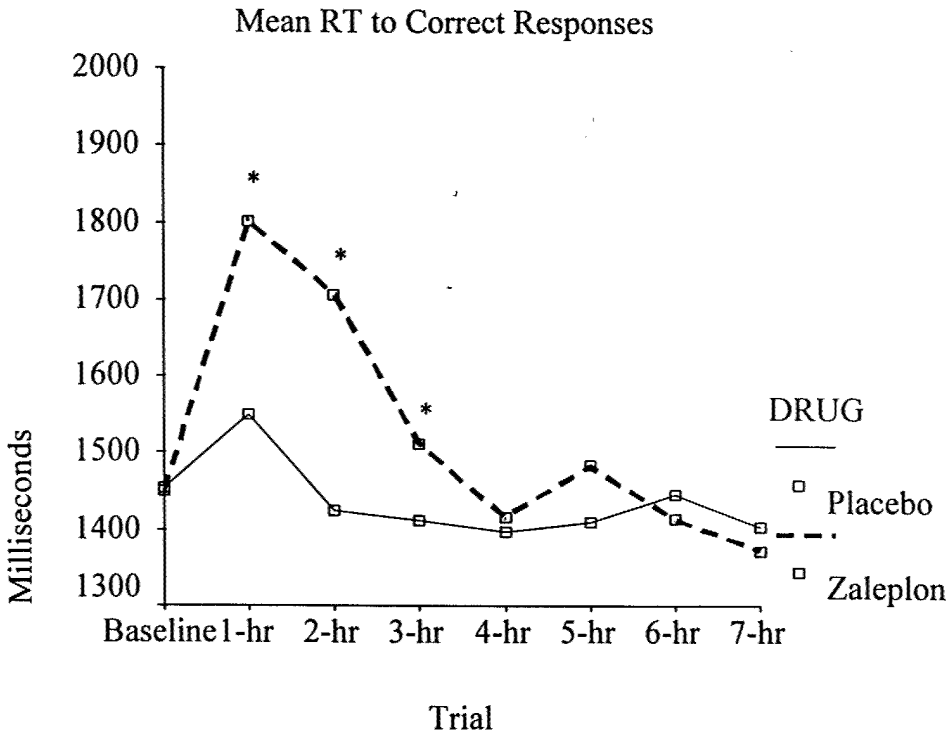

Figure 8 Math Processing Test
* sig. difference between drugs in the change from baseline

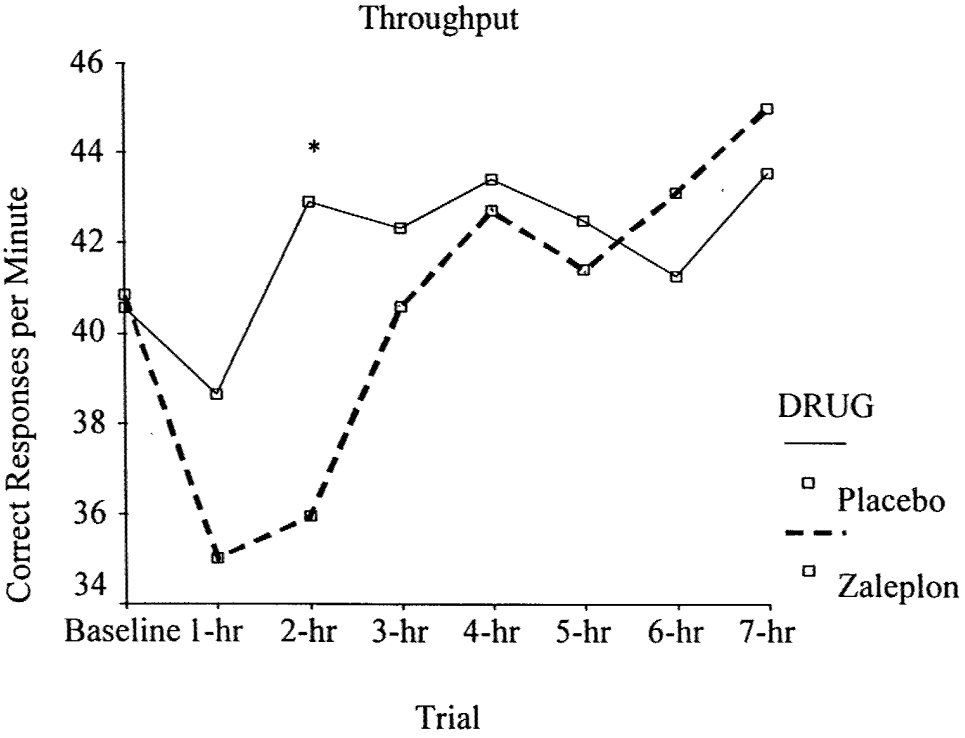

Figure 9 Math Processing Test
* sig. difference between drugs in the change from baseline

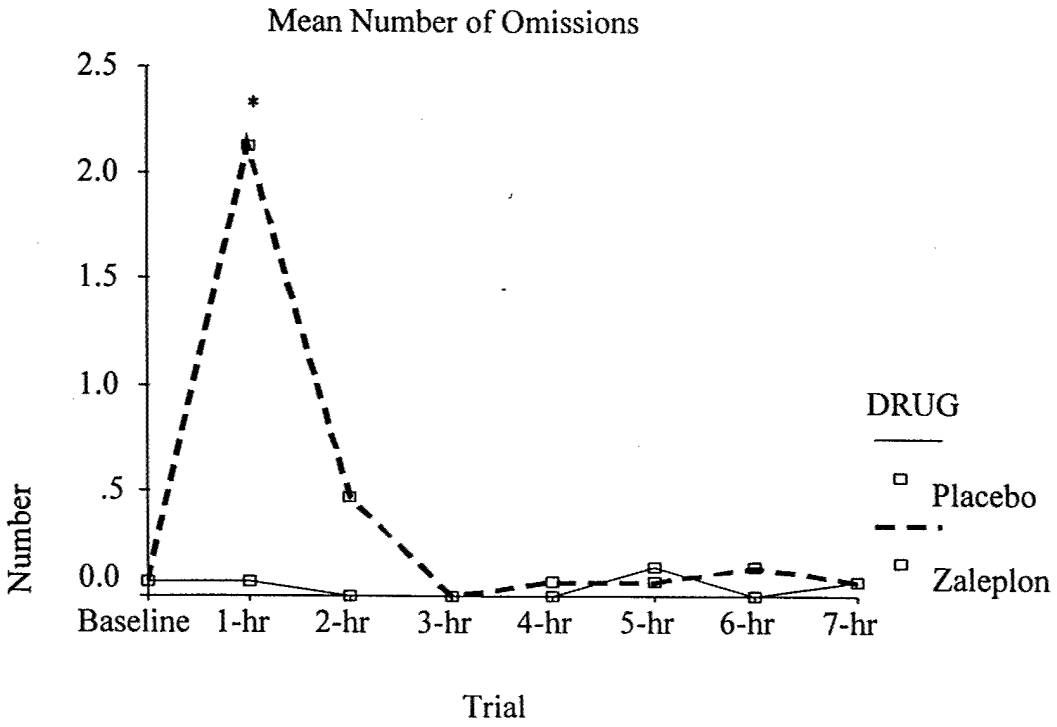

Figure 10 Math Processing Test
* sig. difference between drugs in the change from baseline. Wilcoxon Test was performed on the signed ranks of the differences, not on the mean omissions.

Logical Reasoning Test– Significant drug by trial interactions were detected for accuracy (Huyhn-Feldt F(2,27.9)=4.21, MSE=62.8), MRTC (Huyhn-Feldt F(3.1,42.9)=7.91, MSE=66955.1), SDRTC (Huyhn-Feldt F(5.3,74.4)=6.89, MSE=12899.6), and throughput (F(7,98)=9.38, MSE=18.7). Under zaleplon, accuracy significantly decreased from baseline at the 1-hr (t(14)=2.51) post-dose trial when compared to placebo (see Fig 11). Under zaleplon, MRTC significantly increased from baseline values at the 1-hr (t(14)=3.52) and 2-hr (t(14)=2.71) post-dose trials when compared to placebo(see Fig 12). Under zaleplon, SDRTC significantly increased from baseline values at the 1-hr (t(14)=3.97) and 2-hr (t(14)=2.73) post-dose trials when compared to placebo(see Fig 13). Under zaleplon, throughput significantly decreased from baseline values at the 1-hr (t(14)=4.83) and 2-hr (t(14)=4.08) post-dose trials when compared to placebo(see Fig 14).

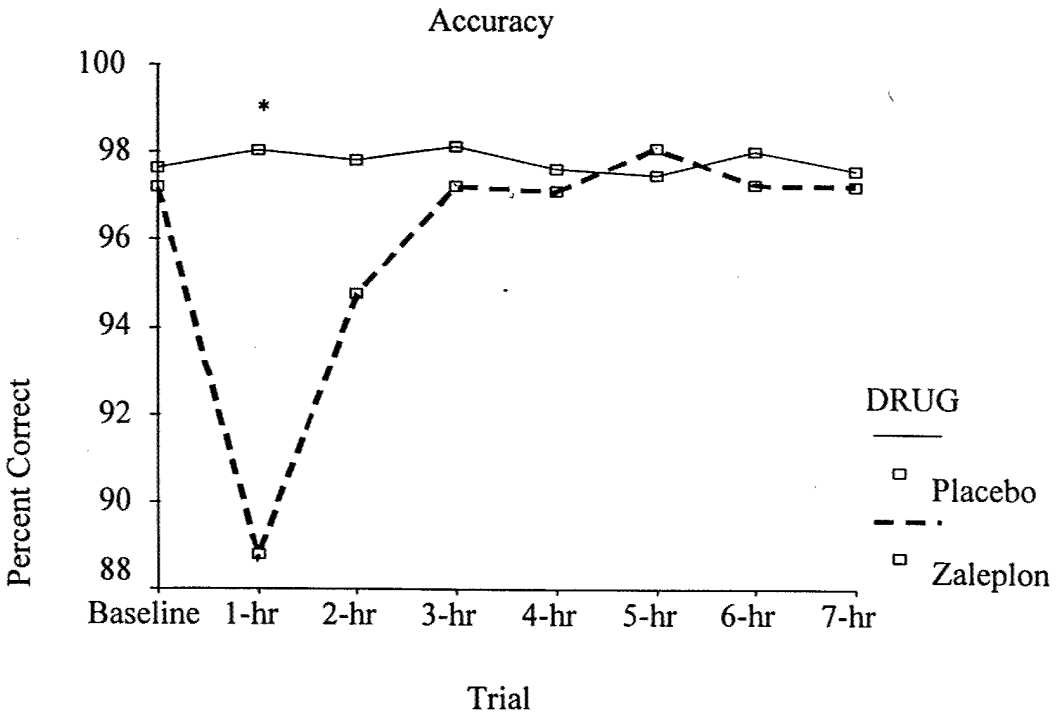

Figure 11 Logical Reasoning Test
* sig. difference between drugs in the change from baseline

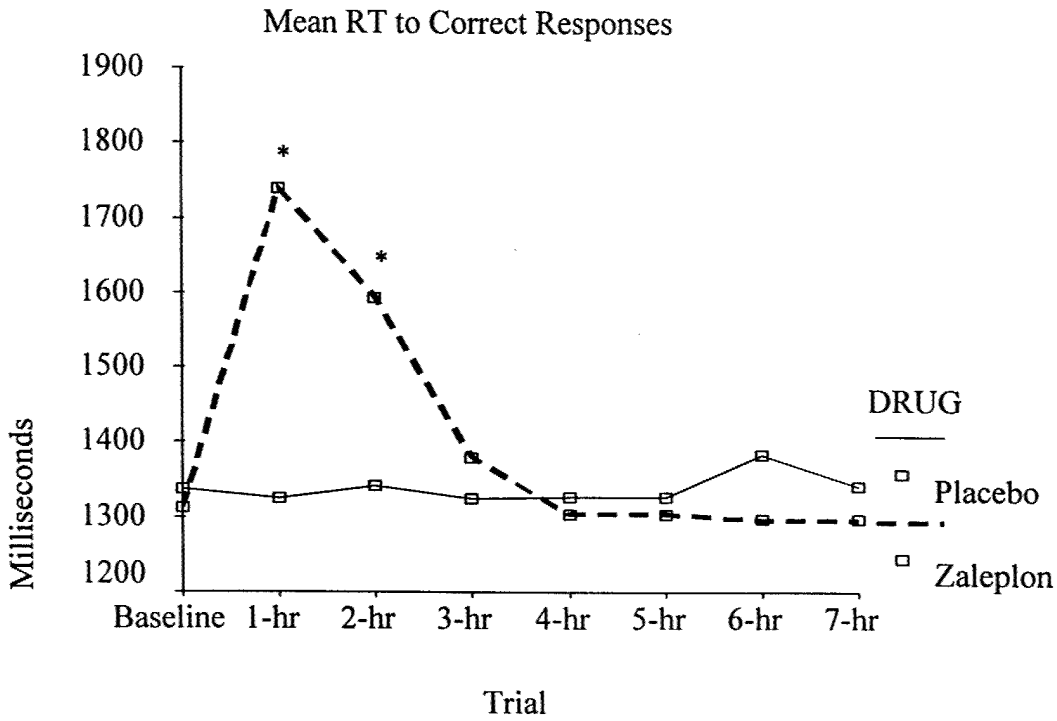

Figure 12 Logical Reasoning Test
* sig. difference between drugs in the change from baseline

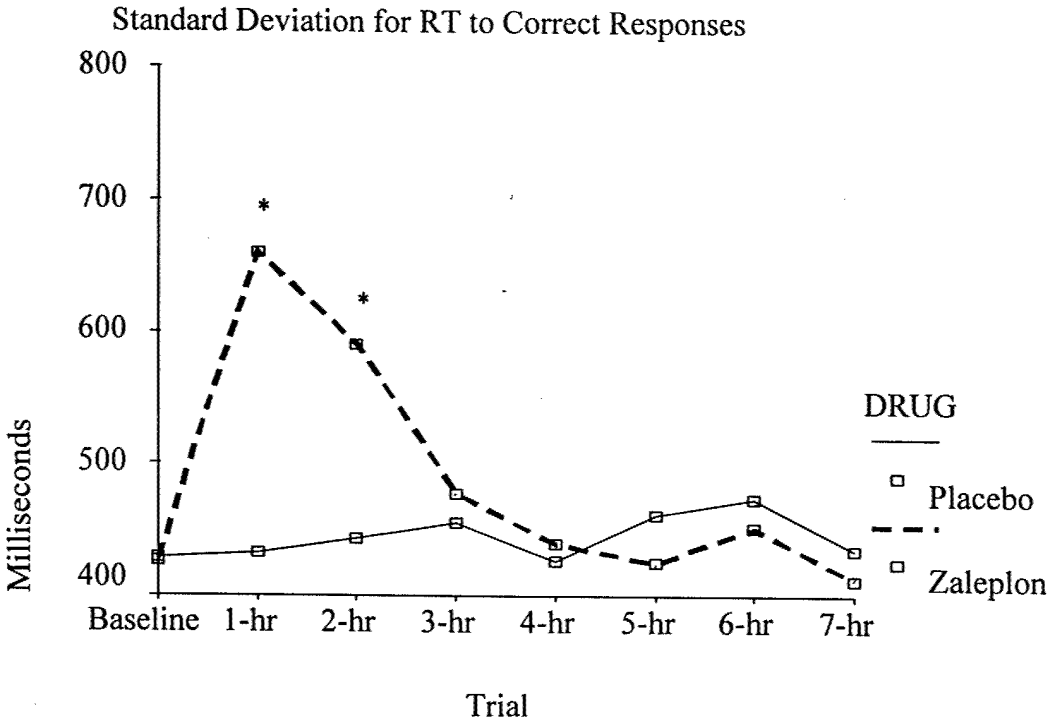

Figure 13 Logical Reasoning Test
* sig. difference between drugs in the change from baseline

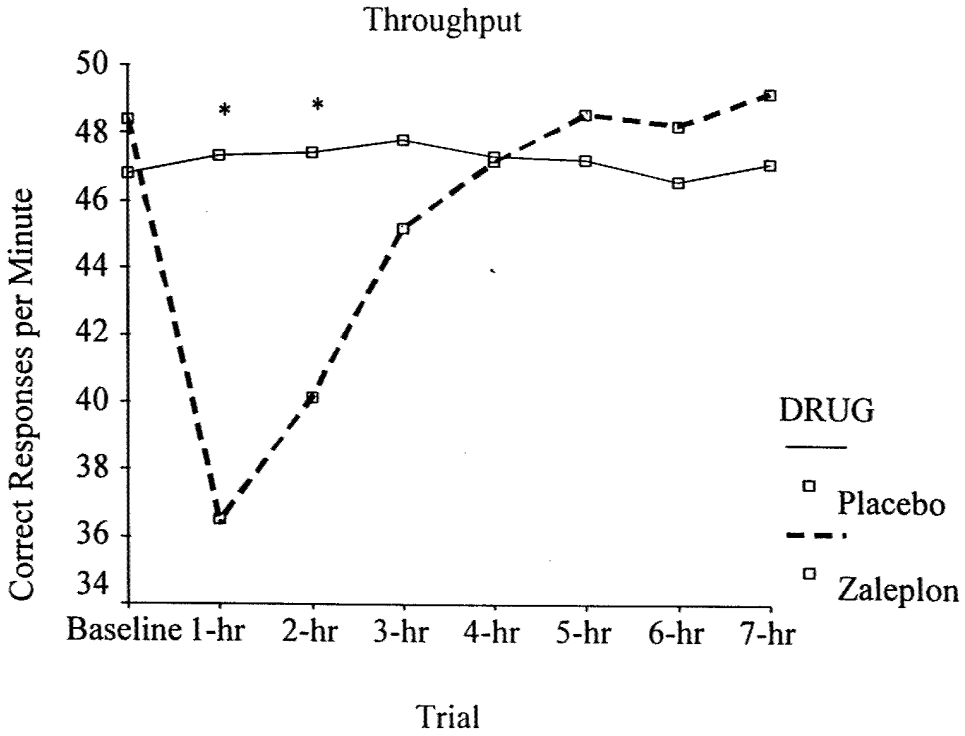

Figure 14 Logical Reasoning Test
* sig. difference between drugs in the change from baseline

Match to Sample Test– Significant drug by trial interactions were detected for MRTC (Huyhn-Feldt F(4.8,67.8)=3.96, MSE=89861.4), and throughput (Huyhn-Feldt F(5.4,76.3)=4.46, MSE=57.3. Under zaleplon, MRTC significantly increased from baseline values at the 1-hr (t(14)=2.21), 2-hr (t(14)=2.36) and 3-hr (t(14)=3.06) post-dose trials when compared to placebo (see Fig 15). Under zaleplon, throughput significantly decreased from baseline values at the 1-hr (t(14)=2.63), 2-hr (t(14)=2.26), and 3-hr (t(14)=3.56) post-dose trials when compared to placebo (see Fig 16).

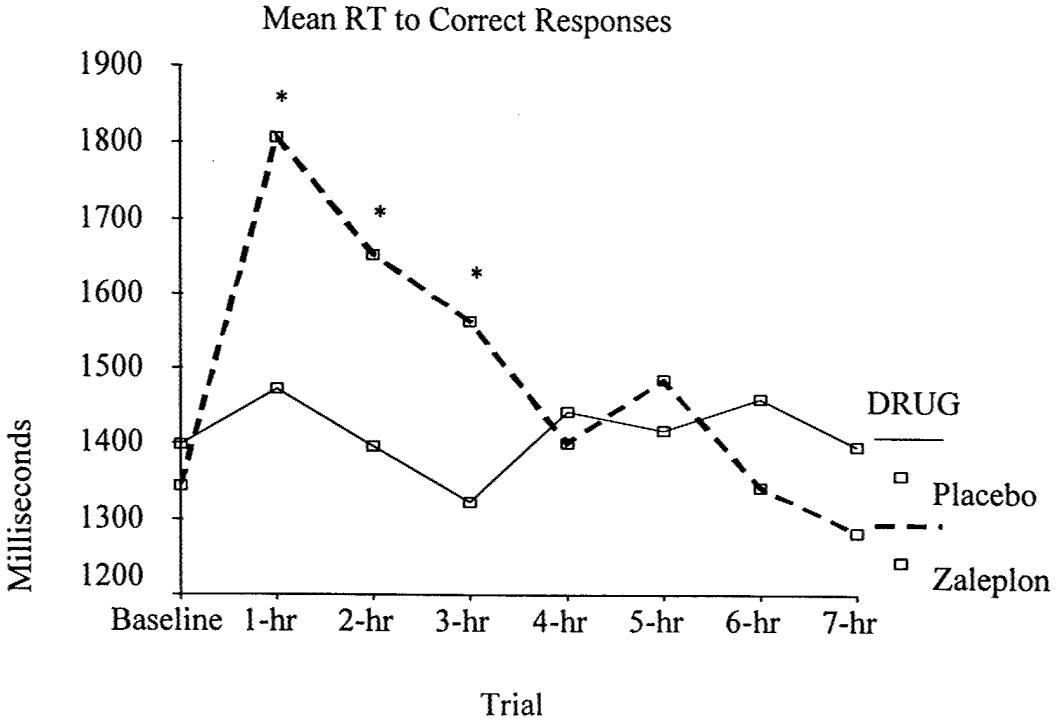

Figure 15 Matching to Sample Test
* sig. difference between drugs in the change from baseline

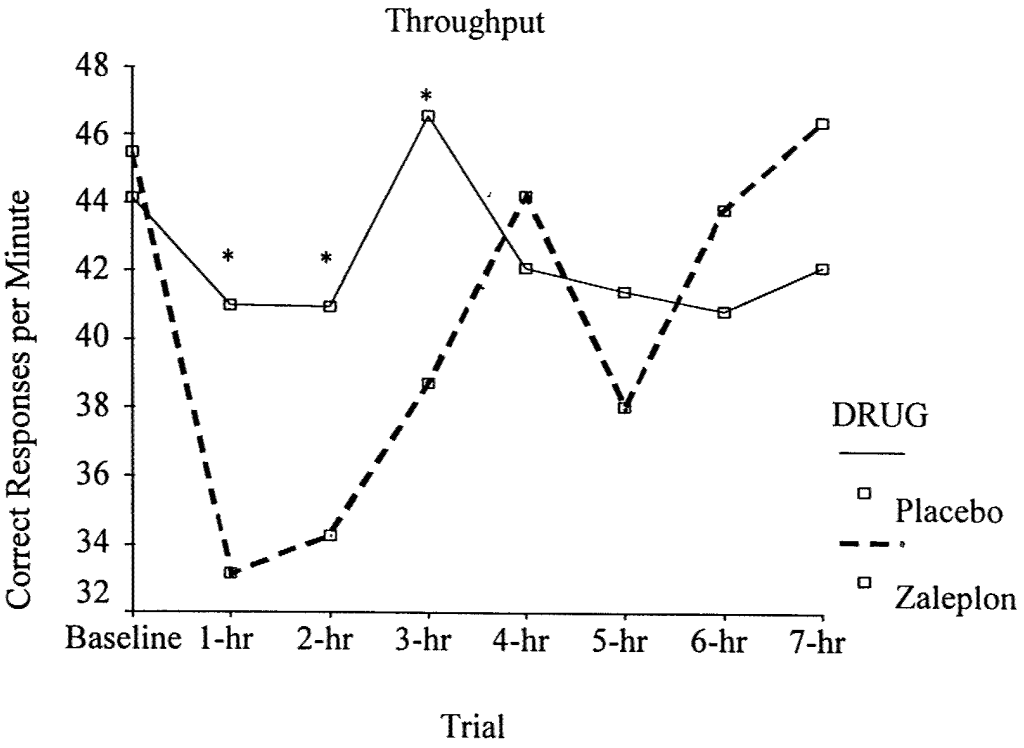

Figure 16 Matching to Sample Test
* sig. difference between drugs in the change from baseline

Simple Reaction Time Test– A significant drug by trial interaction was detected for MRT ($F(7,98)=2.79$, $MSE=324.0$). There were no significant post-hoc comparisons (see Fig 17).

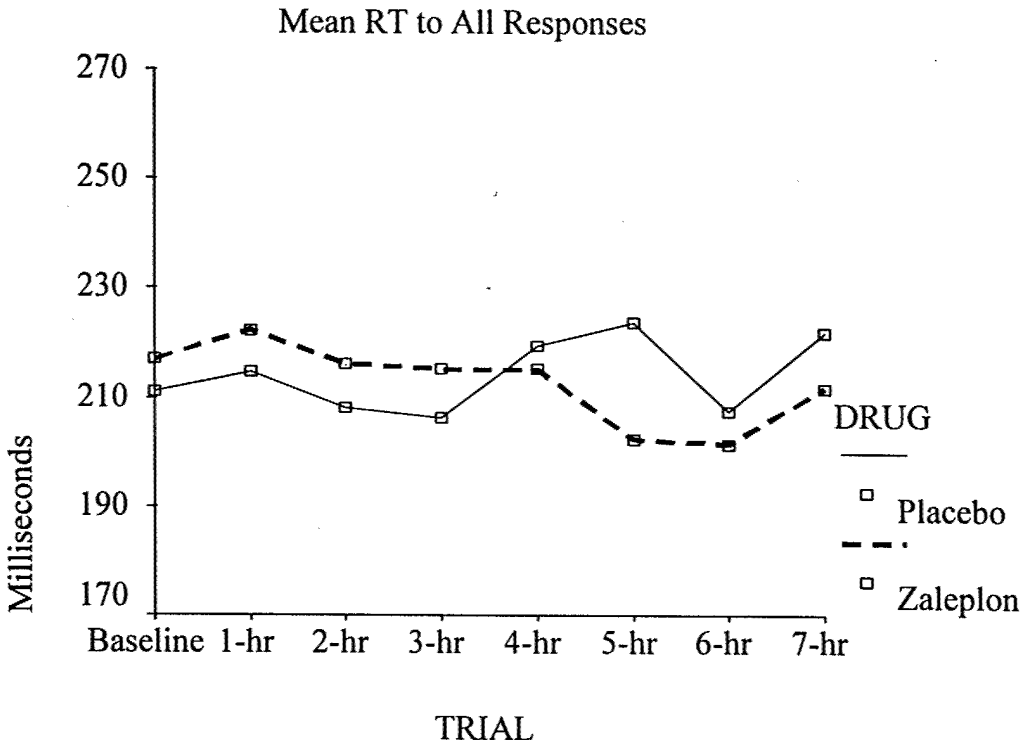

Figure 17 Simple Reaction Time Test
There were no significant post-hoc comparisons.

Psychomotor Vigilance Test– A significant drug by trial interaction was detected for RRT ($F(7,98)=3.73$, $MSE=.0448$). Under zaleplon, RRT significantly decreased from baseline values at the 1-hr ($t(14)=2.86$), and 2-hr ($t(14)=2.85$) post-dose trials when compared to placebo (see Fig 18).

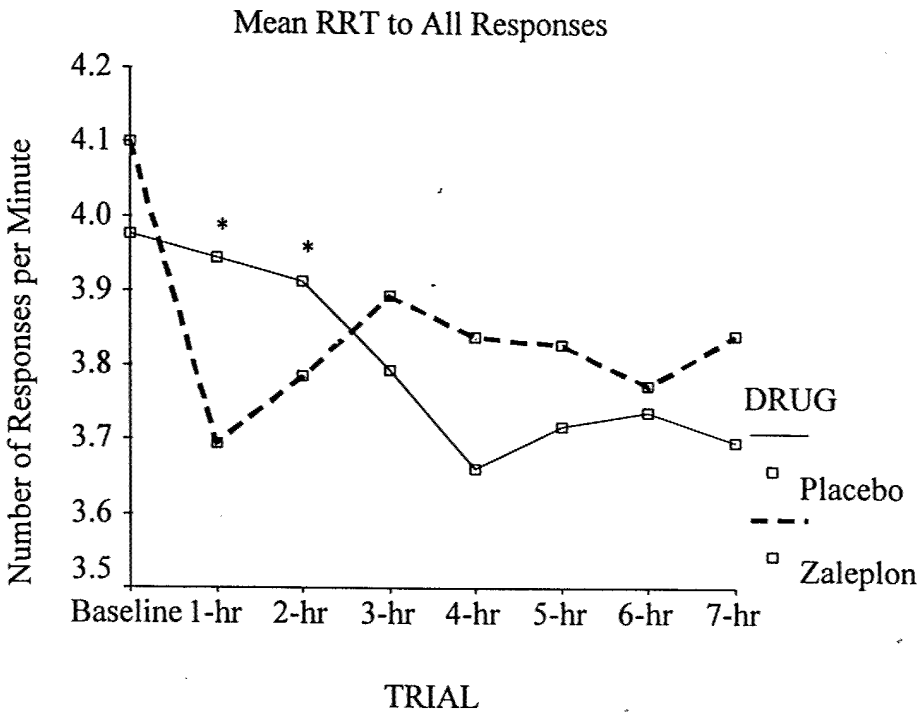

Figure 18 PVT
* sig. difference between drugs in the change from baseline

There was no within-session baseline for the Williams Word Memory Test. Consequently, evaluations were made by comparing the number correct between placebo and zaleplon at each time point, separately (See Fig 19). Given the discrete nature of the data a Wilcoxon Signed Rank Test was utilized. Significant drug differences were found for both trials (1-hr, Wilcoxon z=2.20, 4-hr, Wilcoxon z=2.02).

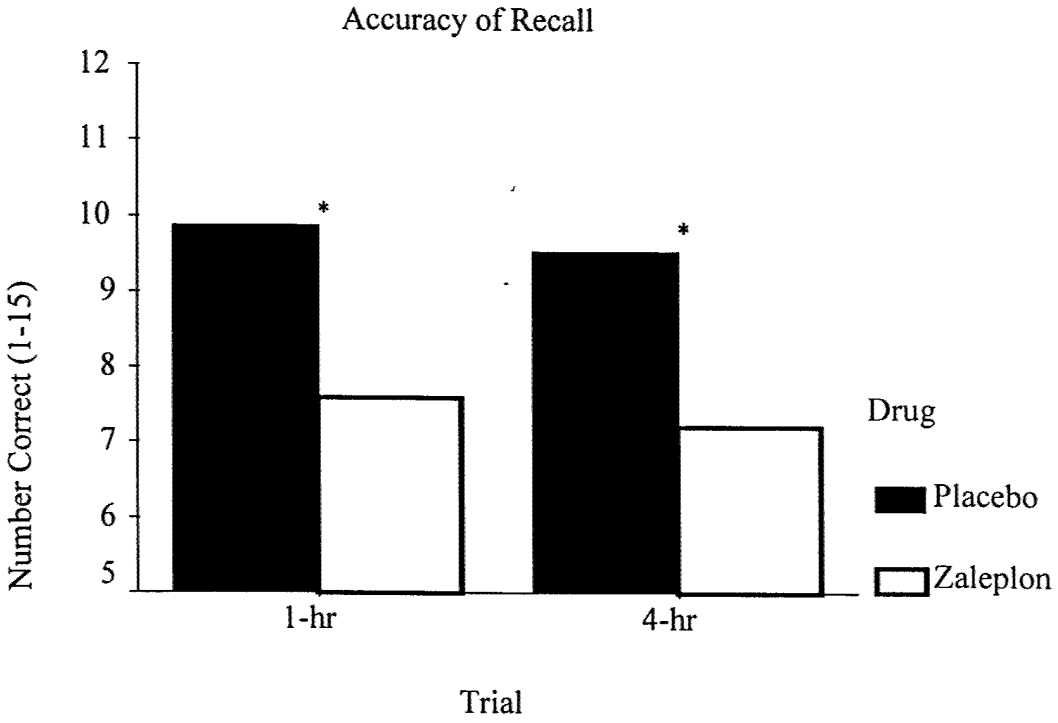

Figure 19 Word Memory Test
* sig. difference between drug conditions

Balance & Strength
Force Platform Test– There was no statistical evidence of effects due to eyes open or eyes closed, both were affected similarly. Consequently the eye conditions were combined. A significant drug by trial interaction was detected for A95 ($F(7,98)=6.36$, $MSE=2.48$). Under zaleplon, A95 significantly increased from baseline values at the 1-hr ($t(14)=4.49$), and 2-hr ($t(14)=3.62$) post-dose trials when compared to placebo(see Fig 20).

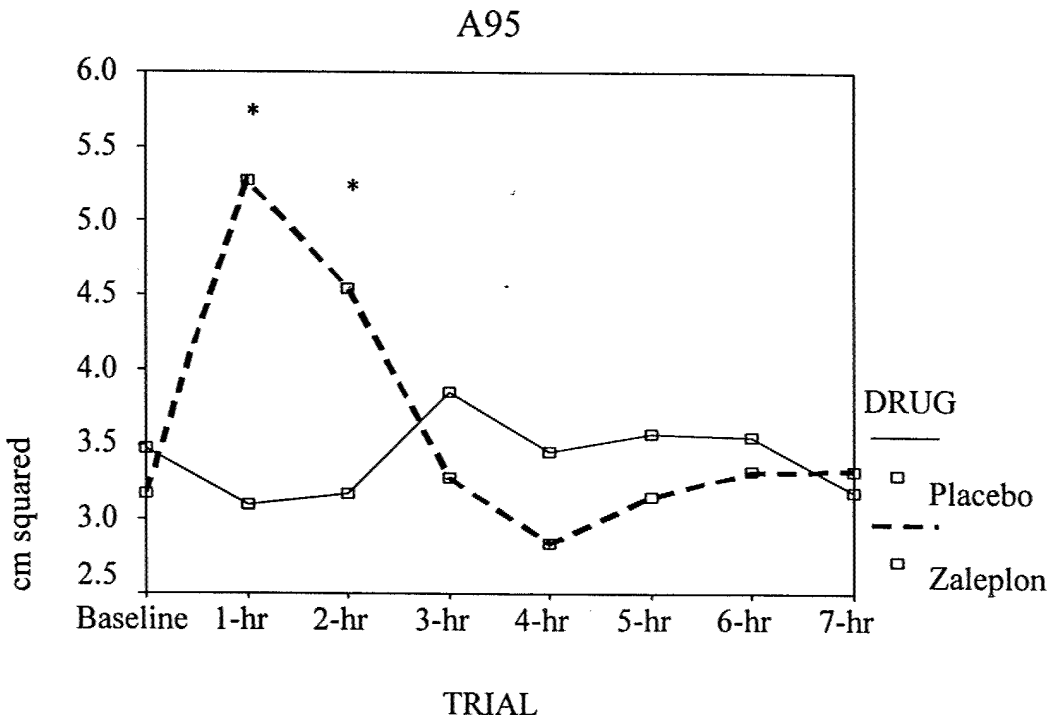

Figure 20 Force Platform Test
* sig. difference between drugs in the change from baseline

Grip Strength-There were no significant changes in Grip Strength performance between the drug groups. Indeed, there was no clear trend with the means ranging from 19.91 kg to 19.23 kg.

Subjective Data
Under zaleplon, SSS ratings significantly increased from baseline values at the 1-hr (Wilcoxon z=2.33), and 2-hr (Wilcoxon z=2.38). post-dose trials when compared to placebo. Much of this result may be due to the placebo condition's reduction in sleep ratings for the 2-hr and 3-hr post-dose trials. Of course, a reduction in sleepiness should be expected for some period following a nap (see Fig 21).

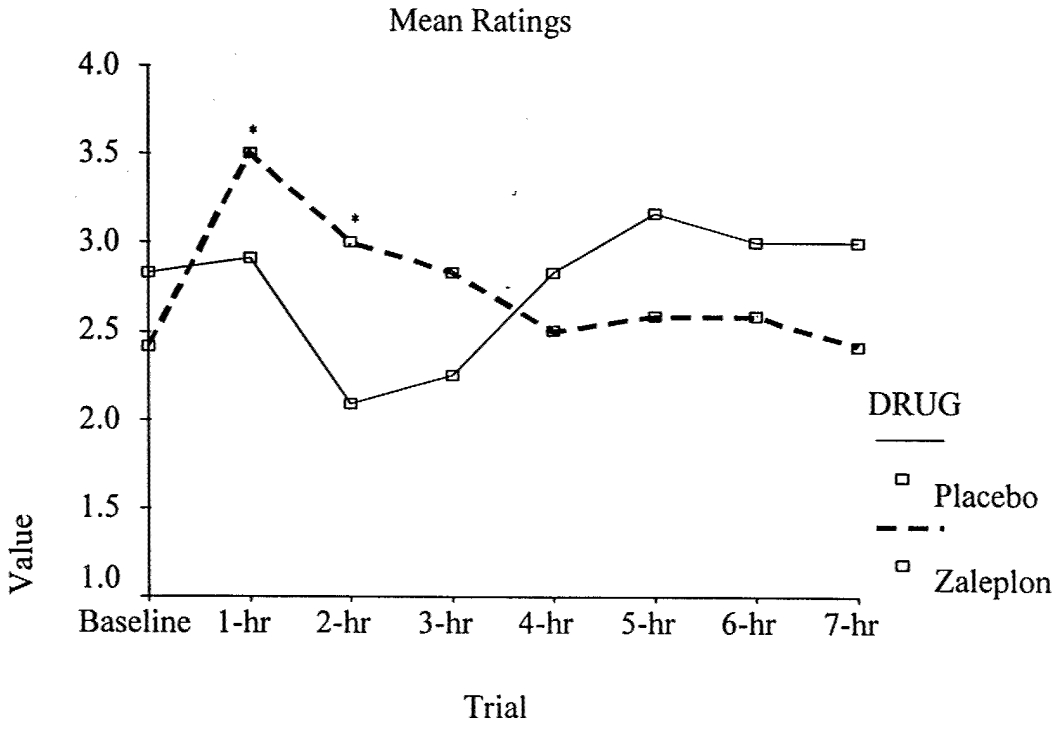

Figure 21 Stanford Sleepiness Scale
* sig. difference between drugs in the change from baseline. Wilcoxon Test was performed on the signed ranks of the differences, not on the mean ratings.

Profile of Mood States- Due to missing data during the last three trials, the POMS data was analyzed using just the first five trials. A significant drug by trial interaction was detected for only one of the six subscales, Confusion (Huyhn-Feldt $F(2.6,26.3)=6.06$, $MSE=7.96$) . Under zaleplon, Confusion ratings significantly increased from baseline values at the 1-hr ($t(10)=2.39$), 2-hr ($t(10)=2.89$), and 3-hr ($t(10)=3.19$) post-dose trials when compared to placebo (see Fig 22).

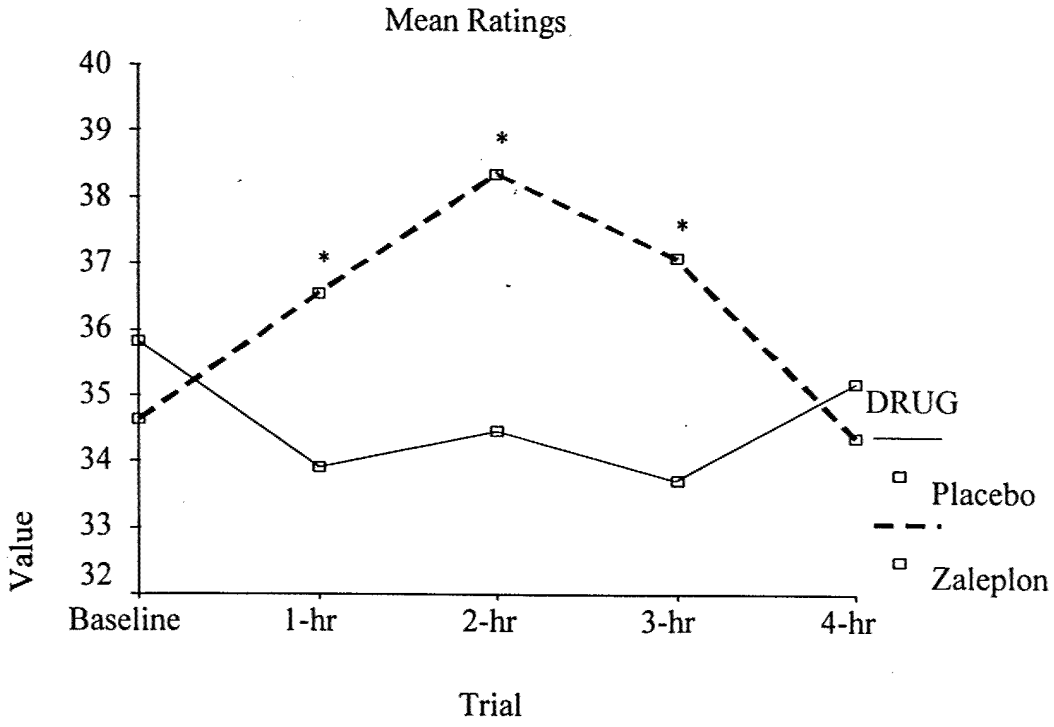

Figure 22 POMS Confusion Scale Results
* sig. difference between drugs in the change from baseline

To prepare for significance testing on the Sleep-Aid Symptoms Questionnaire, difference scores indicating the change from baseline to each of the post-awakening trials were calculated. A Wilcoxon signed-rank test was then performed comparing the drug conditions. Responses to The Sleep-Aid Effects Questionnaire indicated several significant differences between the drug conditions. Since this was a safety study, in addition to the significant results, we included any case where 3 or more out of the 16 participants (19%) indicated a change from baseline (Table 3). Significant increases under the zaleplon condition relative to placebo were found for the Drowsy, Drugged Feeling, Headache, Light Headed, and Difficulty Staying Awake symptoms. A number of other symptoms showed non-significant increases for the zaleplon to placebo comparison. One symptom, congestion, showed a non-significant increase in the placebo compared to zaleplon. At the end of the questionnaire participants were asked to guess whether they had received placebo or zaleplon. Fifteen of 15 participants accurately guessed during which session they received zaleplon.

Symptom	1-hr		2-hr		3-hr		4-hr		5-hr		6-hr		7-hr	
	Z	P	Z	P	Z	P	Z	P	Z	P	Z	P	Z	P
Loss of Balance	19	6	19	0										
Chills	19	0	19	0										
Confusion	19	0												
Congestion	0	19												
Dizzy	19	0	19	0										
Drowsy	69	6*	63	0*	56	0*	38	13	44	13	44	13	50	13
"Drugged" Feeling	44	0*	44	0*	38	0*								
Headache	31	13	44	6*	31	6								
Illusions	19	0												
Light Headed	31	0*	31	0*	31	0*								
Nausea			19	0										
Difficulty Staying Awake	63	0*	63	0*	56	0*	44	19					44	13

Table 3 Sleep-aid effects questionnaire results for zaleplon and placebo. Values in a given drug column indicate the percent of participants who worsened relative to the other condition. * Significant difference between drug conditions ($p<.05$).
Blank fields indicate a response of less than 19% under both drug conditions.

Sleep Inertia Results

Code Substitution Test-Learning–Significant trial main effects were detected for MRTC (Huyhn-Feldt $F(1.4,19.1)=8.71$, $MSE=11516.8$), SDRTC ($F(2,28)=4.08$, $MSE=5704.3$), and throughput ($F(2,28)=10.91$, $MSE=13.6$). MRTC significantly increased from baseline at the 1-hr ($t(14)=3.52$) post-dose trial (see Fig 24). SDRTC significantly increased from baseline at the 1-hr ($t(14)=2.50$) post-dose trial (see Fig 25). Throughput significantly decreased from baseline at the 1-hr ($t(14)=5.06$) post-dose trial (see Fig 26).

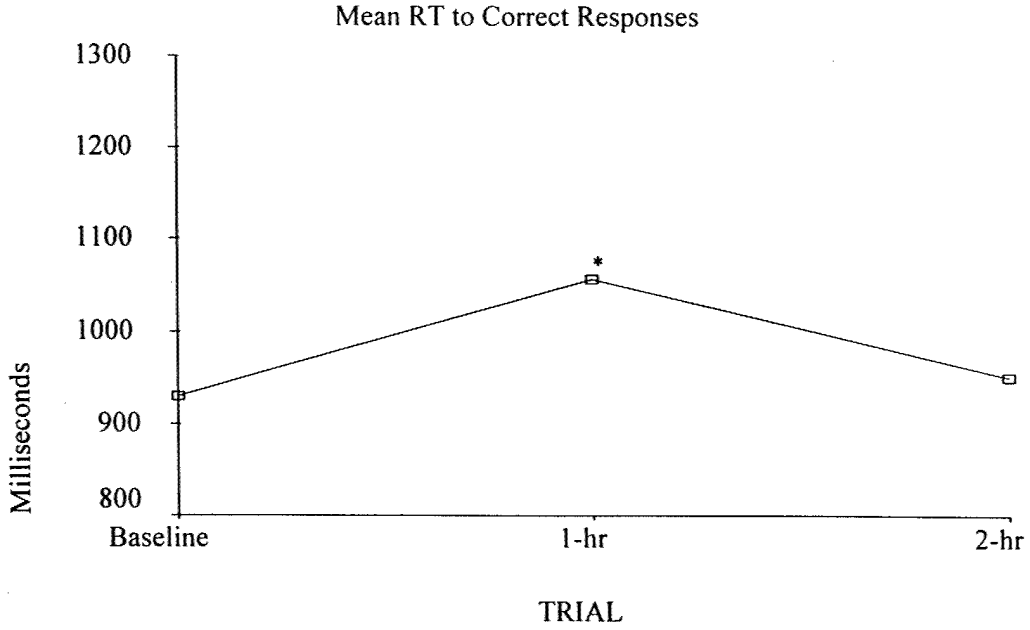

Figure 24 Code Substitution Test-Learning
* sig. change from baseline

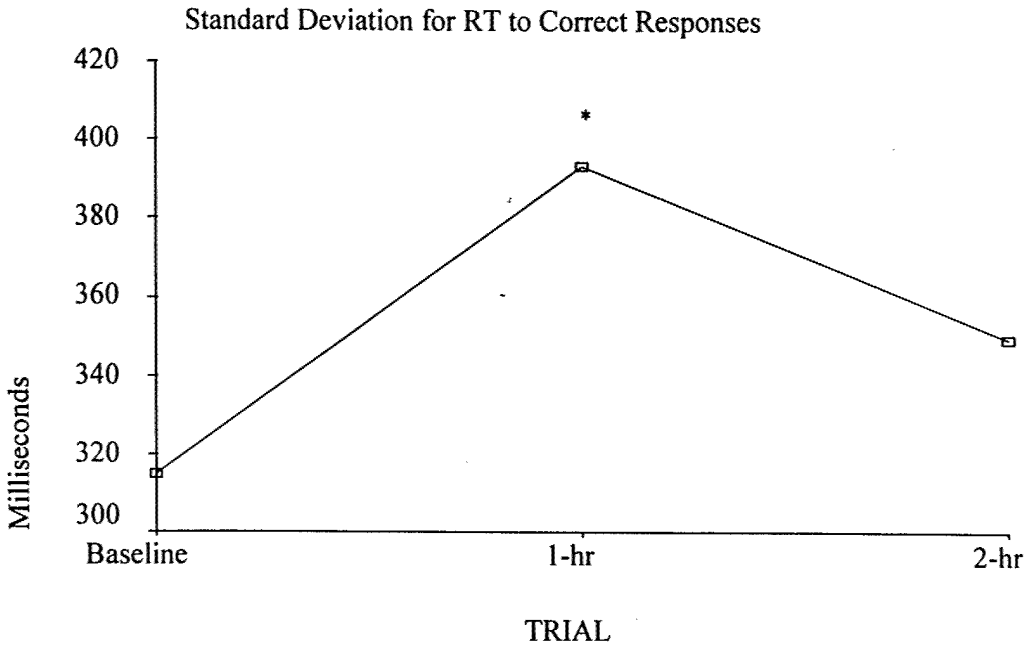

Figure 25 Code Substitution Test-Learning
* sig. change from baseline

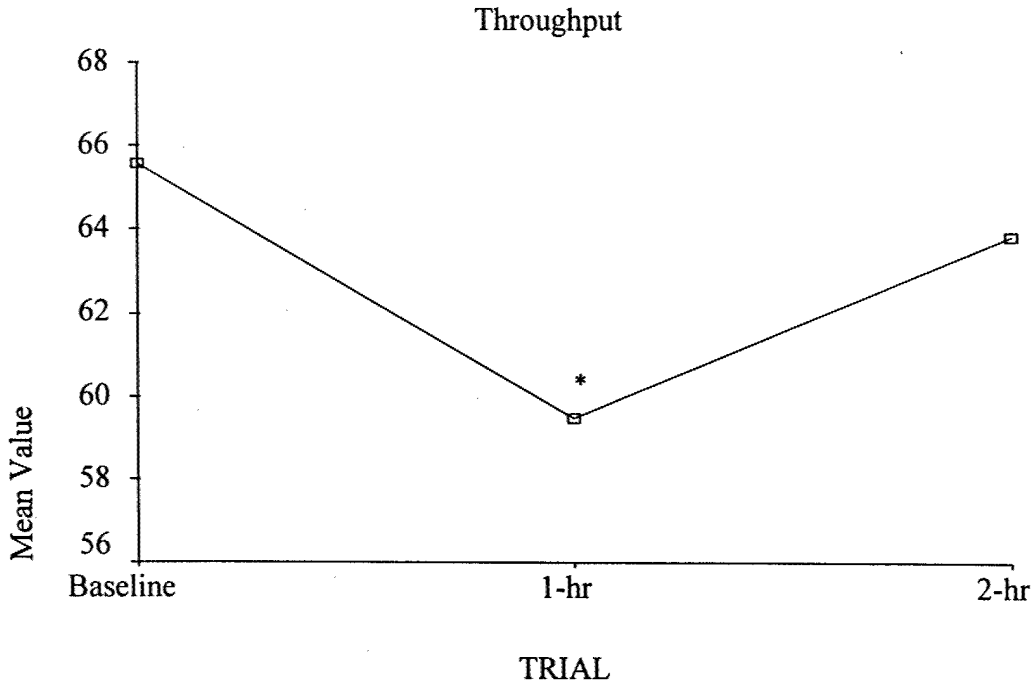

Figure 26 Code Substitution Test-Learning
* sig. change from baseline

Code Substitution Test-Immediate–Significant trial main effects were detected for SDRTC ($F(2,28)=4.62$, $MSE=52131.5$), and throughput ($F(2,28)=4.40$, $MSE=99.1$). Post-hoc

comparisons on SDRTC revealed no significant changes (see Fig 27). Throughput significantly decreased from baseline at the 1-hr (t(14)=2.40) post-dose trial (see Fig 28).

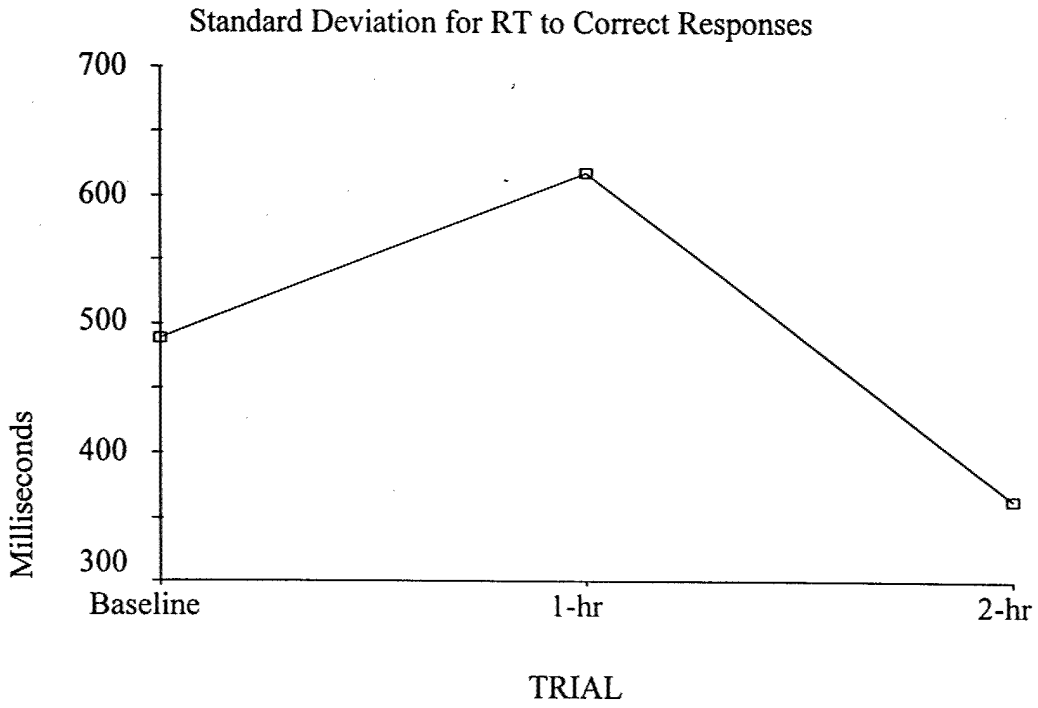

Figure 27 Code Substitution Test-Immediate
No significant changes from baseline were detected.

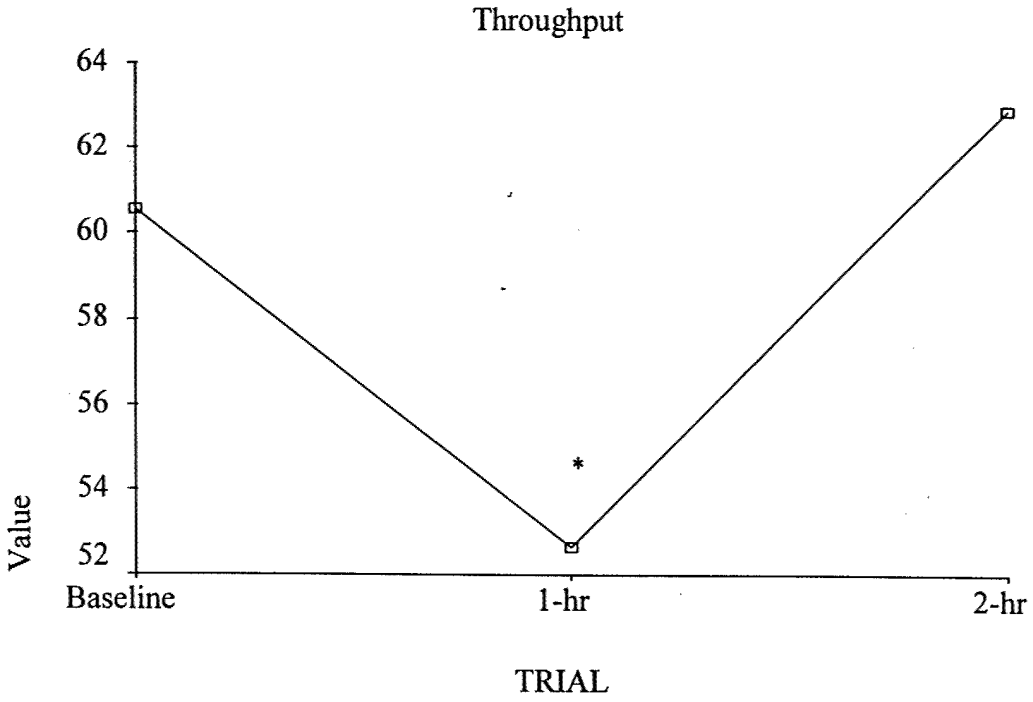

Figure 28 Code Substitution Test-Immediate
* sig. change from baseline

Code Substitution Test-Delayed– No significant trial main effects were detected for any of the four outcome measures.

Math Processing Test- Significant trial main effects were detected for accuracy ($F(2,28)=4.38$, $MSE=3.7$), MRTC ($F(2,28)=6.61$, $MSE=9533.4$), and throughput ($F(2,28)=9.00$, $MSE=7.63$). Accuracy significantly increased from baseline at the 2-hr ($t(14)=2.8$) post-dose trial(see Fig 29). MRTC significantly increased from baseline at the 1-hr ($t(14)=2.22$) post-dose trial(see Fig 30). Throughput significantly increased from baseline at the 2-hr ($t(14)=2.70$) post-dose trial(see Fig 31).

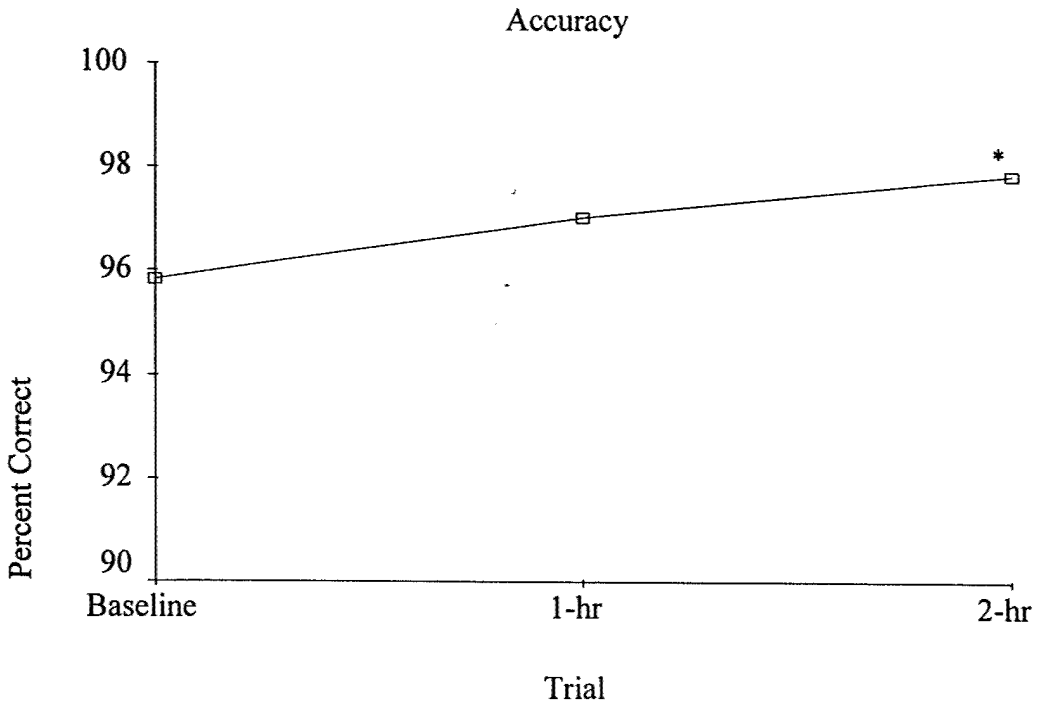

Figure 29 Math Processing Test
sig. change from baseline

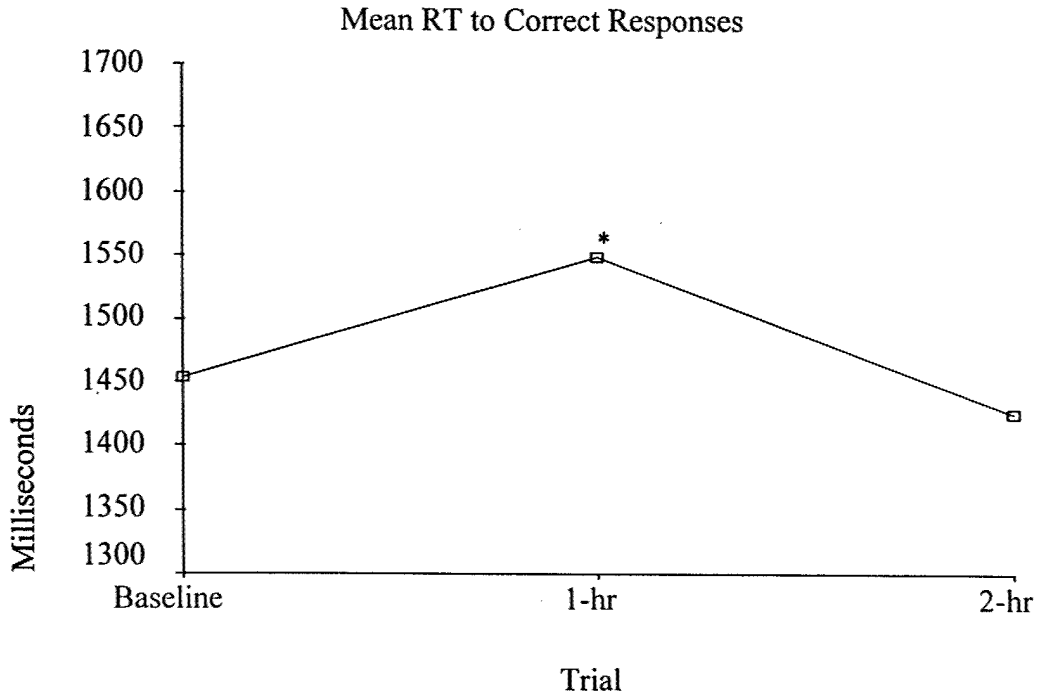

Figure 30 Math Processing Test
* sig. change from baseline

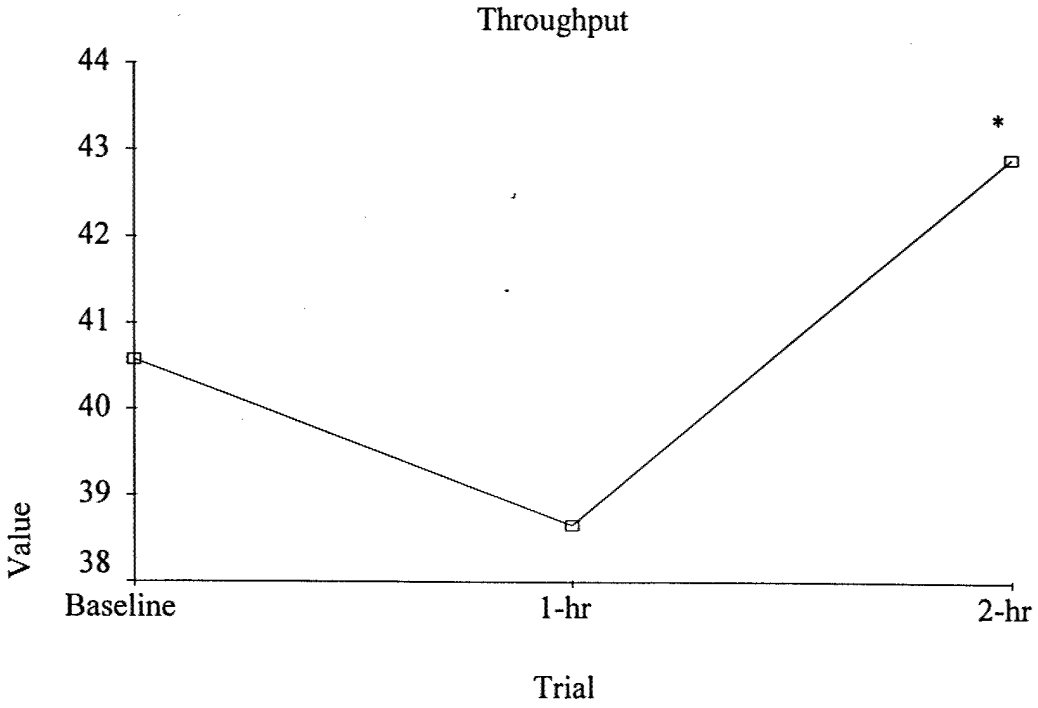

Figure 31 Math Processing Test
* sig. change from baseline

None of the remaining performance tests, ANAM or otherwise, showed any significant changes from baseline for the 1-hr and 2-hr post-dose trials.

DISCUSSION

Zaleplon vs. Placebo

There was no significant sleep latency difference between drug conditions. The mean sleep latency for the placebo group was 12.5min. Thus, the finding of no difference is not surprising because it is doubtful that, for the drug condition, zaleplon was present in the participants' system at any significant amount by this time. Digestion time of the Sonata® capsule within a gel-cap would be between 10-30 min. Thus one would not expect sleep latency to be affected.

Out of a total 25 outcome measures of performance in the ANAM, 14 showed significant decrements under zaleplon at the 1-hr and/or 2-hr post-dose trial when compared to placebo results. Many of the outcome measures that did not reach statistical significance evinced a similar trend. Three of the outcome measures continued to indicate decreased performance for the zaleplon condition at the 3-hr post-dose trial. Keep in mind that the trial labeled 1-hr post-dose includes any test performed between one and two hours post-dose. These findings suggested that performance in an operational setting may be negatively impacted under similar conditions involving zaleplon. An examination of this phenomenon in a more operational setting where cognitive components (similar to those assessed by the ANAM tests) are important may be warranted. Research performed in high-fidelity simulators (i.e. flight simulators, driving simulators, navigational simulators) would be one approach. Tasks involving time critical components (i.e. emergency procedures, re-targeting) might be particularly useful.

The only test within the ANAM to show no significant performance changes for the 1-hr, 2-hr, or 3-hr post-dose trials was the Simple Reaction Time Test. However, significantly increased reaction times were observed for the remaining, more complex, ANAM tests. This suggests that zaleplon may have a differential impact upon levels of cognition and ability.

Significant decrements in word memory were observed both shortly following awakening and again four hours later. Other shorter-term memory tests within the ANAM revealed significant decrements for the first 2 post-dose trials but no effect after that. This could lead one to conclude that memory was impaired in some way in the hours immediately following dosing which may have prevented the information from being stored. Thus, at the four hour word memory trial, recall may not have been impaired. It may be that there was simply nothing more to recall due to ineffective encoding during the word memorization period.

The Grip Strength results indicate that individuals using zaleplon, whether rapidly awakened or not, are fully capable of performing gross physical actions. The Grip Strength test had been included to discern whether flight passengers, for example, would have the ability to grasp a rope ladder during an emergency evacuation of an aircraft. Thus, from a basic functioning perspective (simple strength and reaction tasks) it appears that use of zaleplon would result in little increased risk.

Balance was significantly impaired up to 3-hrs post-dose (i.e. significant performance decrement at the 1-hr and 2-hr post-dose trial), as indicated by the A95 measure of the Force Platform Test. Additionally, several participants under the zaleplon condition, were observed

steadying themselves as they walked through the hallway leading from the bedrooms to the Force Platform room by placing a hand on the wall. However, when asked to stand still with their eyes closed for 1-min, participants were able to remain standing without moving their feet or stepping off the platform.

The SSS showed a significant rating increase under Zaleplon whereas the POMS Fatigue Scale did not. While both measures show the same trend in this study, the SSS was much more sensitive to the affect induced by zaleplon in the participants. This may represent a fine line between being tired and being sleepy. Zaleplon seems to induce sleepiness and, to a lesser amount, tiredness.

Zaleplon brought about significant increases in the levels of several subjective symptoms. Some of these symptoms are desirable in situations where a person is expecting to sleep (i.e., drowsy and difficulty staying awake). However, this sleepiness plus the other significantly reported symptoms (i.e., drugged feeling, headache, and light headed) would be undesirable in operational settings where alertness and clear thinking are required following a 10-mg dose of zaleplon.

Evaluating zaleplon's hypnotic efficacy, both in terms of sleep latency and sleep duration, during the day in a population of normal individuals would be useful. Hedner, Yaeche, Emilien, Farr, & Salinas (2000) showed an increase in subjective sleep quality and subjective total sleep time for nighttime sleep in elderly insomniacs. Certainly one of the difficulties with unassisted daytime sleep is the propensity to awaken relatively soon after beginning sleep. Were zaleplon to prove effective at increasing daytime sleep length its operational utility would be greatly increased.

The results from this study are intended for use in an operationally oriented environment where the risk of using zaleplon must be balanced with the risk of lost sleep due to insomnia. In this regard, the above results suggest that 'basic' performance (e.g. gross motor and muscular control) is not greatly impacted. However, 'higher' performance (e.g. logical reasoning) seems to suffer significantly. Thus, caution is advised regarding daytime zaleplon usage in operational settings involving extreme environments or emergency procedures that include higher cognitive tasks.

Sleep Inertia

Ferrara & De Gennaro (2000), describe sleep inertia as a transitional state, between sleep and wakefulness, the degree of which is modulated by the stage of sleep upon awakening and circadian factors. Certainly waking from deep sleep or a night of sleep may result in large decrements for extended periods (Hartman, & Langdon, 1965, Hartman, Langdon, & McKenzie, 1965 and Langdon, & Hartman, 1962, Ferrara, De Gennaro, & Bertini, 2000). Given the brief duration for sleep in this study, no long-lasting effects due to sleep inertia were expected.

The changes in performance for the 1-hr post-dose trial on the Code Substitution Test were noteworthy. The learning portion of the test, which occurred immediately after awakening, showed decrements from baseline for three out of four outcome measures. The immediate

recall portion, which occurred immediately following the learning portion (from 3-4 min post-awakening), showed two significant decrements from baseline. The delayed portion of the test, which occurred approximately 15min post-awakening, showed no significant changes from baseline. The CST also provided a good opportunity for examining the nature of sleep inertia effects. While the test changed slightly from the learning phase to the immediate recall phase to the delayed recall phase, all phases were given within the first fifteen minutes after awakening. The results for the learning portion of the test provided evidence that it took longer to encode the pairings after awakening than during baseline. The results from the immediate recall portion indicated that it took longer to recall items from memory after awakening than during baseline. The lack of performance change in the delayed portion of the test suggested that participants were able to memorize the pairings immediately following awakening (during the learning phase) and then, at this later time, recall them just as quickly and accurately as during baseline.

There was no significant change in the SRT RT from baseline to the 1-hr post-dose trial. There was a significant increase in RT for the Math Processing test. This combined with the CST results may indicate that higher cognitive functions may be more impaired than lower functions by sleep inertia. This result agrees with the result found by Ferrara, De Gennaro, & Bertini.

No significant changes were detected beyond the Math Processing Test. This does not imply that the subsequent measures were insensitive to sleep inertia, but probably indicates a diminishing sleep inertia effect.

Given that participants slept for approximately 42-min, during a period of normal wakefulness, and that they were well rested prior to the experimental sessions it wasn't surprising to observe little deep sleep in the EEG recordings. In general, the participants were waking from Stage-I or Stage-II sleep. Thus, it was not unexpected that sleep-inertia effects would be short lived. No significant performance impairment was seen beyond 6-min of testing. Given that testing may not have begun for up to 3-min post-awakening a conservative interpretation of the data would be that tasks occurring within the first 10-min after awakening from a nap (sleep < 1-hr) are at considerable risk for impaired performance.

CONCLUSIONS AND RECOMMENDATIONS

Performance was generally affected for up to 3-hrs following a 10-mg dose of zaleplon. Caution is advised regarding daytime zaleplon usage in operational settings involving extreme environments or emergency procedures that include higher cognitive tasks. Unlike higher performance, basic performance does not appear affected.

Sleep inertia was short-lived following a daytime nap (< 1-hr). The findings from this study support the insertion of a minimum of 10-min recovery time prior to any work activities which may follow a daytime nap.

ADDITIONAL INFORMATION

Appendix A contains data summaries of two cognitive tests, Logical Reasoning and Math Processing, given as a percentage of baseline performance. These data are shown with the

results from the FAST™ scheduling tool which is based upon the SAFTE® performance prediction model. Overall, the placebo performance correlated with the FAST™ prediction at r=.73 when the final trial was discarded. It was felt that the final trial should be dismissed due to the 'going-home' effect often seen in studies like this one. The zaleplon data is furnished as a published record of data that may be incorporated into the FAST™ model.

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APPENDIX A
Data and FAST™ Predictions

	Baseline 1200	1-hr 1400	2-hr 1500	3-hr 1600	4-hr 1700	5-hr 1800	6-hr 1900	7-hr 2000
Placebo	100	98.19253	103.5855	103.252	104.1005	102.8562	100.6942	104.0487
Zaleplon	100	80.55933	85.44215	96.40701	101.0394	100.9143	102.6475	105.9603
FAST™	100	96.7852	102.2948	103.4836	104.693	105.3442	104.8997	102.9771