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Cognitive, Psychomotor, and Polysomnographic Effects of Trazodone in Primary Insomniacs

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Summary

Trazodone is widely prescribed as a sleep aid, although it is indicated for depression, not insomnia. Its daytime cognitive and psychomotor effects have not been systematically investigated in insomniacs. The primary goal of this study was to quantify, in primary insomniacs, the hypnotic efficacy of trazodone and subsequent daytime impairments. Sixteen primary insomniacs (mean age 44 years) participated, with insomnia confirmed by overnight polysomnography (sleep efficiency ≤ 85%). Trazodone 50 mg was administered to participants 30 minutes before bedtime for seven days, in a three-week, within-subjects, randomized, double-blind, placebo-controlled design. Subjective effects, equilibrium (anterior/posterior body sway), short-term memory, verbal learning, simulated driving, and muscle endurance were assessed the morning after Days 1 and 7 of drug administration. Sleep was evaluated with overnight polysomnography and modified Multiple Sleep Latency Tests (MSLT) on Days 1 and 7. Trazodone produced small but significant impairments of short-term memory, verbal learning, equilibrium, and arm muscle endurance across time points. Relative to placebo across test days, trazodone was associated with fewer nighttime awakenings, minutes of Stage 1 sleep, and self-reports of difficulty sleeping. On Day 7 only, slow wave sleep was greater and objective measures of daytime sleepiness lower with trazodone than with placebo. Although trazodone is efficacious for sleep maintenance difficulties, its associated cognitive and motor impairments may provide a modest caveat to healthcare providers.

Keywords

trazodone; insomnia; short-term memory; verbal learning; posturography

Introduction

Chronic insomnia is frequently comorbid with a psychiatric disorder. However, insomnia without any identifiable etiology is considered primary insomnia (Buysse *et al.*, 1994). In addition to experiencing significant sleep reduction, primary insomniacs report numerous daytime impairments. These perceived impairments include attention deficits, memory loss, daytime sleepiness, or driving accidents (Edinger *et al.*, 2004). Non-benzodiazepine

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hypnotics such as zolpidem, zaleplon, and eszopiclone are indicated for the pharmacological treatment of insomnia. However, trazodone was recently the most widely prescribed sleep aid in the United States, despite being indicated for depression by the Food and Drug Administration (FDA; Schweitzer *et al*., 2010). Although physicians may perceive trazodone to be safer than its hypnotic counterparts, little testing has been reported of its impairing effects or therapeutic efficacy for insomnia.

Trazodone's preferential prescription may be related to its perception as a safer substitute for other hypnotics. Standard hypnotics have been implicated in increased risk of motor vehicle accidents and memory problems (Leufkens *et al*., 2009). In contrast, trazodone's adverse behavioral effects have rarely been studied. Inconsistent effects on recall have been observed after daytime dosing of trazodone (Rush *et al*., 1997, 1999). High doses of trazodone (200–300 mg) produced no impairments of digit-enter-and recall, immediate picture recall, or delayed picture recall in healthy controls (Rush *et al*., 1997). However, these doses impaired balance, digit-symbol substitution, and digit-enter-and-recall in participants with a history of substance or alcohol abuse (Rush *et al*., 1999). Single doses of trazodone have also been associated with impaired critical flicker fusion in dysthymic insomniacs (Saletu-Zyhlarz *et* al., 2001). Thus, while there is modest evidence of trazodone-induced psychomotor impairment, the most clinically relevant population that will be prescribed the drug—primary insomniacs—is understudied.

Our primary goal was to examine the next-day impairments associated with nighttime dosing of trazodone 50 mg in primary insomniacs. The 50 mg dose was selected because it is commonly prescribed for sedative/hypnotic purposes (Walsh et al., 1998). We tested the hypothesis that trazodone would increase daytime sleepiness and impairment of simulated driving, short-term memory, verbal learning, equilibrium, and muscle endurance.

Methods

Participants

Adults 18–65 years were recruited through media advertisements and outpatient clinics of Wake Forest University Health Sciences. Inclusion criteria were primary insomnia (American Psychiatric Association, 1994) as determined by an unstructured interview with a board-certified sleep physician who followed appropriate DSM-IV and Research Diagnostic Criteria (Edinger *et al*., 2004), a score of zero on Patient Health Questionnaire (Kroenke *et al*., 2001) items 1 ("Little interest or pleasure in doing things") and 9 ("Thoughts that you would be better off dead, or of hurting yourself in some way"), no psychotropic medications within two weeks of initial screening, and either self-reported mean sleep latency ≥ 30 minutes or self-reported WASO ≥ 45 minutes. Exclusion criteria—determined from the Structured Clinical Interview for the DSM-IV (Research Version; First *et al*., 2002), urinalysis, seven days of sleep diaries, and a physical examination conducted by a study physician—were any active psychiatric disorder or therapy; uncontrolled asthma, chronic obstructive pulmonary disease, thyroid disease, or symptoms of menopause; chronic sleep-disturbing pain; poorly controlled diabetes; cardiac disease; use of medications or herbal treatments known to facilitate or interfere with sleep; pregnancy or breast feeding; self-reported bedtime earlier than 9 pm or later than 1 am > 2 times per week; self-reported habitual rising time later than 9 am > 2 times per week; body mass index > 35; Alcohol Use Disorders Identification Test score > 11 (Saunders *et al*., 1993); habitual smoking between 11 pm and 7 am; and use of illicit drugs.

Of the 63 individuals who gave informed consent to participate, 47 did not complete the entire study. The most common reasons for exclusion were sleep efficiency > 85% (19% of 47 participants); did not show up for laboratory visit (17%); tested positive for illicit drugs

(15%); evidence of sleep apnea (15%); and current major depressive episode (9%). Thus, 16 adults (mean age = 44 years, SD = 11; 9 Caucasian women, 2 African-American women, 1 Hispanic woman, 3 Caucasian men, 1 African-American man) were included in the final study sample.

Procedure

Participants who met requirements for further participation spent two polysomnography nights in the sleep laboratory before drug administration weeks. The first (Acclimation) allowed the participant to become accustomed to the laboratory environment. The second (Screening) was used for identification of primary insomnia, sleep apnea or periodic limb movements (PLMs), and next-day practice of behavioral tasks. Participants were required to have sleep efficiency (total time asleep divided by time in bed) <85%. Apneas were defined as a decrease >90 in thermistor signal amplitude for >10 seconds, and hypopneas were defined as a 30–90% decrease in thermistor signal for >10 seconds. PLMs were scored according to standard criteria (Coleman, 1982). An Apnea/Hypopnea Index of ≥ 10 or a PLM arousal index of ≥ 10 per hour were grounds for exclusion (Iber *et al.*, 2007).

Upon arrival to the laboratory at approximately 9:30 pm, the absence of orthostatic hypotension, defined as a systolic blood pressure drop of ≥ 20 mmHg from sitting to standing, was confirmed. Expired breath alcohol measurements were taken to confirm abstinence from recent alcohol use (INTOXILYZER 5000, CMI, Inc., Owensboro, KY). Urine samples were collected to confirm the absence of illicit drugs (Multi-drug 6 line urine screen; Innovacon, Inc., San Diego, CA) and pregnancy (QuickVue, Quidel, San Diego, CA). Following polysomnography from 11 pm–7 am, standing and sitting systolic and diastolic blood pressure were re-assessed and a standard breakfast (plain bagel, cream cheese, and apple juice) was given to the participant.

Participants not excluded after the Screening Night were invited to participate in four drug study sessions (two trazodone, two placebo) over the course of three weeks. Nighttime procedures were identical to that of Acclimation and Screening Nights, except leg EMG and respiratory data were not collected. Additionally, participants ingested either trazodone or placebo at 10:30 pm. Participants received five additional capsules of that week's study drug with instructions to take one pill nightly 30 minutes before bedtime for the next five nights. On each of these nights (Days 2–6), a study staff member telephoned the participant as a reminder to take the pill and to verify the absence of serious adverse events. Participants then returned to the laboratory on Day 7 to complete the same procedures as on Day 1.

Week 2 served as a drug- and session-free washout period. Week 3 procedures were identical to those of Week 1, with the converse drug administered. The order of drug weeks was randomized. Nine of the 16 subjects received trazodone in Week 1 and placebo in Week 3. All procedures were approved by the Institutional Review Board at Wake Forest School of Medicine.

Drug Administration

Trazodone (Desyrel®, Cardinal Health Inc, Richland, MS) capsules were prepared by fitting two halves of a 50mg tablet in an empty gelatin capsule and adding methylcellulose. Placebo pills were comprised of methylcellulose in an identically appearing empty gelatin capsule. All pills were prepared and randomized by the institution's clinical trials pharmacy.

Polysomnography

Overnight PSG data were collected using an 11-channel montage of the Nicolet Ultrasom™ (Viasys Healthcare, Madison, WI) with central and occipital EEG, bilateral

electrooculograms, and submental and bilateral tibial EMG. Respiratory activity was monitored using nasal thermocouple sensors. PSG data were manually scored according to standardized criteria (Iber *et al*., 2007) by a sleep-medicine- certified dose-blinded physician. Sleep latency (minutes between lights off and the first 20 consecutive epochs of sleep), REM latency (time from sleep latency to first epoch of REM), minutes and percent-of-total-sleep-time for Stage 1, Stage 2, REM, and slow-wave sleep (SWS), total awakenings (one or more continuous epochs scored wake), WASO, and sleep efficiency were measured.

Test Battery

Multiple Sleep Latency Test (MSLT)—A modified research-oriented version of this task (Carskadon *et al*., 1986) quantified physiologic sleep tendency. Participants were asked to take a nap one and three hours after arising (8:00 am and 10:00 am). Sleep latency was calculated as the elapsed time from "lights out" to the first 30-second epoch scored as sleep. Participants who did not fall asleep within the 20 minutes had their latency scored as 20 minutes. All other behavioral testing occurred between the two naps.

Visual Analog Scales—Participants drew a vertical line to intersect a 100-mm horizontal line representing the range of responses from "not at all" to "extremely." The 10 items were "depressed," "difficulty sleeping," "energetic," "friendly," "impaired," "irritable," "mellow," restless," "social," and "tired." Scores were calculated by measuring the distance in millimeters from the left of the line ("not at all") to the intersecting line.

Dynamic Posturography—During this test of balance and risk for falls (EquiTest, NeuroCom, Clackamas, OR, USA; Buatois *et al.*, 2006; Whitney et al., 2006), the participant stood on a platform and faced a surrounding wall as the following were manipulated: a) eyes opened or closed, b) platform fixed or sway-referenced, 3) vision normal, absent, or sway-referenced. Each of these conditions included three 20-second trials. When the platform or vision was "sway-referenced," it moved in direct relation to the anteroposterior body movements that maintain upright posture. For each trial, a computer-generated "equilibrium score" was calculated as $((12.5 - (\text{maximum anterior sway} + \text{maximum posterior sway}))/12.5) \times 100$. This score ranged from 0 (fell down) to 100 (no sway at all). The mean of the three trial scores for condition 1 (open eyes, fixed platform, normal vision), the mean of the three trial scores for condition 2 (closed eyes, fixed platform, absent vision), and individual trial scores from the remaining four eyes/platform/vision conditions (open/fixed/sway-referenced, open/sway-referenced/normal, closed/sway-referenced, absent, and open/sway-referenced/sway-referenced) were averaged to derive a composite equilibrium score that was used in analyses.

Verbal Learning—In the Buschke Selective Reminding Test (SRT; Buschke, 1973; Buschke & Fuld, 1974), a list of 12 common words was read to the participant, who was then given 60 seconds to repeat the entire list. Next, the participant was reminded of the words that were not previously recalled, and given another 60 seconds to recall all 12 words. This reminding/recall cycle continued until 12 trials had been completed or the participant recalled all 12 words on three consecutive trials. A word enters long-term storage (LTS) if it is recalled on two consecutive trials (Buschke, 1973).

Short-Term Memory—The Brown-Peterson Memory Test (Brown, 1958; Peterson & Peterson, 1959) measured recall of consonant trigrams without established mnemonic meaning (e.g., QLX, SZB, etc.). After hearing each trigram, the participant counted out loud backwards by threes from a randomly dictated number. After a delay of 9, 18, or 36 seconds,

the participant attempted to recall the consonant trigram. The order of delay intervals was randomized, and there were five trials per delay interval.

Simulated Driving—The STISIM Drive™ (Systems Technology, Inc., Hawthorne, CA) is a computer-based simulator in which the driver controlled speed and steering in a programmed suburban/highway setting with moderate traffic. The task was interactive, with visual and auditory feedback provided to the driver. Participants who finished the simulated 9-mile drive in 16.5 minutes or less earned a $20 bonus ($80 maximum across the four study visits). However, participants were also penalized $2 from this bonus for each collision, time caught speeding, caught driving through a stop sign, or caught driving through a red light. Any participant with ten or more penalties received no bonus but did not lose additional money.

Muscle Endurance—In the test of upper limb function (Agarwal & Kiely, 2006), the seated participant held a 2 kg weight with shoulder adducted, elbow fully flexed, and forearm supine. The participant alternated between lifting the arm above the head until the elbow was fully extended, then dropping the arm back down, for 30 seconds. In the test of lower limb function (Agarwal & Kiely, 2006), the participant alternated between standing upright from a chair with arms folded across the chest, then sitting, for 30 seconds.

Data Analysis

Overnight polysomnography parameters, mean MSLT latency, visual analog scale scores, Selective Reminding Test recall (long-term storage), consonant trigram recall (36 second delay), composite equilibrium score, simulated driving measures (time speeding and total errors), and muscle endurance (mean arm lifts and total stands) were analyzed using 2 X 2 repeated measures analyses of variance (ANOVA) with drug (trazodone/placebo) and time (Day 1/Day 7) factors. Holm-Sidak *post hoc* pairwise comparisons were made after each significant interaction. All tests were two-tailed, and all analyses were considered significant at $p < 0.05$. The six primary outcomes, in descending order of hierarchy, were main effects of trazodone on total driving errors, long-term storage, consonant trigram recall (36 second delay), composite equilibrium score, sleep latency, and muscle endurance. Overall experiment-wise significance required $P < 0.05/6 = 0.008$ for at least one of these six primary endpoints.

Results

Polysomnography and MSLT

Stage 1 minutes decreased from Day 1 to Day 7, regardless of drug (main effect of time, $F(1,15)=7.17$, *post hoc* $t=2.7$, $p=0.017$, Table 1). Trazodone (main effect) significantly reduced total awakenings ($F(1,15)=10.35$, *post hoc* $t=3.2$, $p=0.006$), Stage 1 minutes ($F(1,15)=9.90$, *post hoc* $t=3.1$, $p=0.007$), and Stage 1% ($F(1,15)=9.41$, *post hoc* $t=3.1$, $p=0.008$, Table 1, Figure 1). On Day 7, there were significantly more SWS minutes with trazodone than with placebo (interaction $F(1,15)=4.92$, *post hoc* $t=2.9$, *post hoc* $p=0.007$, Table 1). There were no statistically significant main effects or drug-time interactions on sleep latency, REM latency, WASO, Stage 2 minutes, Stage 2%, REM minutes, REM%, SWS%, or sleep efficiency. A significant interaction of drug and time on MSLT latency ($F(1,15)=4.64$, $p=0.048$) was due to longer mean latencies on Day 7 with trazodone than with placebo (*post hoc* $t=2.3$, $p=0.033$; Table 1).

Visual Analog Scales

There was a main effect of trazodone on ratings of “difficulty sleeping” ($F(1,15)=8.16$, *post hoc* $t=2.9$, $p=0.012$; Table 1). Regardless of drug, ratings of “restless” decreased over time

(main effect, $F(1,15)=8.42$, *post hoc* $t=2.9$, $p=0.011$; Table 1). There were no statistically significant main effects or drug-time interactions on any other items.

Equilibrium

One individual reported nausea on the EquiTest and was excused from further participation in that task. Composite equilibrium scores were significantly lower with trazodone than with placebo (main effect, $F(1,14)=5.34$, *post hoc* t=2.3, p=0.037; Table 1). There was no significant main effect of time and no drug-time interaction on this measure.

Verbal Learning and Short-Term Memory

Trazodone significantly decreased long-term storage on the SRT (main effect, $F(1,15)=5.01$, $p=0.037$; *post hoc* $t=2.2$, $p=0.041$; Table 1) and consonant trigram recall (main effect, $F(1,15)=17.3$, *post hoc* $t=4.2$, $p<0.001$; Table 1). There were no significant main effects of time or drug-time interactions on these measures.

Simulated Driving

There were no significant main effects and no drug-time interactions on driving errors or speeding.

Muscle Endurance

Although mean (±SD) arm lifts increased from Day 1 (24±6) to Day 7 (26±7; main effect of time, $F(1,15)=14.12$, *post hoc* $t=3.8$, $p=0.002$), trazodone significantly decreased arm lifts across days (main effect of drug, $F(1,15)=5.98$, *post hoc* $t=2.4$, $p=0.027$; Table 1). There was no significant drug-time interaction on mean arm lifts. There were no significant main effects or drug-time interactions on lower body muscle endurance.

Discussion

Consistent with its popularity as a medication for insomnia, trazodone decreased nighttime awakenings, Stage 1 sleep, and reports of difficulty sleeping relative to placebo. In addition, slow wave sleep was greater with trazodone than with placebo after a week's dosing, and simulated driving was unaffected by trazodone. These findings complement studies in which trazodone had no negative impact on insomniacs' work, social, or family life, or self-report ratings of post-waking behavior (Paterson *et* al., 2009a; Walsh *et* al., 1998). However, in partial support of our hypothesis, impairing effects of trazodone were found on short-term memory, verbal learning, body sway, and arm muscle endurance. These were modest impairments with low-to-moderate effect sizes. The discrepancy between self-reported and observed impairment is not unexpected. Our laboratory has previously reported that self-reported "impaired" ratings following alcohol are often less severe than actual observed psychomotor impairments in the same individuals (Liguori et al., 1999).

Both memory assessments—the Brown-Peterson test and the Selective Reminding Test (SRT)—were impaired by trazodone. Although generally used to assess deficits in short-term memory, the Brown-Peterson test is also a measure of divided attention. This task replicates the acquisition of information, interrupted by temporary distraction, followed by the loss of the information previously acquired (Crowder, 1982). At the lengthiest delay, trazodone significantly impaired recall, suggesting that the drug may also increase distraction. In addition to the observed short-term memory impairment, significantly fewer words entered long-term storage after trazodone use. During the SRT, participants are not reminded of recently recalled words; thus, recalling one of those words demonstrates retrieval from long-term memory (Buschke, 1973). The decrease of long-term storage scores observed here demonstrates a slowed learning process following trazodone use. These

particular results are potentially clinically significant, as sleep-related memory consolidation is already significantly impaired among primary insomniacs in the absence of treatment (Nissen et al., 2010).

The effect of trazodone on body sway was equivalent to one third of the impairment from a 0.05% breath alcohol concentration (Liguori et al., 1999). The decrease in arm lifts with trazodone reflects proximal muscle function impairment and may indicate an additional peripheral balance effect of trazodone. However, the extent to which this particular effect is due directly to trazodone rather than daytime sleepiness or loss of motivation is unclear. The balance and muscle function impairments were also noteworthy because our sample's mean age was at least 20 years younger than elderly individuals typically sensitive to these tasks (Buatois et al., 2006). Consequently, further investigations of muscle endurance and balance are needed in older individuals who may be more sensitive to trazodone's impairing effects than our sample was.

Our polysomnographic data substantiate previous findings of trazodone's efficacy as a treatment for primary insomnia. Subjective reports of difficulty sleeping improved after trazodone use regardless of day of dosing. This result is consistent with other findings of improved self-reported sleep quality after both acute and chronic use of trazodone (Paterson *et al*., 2009a; Walsh *et al*., 1998). Trazodone's effects on perceived sleep quality appear related to reduction of nighttime awakenings, decreased Stage 1 sleep (drowsiness), and increased slow wave sleep. Other studies have also demonstrated reduction by trazodone (50–150 mg) of nighttime awakenings, Stage 1, or both in primary insomniacs and self-reported poor sleepers (Montgomery, *et al.*, 1983; Walsh *et al.*, 1998). Additionally, trazodone 100 mg has reduced nighttime awakenings in participants with insomnia secondary to depression (Saletu-Zyhlarz *et al.*, 2001). Increased slow-wave sleep following trazodone 100 mg has been reported in healthy participants versus placebo (Yamadera *et al.*, 1998) and when added to caffeine (Paterson et al., 2009b). Both of these studies measured polysomnography after 1–2 days of drug administration. In contrast, we observed significant increases in slow wave sleep only after seven days of trazodone 50 mg. This discrepancy suggests that a higher starting dose of trazodone may be needed for quicker facilitation of deep sleep.

Higher doses or longer regimens could also augment the observed psychomotor effects of trazodone. Trazodone effects on behavior have been reported at doses up to 300 mg (Paterson *et al*., 2009a; Rush *et al*., 1997, 1999). Another limitation is the time course we chose for drug administration. Our study was constrained by its examination of only seven days of dosing. The extent to which the observed behavioral effects peak and decline are better identified with longer time courses than that in the present study. Conversely, sustained use of trazodone may present novel risks not evident in the short time period we examined. Also, the administration of trazodone 30 minutes before bedtime may impact the observed efficacy. Earlier dosing, in allowing additional time to peak effect, may have improved the likelihood of observing a therapeutic effect on sleep latency.

In summary, low-dose trazodone decreased nighttime awakenings and Stage 1 sleep, reduced perceived sleep difficulty, and increased slow wave sleep in primary insomniacs. Yet trazodone also impaired next-day memory performance, equilibrium, and muscle endurance. When these impairments are considered with other potential side effects, including priapism, cardiac arrhythmias, and weight gain, trazodone may be a less attractive treatment option for insomnia. While the present results suggest novel caveats of trazodone in comparison to benzodiazepines, the absence of an active control condition did not allow us to establish assay sensitivity or differentiate relative risk. Furthermore, non-pharmacological treatment options such as cognitive behavioral therapy may be efficacious

alternatives to any pharmacotherapy (Jacobs et al., 2004). For further characterization of the relative risks and rewards of trazodone, direct comparisons of multi-week regimens of trazodone, benzodiazepine receptor agonists, and cognitive behavioral therapy are warranted.

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Table 1

Outcome measures for participants receiving placebo and trazodone

	Placebo		Trazodone		Cohen's *d*		*P* Values	
Measure	**Day 1**	**Day 7**	**Day 1**	**Day 7**	**Day 1**	**Day 7**	**Drug main effect**	**Drug X time**
Polysomnography and MSLT								
Sleep latency (mins)	23.5±15.8	24.5±18.7	28.3±20.4	26.2±28.6	0.27	0.07	0.556	0.697
REM latency (mins)	92.4±51.5	84.3±40.8	85.8±49.1	93.0±53.1	0.13	0.19	0.905	0.385
WASO (mins)	49.4±37.8	74.3±61.1	51.8±51.8	52.9±54.9	0.05	0.37	0.401	0.220
Stage 1 (mins)	28.9±15.2	28.8±11.6	26.7±11.5	17.9±9.5	0.16	1.03	0.007*	0.112
Stage 2 (mins)	223.3±36.6	216.0±58.2	218.4±49.1	223.1±47.2	0.11	0.13	0.923	0.414
REM (mins)	85.2±30.6	79.4±28.4	83.3±27.1	78.0±22.5	0.07	0.06	0.688	0.948
SWS (mins)	76.9±38.9	67.9±41.4	77.6±29.4	90.4±33.8	0.02	0.60	0.073	0.042*
Stage 1%	7.2±4.2	7.6±3.6	6.9±3.4	4.4±2.2	0.08	1.10	0.008*	0.077
Stage 2%	54.3±9.6	54.7±12.6	53.7±8.9	54.3±8.1	0.06	0.04	0.811	0.922
REM%	20.4±6.8	19.9±5.4	20.1±4.6	19.1±4.7	0.05	0.16	0.474	0.762
SWS%	18.2±8.3	17.8±12.4	19.3±7.9	22.3±8.7	0.14	0.43	0.140	0.164
Sleep efficiency (%)	86.3±8.2	81.7±12.0	85.1±11.1	85.3±11.0	0.12	0.31	0.642	0.288
Total awakenings	21.6±14.5	20.0±9.9	16.2±9.8	12.7±6.5	0.44	0.89	0.006*	0.473
MSLT latency (mins)	9.9±5.4	8.6±4.2	11.0±6.4	12.7±6.2	0.19	0.79	0.139	0.048*
Visual Analog Scales								
Depressed	7.3±12.2	8.4±10.1	6.3±8.2	10.7±17.7	0.10	0.17	0.775	0.391
Difficulty sleeping	57.9±27.9	60.4±18.8	46.8±22.7	36.1±28.1	0.44	1.04	0.012*	0.272
Energetic	37.1±24.1	36.8±19.3	27.4±17.9	34.0±25.0	0.46	0.13	0.161	0.242
Friendly	58.9±21.9	61.9±17.6	57.4±21.1	56.8±25.5	0.07	0.24	0.329	0.616
Impaired	27.8±22.6	28.9±25.1	38.4±20.3	31.9±25.9	0.49	0.12	0.108	0.301
Irritable	24.9±21.4	22.4±20.6	25.5±21.2	23.4±24.4	0.03	0.04	0.876	0.954
Mellow	55.8±23.1	49.1±19.5	55.7±23.7	52.1±20.9	0.00	0.15	0.722	0.429
Restless	30.4±21.4	23.0±22.4	30.1±25.4	21.6±22.2	0.01	0.06	0.872	0.868
Social	44.8±26.5	47.9±22.3	45.6±25.0	47.6±28.7	0.03	0.01	0.954	0.859
Tired	61.4±20.9	58.8±26.3	60.9±23.5	61.5±24.8	0.02	0.11	0.852	0.663
Body Sway								

	Placebo		Trazodone		Cohen's *d*		*P* Values	
Measure	**Day 1**	**Day 7**	**Day 1**	**Day 7**	**Day 1**	**Day 7**	**Drug main effect**	**Drug X time**
Equilibrium score	83.3±4.7	83.3±4.7	81.0±5.1	81.7±4.0	0.47	0.37	0.037*	0.479
Selective Reminding Test								
Words in LTS	115.4±25.5	115.2±20.4	111.1±24.7	109.6±22.2	0.17	0.26	0.041*	0.804
Brown-Peterson Memory Test								
Trigrams (36s delay)	11.7±3.1	11.6±3.8	11.1±3.7	10.0±4.0	0.18	0.41	<0.001*	0.358
Simulated Driving								
Errors	3.4±2.7	3.2±2.3	3.6±1.9	3.3±2.1	0.09	0.05	0.808	1.000
Time speeding (secs)	23.8±29.9	18.2±14.7	19.7±22.0	21.2±18.2	0.16	0.18	0.901	0.372
Muscle Endurance								
Mean arm lifts (/30s)	25.8±6.8	27.0±7.7	23.0±6.9	25.7±6.9	0.41	0.18	0.027*	0.133
Mean stands (/30s)	16.4±5.4	16.6±6.4	15.0±4.8	16.1±5.9	0.27	0.08	0.220	0.312

Data are expressed as mean ± SD for 16 participants, except for equilibrium score (*N*=15). Maximum possible scores: Visual Analog Scales=100; Selective Reminding Test=144; Consonant Trigram Recall=15; Equilibrium Score=100. *P* values for drug main effects and drug X time interactions are based on 2 X 2 repeated measures analyses of variance (ANOVA) with drug (trazodone/placebo) and time (Day 1/Day 7) factors.

*$P < 0.05$

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