

ORIGINAL INVESTIGATION

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Acute behavioral effects and abuse potential of trazodone, zolpidem and triazolam in humans

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Abstract The present study examined the acute behavioral effects and abuse potential of three drugs commonly used to treat sleep disorders, trazodone, zolpidem and triazolam, and placebo in ten male volunteers with histories of alcohol and drug abuse. Trazodone (100, 200 and 300 mg), a triazolopyridine antidepressant, was included because antidepressants are being used more frequently to treat sleep disorders, but it is unclear whether they have a distinct behavioral pharmacologic profile relative to benzodiazepine hypnotics. Zolpidem (15, 30 and 45 mg), an imidazopyridine hypnotic, was tested because it is the most commonly prescribed hypnotic and purportedly has a unique benzodiazepine-receptor binding profile. Triazolam (0.25, 0.5 and 0.75 mg), a triazolobenzodiazepine hypnotic, was included as the standard component because previous laboratory studies have demonstrated that it has at least some abuse potential. Trazodone, zolpidem and triazolam generally produced comparable dose-related increases in scores on the PCAG scale of the ARCI, which suggests the doses tested were equivalent on some behavioral dimension. The effects of trazodone on subject-rated items thought to measure abuse potential (e.g., subject ratings of Willing to Take Again) were less than those observed with triazolam. Zolpidem and triazolam produced comparable effects on these measures. The highest dose of zolpidem, but not triazolam, increased ratings of Like Drug, Happy, Good Effects, Friendly, Elated,

Carefree and Bad Effects. Triazolam and zolpidem produced dose-dependent impairment on all of the performance tasks. Trazodone impaired performance on some, but not all, of these tasks. Consistent with the pharmacokinetics of these compounds, the time-action functions of trazodone, zolpidem and triazolam were similar on these measures. These data suggest that trazodone has less abuse potential than triazolam, and may be a viable alternative to benzodiazepine hypnotics in individuals with histories of alcohol or drug abuse. By contrast, despite its unique neuropharmacological profile, the acute behavioral effects and abuse potential of zolpidem are comparable to those of triazolam.

Key words Trazodone · Zolpidem · Triazolam · Hypnotics · Abuse potential · Behavioral effect

Introduction

Serious sleep disorders affect at least 15 percent of the adult population (e.g., Balter and Uhlenhuth 1992). Benzodiazepines, including triazolam, temazepam, quazepam, flurazepam and estazolam, are among the most commonly prescribed medications for treating sleep disorders. Benzodiazepines are effective in the treatment of sleep disorders in that they decrease sleep latency, nocturnal awakenings and wake time after sleep onset, increase total sleep time, and improve subject ratings of quality of sleep (for a review see Hollister et al. 1993). Importantly, the benzodiazepines are much safer than their predecessors, the barbiturates.

While they are clinically effective in the management of sleep disorders and safer than the barbiturates, the use of benzodiazepines poses a number of problems (Woods et al. 1987, 1992). First, the benzodiazepines have some potential for abuse, although less than the

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barbiturates (Griffiths et al. 1980; Woods et al. 1987, 1992; Griffiths and Weerts 1997). The non-medical use/abuse of benzodiazepines is common among individuals with histories of alcohol, opioid and sedative abuse (for reviews see Woods et al. 1987, 1992; Griffiths and Weerts 1997). Second, acute administrations of benzodiazepines dose-dependently impair human performance (Lister 1985; Cole 1986; Ghoneim and Mewaldt 1990; Roth et al. 1990; Curran 1991). Third, repeated administrations of benzodiazepines produce tolerance and dependence (Woods et al. 1987, 1992).

The abuse potential, performance-impairing effects and dependence liability of benzodiazepines have prompted many clinicians to explore the use of alternative pharmacotherapies to treat sleep disorders. For example, antidepressants are being used more frequently to treat sleep disorders (Wysowski and Baum 1991; Nierenberg et al. 1994; Hartmann 1995). In 1970, antidepressants accounted for approximately 6% of the drugs prescribed as sleep therapies. This number increased to approximately 11% in 1989 (Wysowski and Baum 1991). Antidepressants, like benzodiazepines, appear to be effective hypnotics. In a recent study, primary insomniacs were treated with 50 mg trazodone, a triazolopyridine antidepressant (Walsh et al. 1998). Relative to baseline, trazodone decreased subject ratings of latency to sleep.

Trazodone, like the benzodiazepines, impairs performance on several laboratory tasks (for reviews see Woods et al. 1987, 1992; Amado-Boccaro et al. 1994; Volz and Sturm 1995). Whether the magnitude of impairment is less than that observed with benzodiazepines is unclear. To the best of our knowledge, there are only two published reports that directly compared the performance-impairing effects of trazodone and a benzodiazepine (Karniol et al. 1976; Rush et al. 1997). The results of these studies are mixed. In the first study, trazodone (47 mg/70 kg), but not diazepam (4.7 mg/70 kg), significantly impaired symbol-copying performance and increased subject ratings of sedation relative to placebo in healthy volunteers. In the second study, triazolam (0.125–0.5 mg), but not trazodone (50–200 mg), dose-dependently impaired performance in healthy, non-drug abusing volunteers (Rush et al. 1997). Triazolam and trazodone produced comparable dose-related increases in subject-ratings of drug effect, which suggests equivalent doses were tested.

The present experiment was designed to characterize further the acute behavioral effects of trazodone (Desyrel) relative to triazolam (Halcion), a triazolobenzodiazepine hypnotic. To accomplish this aim, the acute subject-rated effects, performance-impairing effects and abuse potential of trazodone and triazolam were compared across a 3-fold range of doses in volunteers with histories of alcohol and drug abuse. Drug effects were assessed in volunteers with histories of drug and alcohol because, as noted above, these individuals

are at increased risk to abuse sedative/hypnotic drugs. While the extant literature suggests that trazodone has little abuse potential (Anseau and De Roeck 1993; Liebowitz and El-Mallakh 1989), to the best of our knowledge, this has not been determined prospectively in subjects with histories of alcohol or drug abuse using laboratory methods specifically designed to assess the abuse potential of drugs (Fischman and Mello 1989). Drug effects were assessed before drug administration and repeatedly afterwards for 5 h with a battery of subject-rated and performance measures previously demonstrated to be sensitive to the effects of benzodiazepine and non-benzodiazepine compounds in individuals with histories of alcohol and drug abuse (e.g., Evans et al. 1990, 1994; Mumford et al. 1995a, b; Rush et al. 1998).

To provide a more comprehensive assessment of the abuse potential of hypnotics, a 3-fold range of doses of zolpidem (Ambien) was also tested. Zolpidem, an imidazopyridine, is now the most commonly prescribed hypnotic (Cardinale 1996). The hypnotic actions of zolpidem, like benzodiazepine hypnotics, are mediated at the benzodiazepine recognition site of the gamma-aminobutyric acid-A ($GABA_A$) receptor complex (Synder et al. 1977; Olsen et al. 1984; Haefely 1989; Benavides et al. 1996; Besnard et al. 1996). However, the neuropharmacological profile of zolpidem is somewhat different from that of most benzodiazepines in that it binds with low affinity to certain α_5 -containing $GABA_A$ -receptor subtypes (Benavides et al. 1996; Besnard et al. 1996). Triazolam, by contrast, binds with high affinity to these $GABA_A$ -receptor subtypes. Whether zolpidem's unique neuropharmacological profile reduces its abuse potential and performance-impairing effects is unclear (for reviews see Lader and Hindmarch 1996; Stephens and Sanger 1996; Rush 1998).

Materials and methods

Subjects

Ten adult male volunteers with histories of drug and alcohol abuse were recruited via flyers and word-of-mouth, and were paid to participate in this experiment. One additional volunteer was enrolled, but was discharged before completing the protocol due to behavioral problems on the General Inpatient Psychiatry Unit. Prior to participation, all potential volunteers completed a comprehensive medical-history questionnaire, drug-use questionnaire, a mental status examination and vital sign assessment, and were examined by a psychiatrist (R.W.B.). Routine clinical laboratory blood chemistry tests and an electrocardiogram were conducted on all potential volunteers. Potential volunteers with histories of serious physical disease, current physical disease, impaired cardiovascular functioning, chronic obstructive pulmonary disease, seizure, head trauma or CNS tumors, or current or past histories of serious psychiatric disorder (i.e., axis I, DSM IV), other than substance abuse or dependence, were excluded from participation. All subjects were in good health with no contraindications to sedative/hypnotic drugs. This study was approved by the Institutional Review Board of the University of Mississippi Medical Center, and subjects gave their written informed consent prior to participating.

The ten subjects who completed this protocol ranged in age from 33 to 48 years (mean = 40) and in weight from 60 to 101 kg (mean = 78). Subjects reported lifetime experience with a wide range of commonly abused drugs including amphetamines, barbiturates, benzodiazepines, cocaine, marijuana and opiates, and scored between 5 and 24 (mean = 15) on the Drug Abuse Screening Test (DAST) (Skinner 1982). Subjects reported consuming 0–106 alcohol-containing beverages during the week preceding admission (mean = 34), and scored between 6 and 43 (mean = 24) on the Michigan Alcohol Screening Test (MAST) (Selzer 1971). Nine subjects reported smoking tobacco cigarettes daily (range = 10–30, mean = 18). Eight subjects reported consuming at least some caffeine daily (range = 136–1,224 mg, mean = 589 mg).

General procedures

Subjects resided on the General Inpatient Psychiatry Unit at the University of Mississippi Medical Center while participating in this experiment, and two subjects generally participated concurrently. The General Inpatient Psychiatry Unit at the University of Mississippi Medical Center is a locked unit for patients with psychiatric or substance-abuse problems. Subjects completed ten experimental sessions across a 2-week period.

Subjects were informed that during their participation they would receive various drugs and that these could include placebo, sedatives, muscle relaxants, anxiolytics, stimulants and weight loss medications, antidepressants, and antihistamines. Other than receiving this general information, subjects were blind to the type of drug administered. Subjects were told that the purpose of the study was to see how different drugs affect mood and behavior. Other than this general explanation of purpose, subjects were given no instruction of what they were "supposed" to do or of what outcomes might be expected.

On the day of admission to the General Inpatient Psychiatry Unit, subjects provided a urine sample which was screened for the presence of amphetamines, barbiturates, benzodiazepines, cocaine, opioids and THC. Subjects were then allowed to acclimate to the General Inpatient Psychiatry Unit for 3–8 days (mean = 5). During this acclimation period, subjects were observed for signs of drug or alcohol withdrawal. All subjects were without evidence of physiological dependence. During the acclimation period, subjects completed one to four "practice" sessions (mean = 2). These "practice" sessions were used to familiarize subjects with the behavioral measures and daily laboratory routine. No medications were administered on these days. During the acclimation period, subjects provided a urine sample daily which was screened for the presence of those drugs detected in their urine on the day of admission. Drug testing began after subjects provided urine sample free of the drugs detected on the day of admission, except THC.

Experimental sessions were conducted Monday through Friday. There were no scheduled experimental activities on Saturday and Sunday. On experimental session days, subjects followed a daily routine. Each experimental-session day, subjects consumed a standard hospital breakfast at approximately 0700 hours. Subjects were then escorted off the General Inpatient Psychiatry Unit and allowed to smoke tobacco cigarettes between 0730 and 0800 hours. Subjects were not allowed to smoke again until after completing the experimental session. Subjects were escorted to the test room at approximately 0815 hours. The test room was located on the General Inpatient Psychiatry Unit and consisted of a desk and chair for the research assistant and nurse, a cushioned chair for the subject, an Apple Macintosh microcomputer (Quadra 605, Apple Computer, Inc., Cupertino, Calif., USA) and an automated blood pressure monitor (DINAMAP Model 9300, Johnson & Johnson Medical Inc., Tampa, Fla., USA). Each morning subjects provided a urine sample which was screened on a random, unannounced basis for the presence of amphetamines, barbiturates, benzodiazepines, cocaine, opioids and THC. Each subject's urine sample was screened at least once (range = 1–5; mean = 2). Subjects also provided an expired air specimen which was assayed for the presence of

alcohol using a hand-held breathalyzer (Alco-Sensor, Intoximeters, Inc., St Louis, Mo., USA).

On experimental sessions days, subjects completed the subject-rated drug-effect questionnaires and performance tasks at approximately 0830 hours. Between 0830 and 0900 hours subjects sat quietly in a semi-reclined position and their heart rate and blood pressure was monitored. Subjects ingested drug at approximately 0900 hours, and completed the subject-rated drug-effect questionnaires and performance tasks periodically for 5 h after drug administration. A standard hospital lunch was provided after the subject completed the subject-rated drug-effect questionnaires and performance tasks at the 3-h observation (i.e., approximately 1215 hours). After completing the subject-rated drug-effect questionnaires and performance tasks at the 5-hour observation, subjects were escorted back to the General Inpatient Psychiatry Unit. No other activities were scheduled for subjects for the remainder of the day, but they were encouraged to engage in art, occupational or recreational activities provided by the staff of the General Inpatient Psychiatry Unit.

Behavioral measures and vital signs

Unless otherwise noted, all subject-rated drug-effect questionnaires and performance tasks were completed on an Apple Macintosh microcomputer. Behavioral measures were completed approximately 30 min before drug administration, and 0.5, 1, 1.5, 2, 2.5, 3, 4, and 5 h after drug administration. Subjects completed the tasks in fixed order. The order in which the subject-rated drug-effect questionnaires and performance tasks are described corresponds to the order in which the subjects completed them.

Addiction research center inventory (ARCI)

The short form of the ARCI consisted of 49 true/false questions and contained five major subscales: Morphine-Benzedrine Group (MBG) (a measure of euphoria); Pentobarbital, Chlorpromazine, Alcohol group (PCAG) (a measure of sedation); Lysergic Acid Diethylamide (LSD) (a measure of dysphoria); and Benzedrine group (BG) and Amphetamine (A) scales (empirically derived amphetamine-sensitive scales) (Martin et al. 1971; Jasinski 1977). Subjects used a computer mouse to point to and select among the two response options displayed on the screen, True or False.

Adjective rating scale

The adjective rating scale consisted of 32 items and contained two subscales: Stimulant and Sedative (Oliveto et al. 1992). Subjects rated each item using the computer mouse to point to and select among one of five response options: Not At All, A Little Bit, Moderately, Quite A Bit and Very Much (scored numerically from 0 to 4, respectively). The Sedative subscale consisted of the following 16 adjectives: Clumsy, Dizzy, Confused, Dazed, Sleepy, Depressed, Difficulty Walking, Drowsy, Nausea, Drunk, Fatigued, Lazy, Relaxed, Tired, Sluggish and Spaced Out. The Stimulant subscale consisted of the following 16 adjectives: Active, Alert, Irregular Heartbeat, Good Mood, Muscles Twitching, Agitated, Energetic, Excited, Euphoric, Irritable, Nervous, Restless, Shaky, Sweaty, Talkative, and Heart Racing. Scores for the Sedative and Stimulant subscales were calculated by summing the responses to the individual items. The maximum possible score on each subscale was 64.

Subject-rated drug-effect questionnaire

This questionnaire consisted of 32 items that were presented on the video screen, one at a time. Subjects rated each of the items

using a 5-point scale similar to the one described above. The items rated were: Strong, Bad Effects, Good Effects, High, Rush, Like the Drug, Vigorous, Elated, Friendly, Carefree, Relaxed, Impairing Your Ability to Concentrate, Improving Your Ability to Concentrate, Hear Voices, Repeating a Ritual, More Hungry, Less Hungry, Motivated, Turning in Your Stomach, Frightened, Danger, Mentally Sharp, Mentally Slow, Happy, Sad, Bad Mood, Paranoid, People are Talking About You, Impairing Your Performance, Improving Your Performance, Take this Drug Again and Pay For this Drug.

End-of-day questionnaire

Approximately 5 h after oral drug administration, subjects completed an End-of-Day Questionnaire that consisted of two parts. The first part consisted of five items: 1) rate the overall Strength of today's drug, 2) rate your overall Liking of today's drug, 3) rate the overall Good effects of today's drug, 4) rate the overall Bad effects of today's drug, and 5) rate the degree to which you would Like to take today's drug again. These items were rated using a 5-point scale similar to the one described above. The second part of the questionnaire consisted of two items: 1) estimate the amount of money you think the drug would be worth on the street and 2) estimate the amount of money that you would personally be willing to pay for the drug on the street. Subjects used the numeric keypad on the computer keyboard to input any numeric value in dollars and cents.

Pharmacological-class questionnaire

Approximately 5 h after oral drug administration, subjects completed a pharmacological-class questionnaire. This questionnaire asked subjects to "Select the drug class that best describes the drug you received today". The options included: blank or placebo, opiate (like morphine, heroin), stimulant (like cocaine, amphetamine), speedball (like heroin and cocaine together), hallucinogen (like LSD), benzodiazepine (like Valium) or barbiturate (like Seconal), alcohol, marijuana, phencyclidine (like PCP), or antidepressant (like Elavil).

Observer-rated drug-effect questionnaire

Observer ratings were completed by a research assistant who was blind to the medications and doses being tested. The research assistant completed the observer-rating scales at approximately the same time the subject completed the Drug-Effect Questionnaire. The observer was instructed to base her ratings on observation of the subject's gross behavior rather than on the subject's verbal reports or ratings. The items were rated using a 5-point scale similar to the one described above. The items rated were: Any Drug Effect, High, Like the Drug Effect, Carefree, Drunk, Speech Slurred, Drowsy, Tired, Sleepy, Stimulated, Nervous, Jittery, Happy, Sad, Good Mood, Bad Mood, Talkative, Restless, Fidgety, Friendly, Relaxed, Excited, Alert, Energetic, Positive Vocalizations, Smiling, Laughing, Paranoid, Compulsive and Hallucinating.

Digit-symbol-substitution test (DSST)

A computerized version of the DSST, which has been described previously, was used in this experiment (McLeod et al. 1982). Briefly, subjects used a numeric keypad to enter a geometric pattern associated with one of 9 digits displayed on a video screen. Subjects had 90 s to enter as many geometric patterns as possible. The dependent measures were the number of geometric patterns the

subject attempted to enter (i.e., number of trials completed) and the number of patterns the subject entered correctly (i.e., number of trials correct).

Digit-enter-and-recall procedure

This was a modified version of the number recall task, which has been described previously (Roache and Griffiths 1985; Evans et al. 1990; Mumford et al. 1995a,b). Briefly, subjects used a numeric keypad to reproduce randomly selected 8-digit numbers which were displayed on the computer screen one at a time. The task consisted of two components, an enter component in which subjects copied (entered) the 8-digit number while it was displayed on the screen, and a second component in which the subject recalled the 8-digit number from memory after it disappeared from the screen. At the beginning of each trial, an 8-digit number appeared on the computer screen. If the subject entered the number incorrectly, the trial was discontinued, and a different 8-digit number was presented. If the number was entered correctly, the trial continued to the second component; the number disappeared from the screen and, either immediately (five trials) or after a 10-s delay (five trials), the subject was required to recall (i.e., re-enter the 8-digit number using the numeric keypad) the number. The task continued until the subject had correctly entered ten 8-digit numbers in the first component (i.e., ten trials were initiated) or 25 incorrect attempts were made. The dependent measure was the total number of 8-digit numbers correctly reproduced in the second (recall) component. The maximum possible score was 10.

Balance

This task assessed the subject's ability to stand upright on one foot with his eyes closed and arms extended to the side at shoulder height. The subject was required to balance on one foot for a maximum of 30 s; if the subject touched the raised foot to the floor before 30 s elapsed, that time was taken as the score for that foot. The subject was required to balance on each foot, and scores for both the right and left foot were summed so that the maximum possible total score was 60 s.

Picture recall/recognition

This was a modified version of the Delayed Recognition Task, which has also been described previously (Roache and Griffiths 1985; Evans et al. 1990; Mumford et al. 1995a,b). Approximately 1.5 h after drug administration, subjects were given 120 s to study a sheet of paper with 18 pictures. After 120 s the sheet of paper was taken from the subject, and he was instructed to write down as many of the names of the pictures as he could remember (immediate recall). At 5½ h after drug administration, subjects were tested for both delayed recall and delayed recognition of the pictures presented 4 h previously. Subjects were first asked to write down the names of as many of the pictures as they could remember and then were presented with a chart containing 198 pictures and asked to identify the 18 pictures which they had been shown 4 h previously. The maximum possible score for each recall or recognition test was 18.

Vital signs

Heart rate and blood pressure were recorded for safety purposes using an automated blood-pressure monitor. Heart rate and blood pressure were recorded approximately 30 min before drug administration and 0.5, 1, 1.5, 2, 2.5, 3, 4 and 5 h after drug

administration. Heart rate and blood pressure were recorded immediately before subjects completed the subject-rated drug-effect questionnaires and performance tasks described above.

Drug administration

Ten dose conditions were studied in the present experiment: 1) placebo, 2) 0.25 mg triazolam, 3) 0.5 mg triazolam, 4) 0.75 mg triazolam, 5) 15 mg zolpidem, 6) 30 mg zolpidem, 7) 45 mg zolpidem, 8) 100 mg trazodone, 9) 200 mg trazodone and 10) 300 mg trazodone. All dose conditions were administered in a double-blind fashion. Drug doses were prepared by encapsulating 0.25 mg triazolam (Pharmacia Upjohn Company, Kalamazoo, Mich., USA), 5 or 10 mg zolpidem (Searle and Co., Chicago, Ill., USA) or 100 mg trazodone (Cardinal Health Inc., Richland, Miss., USA) in a size 00 capsule. Lactose was then used to fill the remainder of all the capsules. Placebo capsules contained only lactose.

The commonly used hypnotic doses of triazolam, zolpidem and trazodone are 0.125–0.25 mg, 5–10 mg and 50–100 mg, respectively. Supratherapeutic doses were tested because they are often used by drug abusers.

During each experimental session subjects ingested five capsules. Dose was varied by administering the appropriate number of active and placebo capsules. Capsules were taken orally with approximately 150 ml water, and at least 24 h separated all drug administrations. Order of drug administration was determined by a 10×10 Latin Square.

Data analysis

Time-course and peak-effect data were analyzed as raw scores for all measures. Effects were considered significant for $P \leq 0.05$. For repeated measures ANOVAs, Huynh-Feldt corrected P values were used.

Time-course data were analyzed by two-factor, repeated measures ANOVA with Dose condition (placebo and the nine drug conditions) and Time (pre-drug, 0.5, 1, 1.5, 2, 2.5, 3, 4 and 5 h post-drug) as factors (SuperANOVA, Abacus Concepts, Inc., Berkeley, Calif., USA). The mean square error term was then used to conduct Dunnett's post hoc test comparing placebo with each of the drug conditions at each post-drug time point.

Peak-effect data were calculated and analyzed by one-factor repeated measures ANOVA with Dose condition (i.e., placebo and the nine active dose conditions) as the factor. For the ARCI, Subject-Rated Drug-Effect Questionnaire and Observer-Rated Drug-Effect Questionnaire, peak effect was defined as the maximum value from 0.5 to 5 h after drug administration. For the DSST, Digit-Enter-and-Recall Procedure and Balance Task, peak effect was defined as the minimum value from 0.5 to 5 h after drug administration. The mean square error term was then used to conduct Dunnett's post-hoc test comparing placebo to each of the active dose conditions. Differences between trazodone and triazolam were determined using a two-factor repeated measure ANOVA with Drug (i.e., trazodone and triazolam) and Dose (i.e., the three active doses of each drug) as factors. Placebo data were excluded from these analyses. Trazodone-triazolam differences were inferred if the main effect of Drug or the interaction between Drug and Dose attained statistical significance. Zolpidem-triazolam differences were determined in a similar fashion. Data from the Picture Recall/Recognition and End-of-Day Questionnaire were analyzed in the same fashion as peak-effect data.

Results

Time course

Figure 1 shows triazolam, zolpidem and trazodone time-course functions for three measures: scores from the PCAG subscale of the ARCI, trials completed on the DSST and trials correct on the Digit-Entry-and-Recall procedure. This figure shows that the time-action functions of triazolam, zolpidem and trazodone were generally similar. Significant drug effects were evident by 0.5–2.5 h after drug administration, peaked 1.5–3 h after drug administration, and progressively abated during the remainder of the experimental session.

Peak effect

ARCI

The highest dose of triazolam and zolpidem, and the intermediate dose of trazodone, increased PCAG scores significantly above placebo levels ($F_{(9,81)} = 3.8$, $P = 0.001$; Dunnett's = 2.8) (Fig. 2). Neither the zolpidem nor the trazodone dose-response functions differed significantly from the triazolam dose-response function. None of the other scales from the ARCI was significantly affected by any of the dose conditions.

Adjective rating scale

The highest dose of triazolam and zolpidem, but none of the doses of trazodone, increased Sedative scores from the Adjective-Rating Scale significantly above placebo levels ($F_{(9,81)} = 2.7$, $P = 0.02$; Dunnett's = 7.8) (Fig. 2). The zolpidem and triazolam dose-response functions did not differ significantly. The effects of trazodone tended to be less than those of triazolam ($F_{(2,18)} = 3.2$, $P = 0.06$).

The highest dose of triazolam, but none of the doses of zolpidem or trazodone, increased Stimulant scores significantly above placebo levels ($F_{(9,81)} = 3.4$, $P = 0.05$; Dunnett's = 7.8) (data not shown). Zolpidem and triazolam produced comparable dose-related effects on this measure. The effects of trazodone were significantly less than those observed with triazolam ($F_{(2,18)} = 4.8$, $P = 0.02$).

Subject-rated drug-effect questionnaire

Table 1 shows that 17 items from the Subject-Rated Drug-Effect Questionnaire were significantly affected by at least one of the dose conditions. Figure 2 shows dose-response functions for six of these items: Mentally Slow, Performance Impaired, Willing to Take Again, Elated, Like Drug and Good Effects. This figure

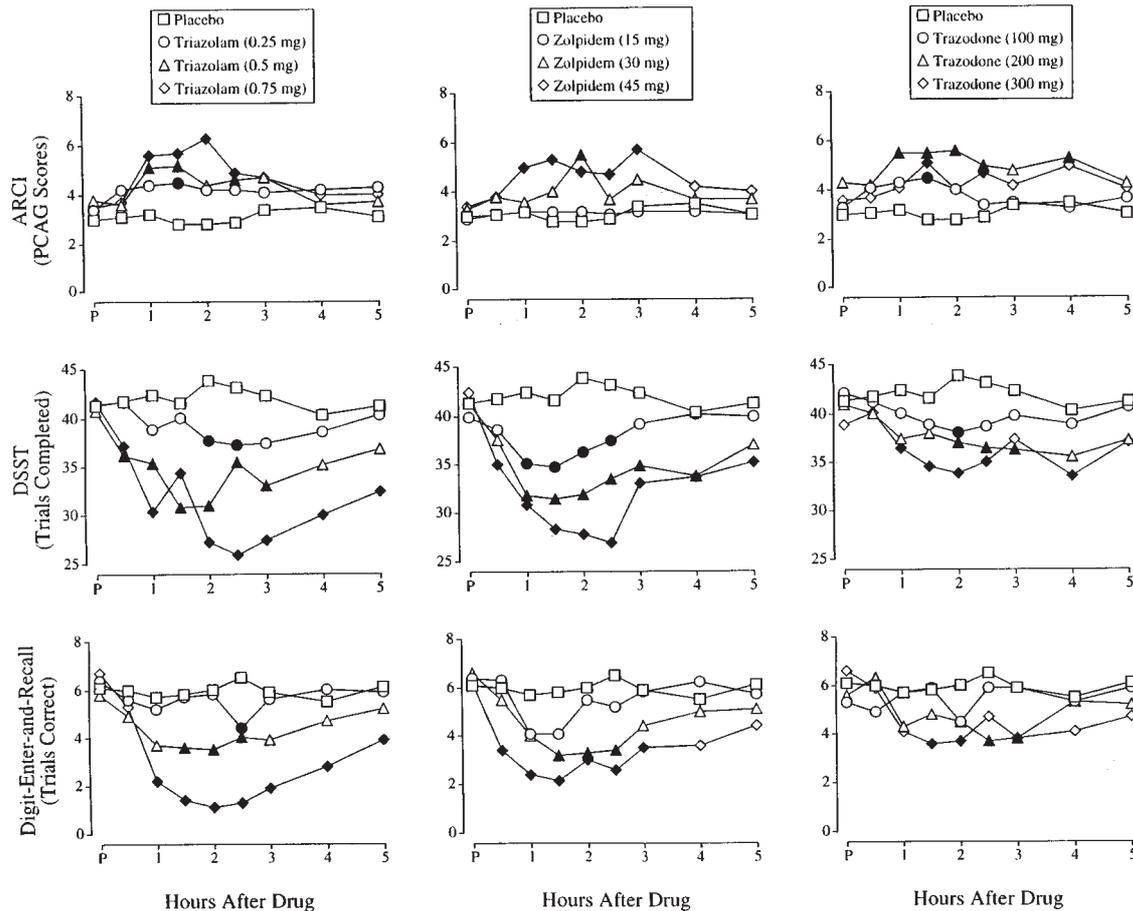


Fig. 1 Time-course functions and dose effects for triazolam (*left column*), zolpidem (*middle column*) and trazodone (*right column*) for PCAG scores from the ARCI, number of trials completed on the DSST, and trials correct Digit-Enter-and-Recall task. *X-axes*: time after drug administration in hours; *P* indicates pre-drug. Data points show means of ten subjects. *Filled symbols* indicate those values that are significantly different from the corresponding placebo value at the same time-point ($P \leq 0.05$, Dunnett's post hoc test). Standard error bars are omitted for clarity

shows that in general the highest dose of triazolam and zolpidem increased ratings of Mentally Slow, Performance Impaired, Willing to Take Again and Elated significantly above placebo levels. The higher doses of zolpidem, but none of the doses of triazolam, increased ratings of Like Drug and Good Effects significantly above placebo levels. However, the zolpidem and triazolam dose-response functions did not differ significantly on these measures.

None of the doses of trazodone tested increased ratings of Mentally Slow, Performance Impaired, Willing to Take Again, Elated, Like Drug and Good Effects significantly above placebo levels (Fig. 2; Table 1). For subject ratings of Willing to Take Again, Like Drug and Good Effects, the effects of trazodone were significantly less than those observed with triazolam ($F_{(2,18)}$ values > 4.1 , P values < 0.05). For subject ratings of Performance Impaired, the effects of trazodone

tended to be less than those of triazolam ($F_{(2,18)} = 3.2$, $P = 0.06$). The effects of trazodone and triazolam did not differ significantly for subject ratings of Mentally Slow and Elated.

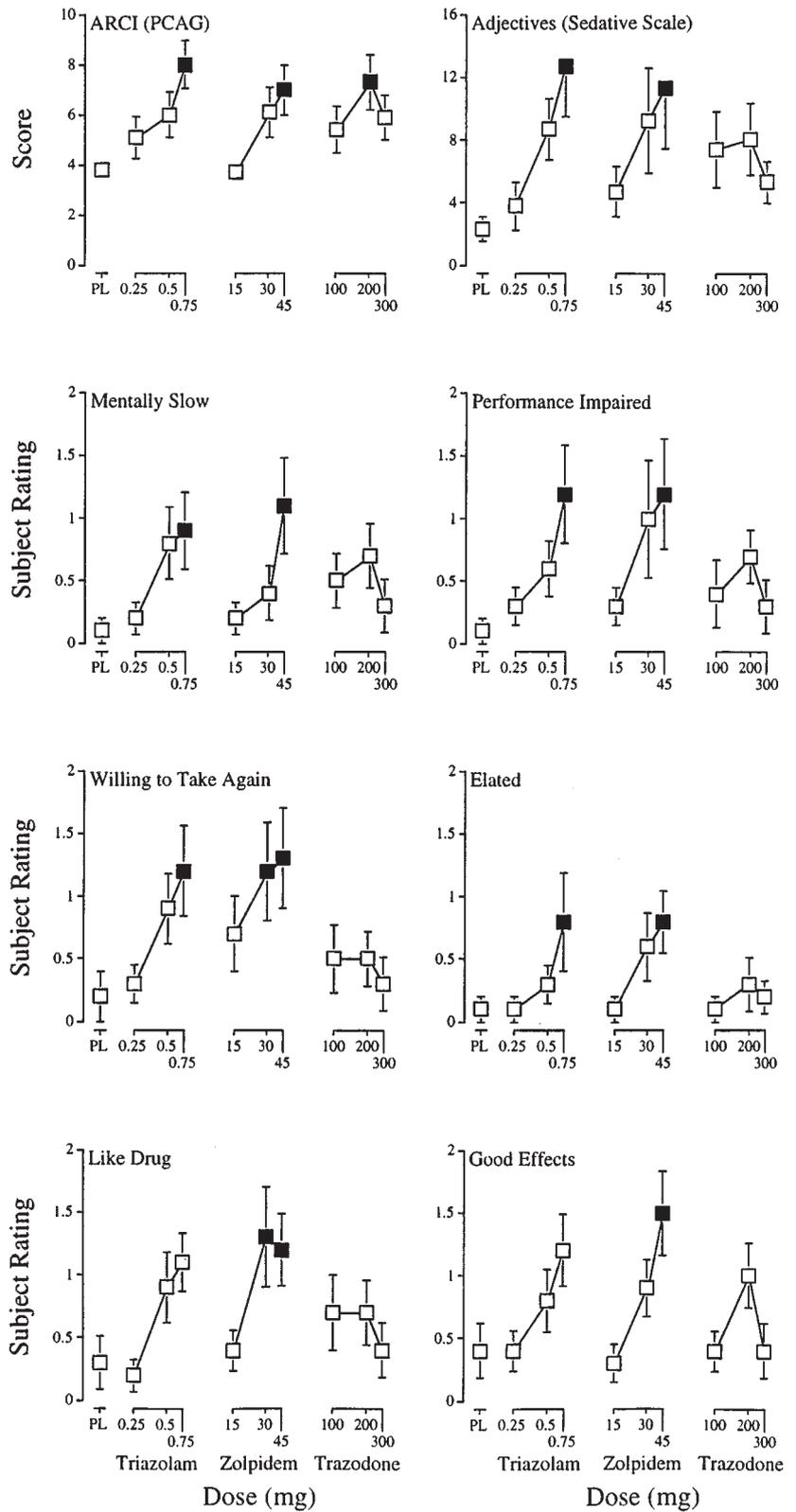
End-of-day questionnaire

The two highest doses of trazodone, but none of the doses of triazolam or zolpidem increased ratings of Drug Strength on the End-of-Day Questionnaire significantly above placebo levels ($F_{(9,81)} = 4.1$, $P = 0.006$; Dunnett's = 0.9) (data not shown). The zolpidem and trazodone dose-response functions did not differ significantly from the triazolam dose-response function. None of the other items on the End-of-Day Questionnaire were significantly affected by any of the dose conditions.

Pharmacological-class questionnaire

Table 2 shows that all three drugs generally decreased placebo identifications on the Pharmacological-Class Questionnaire as a function of dose. Triazolam, zolpidem and trazodone were most often identified as a benzodiazepine or barbiturate.

Fig. 2 Dose effects for scores from the PCAG scale of the ARCI and sedation scale from the Adjective Rating Scale, and subject ratings of Mentally Slow, Performance Impaired, Willing to Take Again, Elated, Like Drug and Good Effects from the Subject-Rated Drug-Effect Questionnaire. Data are expressed as peak effect. *X-axes*: dose in mg; data points above “PL” designate placebo values. Data points show means of ten subjects; brackets show ± 1 SEM. *Filled symbols* indicate those values that are significantly different from the placebo value ($P \leq 0.05$, Dunnett’s post hoc test)



Observer-rated drug-effect questionnaire

Table 1 shows that 13 items from the Observer-Rated Drug-Effect Questionnaire were significantly affected by

at least one of the dose conditions. Figure 3 shows triazolam, zolpidem and trazodone dose-response functions for four of these items: Drug Effect, High, Drowsy and Sleepy. This figure shows that the two highest doses

Table 1 Peak means for the 17 items from the Subject-Rated Drug-effect Questionnaire and the 13 items from the Observer-Rated Drug-Effect Questionnaire that were significantly affected by at least one of the dose conditions. *Column 1* indicates the item. *Column 2–11* display the means from the ten dose conditions. *Column 12*

shows the critical difference obtained from Dunnett's post-hoc test. This value can be used to determine which data points differ significantly from the placebo value. *Bold values* are significantly different from the placebo value

Scale and item	Placebo	Triazolam (mg)			Zolpidem (mg)			Trazodone (mg)			Dunnett's Post-hoc test
		0.25	0.50	0.75	15	30	45	100	200	300	
<i>Subject-rated drug-effect-questionnaire</i>											
Bad effects	0.10	0.10	0.20	0.30	0.10	0.60	0.80	0.50	0.40	0.20	0.62
Bad mood	0.00	0.10	0.40	0.90	0.10	0.50	0.30	0.00	0.10	0.10	0.67
Carefree	0.20	0.20	0.80	0.80	0.30	0.80	1.00	0.60	0.40	0.40	0.75
Concentration impaired	0.00	0.30	0.70	1.20	0.30	1.00	0.90	0.40	0.90	0.50	1.00
Elated	0.10	0.10	0.30	0.80	0.10	0.60	0.80	0.10	0.30	0.20	0.69
Friendly	0.20	0.50	1.00	0.90	0.30	0.80	1.20	0.40	0.60	0.30	0.92
Good effects	0.40	0.40	0.80	1.20	0.30	0.90	1.50	0.40	1.00	0.40	0.82
Happy	0.10	0.20	0.70	1.00	0.40	1.00	1.10	0.30	0.30	0.30	0.91
High	0.40	0.40	0.90	1.40	0.40	0.90	1.30	1.10	1.60	1.00	1.00
Like drug	0.30	0.20	0.90	1.10	0.40	1.30	1.20	0.70	0.70	0.40	0.88
Mentally sharp	0.10	0.10	0.40	1.20	0.40	0.60	0.70	0.10	0.10	0.00	0.68
Mentally slow	0.10	0.20	0.80	0.90	0.20	0.40	1.10	0.50	0.70	0.30	0.75
Performance impaired	0.10	0.30	0.60	1.20	0.30	1.00	1.20	0.40	0.70	0.30	1.00
Strong	0.50	0.60	1.40	1.50	1.00	1.60	1.90	1.30	1.80	1.30	1.07
Talking about me	0.00	0.00	0.40	0.50	0.10	0.60	1.10	0.00	0.10	0.00	0.84
Willing to pay for	0.10	0.30	0.80	1.30	0.40	1.20	0.80	0.30	0.30	0.20	0.85
Willing to take again	0.20	0.30	0.90	1.20	0.70	1.20	1.30	0.50	0.50	0.30	0.92
<i>Observer-rated drug-effects questionnaire</i>											
Alert	2.40	1.90	2.00	1.80	0.10	1.80	2.00	2.00	2.20	2.20	0.46
Carefree	1.80	2.20	2.60	2.50	0.20	2.30	2.40	2.00	2.00	2.10	0.73
Bad mood	0.00	0.00	0.20	0.00	0.30	0.10	0.90	0.20	0.10	0.10	0.53
Drowsy	0.30	0.90	2.10	2.90	0.80	1.90	2.00	1.10	1.00	1.10	1.00
Drug effect	0.50	1.00	2.20	2.90	1.00	2.00	2.30	1.40	1.20	1.20	0.90
Drunk	0.00	0.10	0.70	0.50	0.20	0.50	0.50	0.10	0.10	0.10	0.62
High	0.30	0.40	1.60	2.10	0.70	1.40	2.10	0.70	0.70	0.90	1.00
Like drug	0.50	0.60	1.20	1.20	0.20	1.20	1.60	0.70	0.80	0.70	0.83
Nervous	0.00	0.00	0.10	0.00	0.00	0.10	0.50	0.10	0.00	0.10	0.35
Sleepy	0.50	1.10	2.10	2.70	0.70	1.70	1.80	1.00	0.70	0.90	0.96
Speech slurred	0.00	0.10	0.30	0.60	0.10	0.20	0.80	0.00	0.00	0.00	0.70
Talkative	0.00	0.00	0.20	0.00	0.30	0.10	0.90	0.20	0.10	0.10	0.53
Tired	0.20	0.90	1.50	2.20	0.60	1.30	1.30	0.90	0.70	0.80	0.97

of triazolam and zolpidem, but none of the doses of trazodone, increased these observer ratings significantly above placebo levels. The triazolam and zolpidem dose-response functions did not differ significantly on these observer-rated items [$F_{(2,18)}$ values 1.4, P values > 0.29]. The effects of trazodone on these observer-rated items were significantly less than those observed with triazolam [$F_{(2,18)}$ values > 5.8 , P values ≤ 0.01].

DSST

The two highest doses of triazolam, and all three doses of zolpidem tested, decreased the number of trials completed and the number of trials correct significantly below placebo levels [$F_{(9,81)} = 11.4$ and 16.6 , respectively, $P = 0.001$; Dunnett's = 6.5 and 7.8 , respectively] (Fig. 4). The two highest doses of trazodone decreased the number of trials completed significantly below placebo levels, but none of the doses tested significantly decreased the number of trials correct. Triazolam and

zolpidem did not differentially impair DSST performance. Trazodone and triazolam did not produce significantly different effects for the number of trials completed. Trazodone produced significantly less impairment than triazolam on number of trials correct [$F_{(2,18)} = 13.3$, $P = 0.0003$].

Digit-enter-and-recall

The two highest doses of each drug decreased the number of trials correct significantly below placebo levels [$F_{(9,81)} = 4.7$, $P = 0.008$; Dunnett's = 1.9] (Fig. 4). Neither the zolpidem nor the trazodone dose-response function differed significantly from the triazolam dose-response function.

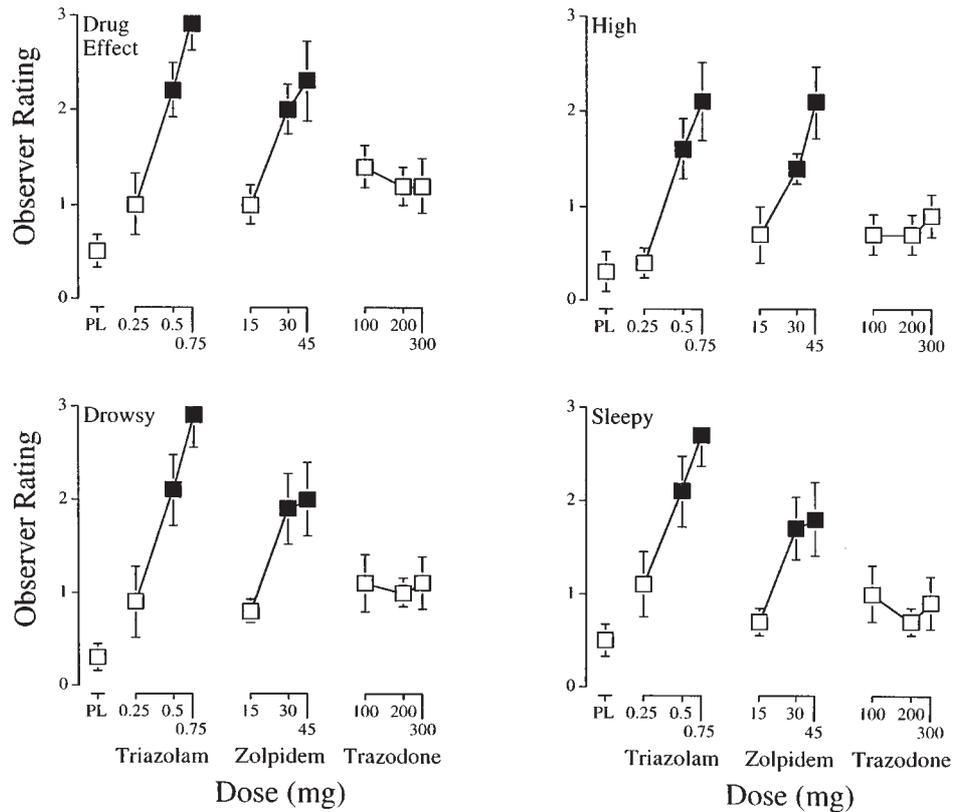
Balance

The two highest doses of each drug significantly impaired balance relative to placebo [$F_{(9,81)} = 4.5$,

Table 2 Approximately 5 h after oral drug administration, subjects were asked to identify the drug effect as being most similar to one of several categories of psychoactive drugs. Data are derived from ten subjects. Each value in the table shows the total number of subjects that selected a given drug category. Categories that were not selected at all are omitted

Scale and item	Placebo	Triazolam (mg)			Zolpidem (mg)			Trazodone (mg)		
		0.25	0.50	0.75	15	30	45	100	200	300
Blank placebo	6	5	2	2	5	3	3	2	1	2
Opiate	0	0	0	0	0	0	0	0	0	1
Stimulant	1	1	2	0	1	0	1	0	0	0
Hallucinogen	0	0	0	0	0	0	0	1	0	0
Benzodiazepine or barbiturate	2	3	3	6	4	5	4	4	4	3
Alcohol	1	0	0	0	0	0	0	0	1	0
Marijuana	0	0	0	1	0	0	1	1	1	1
Phencyclidine	0	0	0	0	0	0	1	0	0	0
Antidepressant	0	1	3	1	0	2	0	2	3	3
Total	10	10	10	10	10	10	10	10	10	10

Fig. 3 Dose effects for ratings of Drug Effect, High, Drowsy and Sleepy from the Observer-Rated Drug-Effect Questionnaire. Other details are the same as in Fig. 2



$P = 0.01$; Dunnett's = 15.4] (Fig. 4). Neither the zolpidem nor the trazodone dose-response function differed significantly from the triazolam dose-response function.

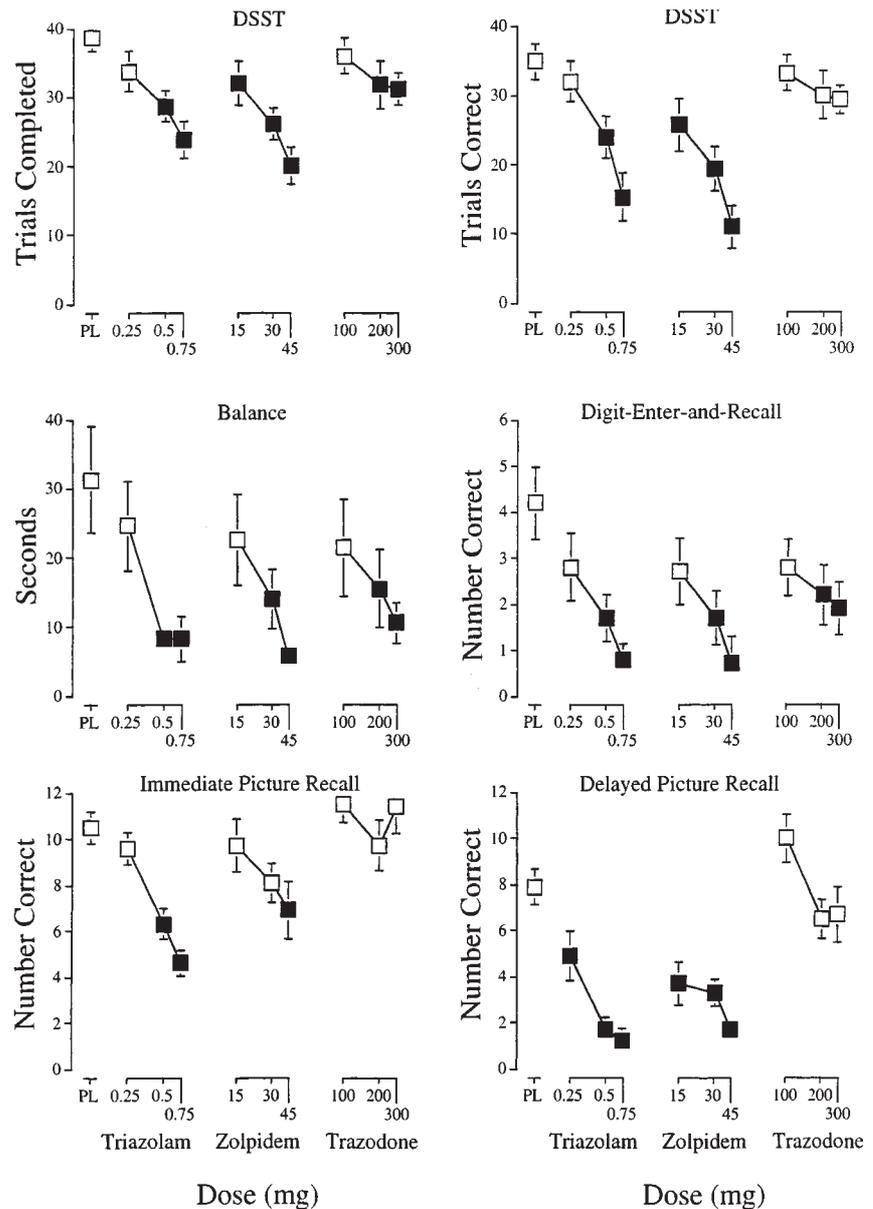
Picture recall/recognition

The two highest doses of triazolam and the highest dose of zolpidem significantly impaired immediate-picture recall relative to placebo [$F_{(9,81)} = 11.6, P = 0.001$; Dunnett's = 2.6], while all doses of triazolam and zolpidem tested significantly impaired delayed-picture recall [$F_{(9,81)} = 15.6, P = 0.0001$; Dunnett's = 2.9] (Fig. 4).

None of the doses of trazodone significantly impaired immediate- or delayed-picture recall (Fig. 4). Zolpidem and triazolam produced comparable dose-related effects on the immediate-picture and delayed-picture-recall tasks. Trazodone produced significantly less impairment than triazolam on the immediate-picture-recall [$F_{(2,18)} = 7.4, P = 0.017$] and delayed-picture-recall tasks [$F_{(1,9)} = 43.5, P = 0.0001$].

The two highest doses of triazolam and all doses of zolpidem, but none of the doses of trazodone, significantly impaired performance on the delayed-recognition task relative to placebo [$F_{(9,81)} = 10.6, P = 0.0001$; Dunnett's = 2.8] (data not shown). The effects of zolpidem were significantly greater than

Fig. 4 Dose effects for trials completed and trials correct from the DSST, (seconds balanced), trials correct from the Digit-Enter-and-Recall task, and number correct from the immediate- and delayed-picture recall task. Other details are the same as in Fig. 2



those observed with triazolam [$F_{(2,18)} = 9.2$, $P = 0.002$]. The effects of trazodone were significantly less than those observed with triazolam [$F_{(2,18)} = 10.1$, $P = 0.001$].

Discussion

The present study examined the acute behavioral effects and abuse potential of trazodone, a triazolopyridine antidepressant, zolpidem, an imidazopyridine hypnotic, and triazolam, a triazolobenzodiazepine hypnotic, across a 3-fold range of doses. As noted above, antidepressants like trazodone are being used more frequently to treat sleep disorders, but it is unclear whether they have a distinct behavioral pharmacological profile relative to benzodiazepine hypnotics.

Zolpidem was included because it is the most commonly prescribed hypnotic and reportedly has a unique benzodiazepine-receptor binding profile. Trazodone, zolpidem and triazolam produced comparable dose-related increases on the PCAG scale of the ARCI, which suggests that the drug doses tested were equivalent on some behavioral dimension. The effects of trazodone on subject-rated items thought to measure abuse potential (e.g., subject ratings of Willing to Take Again) were significantly less than those observed with triazolam, while the effects of zolpidem and triazolam were comparable. Triazolam and zolpidem produced dose-dependent impairment on all of the performance tasks. Trazodone impaired performance on some, but not all, of these tasks. Consistent with the pharmacokinetics of these compounds, the time-action functions of trazodone, zolpidem and triazolam

were similar on these measures (Brogden et al. 1981; Greenblatt et al. 1989; Anker et al. 1991; Nilsen and Dale 1992; Haria et al. 1994; Fraisse et al. 1996). Below, we discuss these findings in terms of trazodone-triazolam differences and similarities, and zolpidem-triazolam similarities.

Trazodone versus triazolam

Triazolam and trazodone increased scores on the PCAG scale of the ARCI, a putative measure of sedation (Martin et al. 1971; Jasinski 1977). Across the range of doses tested, trazodone and triazolam produced comparable effects, which suggests the doses tested were equivalent on some behavioral dimension. Demonstrating that the doses of trazodone and triazolam tested are equivalent on some dimension is important, especially when between-drug differences emerge on other measures (Greenblatt 1995).

While trazodone and triazolam produced similar increases on PCAG scores of the ARCI, subject-rated items thought to measure the abuse potential of drugs clearly-differentiated these compounds. For example, triazolam, but not trazodone, increased subject ratings of Willing to Take Again, Like Drug and Good Effects. These items are thought to be indirect measures of drug reinforcement that may be used to infer a relative abuse potential. The finding that trazodone may have less abuse potential than triazolam is concordant with epidemiological data. To the best of our knowledge, there are no reports of trazodone abuse. The finding that trazodone may have less abuse potential than triazolam is also concordant with clinical observations in patients at risk to abuse benzodiazepines (Liebowitz and El-Mallakh 1989; Ansseau and De Roeck 1993). In one study, for example, patients with histories of drug abuse were treated with trazodone for anxiety or sleep disorders (Liebowitz and El-Mallakh 1989). There was no evidence of trazodone abuse or dose escalation.

Triazolam produced dose-related performance impairment on all of the performance tasks used in the present experiment. Significant impairment generally was observed only with the two highest doses of each drug. These findings systematically replicate previous reports that used similar measures to assess the acute behavioral effects of triazolam in individuals with histories of drug or alcohol abuse (e.g. Roache and Griffiths 1985; Evans et al. 1990; Rush et al. 1998). Trazodone produced significant impairment on some, but not all, of the performance tasks. The finding that trazodone also impaired performance is concordant with some previous studies (e.g., Curran et al. 1988; Longmore et al. 1988; Sakulsripong et al. 1991; Volz and Sturm 1995), but discordant with other studies (e.g., Warrington et al. 1984; Amado-Boccaro et al. 1994; Rush et al. 1997). The reason for the discrepancy between the present experiment and some previous experiments is unknown, but may be due to the meth-

ods used. Most notably, these previous experiments employed healthy, non-drug-abusing individuals as volunteers. The present study, by contrast, employed individuals with histories of alcohol or drug abuse.

The finding that trazodone has less abuse potential and impairs performance to a lesser extent than triazolam is consistent with the neuropharmacological mechanisms of action of these drugs. Benzodiazepines exert their behavioral and clinical effects primarily via the GABA_A receptor complex (e.g., Synder et al. 1977; Olsen et al. 1984; Haefely 1989), while trazodone exerts its behavioral and clinical effects primarily *via* serotonin systems (Brogden et al. 1981). Several previous studies have demonstrated that serotonin drugs have less abuse potential than benzodiazepines (e.g., Cole et al. 1982; Sellers et al. 1992; Troisi et al. 1993; Evans et al. 1994). For example, lorazepam (1–8 mg/70 kg), a benzodiazepine agonist, and buspirone (15–120 mg/70 kg), a partial agonist at the serotonin 5-HT_{1A} receptor, produced comparable dose-related increases in subject ratings of Drug Strength in volunteers with histories of drug abuse (Troisi et al. 1993). By contrast, lorazepam, but not buspirone, significantly increased subject ratings of Drug Liking.

In summary, the present experiment assessed the acute behavioral effects and abuse potential of trazodone relative to triazolam. The effects of trazodone on subject-rated items thought to measure abuse potential (e.g., subject ratings of Willing to Take Again) were significantly less than those observed with triazolam. These data, along with epidemiological and clinical data, suggest that trazodone has less abuse potential than triazolam and may be a viable alternative to benzodiazepines in individuals with histories of alcohol or drug abuse.

Zolpidem versus triazolam

Zolpidem and triazolam produced sedative-like subject-rated drug effects (e.g., increased ratings of Mentally Slow and Performance Impaired on the Subject-Rated Drug-Effect Questionnaire, increased Sedation scores on the Adjective Rating Scale, and increased scores on the PCAG scale of the ARCI), although significant effects were observed only with the highest dose of each drug. The absolute magnitude of these sedative-like subject-rated drug effects was similar for the highest dose of zolpidem and triazolam. The findings that zolpidem and triazolam produce comparable sedative-like subject-rated drug effects across the range of doses tested systematically replicates a previous study that tested the same doses in individuals with histories of drug abuse (Evans et al. 1990).

To the best of our knowledge, there is only one published report that directly assessed the abuse potential of zolpidem relative to triazolam (Evans et al. 1990). In that study, 15 volunteers with histo-

ries of drug abuse participated in a double-blind, placebo-controlled, crossover study that assessed the acute effects of zolpidem (15, 30 or 45 mg), triazolam (0.25, 0.5 or 0.75 mg) and placebo. The highest dose of zolpidem and triazolam produced comparable dose-related increases in subject ratings of Drug Effect, which suggest equivalent doses were tested. Interestingly, however, the highest dose of zolpidem, but not triazolam, increased subject ratings of Drug Liking, Good Effects and Easy-Going/Mellow significantly above placebo levels. Zolpidem, but not triazolam, also produced a constellation of "negative" effect (e.g., increased subject ratings of Anxious/Nervous, Bad Effects, Blurred Vision, Lightheaded/Dizzy, and Queasy/Sick to Stomach). The highest dose of zolpidem, but not triazolam, increased scores on the Lysergic Acid Diethylamide (LSD) scale from the Addiction Research Center Inventory (ARCI), a putative measure of dysphoria. Zolpidem, but not triazolam, produced emesis. The authors of this report speculated that these "negative" subject-rated and physiological effects might limit zolpidem's abuse potential.

In the present experiment, the highest dose of zolpidem, but not triazolam, increased subject ratings of Drug Liking and Good Effects significantly above placebo levels, which is concordant with the findings of the Evans et al. (1990) study. The highest dose of zolpidem, but not triazolam, also increased subject ratings of Bad Effects significantly above placebo levels, and there was one instance of emesis following zolpidem administration. Thus, zolpidem did not produce a wide constellation of "negative" drug effects. Whether the increased ratings of Bad Effects observed with zolpidem in the present experiment is sufficient to offset the "positive" drug effects (e.g., increased ratings of Drug Liking and Good Effects) and reduce its abuse potential is unknown. Additional research is obviously needed. However, until such studies are available, the most parsimonious conclusion is that the abuse potential of zolpidem is comparable to that of triazolam.

Zolpidem and triazolam produced comparable dose-related performance impairment on a battery laboratory tasks. The findings that zolpidem and triazolam produced comparable dose-related impairment is concordant with previous studies that compared these drugs using different methods, performance tasks and subject populations (for reviews see Lader and Hindmarch 1996; Rush 1998).

In summary, the present experiment assessed the acute behavioral effects and abuse potential of zolpidem relative to triazolam. Across the range of doses tested, zolpidem and triazolam produced comparable dose-related performance impairment and subject-rated drug effects. These data suggest that despite its somewhat unique benzodiazepine-receptor-binding profile, zolpidem's acute behavioral effects

and abuse potential are generally similar to those of triazolam.

Summary and conclusions

The present study examined the acute behavioral effects and abuse potential of three drugs commonly used to treat sleep disorders, trazodone, zolpidem and triazolam, and placebo in volunteers with histories of alcohol and drug abuse. Zolpidem and triazolam, but not trazodone, increased subject ratings on items thought to measure abuse potential (e.g., ratings of Willing to Take Again). The findings of the present study suggest that trazodone has less abuse potential than triazolam, and may be a viable alternative to benzodiazepine hypnotics in individuals with histories of alcohol or drug abuse. By contrast, the acute behavioral effects and abuse potential of zolpidem are comparable to those of triazolam.

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