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## Acute performance-impairing and subject-rated effects of triazolam and temazepam, alone and in combination with ethanol, in humans

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The acute behavioural effects of triazolam (0.125 and 0.25 mg), temazepam (15 and 30 mg), and placebo, alone and in combination with ethanol (0 and 0.5 g/kg), were assessed in 10 volunteers. Ethanol alone did not impair performance and produced only a few subject-rated drug effects. Triazolam and temazepam alone produced some performance impairment and a few subject-rated drug effects. These effects tended to be dose-dependent and were comparable for the two drugs across the range of doses tested. The triazolam–ethanol and temazepam–ethanol combinations produced robust performance impairment and sedative-like subject-rated drug effects that were similar in magnitude. The findings of the present study suggest that even a moderate amount of ethanol in combination with a clinical dose of triazolam or temazepam can cause performance impairment that might diminish an individual's ability to respond adequately to unexpected demands (e.g. smoke alarms or middle-of-the-night child care).

**Key words:** alcohol, benzodiazepines, drug interactions, ethanol, hypnotics and sedatives, performance, subjective effects, temazepam, triazolam

### Introduction

Insomnia is common among adults in the USA. Across populations, prevalence estimates for some level of insomnia in the past year range from 10% to more than 40% (Foley *et al.*, 1995; Simon and VonKorff, 1997; Johnson *et al.*, 1998; Ancol-Israel and Roth, 1999; Shochat *et al.*, 1999). Insomnia and related sleep disturbances account for approximately 3.3 million visits to primary care physicians annually (Radecki and Brunton, 1993), and the direct economic impact of sleep disturbance in the USA has been estimated at more than US\$13 billion annually (Walsh and Engelhardt, 1999). Prescription hypnotics are effective in the treatment of insomnia (National Sleep Foundation/Gallup Organization, 1995; Ancol-Israel and Roth, 1999; Mitler, 2000; Richardson, 2000). Benzodiazepine hypnotics have been the most commonly prescribed pharmacotherapy for sleep disturbance, with trends towards shorter-acting compounds that have fewer residual daytime effects (Wysowski and Baum, 1991; Mitler, 2000). Consistent with this trend, triazolam (HALCION), a triazolobenzodiazepine, and temazepam (RESTORIL), a 1,4-benzodiazepine, both fast-acting, have been widely prescribed hypnotics (Wysowski and Baum, 1991; Mitler, 2000).

Due largely to the traditional association of sedating drugs with problems of abuse and dependence, the widespread use of benzodiazepines has been a source of concern (Woods *et al.*, 1988). Epidemiological data do not support such concerns, but

instead suggest that the non-medical or recreational use of benzodiazepines is rare in the general population, with most use of these drugs being appropriate (for a review, see Woods *et al.*, 1992).

While the benzodiazepines are safer and have less abuse potential than their predecessors, the barbiturates, they produce a myriad of untoward effects (for a review, see Woods *et al.*, 1992). Most notably, the benzodiazepines impair various aspects of human performance in patients suffering from sleep disturbances as well as healthy individuals. Acute doses of benzodiazepines have consistently been shown to dose-dependently impair performance in healthy individuals (van der Kroef, 1979; Morris and Estes, 1987; Huff and Plunkett, 1989). Understanding the performance-impairing effects of these benzodiazepines in healthy individuals is important because these individuals often use these compounds to manage transient sleep difficulties, such as promotion of sleep during extended travel or to manage insomnia in rotating shift work (Walsh *et al.*, 1984; Roehrs *et al.*, 1990).

Concerns remain regarding differences in behavioural impairment profiles among available benzodiazepines, and some investigators have cited the need for the systematic study of differences between available benzodiazepines in terms of their amnesic effects, as well as impairment of learning and recall (Woods *et al.*, 1992; Roache *et al.*, 1993; Woods and Winger, 1995). Initial comparisons of triazolam and temazepam, for example, found greater and more frequent impairment in learning,

memory, recall and performance by triazolam than temazepam (Bixler *et al.*, 1987; Greenblatt *et al.*, 1989; Bixler *et al.*, 1991; Wysowski and Baum, 1991). However, these early studies were limited in several ways, including reliance on single-doses of triazolam and temazepam, use of relatively higher doses of triazolam than temazepam and limited assessment of performance-impairing effects. Subsequent studies found the performance-impairing effects of these drugs to be comparable in magnitude (Rush *et al.*, 1993a; Rush and Griffiths, 1996). These more recent studies used double-blind, placebo-controlled designs to characterize the dose–response functions derived from the clinically recommended doses of triazolam (i.e. 0.25 mg) and temazepam (i.e. 30 mg) (Physician's Desk Reference, 2000). These more recent studies also used more comprehensive batteries to assess performance impairment, including measures of psychomotor impairment (e.g. balance, circular lights) and impairment of recall and recognition (e.g. Digit-Symbol Substitution, Digit-Enter and Recall, Repeated Acquisition). When clinically equivalent doses of triazolam (0.125, 0.25 and 0.5 mg) and temazepam (15, 30 and 60 mg) were evaluated, comparable impairment profiles were observed across the dose–response curve. There were no significant differences in the absolute magnitude of the peak effects produced by triazolam and temazepam (Rush *et al.*, 1993a; Rush and Griffiths, 1996). These findings suggest that differences shown earlier in the behavioural impairment profiles of triazolam and temazepam were likely to be more representative of non-equivalent dose comparisons, rather than of inherent differences in compounds (Rush and Griffiths, 1996). However, whether triazolam and temazepam might differ under other conditions, for example, in combination with ethanol, is unknown.

The purpose of the present study was to investigate the behavioural effects of triazolam and temazepam, alone and in combination with ethanol. Triazolam and temazepam were chosen for this comparison because both are widely used benzodiazepine hypnotics whose impairing effects are increased with concurrent use of ethanol (Kuitunen *et al.*, 1990; Lehmann and Lilienberg, 1991; Kunsman *et al.*, 1992; Kuitunen, 1994). We chose to study these drugs in combination with ethanol because the combined use of anxiolytics (e.g. benzodiazepines) and ethanol is widespread and well-documented (Grant and Harford, 1990), and benzodiazepines are often prescribed without adequate information concerning the patient's ethanol use (Graham *et al.*, 1992). To our knowledge, no controlled studies have directly compared the behavioural impairment profiles of triazolam–ethanol and temazepam–ethanol combinations within a single-study sample. Comparing the effects of triazolam–ethanol and temazepam–ethanol combinations across studies is not possible because the effects of comparable doses of triazolam and temazepam have not been assessed in combination with the same dose of ethanol.

In the present study, we assessed the acute performance-impairing and participant-rated effects of 10 drug–ethanol combinations that included a moderate dose of ethanol (i.e. 0.5 g/kg, the equivalent to two to three standard drinks) and clinically equivalent doses of triazolam (i.e. 0.125 and 0.25 mg) and temazepam (15 and 30 mg). The acute performance-impairing and participant-rated effects of triazolam and temazepam, alone and in combination with ethanol, were assessed in non-drug-abusing volunteers using a within-subject, double-blind, double-dummy, placebo-controlled cross-over design. Drug effects were assessed using a battery of subject-rated, behavioural and observer-rated measures that have

previously been shown to be sensitive to the effects of ethanol and benzodiazepines in non-drug-abusing volunteers (Kirk *et al.*, 1990; Roache *et al.*, 1993; Rush *et al.*, 1993b; Rush and Griffiths, 1997; Rush and Ali, 1999).

## Methods

### Volunteers

Ten healthy adult volunteers (five males and five females) were recruited via newspaper advertisements, flyers and word-of-mouth and were paid (US\$30 per session) to participate in the experiment. Medical history, physical examinations, laboratory blood chemistry tests and electrocardiograms indicated that all volunteers were in good health with no contraindications to ethanol or study medications. All potential volunteers were interviewed by a psychiatrist, and individuals with current or past histories of serious psychiatric disorder, except nicotine dependence, were excluded. Potential volunteers with current or past history of drug or ethanol abuse or dependence were excluded from study participation. Drug urine screens conducted during initial screening were negative for amphetamine, benzodiazepines, barbiturates, cocaine and opioids (ONTRAK Abusscreens, Roche Diagnostic Systems, Nutley, NJ), USA. In the female volunteers, human chorionic gonadotropin urine pregnancy tests before and periodically during study participation were negative (Abbott TestPack+ Plus, Abbott Laboratories, Abbott Park, IL, USA). This study was approved by the Institutional Review Board of the University of Mississippi Medical Center, and volunteers gave their written informed consent prior to participating.

Volunteers were aged between 25 and 50 years (mean 36 years) and weighed between 65 and 90 kg (mean 80 kg). Volunteers reported consuming between one and 20 ethanol-containing beverages per week (mean 9) and between 21 and 476 mg of caffeine per day (mean 181 mg). Five volunteers reported smoking between five and 30 tobacco cigarettes per day (mean 19). These volunteers were allowed to smoke *ad libitum* except while completing the computer tasks. Finally, volunteers reported between 12 and 20 years of education (mean 15 years).

### General procedures

Volunteers participated as outpatients at the Laboratory of Human Behavioral Pharmacology at the University of Mississippi Medical Center Monday through Friday. Data reported in the present manuscript are from 10 experimental sessions. Volunteers also completed an additional five experimental sessions in which triazolam, temazepam and placebo were combined with a higher dose of ethanol (1.0 g/kg). Data from these additional experimental sessions are not reported because several volunteers were unable to tolerate this dose of ethanol (i.e. volunteers vomited either during or shortly after the administration of ethanol). Data from the 10 experimental sessions reported herein represent those sessions in which the drug conditions were tested in combination with either the placebo beverage or the moderate dose of ethanol (0.5 g/kg).

Volunteers were instructed that during their participation they could receive various drugs including placebo, various sedatives, muscle relaxants, antihypertensives, anxiolytics, stimulants and weight loss medications, antidepressants and antihistamines, alone and in combination with alcohol. Other than receiving this general

information, volunteers were blind to the type of drug administered. Volunteers were told that the purpose of the study was to see how different drugs affect mood and behaviour. Other than this general explanation of purpose, volunteers were given no instruction of what they were 'supposed' to do or of what outcomes might be expected.

Volunteers were requested to refrain from using all psychoactive drugs (with the exception of tobacco and caffeinated products) throughout the entirety of the study. Volunteers were requested to refrain from caffeine and solid food for 4 h prior to a scheduled experimental session and to refrain from ethanol for 12 h prior to a scheduled experimental session day. On each experimental session day, volunteers arrived at the laboratory at approximately 08.00 h and were provided a light breakfast with a decaffeinated beverage between 08.00 h and 08.30 h. Urine samples were screened on a random unannounced basis for the use of amphetamines, barbiturates, benzodiazepines, cocaine and opioids outside the laboratory. Each volunteer's urine sample was screened 3–8 times (mean 6). All urine specimens were negative for amphetamines, barbiturates, cocaine and opioids, which indicated that volunteers had complied with our requests. Urine specimens were occasionally positive for benzodiazepines, which likely was due to the administration of the study medications. Volunteers also provided an expired air specimen that was assayed for the presence of ethanol using an Alco-Sensor hand-held breathalyser (Intoximeters, Inc., St Louis, MO, USA). None of the expired air specimens were positive for ethanol.

On experimental session days, volunteers completed the subject-rated questionnaires and performance tasks at approximately 08.30 h, ingested capsules at approximately 09.00 h, ingested ethanol- or water-containing drinks between 09.00 h and 09.30 h, and completed the subject-rated questionnaires and performance tasks periodically after ethanol/placebo drink administration for 5 h. A light lunch with a decaffeinated beverage was provided after the volunteer completed the behavioural tasks and subject-rated questionnaires at the 3-h observation (i.e. approximately 12.45 h). A minimum of 24 h separated all drug administrations.

Prior to their release from the experimental session, all volunteers were required to return to pre-drug performance levels on a field sobriety task, the experimental performance measures, and to have a breath-alcohol level of less than 0.02 g/dl. Volunteers were not allowed to drive to or from the experimental sessions. Volunteers were instructed to refrain from driving or engaging in risky activities for a minimum of 6 h following their release from the laboratory. All driving and risky activities restrictions and session release requirements were described clearly in the informed consent document signed by the volunteer.

### Performance measures

All behavioural tasks, except balance, circular lights, and picture recall and recognition, were administered on an Apple Macintosh microcomputer (Apple Computer, Inc., Cupertino, CA). Unless otherwise noted, all tasks were completed in fixed order approximately 60 min before drug administration and 0, 0.5, 1, 1.5, 2, 2.5, 3, 4 and 5 h following ethanol/placebo drink administration.

### Digit-Symbol Substitution Test (DSST)

The DSST is a widely used measure of performance impairment

that is sensitive to the effects of benzodiazepines (Stone, 1984; Evans *et al.*, 1990; Rush *et al.*, 1999). This was a computerized version of the DSST in which the volunteer used a numeric keypad to enter a geometric pattern associated with one of nine digits displayed on a video screen (McLeod *et al.*, 1982). At each administration, the sequences of geometric patterns were randomly determined by the computer program. Volunteers had 90 s to enter as many geometric patterns as possible. The dependent measure was the number of geometric patterns the volunteer was able to enter correctly (i.e. trials correct).

### Digit-enter and recall

This task was a modified version of the number recall task described previously (Roache and Griffiths, 1985). Volunteers used a numeric keypad to reproduce randomly selected eight-digit numbers which were displayed on the computer screen one at a time. The task consisted of two components, an enter component in which volunteers copied (i.e. entered) the eight-digit number while it was displayed on the screen, and a second component in which the volunteer recalled the eight-digit number from memory after it disappeared from the screen. At the beginning of each trial, an eight-digit number appeared on the computer screen. If the volunteer entered the number incorrectly into the computer, the trial was discontinued, and a different eight-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 volunteer was required to recall the number (i.e. re-enter the eight-digit number using the numeric keypad). The task continued until the volunteer had correctly entered 10 eight-digit numbers in the first component (i.e. 10 trials were initiated) or 25 incorrect attempts were made. The dependent measure was the total number of eight-digit numbers correctly reproduced in the second (recall) component out of a maximum possible 10.

### Repeated Acquisition

This was a modified version of the Repeated Acquisition procedure, which has been shown to be sensitive to the performance impairing effects of benzodiazepines (Higgins *et al.*, 1987; Kelly *et al.*, 1997). The task has been described in detail previously (Rush and Griffiths, 1996). Briefly, volunteers used a computer mouse to point to and click on three buttons (i.e. Left, Centre, Right) on the computer screen. Volunteers were required to click on the buttons in a novel predetermined sequence (e.g. Centre, Left, Right, Left, Right, Centre, Left, Right, Centre, Left) as the numbers 1–10 appeared sequentially in the centre of the video screen. Incorrect responses produced a 2-s time-out but did not reset the sequence. Volunteers were exposed to a novel, computer-generated 10-response sequence each time they performed the task, which was 10 times each experimental session. The task continued until the volunteer had completed the novel sequence 20 times or 300 s elapsed, whichever occurred first. The dependent measure was percentage errors, which was calculated by dividing the total number of errors by the total number of responses and multiplying by 100.

### Picture recall and recognition

This task was a modified version of the Delayed Recognition Task, which has been described previously (Roache and Griffiths, 1985),

and has been shown to be sensitive to the impairing effects of benzodiazepines (Rush *et al.*, 1999). Approximately 1 h after drug administration, volunteers were given 90 s to study a card with 18 pictures. After a 90-s delay, the volunteer was instructed to return the card and to write down as many names of the pictures as he or she could remember (immediate recall). Approximately 5 h after drug administration, volunteers were tested for both delayed recall and delayed recognition of the pictures presented 4 h previously. Volunteers were first asked to write down the names of as many of the pictures as they could remember. Volunteers then were presented with a chart containing 198 pictures and were asked to identify the 18 pictures that they had been shown 4 h previously. The maximum possible score for each recall or recognition test was 18.

### *Circular lights*

The circular lights task is a widely used measure of psychomotor performance impairment. This task has been previously described (Griffiths *et al.*, 1983) and involved rapid hand-eye coordinated movements in which volunteers pressed a series of 16 buttons (circularly arranged around a 54 cm diameter) as rapidly as possible in response to the randomly sequenced illumination of their associated lights. Required response sequences were randomly pre-determined electronically for each trial. The dependent measure was the number of correct button presses during a 60-s trial.

### *Balance task*

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

### **Subject-rated and observer-rated measures**

All subject- and observer-rated measures were obtained on an Apple Macintosh microcomputer, and the volunteer or observer used a computer mouse to point to and select among the various response options displayed on the screen. Unless otherwise stated, all measures were completed approximately 1 h before drug administration, and 0, 0.5, 1, 1.5, 2, 2.5, 3, 4 and 5 h following ethanol/placebo drink administration. These questionnaires were completed in fixed-order corresponding to the order in which they are described below.

### *Profile of Mood States (POMS)*

The POMS Questionnaire, a 65-item, adjective-rating scale, is considered to be a standardized mood-state inventory (McNair *et al.*, 1971) and has been shown to have excellent discriminant and convergent validity in general population samples (Nyenhuis *et al.*, 1999). On the POMS, individual adjectives were presented sequentially, one at a time. Volunteers were instructed to rate each adjective on the basis of how they felt at the present time on a scale with five response options: 'Not at all', 'A little bit', 'Moderately', 'Quite a bit' and 'Very much' (scored numerically from 0 to 4, respectively). From the 65 items, eight factors were determined: Anger–Hostility; Confusion–Bewilderment; Depression–Dejection; Fatigue; Friendly; Tension–Anxiety; Vigor; and Total-mood disturbance.

### *Addiction Research Center Inventory (ARCI)*

The ARCI is an empirically derived self-report questionnaire that is sensitive to different classes of abused drugs (Haertzen, 1974). 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).

### *Subject-rated drug-effect questionnaire*

This questionnaire consisted of 34 100-mm visual-analog scales that were presented on the computer screen, one at a time. Volunteers were instructed to rate each item on the basis of how they felt at the present time. Each visual-analog scale was anchored at the left-most extreme with 'Not at all' and at the right-most extreme with 'An awful lot'. The items rated were: 'Drug effect', 'Bad effects', 'Good effects', 'High', 'Like drug', 'Alert-energetic', 'Drunk', 'Vigorous', 'Elated', 'Friendly', 'Drowsy', 'Stimulated', 'Confused', 'Restless', 'Jittery', 'Nervous', 'Carefree', 'Relaxed', 'Able to concentrate', 'Fidgety', 'Hungry', 'Dizzy/light-headed', 'Itchy skin', 'Tired', 'Excited', 'Motivated', 'Sweaty', 'Thirsty', 'Stomach turning', 'Sleepy', 'Happy', 'Good mood', 'Need or desire to talk' and 'Performance impaired'.

### *End-of-day questionnaire*

Approximately 5 h after ethanol/placebo drink administration, volunteers completed an end-of-day questionnaire. The end-of-day questionnaire asked volunteers to rate the overall effect of the drug they had received. The end-of-day questionnaire consisted of five items: (1) rate the overall STRENGTH of today's drug effect; (2) rate your overall LIKING of today's drug effect; (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 visual-analog scale identical to those described above.

### *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 volunteer completed the visual-analog scales. The items rated were: (1) estimate the strength of DRUG EFFECT you think the subject is experiencing; (2) is the subject CONFUSED/DISORIENTED?; (3) is the subject's POSTURE IMPAIRED?; (4) is the subject SEDATED?; (5) is the subject's SPEECH SLURRED?; and (6) is the subject STIMULATED? These items were rated using a visual-analog scale identical to those described above. The observer also estimated the time in minutes that the volunteer spent sleeping during the previous assessment period. The observer was instructed to base her ratings on observation of the volunteer's gross behaviour rather than on the volunteer's verbal reports or ratings.

### **Breath-alcohol, heart rate and blood pressure**

Breath-alcohol levels were recorded approximately 60 min before drug administration, and 0, 0.5, 1, 1.5, 2, 2.5, 3, 4 and 5 h

following ethanol/placebo drink administration using a handheld breathalyser (Intoximeters, Inc.). Heart rate and blood pressure were recorded at these same times using a Vital-Check (Model 4200) automated blood-pressure cuff (IVAC corporation, San Diego, CA, USA).

### Drug administration

Ten drug-ethanol conditions were studied in the present experiment: (1) placebo ethanol plus placebo drug; (2) 0.5 g/kg ethanol plus placebo drug; (3) placebo ethanol plus 0.125 mg triazolam; (4) 0.5 g/kg ethanol plus 0.125 mg triazolam; (5) placebo ethanol plus 0.25 mg triazolam; (6) 0.5 g/kg ethanol plus 0.25 mg triazolam; (7) placebo ethanol plus 15 mg temazepam; (8) 0.5 g/kg ethanol plus 15 mg temazepam; (9) placebo ethanol plus 30 mg temazepam; and (10) 0.5 g/kg ethanol plus 30 mg temazepam. Each volunteer received all 10 possible ethanol-drug combinations in random order. Volunteers received capsules and drinks during each session to maintain volunteer and staff blindness as to whether the drugs and ethanol were being administered alone or in combination.

References below to placebo pertain to sessions in which placebo doses of both ethanol and drug (i.e. triazolam or temazepam) were administered. References to ethanol alone pertain to sessions in which an active dose of ethanol was administered in combination with placebo drug. References to triazolam or temazepam alone pertain to sessions in which an active dose of drug was administered in combination with the placebo dose of ethanol.

### Ethanol

The ethanol dose conditions were 0 and 0.5 g/kg of absolute (95%) ethanol. Fruit juice was added to both drinks (0 and 0.5 g/kg) at a ratio of five parts juice per one part ethanol dose. Tap water was used to equate the total volume of the 0 and 0.5 g/kg ethanol drinks. One milliliter of ethanol was floated on the surface of all drinks in an attempt to maintain volunteer and staff blindness. Volunteers consumed six equal volume drinks over a 30-min period (i.e. one drink every 5 min).

### Triazolam and temazepam

The drug conditions were triazolam (0.125 and 0.25 mg), temazepam (15 and 30 mg) and placebo. Triazolam and temazepam doses were prepared by over-encapsulating commercially available 0.125 and 15 mg tablets/capsules, respectively, in a size 00 capsule (Pharmacia-UpJohn Co., Kalamazoo, MI, USA; Sandoz Pharmaceutical Corporation, East Hanover, NJ, USA, respectively). Lactose was used to fill the remainder of all the capsules. Placebo capsules contained only lactose. During each experimental session, volunteers ingested two capsules. Administering the appropriate number of drug- or placebo-containing capsules varied dose. Capsules were taken orally with approximately 150 ml of water immediately before beginning to consume the ethanol- or water-containing drinks.

### Statistical analysis

Analyses were conducted on raw scores. For all statistical analyses,  $p < 0.05$  was considered statistically significant. All statistical analyses were conducted using StatView (SAS Institute Inc., Cary, NC, USA). Because the absorption rates of triazolam and

temazepam often differ within and across individuals, peak-effect data (i.e. the post-drug value representing the greatest change from the pre-drug value for each volunteer) were calculated to allow for comparison of drug effects separate from drug kinetics. Peak effect data were analysed with one-factor repeated measure ANOVA with Dose Condition (placebo and the nine drug-combination conditions) as the factor. If Dose Condition produced a statistically significant effect, the mean square error term was used to conduct Fisher's protected least significant difference (PLSD) post-hoc test to compare each of the nine drug-ethanol conditions to the placebo condition. Corresponding drug-ethanol conditions (e.g. placebo ethanol plus 0.25 mg triazolam versus placebo-ethanol plus 30 mg temazepam; 0.5 g/kg ethanol plus 0.25 mg triazolam versus 0.5 g/kg ethanol plus 30 mg temazepam) were also compared using Fisher's PLSD post-hoc test when appropriate. Data from the end-of-day questionnaire were analysed in the same fashion as peak-effect data.

Time-course data were analysed by repeated measures ANOVA with Dose Condition (placebo and the nine drug-ethanol combination conditions) and Time (pre-drug, 0, 1, 2, 3, 4 and 5 h after ethanol administration) as factors. If the Dose Condition-Time interaction attained statistical significance, the mean square error term was used to conduct Fisher's Protected LSD post-hoc test comparing placebo with each of the dose conditions at each post-drug time point.

## Results

### Performance measures

#### Balance

Balance was significantly impaired relative to placebo following the administration of 0.5 g/kg ethanol plus 0.25 mg triazolam, and 0.5 g/kg ethanol plus 15 mg temazepam (Table 1). None of the corresponding triazolam-ethanol and temazepam-ethanol conditions differed significantly.

#### Circular lights

Circular lights performance was significantly impaired relative to placebo following the administration of 0.25 mg triazolam alone, 0.5 g/kg ethanol plus 0.25 mg triazolam, 0.5 g/kg ethanol plus 15 mg temazepam and 0.5 g/kg ethanol plus 30 mg temazepam (Table 1). None of the corresponding triazolam-ethanol and temazepam-ethanol conditions differed significantly.

#### Digit-enter and recall

Performance on the digit-enter and recall task was significantly impaired relative to placebo following the administration of 0.5 g/kg ethanol plus 30 mg temazepam (Table 1). None of the corresponding triazolam-ethanol and temazepam-ethanol conditions differed significantly.

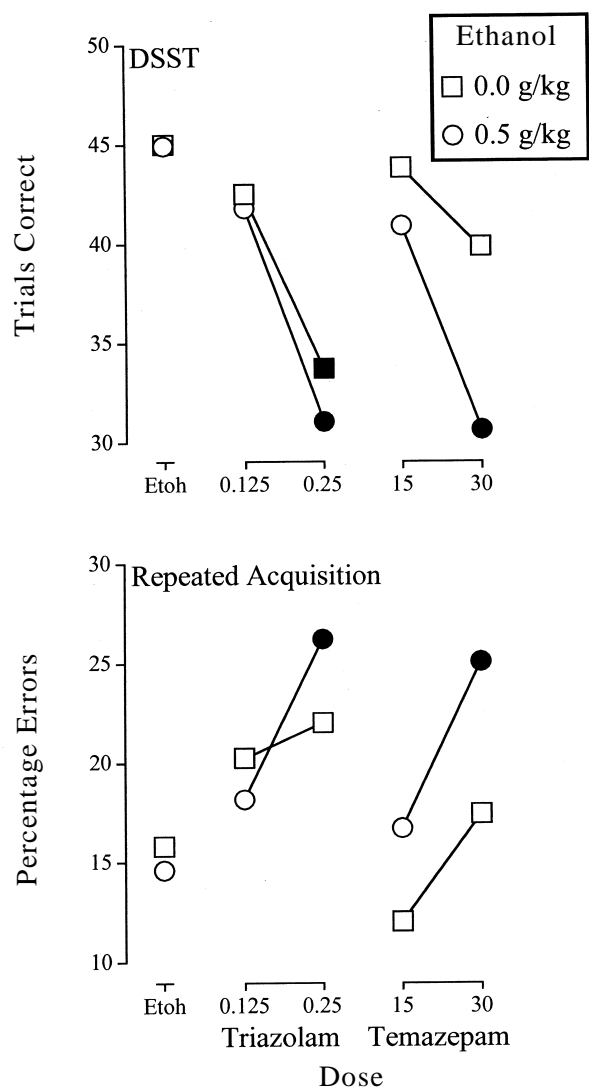
#### DSST

Performance on the DSST was significantly impaired relative to placebo following the administration of 0.25 mg triazolam alone, 0.5 g/kg ethanol plus 0.25 mg triazolam and 0.5 g/kg ethanol plus 30 mg temazepam (Table 1 and Fig. 1). None of the corresponding triazolam-ethanol and temazepam-ethanol conditions differed significantly.

**Table 1.** Summary of means for the 10 ethanol-drug conditions. Summary statistics are not included for a particular measure if the initial one-way ANOVA that included all 10 dose conditions failed to reveal a significant effect of Dose Condition. The two rightmost columns show the F values obtained from the one-way ANOVA and values for Fisher's Protected Least Different post-hoc test. An asterisk indicates that the value differed significantly from the placebo-placebo condition

	Ethanol (0 g/kg) Plus					Ethanol (0.5 g/kg) Plus					F(9,81)	Fisher's PLSD
	Placebo	Triazolam (0.125 mg)	Triazolam (0.25 mg)	Temazepam (15 mg)	Temazepam (30 mg)	Placebo	Triazolam (0.125 mg)	Triazolam (0.25 mg)	Temazepam (15 mg)	Temazepam (30 mg)		
Performance measures												
Balance	13.4	9.5	11.2	12.0	9.9	15.7	10.9	7.5*	8.9*	9.9	2.3	4.4
Circular lights	109.7	106.7	96.6*	104.7	101.3	106.3	101.7	88.3*	96.5*	91.6	3.9	9.9
Digit-enter-and-recall	5.2	5.9	4.0	4.6	4.5	5.1	4.9	4.2	4.2	3.5*	2.4	1.3
DSST	45.0	42.5	33.7*	43.8	39.8	44.9	41.8	31*	40.9	30.6*	5.3	6.8
Repeated acquisition	15.8	20.2	22.0	12.0	17.4	14.6	18.1	26.2*	16.7	25.1*	2.9	7.6
ARCI												
LSD	3.9	3.5	5.3*	3.7	5.0	4.7	4.9	5.5*	5.2	5.7*	2.6	1.4
Subject-rated												
Drug-effect questionnaire												
Bad effects	14.0	16.5	25.0	13.8	16.7	17.7	27.2	37.3*	27.7	26.1	2.4	13.9
Drug effect	22.6	21.3	43.7*	30.4	26.1	38.2	34.7	48.3*	37.4	38.5*	2.5	15.8
Drunk	3.6	5.7	10.6	11.8	23.3*	26.5*	34.5*	48*	30.1*	36.5*	5.4	17.9
Good effects	26.2	36.2	41.3*	41.5*	27.3	35.4	31.1	55.3*	43.7*	39.2	3.1	13.8
High	12.3	17.7	41.8*	26.7	29.4	38.3*	40.8*	54.9*	38.5*	35.1*	4.0	17.6
Nervous	5.0	3.7	24.3*	6.6	18.1	17.3	29.1*	24.2*	13.9	20.9*	2.8	14.9
Performance impaired	19.6	24.1	24.3	22.1	34.9	33.4	34.3	49.3*	25.5	40.9*	2.5	16.9
Restless	22.1	7.6	26.1	12.4	16.8	27.7	32.3	32.7	23.2	27.9	2.4	15.2
Stomach turning	12.8	12.2	13.4	4.0	28.7*	16.2	38*	35.8*	19.1	17.3	3.8	15.8
Observer-rated												
Drug-effect questionnaire												
Drug-effect	8.1	8.4	11.4	18.9*	9.4	15.2*	17.8*	18.1*	10.2	13.6	2.9	6.9
End-of-day questionnaire												
Drug strength	6.0	10.3	34.7*	26.6*	28.1*	22.2	26.7*	43.6*	31.6*	32.6*	2.9	18.5
Physiological measures												
Breath-alcohol level	0.0	0.0	0.0	1.0	1.0	33*	38*	34*	32*	30*	71.3	5.8

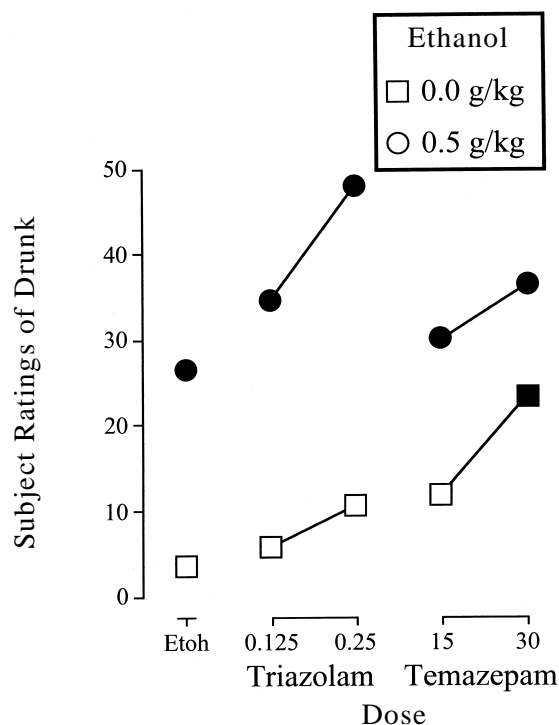
\*Denotes value significantly different from placebo



**Figure 1** Peak-effect data for trials correct on the DSST and percentage errors on the Repeated Acquisition procedure. *x*-axis: Dose: Data points above Etoh represent values when the doses of ethanol were administered in combination with placebo drug. Connected data points above 0.125 and 0.25 represent the effects of the two active doses of triazolam administered in combination with 0.0 g/kg (squares) or 0.5 g/kg (circles) ethanol. Connected data points above 15 and 30 represent the effects of the two active doses of temazepam administered in combination with 0.0 g/kg (squares) or 0.5 g/kg (circles) ethanol. Data points show means of 10 volunteers. Filled symbols indicate those values which are significantly different from the placebo-ethanol/placebo-drug condition (i.e. squares above Etoh) ( $p < 0.05$ , Fisher's PLSD post-hoc test)

#### Repeated Acquisition procedure

Performance on the Repeated Acquisition procedure was significantly impaired relative to placebo following the administration of 0.5 g/kg ethanol plus 0.25 mg triazolam and 0.5 g/kg ethanol plus 30 mg temazepam (Table 1 and Fig. 1). These dose conditions did not differ significantly.



**Figure 2** Peak-effect data for volunteer ratings of Drunk from the Subject-Rated Drug-Effect Questionnaire. *x*-axis: Dose: Data points above Etoh represent values when the doses of ethanol were administered in combination with placebo drug. Connected data points above 0.125 and 0.25 represent the effects of the two active doses of triazolam administered in combination with 0.0 g/kg (squares) or 0.5 g/kg (circles) ethanol. Connected data points above 15 and 30 represent the effects of the two active doses of temazepam administered in combination with 0.0 g/kg (squares) or 0.5 g/kg (circles) ethanol. Data points show means of 10 volunteers. Filled symbols indicate those values which are significantly different from the placebo-ethanol/placebo-drug condition (i.e. squares above Etoh) ( $p < 0.05$ , Fisher's PLSD post-hoc test)

#### Picture recall and recognition

There were no significant effects on the picture recall and recognition task.

#### Subject-rated and observer-rated drug-effect questionnaires

##### ARCI

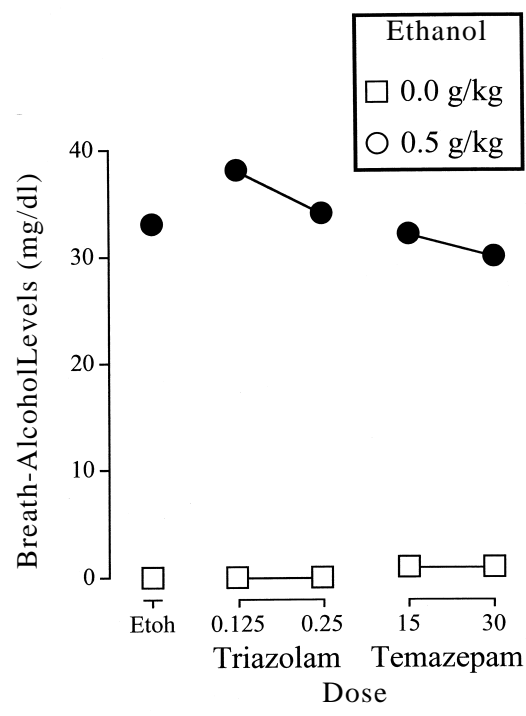
Scores on the LSD scale of the ARCI were significantly increased relative to placebo following the administration of 0.25 mg triazolam alone, 0.5 g/kg ethanol plus 0.25 mg triazolam and 0.5 g/kg ethanol plus 30 mg temazepam (Table 1). The corresponding triazolam-ethanol and temazepam-ethanol conditions did not differ significantly. There were no other significant effects on the ARCI.

##### POMS

There were no other significant effects on the eight factors from the POMS.

##### Subject-rated drug-effect questionnaire

A significant effect of Dose Condition was observed on nine items on the subject-rated drug-effect questionnaire: Bad effects, Drug



**Figure 3** Peak-effect data for Breath Alcohol Levels. x-axis: Dose: Data points above EtOH represent values when the doses of ethanol were administered in combination with placebo drug. Connected data points above 0.125 and 0.25 represent the effects of the two active doses of triazolam administered in combination with 0.0 g/kg (squares) or 0.5 g/kg (circles) ethanol. Connected data points above 15 and 30 represent the effects of the two active doses of temazepam administered in combination with 0.0 g/kg (squares) or 0.5 g/kg (circles) ethanol. Data points show means of 10 volunteers. Filled symbols indicate those values which are significantly different from the placebo-ethanol/placebo-drug condition (i.e. squares above EtOH) ( $p < 0.05$ , Fisher's PLSD post-hoc test)

effect, Drunk, Good effects, High, Nervous, Performance impaired, Restless and Stomach turning (Table 1). In each instance, except for ratings of Restless, at least one of the ethanol-drug conditions increased ratings significantly above levels observed with placebo (Table 1). Figure 2 shows peak-effects for ethanol, triazolam and temazepam alone, and triazolam-ethanol and temazepam-ethanol combinations for volunteer ratings of Drunk. This figure shows that ratings of Drunk were significantly increased relative to placebo following the administration 0.5 g/kg ethanol alone, 30 mg temazepam alone, 0.5 g/kg ethanol plus 0.125 mg triazolam, 0.5 g/kg ethanol plus 0.25 mg triazolam, 0.5 g/kg ethanol plus 0.25 mg triazolam, 0.5 g/kg ethanol plus 15 mg temazepam and 0.5 g/kg ethanol plus 30 mg temazepam.

#### End-of-day questionnaire

Relative to placebo, ratings of Drug Strength were increased significantly following the administration of 0.25 mg triazolam alone, 15 mg temazepam alone, 30 mg temazepam alone, 0.5 g/kg ethanol plus 0.125 mg triazolam, 0.5 g/kg ethanol plus 0.25 mg triazolam, 0.5 g/kg ethanol plus 15 mg temazepam, and 0.5 g/kg ethanol plus 30 mg temazepam (Table 1). There were no significant differences between corresponding conditions.

#### Observer-rated drug-effect questionnaire

Relative to placebo, observer ratings of Drug Effect were significantly increased following the administration of 0.5 g/kg alone, 0.5 g/kg ethanol plus 0.125 mg triazolam and 0.5 g/kg ethanol plus 0.25 mg triazolam.

#### Breath-alcohol, heart rate and blood pressure

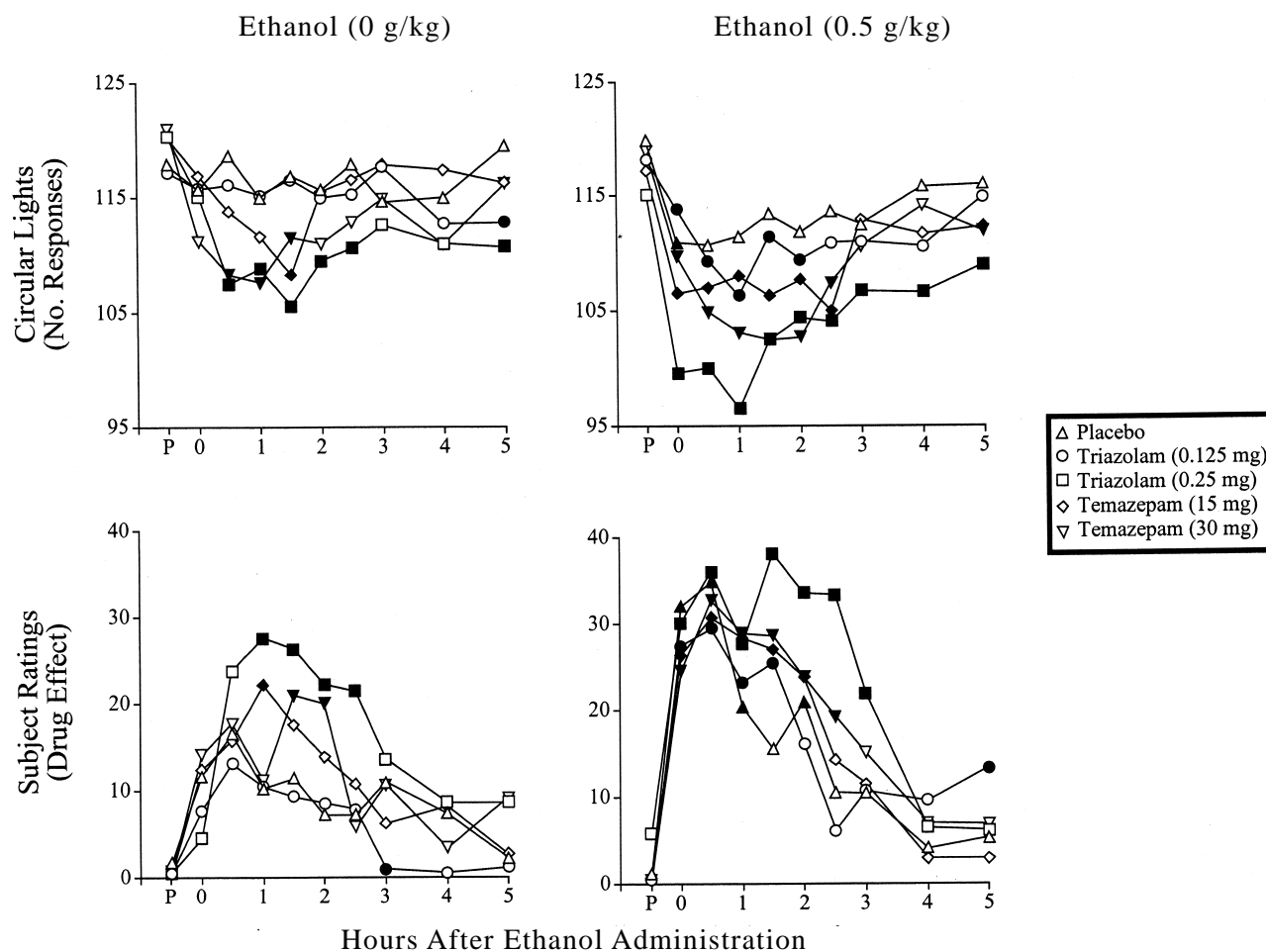
Breath-alcohol levels were significantly increased relative to placebo following the administration of 0.5 g/kg ethanol alone, 0.5 g/kg ethanol plus 0.125 mg triazolam, 0.5 g/kg ethanol plus 0.25 mg triazolam, 0.5 g/kg ethanol plus 15 mg temazepam and 0.5 g/kg ethanol plus 30 mg temazepam (Table 1 and Fig. 3). Breath alcohol levels were significantly higher following the administration of 0.5 g/kg ethanol plus 0.125 mg triazolam than following the administration of 0.5 g/kg ethanol plus 15 mg temazepam. There were no other significant differences between corresponding triazolam-ethanol and temazepam-ethanol conditions. There were no significant effects on heart rate or blood pressure.

#### Time-course

Figure 4 shows time-course functions for ethanol, triazolam and temazepam alone and triazolam-ethanol and temazepam-ethanol combinations for two representative measures: number of responses on the circular lights task and subject-rated drug effect. Two-factor repeated measure ANOVA revealed a significant interaction of Dose Condition and Time on both of these measures [ $F(81,729) = 1.3$  and  $1.6$ , respectively,  $p < 0.04$ ]. Ethanol alone impaired performance on the circular lights task and increased volunteer ratings of drug effect (Fig. 4). Triazolam and temazepam alone also impaired performance on the circular lights task and increased subject ratings of drug effect (Fig. 4). The effects of ethanol, triazolam and temazepam alone were generally evident from 0 to 3 h after the administration of ethanol. Combining triazolam or temazepam with ethanol generally produced greater performance impairment and subject ratings than observed with placebo or the drugs alone, but did not alter the time-course functions of the drugs (Fig. 4).

## Discussion

Combined use of anxiolytics (e.g. benzodiazepines) and ethanol is widespread and well documented (Grant and Harford, 1990). Benzodiazepines often are prescribed without adequate information concerning the patient's ethanol use (Graham *et al.*, 1992). Use of ethanol to facilitate sleep is not uncommon for members of the general population with transient sleep difficulties or for those with clinically significant chronic sleep disturbance (National Sleep Foundation/Gallup Organization, 1995; Johnson *et al.*, 1998; Ancol-Israel and Roth, 1999). To further characterize the effects of combined benzodiazepine and ethanol use, the present study examined the performance-impairing and subject-rated effects of ethanol, triazolam and temazepam alone and triazolam-ethanol and temazepam-ethanol combinations. The doses of triazolam and temazepam administered in the present study were consistent with those commonly used in clinical practice (e.g. Physician's Desk Reference, 2000). The dose of ethanol tested was comparable to amounts that might be consumed



**Figure 4** Time-course functions and dose effects for placebo, triazolam (0.125 and 0.25 mg) and temazepam (15 and 30 mg) in combination with the placebo (left column) and 0.5 g/kg (right column) dose of ethanol for number of responses on the circular lights task and subject-rated drug effect. x-axis: Time after the completion of ethanol administration (h); P indicates pre-drug. Referring to time after ingesting triazolam or temazepam, 0.5 h should be added to each time point. Data points show means of 10 subjects. Filled symbols indicate those values which are significantly different from the corresponding time-points from the placebo-ethanol/placebo-drug condition value (i.e. triangles in left-column panels) ( $p < 0.05$ , Fisher's PLSD post-hoc tests)

as a soporific (i.e. two to three standard drinks). Administered alone, the moderate dose of ethanol tested in the present experiment caused little performance impairment and produced only a few, prototypical subject-rated drug effects. When tested alone, triazolam and temazepam produced some performance impairment, and these effects were generally limited to the higher doses. Triazolam and temazepam alone produced a few sedative-like subject-rated drug effects. Combining either triazolam or temazepam with ethanol produced significant performance impairment. The subject-rated effects of the triazolam-ethanol and temazepam-ethanol combinations also were greater than those observed with the constituent drugs alone. Below, we discuss these findings in terms of the effects of ethanol alone, triazolam and temazepam alone and the effects of the ethanol-drug combinations.

#### Ethanol alone

The dose of ethanol used in the present study was moderate, corresponding to two to three standard drinks. The dose of ethanol tested in the present study is also consistent with the amounts of

reportedly used as a soporific (National Sleep Foundation/Gallup Organization, 1995; Johnson *et al.*, 1998; Ancol-Israel and Roth, 1999). The present study found that this dose of ethanol alone generally did not significantly impair performance, and produced only a few significant subject-rated drug effects. These findings are consistent with previous studies that used similar methods and volunteers (de Wit *et al.*, 1987; Heishman *et al.*, 1989; Higgins *et al.*, 1992, 1993; Rush *et al.*, 1993b; Rush and Griffiths, 1997).

#### Triazolam and temazepam alone

The doses of triazolam and temazepam tested alone generally did not significantly impair performance, and produced only a few significant subject-rated drug effects. The performance-impairing and subject-rated effects observed with triazolam and temazepam alone were comparable in magnitude. The findings of the present experiment are concordant with the results of previously published research that demonstrated comparable performance impairment and subject-rated drug effects using similar doses, methods and volunteers (Rush *et al.*, 1993a; Rush and Griffiths, 1996).

The present findings are discordant with several other previous studies that found that triazolam produced greater behavioural impairment than temazepam (Scharf *et al.*, 1988; Greenblatt *et al.*, 1989; Bixler *et al.*, 1991). The reason for the discrepancy is unknown, but may be due to the methods used in the previously published studies. Most notably, each of the studies tested only a single dose of each triazolam and temazepam, and relatively higher doses of triazolam may have been tested (Scharf *et al.*, 1988; Greenblatt *et al.*, 1989; Bixler *et al.*, 1991). Two of these studies compared 0.5 mg triazolam and 30 mg temazepam (Scharf *et al.*, 1988; Bixler *et al.*, 1991), while the third study compared 0.25 mg triazolam and 15 mg temazepam (Greenblatt *et al.*, 1989). The clinically recommended doses of triazolam and temazepam in non-geriatric patients is 0.25 and 30 mg, respectively (Physician's Desk Reference, 2000). The clinically recommended doses of triazolam and temazepam for geriatric patients is 0.125 and 15 mg, respectively (Physician's Desk Reference, 2000). Testing relatively higher doses of triazolam than temazepam obviously biases the outcome towards greater impairment with the former.

### Triazolam-ethanol and temazepam-ethanol combinations

The results of the present experiment are consistent with several previous studies that used similar methods to assess the combined effects of ethanol and a benzodiazepine (Linnoila *et al.*, 1990; Lehmann and Lilienberg, 1991; Kunsman *et al.*, 1992; Rush and Griffiths, 1997). Worth emphasizing is that the absolute magnitude of impairment observed with the triazolam-ethanol and temazepam-ethanol combinations was comparable. To the best of our knowledge, this is the first study to directly compare the behavioural effects of triazolam and temazepam in combination with ethanol. The findings of the present experiment are concordant with the results of previously published research that demonstrated comparable behavioural effects with triazolam and temazepam when equivalent doses were tested (Rush *et al.*, 1993a; Rush and Griffiths, 1996). The findings of the present experiment extend the results of these previously published reports by demonstrating comparable behavioural effects with triazolam and temazepam under a different set of experimental conditions. Future research should determine whether the performance-impairing effects of triazolam and temazepam, alone and in combination with ethanol, differ in special populations, such as the elderly.

Combining ethanol with either triazolam or temazepam resulted in greater performance impairment and larger magnitude subject-rated drug effects than those observed with the constituent drugs alone. The use of ethanol as a soporific by individuals with both transient and chronic sleep disturbance is well documented, with prevalence rates ranging from 7% to 28% across populations (National Sleep Foundation/Gallup Organization, 1995; Johnson *et al.*, 1998; Ancol-Israel and Roth, 1999). Similarly ethanol is often used in combination with over-the-counter sleep-enhancing drugs by individuals with chronic sleep disturbance (Johnson, 1997). While the percentage of individuals with sleep disturbances who combine ethanol with prescription hypnotics is unknown, the results of the present study underscore the importance of physician assessment of ethanol consumption in patients for whom they intend to prescribe hypnotic medications (Graham *et al.*, 1992). The findings of the present study suggest that even a moderate amount of ethanol in combination with a clinical dose of triazolam or temazepam can cause performance impairment that might diminish an individual's ability to respond to unexpected middle-of-the-night demands (e.g. child care, on-call responsibilities or smoke alarms).

zepam can cause performance impairment that might diminish an individual's ability to respond to unexpected middle-of-the-night demands (e.g. child care, on-call responsibilities or smoke alarms).

The present study employed a double-blind, double-dummy, placebo-controlled design in which the behavioural effects of varying doses of triazolam and temazepam, alone and in combination with a moderate dose of ethanol, were assessed at multiple time-points. However, certain caveats should be considered in the interpretation of these results. The present data represent 10 sessions of an original 15 sessions. Data for five of the original experimental sessions were omitted because several volunteers were unable to tolerate a higher dose of ethanol (i.e. 1.0 g/kg), alone and in combination with triazolam and temazepam. What effect the sessions involving the higher dose of ethanol, alone and in combination with triazolam or temazepam, might have had on responses to the placebo or moderate doses of ethanol, alone and in combination with triazolam or temazepam, is not known.

Finally, while triazolam and temazepam are commonly prescribed hypnotics, novel compounds, such as zolpidem and zaleplon, are now available for the treatment of sleep disorders. Relative to triazolam, both zolpidem and zaleplon have a unique benzodiazepine-receptor binding profile (Greenblatt *et al.*, 1998; Sanger *et al.*, 1999). To the best of our knowledge, there are no published studies that directly compare the behavioural effects of ethanol-zolpidem or ethanol-zaleplon combinations to those of an triazolam-ethanol or temazepam-ethanol combination. Whether the unique binding profile of zolpidem and zaleplon would result in differential effects when combined with ethanol is unknown. Future studies should compare the behavioural effects of these ethanol-drug combinations. Such studies might assist in identifying the safest available compound for the treatment of sleep disorders with patients that might consume ethanol concomitantly.

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