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# The Abuse Potential of Zolpidem Administered Alone and With Alcohol

CANDACE JEAVONS WILKINSON

*Southern California Research Institute, 11914 West Washington Blvd., Los Angeles, CA 90066*

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WILKINSON, C. J. *Abuse potential of zolpidem alone and with alcohol.* PHARMACOL BIOCHEM BEHAV **60**(1) 193–202, 1998.—The abuse potential of zolpidem, alone and in combination with alcohol, was examined in healthy volunteers with a history of social use of alcohol and drugs. Zolpidem, a short-acting imidazopyridine hypnotic with selectivity for a benzodiazepine receptor subtype ($BZ_1$ or $omega_1$), was administered double blind at 0, 10, or 15 mg with alcohol (0.75 g ethanol/kg b.wt.) or with placebo beverage in a randomized, six-way crossover design. Outcome measures included the Drug Effect Questionnaire (DEQ), the Addiction Research Center Inventory (ARCI-40), and the Profile of Mood States (POMS). Blood alcohol concentrations (BACs) were not significantly modified by zolpidem. Relative to placebo, zolpidem and alcohol significantly ($p < 0.05$) increased drug strength perception, drug-liking, and drug-disliking scores on the DEQ. On the ARCI-40, zolpidem and alcohol significantly increased sedation/intoxication and dysphoria/fear scores, but did not significantly change euphoria/well-being scores. Zolpidem and alcohol were rated more unfavorably than placebo on the POMS. Alcohol did not have additive effects on the subjective ratings for zolpidem. It is concluded that, for this population and at the doses tested, the abuse potential of zolpidem appears to be modest and not increased by alcohol. © 1998 Elsevier Science Inc.

Zolpidem  Zolpidem–alcohol interaction  Abuse potential  Healthy volunteers

ZOLPIDEM is a rapid-onset, clinically effective hypnotic with an imidazopyridine structure (19,21). Its mechanism of action presumably involves interaction at specific benzodiazepine binding sites of a certain population of $GABA_A$ receptors (1,3,7,25), resulting in a different preclinical spectrum of action than benzodiazepines (22,30,31,40). At the recommended dose of 10 mg, zolpidem appears to be safe and effective with minimal evidence of tolerance development (34) or occurrence of rebound insomnia in patients with chronic insomnia treated for up to 4 weeks (36).

Preclinical studies have demonstrated that zolpidem produces no antipunishment effects (31,40), and does not increase food intake patterns (22,31). Furthermore, studies in rats and mice have shown that the development of physical dependence and tolerance to sedative-hypnotic, depressant, and anticonvulsant effects evidenced with benzodiazepines is not found with zolpidem (23,29,30,32,33,35). A study in baboons, however, indicated that species differences may exist in terms of abuse potential (13).

In humans, the abuse potential of alcohol is beyond doubt (20,28). A liability for abuse also exists for the benzodiazepines; however, they are reported to have modest abuse potential relative to other drug classes (5,39). In a placebo-controlled comparison to triazolam, zolpidem showed an abuse potential similar to that of triazolam (9) on some subjective measures of drug liking; however, zolpidem also produced increases in subjective ratings of negative effects (e.g., dysphoria and somatic symptoms including dizzy, anxious, queasy, blurred vision) that were not observed with triazolam. These negative effects following zolpidem presumably would mitigate any abuse potential.

Several decades of research have established a standard battery of measures for abuse liability assessment. Experts in the field emphasize the importance of including a variety of subjective and objective measures as well as assessing drug–alcohol interactions (5,8,10). The present author conducted such a comprehensive study to evaluate the effects of zolpidem, given with and without alcohol, on both objective measures of cognitive and psychomotor performance as well as on subjective measures of abuse liability. Given the lengthy scope of the findings from that larger study, the two different sets of data are reported separately. The present article summarizes the abuse liability findings. The findings for the objective measures of cognitive and psychomotor performance

Requests for reprints should be addressed to C. J. Wilkinson, Ph.D., Director, Clinical Research, Southern California Research Institute, 11914 West Washington Blvd., Los Angeles, CA 90066.

have been reported in a prior article (38). Some of zolpidem's dose- and time-related performance deficits demonstrated in that study were recently confirmed in a similar population and found comparable to temazepam and triazolam, with the exception of zolpidem's faster time to peak effect at approximately 60 min (27).

The aim of the present study was to explore the effects of zolpidem alone, and in combination with alcohol, on a variety of validated subject-rated measures to provide a comprehensive evaluation of zolpidem's abuse potential in healthy volunteers with a history of social use of alcohol and drugs.

## METHOD

### *Subjects*

After Institutional Review Board approval and subject-informed consent, 41 healthy male volunteers, 21 to 40 years old, were enrolled in the larger study. To be eligible, subjects had to be nonsmokers who were in good mental and physical health as determined by a psychological inventory, medical history, physical examination, laboratory analyses (blood chemistries and urinalysis), and 12-lead electrocardiogram. Accepted subjects had a reported social use of alcohol at levels indicating the ability to tolerate the alcohol dose in the study [i.e., classified as moderate to low-heavy on the QFV alcohol use scale (6)]. In addition, the majority of subjects had some prior experience with psychoactive drugs (i.e., "recreational" drug use).

All qualified applicants agreed to abstain from psychoactive drug use for 30 days prior to and throughout the study, to abstain from alcohol during the 24 h preceding each study session, and to provide breath and urine samples at each visit for alcohol and drug screening. Breath alcohol tests provided immediate results; all urine samples were tested at screening but then, on a random basis, only 25% of those from the treatment visits were tested. All breath and urine samples tested were negative, indicating that subjects had complied with the study's restrictions.

Subjects were excluded from the study if they had a hypersensitivity to central nervous system depressants, a current or past history of drug abuse or a positive urine drug screen for drugs of abuse, a significant medical or psychiatric disorder, a history of any current significant sleep disorder, or a body weight that deviated by more than 15% from ideal weight according to the Metropolitan Height and Weight Table of 1983. Finally, subjects were excluded if they had used zolpidem previously or an investigational drug within 30 days, an over-the-counter drug within 72 h of study entry, or any medication during the study that might confound the study results.

Based on data from previous studies [cf. (4,37)], a sample size of 24 was considered to be large enough to detect expected treatment differences with a power of 0.80 and an alpha level of 0.05. A total of 12 subjects discontinued prior to randomization: eight because of schedule conflicts, three for failure to meet entry criteria, and one due to questionable alcohol tolerance. Of the 29 randomized subjects, four discontinued due to noncompliance and one due to an adverse event following treatment with alcohol and zolpidem 10 mg. Thus, 24 subjects [mean age 26.1 years, mean weight 76.5 kg (168.4 lbs), 75% Caucasian] completed the study.

### *Study Design*

According to a double-blind, randomized, placebo-controlled, six-way crossover design, each subject underwent six treatment sessions that included administration of a drug (placebo, zolpidem 10 mg, or zolpidem 15 mg) together with a beverage (alcohol 0.75 g ethanol/kg body weight or placebo). Treatment order was arranged as a $6 \times 6$ Latin square with 1-week intervals between treatments. The alcohol dose was selected based on previous studies indicating that this dose would yield a mean blood alcohol concentration (BAC) of 0.08% at approximate peak [cf. (4,37)]. To optimize absorption, beverages were given as a 16% solution (1:1.5 ratio of vodka, or water, to orange juice). To provide alcohol stimulus cues with the placebo beverage, approximately 2 ml of vodka were rubbed around the rim of the placebo beverage cups. To control for effects of drinking rate, beverages were given in three separate portions for paced drinking at 10-min intervals starting at time −30 min (with end of drinking at time 0). Drug treatments were administered after the first 10-min interval at −20 min.

Subjects were scheduled to arrive for each treatment session prior to 0900 h, after an overnight fast. Upon arrival, a urine sample was obtained for substance-abuse screening. BACs (via breath sample using an Alco-Sensor III device; Intoximeters, Inc., St. Louis, MO) were determined during each treatment session at arrival and then at +45, +75, +115, +160, +230, and +300 min following the 30-min drinking period. A standard minimal breakfast (e.g., toast or English muffin with juice) was consumed 30 min before, and a standard lunch (without caffeinated beverages) was served at +170 mins following, the drinking period. Subjects were not permitted to leave the laboratory until all tests were completed, their BACs were below 0.03%, and any adverse effects had abated. As an added safety precaution, taxi transport was provided at each treatment session.

### *Safety*

Vital signs (blood pressure and heart rate) were recorded at four times during each treatment session: upon arrival, and at +30, +160, and +300 min following the 30-min drinking session. Adverse events were recorded as they occurred. A treatment-emergent adverse event was defined as an event that occurred within 24 h after dosing and either was not present (or was less severe) at baseline. Patients completed physical examinations and laboratory tests within 1 week of the last test session.

### *Abuse Liability Measures*

*Drug effect questionnaire (DEQ).* A modified version of the single-dose DEQ developed by Fraser and colleagues (11) was administered at approximately 40 min following the end of the drinking period (i.e., 60 min postdrug) for a "right now" assessment of effects (peak drug effect), and at +300 min (i.e., 320 min postdrug) for a retrospective assessment of "peak effects today." Categorical ratings on five-point scales were obtained for drug strength (range from 0 = "no effect at all" to 4 = "very strong effect"), drug liking (range from 0 = "dislike or feel neutral about the drug" to 4 = "like the drug very much"), and drug disliking (range from 0 = "like or feel neutral about the drug" to 4 = "dislike the drug very much"). The separate scales for drug liking vs. disliking were included to capture subjective drug effects that may be multidimensional and so include both positive and negative aspects.

*Addiction research center inventory (ARCI).* This true-false questionnaire has proven sensitive to various classes of abused drugs (15). Subjects were specifically instructed to rate their

peak effects for the treatment session retrospectively by completing a short 40-item ARCI version (ARCI-40) at +300 min following the drinking period (i.e., 320 min postdrug). The ARCI-40 contains subsets from three scales: the pentobarbital–chlorpromazine–alcohol group (PCAG; scores range 0–15), which reflects sedation and intoxication; the morphine–benzedrine group (MBG; scores range 0–16), which reflects feelings of euphoria and well-being; and the lysergic acid diethylamide specific scale (LSD; scores range 0–14), which reflects dysphoria and feelings of fear.

*Profile of mood states (POMS).* This questionnaire is a 65-item adjective rating scale that is sensitive to drug effects (16,18,26). The bipolar form (POMS-BI) was used. Subjects rate feeling-state adjectives on a four-point scale from 0 = "not at all" to 3 = "extremely." Responses for positive moods are scored with plus values and negative moods are assigned minus values. A total score (range 0–36) is obtained for each of the following bipolar mood scales: elated–depressed, agreeable–hostile, clearheaded–confused, confident–unsure, energetic–tired, and composed–anxious. The questionnaire was completed at +300 min following the drinking period, and specifically required subjects to rate retrospectively their perceived peak effects for that day's session.

*Statistical Methods*

Statistical analyses that included analyses of variance (ANOVAs) and subsequent *t*-tests as well as descriptive statistics were performed on the subjective measures of abuse potential using BMDP statistical software (BMDP Statistical Software, Inc., Los Angeles, CA). Repeated-measures ANOVAs tested main effects of drug (differences between zolpidem 0, 10, and 15 mg) and alcohol (vs. placebo) and alcohol-by-drug interactions [cf. (12)]. According to a planned stepwise analysis scheme, initial analyses included a grouping factor for treatment sequence; results generally showed no significant effects.

In addition, a total of five planned paired comparison *t*-tests of the six means for each drug and alcohol treatment combination were conducted to identify significant ($p < 0.05$) effects. These *t*-tests evaluated the effect of alcohol alone, the zolpidem 10-mg and 15-mg doses alone (drug effects), and the zolpidem 10-mg and 15-mg doses in combination with alcohol (additive effects). Given the study's focus on abuse potential and safety, the *p*-values for the *t*-tests were not adjusted to reduce type I errors because we wanted instead to minimize type II errors (i.e., false conclusions that adverse treatment effects were not significant).

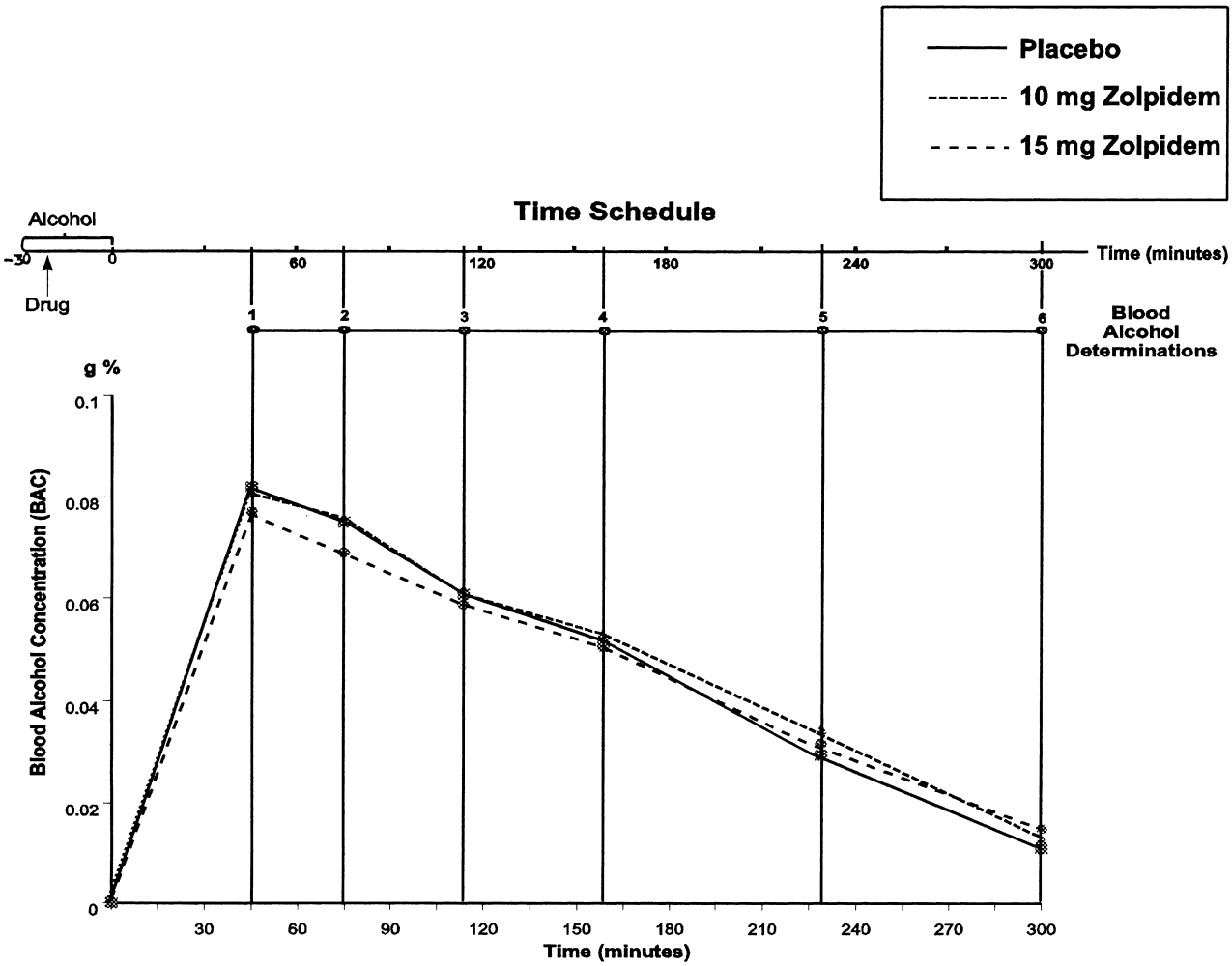


FIG. 1. Mean blood alcohol concentrations (BACs via breath samples) in 24 healthy men as a function of treatment and time.

Clinical laboratory values were classified as low, normal, or high, according to laboratory normal ranges. Changes from prestudy to poststudy were tested by the method of Stuart-Maxwell (for 3-by-3 tables) or by the McNemar Test (for 2-by-2 tables) using SAS version 6.06. Significance tests were two sided and were made at an alpha level of 0.05. Laboratory test results and vital signs were reviewed for potentially clinically significant abnormalities based on the criteria suggested by the FDA Division of Neuropharmacological Drug Products.

## RESULTS

### *Blood Alcohol Concentration (BAC)*

The mean BACs during the three sessions when subjects received alcohol showed a similar pattern over time for all three treatments. As seen in Fig. 1, the mean BACs for each treatment session showed a peak of 0.08% at +45 min, and declined to approximately 0.015% at +300 min. To minimize response variability, this study selected +45 min after the end

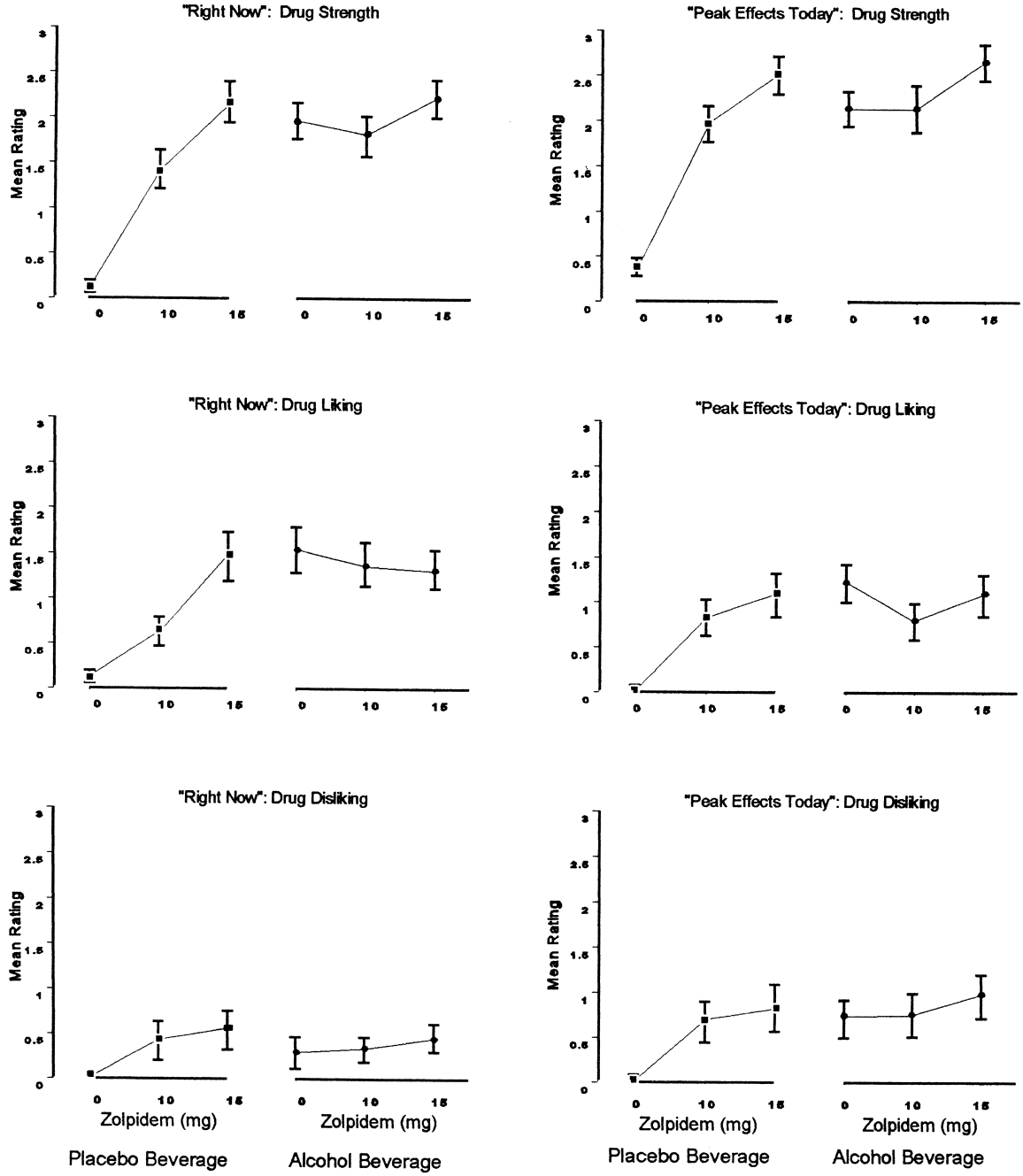


FIG. 2. Mean (± SEM) drug effect questionnaire ratings following zolpidem (0, 10, or 15 mg) with either placebo or alcohol beverage ($n$ = 24). ("Right Now" evaluation +50 min postdrug; "Peak Effects" = retrospective evaluation at +320 min postdrug).

of drinking, rather than the usual +30 min, to ensure that the peak alcohol effect was measured on the descending limb of the BAC.

*The Drug Effect Questionnaire (DEQ)*

Mean scores for the DEQ items at 60 min ("right now") and at 320 min (retrospective "peak effects today") postdrug are presented in Fig. 2. At both points during the placebo beverage sessions, a significant dose–response relationship of zolpidem was observed at the "right now" and "peak effects" assessments, respectively, for drug strength, $F(1, 23) = 29.9$, $p < 0.001$, and $F(1, 23) = 30.39$, $p < 0.001$, and drug liking, $F(1, 23) = 4.61$, $p < 0.05$ and $F(1, 23) = 4.15$, $p < 0.05$. Drug disliking scores were significant for "peak effects" only, $F(1, 23) = 4.4$, $p < 0.05$. In contrast, during alcohol sessions, mean scores following alcohol alone were approximately as high or higher than those following alcohol plus zolpidem 10 mg. These differences in the zolpidem dose–response relationship during alcohol and placebo drinking sessions are also evidenced by significant drug-by-alcohol interactions (all $p < 0.001$) for drug strength and drug liking at both assessment times, $F(1, 23) = 18.88$ and 10.67 for strength "right now" and "peak effects," respectively, and, $F(1, 23) = 11.38$ and 14.39 for liking.

Mean scores for the DEQ indicated a different response for the two assessment times. Numerically, the mean scores for the retrospective "peak effects today" assessment completed at the end of the testing session were higher for drug strength and drug disliking, and lower for drug liking, than scores for the "right now" assessment time.

Results of the paired *t*-tests on the mean scores for all subjective measures are summarized in Table 1. As shown, the retrospectively assessed "peak effects today" scores for the DEQ generally showed significant main effects of drug and of alcohol, but no significant additive effects of alcohol with zolpidem. For the immediate "right now" DEQ assessment, a similar pattern of significant effects was obtained for drug strength. For the "right now" drug disliking scores, however, only the effect of zolpidem 15 mg was significant; zolpidem 10 mg and alcohol alone failed to reach statistical significance ($p = 0.067$ and $p = 0.110$, respectively). For the "right now" drug-liking scores, a significant additive effect of alcohol with zolpidem 10 mg was obtained.

*Addiction Research Center Inventory (ARCI-40)*

Means for the ARCI-40 subscale scores are presented in Fig. 3. On the PCAG subscale (measuring sedation and intoxication), scores increased with increasing zolpidem doses with placebo beverage. In the presence of alcohol alone, the scores were higher than with zolpidem 15 mg. ANOVAs showed significant main effects of drug, $F(1, 23) = 10.63$, $p < 0.001$, and alcohol, $F(1, 23) = 9.09$, $p < 0.01$, and no significant alcohol-by-drug interaction. *t*-tests showed a significant drug effect for zolpidem 15 mg and a significant additive effect for zolpidem 10 mg with alcohol (Table 1).

TABLE 1

SUMMARY OF SUBJECTIVE MEASURES: SIGNIFICANT COMPARISONS OF PAIRED MEANS FOR ZOLPIDEM (0, 10, OR 15 mg), ADMINISTERED WITH AND WITHOUT ALCOHOL, IN 24 HEALTHY MEN

| | Significant Paired *t*-Test ($df = 23$) | | | | |
|---|---|---|---|---|---|
| | Zolpidem | | Alcohol | Zolpidem + Alcohol | |
| | 15 mg | 10 mg | 0.08% | 15 mg | 10 mg |
| Subjective Measures | $P_{15}$–$P_0$ | $P_{10}$–$P_0$ | $A_0$–$P_0$ | $A_{15}$–$P_{15}$ | $A_{10}$–$P_{10}$ |
| DEQ "right now": | | | | | |
| Drug strength | * | * | * | — | — |
| Drug liking | * | * | * | — | * |
| Drug disliking | * | — | — | — | — |
| DEQ "peak effects": | | | | | |
| Drug strength | * | * | * | — | — |
| Drug liking | * | * | * | — | — |
| Drug disliking | * | * | * | — | — |
| ARCI-40 scales: | | | | | |
| PCAG (sedation/intoxication) | * | — | — | — | * |
| MBG (euphoria/well-being) | — | — | — | — | — |
| LSD (dysphoria/fear) | * | * | * | — | * |
| POMS scales: | | | | | |
| Elated–depressed | * | — | — | — | — |
| Agreeable–hostile | — | * | — | — | — |
| Clearheaded–confused | * | * | * | — | — |
| Confident–unsure | * | * | * | — | — |
| Energetic–tired | * | * | — | — | — |
| Composed–anxious | * | — | * | — | — |

*$p < 0.05$, — = Not significant.

Abbreviations: $A_0$ = alcohol with placebo drug; $A_{10}$ = alcohol with zolpidem 10 mg; $A_{15}$ = alcohol with zolpidem 15 mg; ARCI = Addiction Research Center Inventory; DEQ = Drug Effect Questionnaire; *df* = degrees of freedom; LSD = lysergic acid diethylamide specific; MBG = morphine benzedrine group; PCAG = pentobarbital–chlorpromazine–alcohol group; $P_0$ = placebo beverage with placebo drug; $P_{10}$ = placebo beverage with zolpidem 10 mg; $P_{15}$ = placebo beverage with zolpidem 15 mg; POMS = profile of mood states.

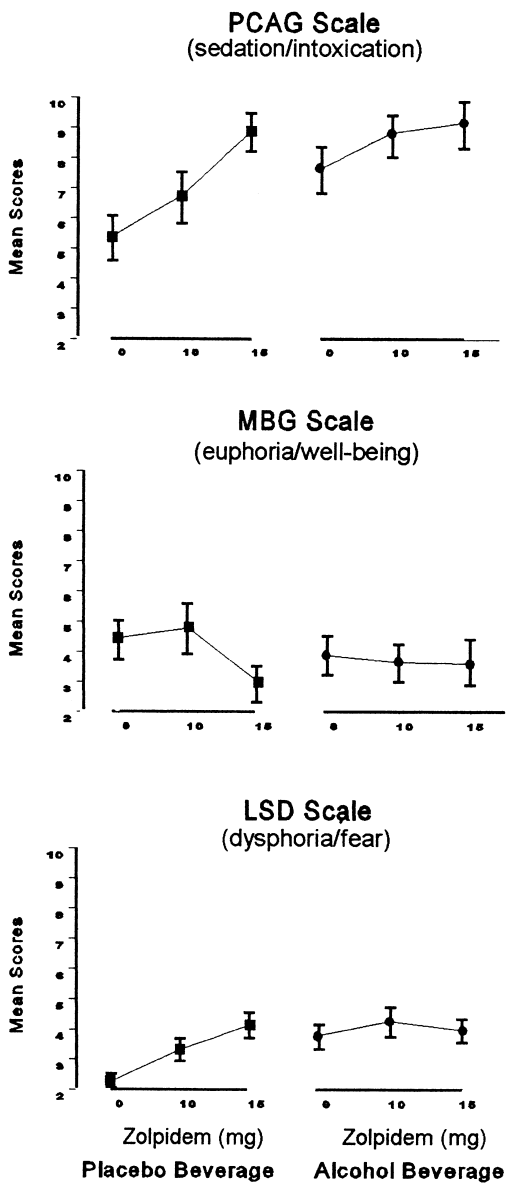


FIG. 3. Mean (± SEM) ARCI-40 Scores following zolpidem (0, 10, or 15 mg), with either placebo or alcohol beverage ($n = 24$; ARCI = Addiction Research Center Inventory; PCAG = pentobarbital–chlorpromazine–alcohol group; MBG = morphine–benzedrine group; LSD = lysergic acid diethylamide.

The MBG subscale scores (measuring euphoria and well-being) were changed only slightly by either zolpidem or alcohol (Table 1). No significant effects were obtained in any of the analyses of these scores. In contrast, the LSD subscale scores (assessing dysphoria and fearful feelings) showed a zolpidem dose–response relationship with placebo beverage but not with alcohol (Fig. 3). Specifically, these scores were increased by alcohol, alone or when given with zolpidem 10 mg, whereas no further increases were seen when alcohol was combined with zolpidem 15 mg. These findings are reflected in the significant drug-by-alcohol interaction, $F(1, 23) = 5.16$, $p < 0.01$, drug effects, $F(1, 23) = 5.16$, $p < 0.01$, and alcohol effects, $F(1, 23) = 6.76$, $p < 0.05$, in the ANOVA for LSD and by the *t*-test comparisons (Table 1).

*Profile of Mood States (POMS)*

In general, mean scores for the six POMS bipolar mood scales (Fig. 4) decreased with increasing zolpidem dose (subjects were less elated, agreeable, clearheaded, confident, energetic, and composed). Furthermore, for each zolpidem dose, alcohol typically decreased POMS scores. Alcohol alone was associated with scores similar to or smaller than scores with zolpidem 10 mg. ANOVAs on the POMS subscores indicated significant alcohol effects ($p < 0.05$) on all but the agreeable–hostile scores and significant drug effects ($p < 0.05$) for all but the elated–depressed and the agreeable–hostile scores. For the clearheaded–confused and the confident–unsure scores, significant drug-by-alcohol interactions were found, $F(1, 23) = 3.67$, $p < 0.05$ and, $F(1, 23) = 5.89$, $p < 0.01$, respectively. For these subscales, placebo drug scores were considerably higher (i.e., more positive mood) than zolpidem scores in sessions with placebo beverage but not in sessions with alcohol consumption.

Results of paired *t*-tests on the POMS subscale scores were significant ($p < 0.05$) for the majority of the drug vs. placebo and alcohol vs. placebo comparisons (Table 1). None of the additive effects of alcohol to zolpidem were significant.

*Safety*

None of the clinical laboratory variables showed statistically significant changes from prestudy to poststudy. According to the FDA Division of Neuropharmacological Drug Products' criteria for identifying abnormal vital signs, a total of 10 potentially clinically significant vital sign measurements were recorded in five subjects, but none were judged to be of clinical relevance.

The incidence of adverse events increased with increasing drug dose and was higher with alcohol beverage than with placebo beverage at each dose of zolpidem (Table 2). The events with the highest incidence were ataxia, diplopia, dizziness, and nausea. The percentage of subjects who experienced one or more adverse events ranged from 8.0% under placebo, 29.6% after alcohol alone, 56% following the highest zolpidem dose (15 mg), and to 62.5% following the combination of alcohol and zolpidem 15 mg.

## DISCUSSION

Based on the DEQ, the ARCI-40, and the POMS, the abuse potential of placebo, zolpidem 10 mg and zolpidem 15 mg was evaluated alone and in combination with alcohol as part of a larger study that included objective measures of cognitive and psychomotor performance. In particular, the combined effect of zolpidem with alcohol was evaluated to assess the safety of this "worst case" combination, which might occur in the misuse of zolpidem. The dose of alcohol (0.75 g ETOH/kg b.wt.) was aimed to achieve a mean peak blood alcohol concentration of 0.08%, a moderately high level for social drinkers and known to affect psychomotor performance significantly (37). As reported previously for the first part of this comprehensive study (38), zolpidem showed a rapid onset, with significant performance impairment at the peak effects (1–2 h postdose), declining impairment postpeak (2–3 h postdose), and essentially no residual impairment effects by the end of the session (4–5 h postdose). Such behavioral effects are consistent with those reported and cited in other zolpidem

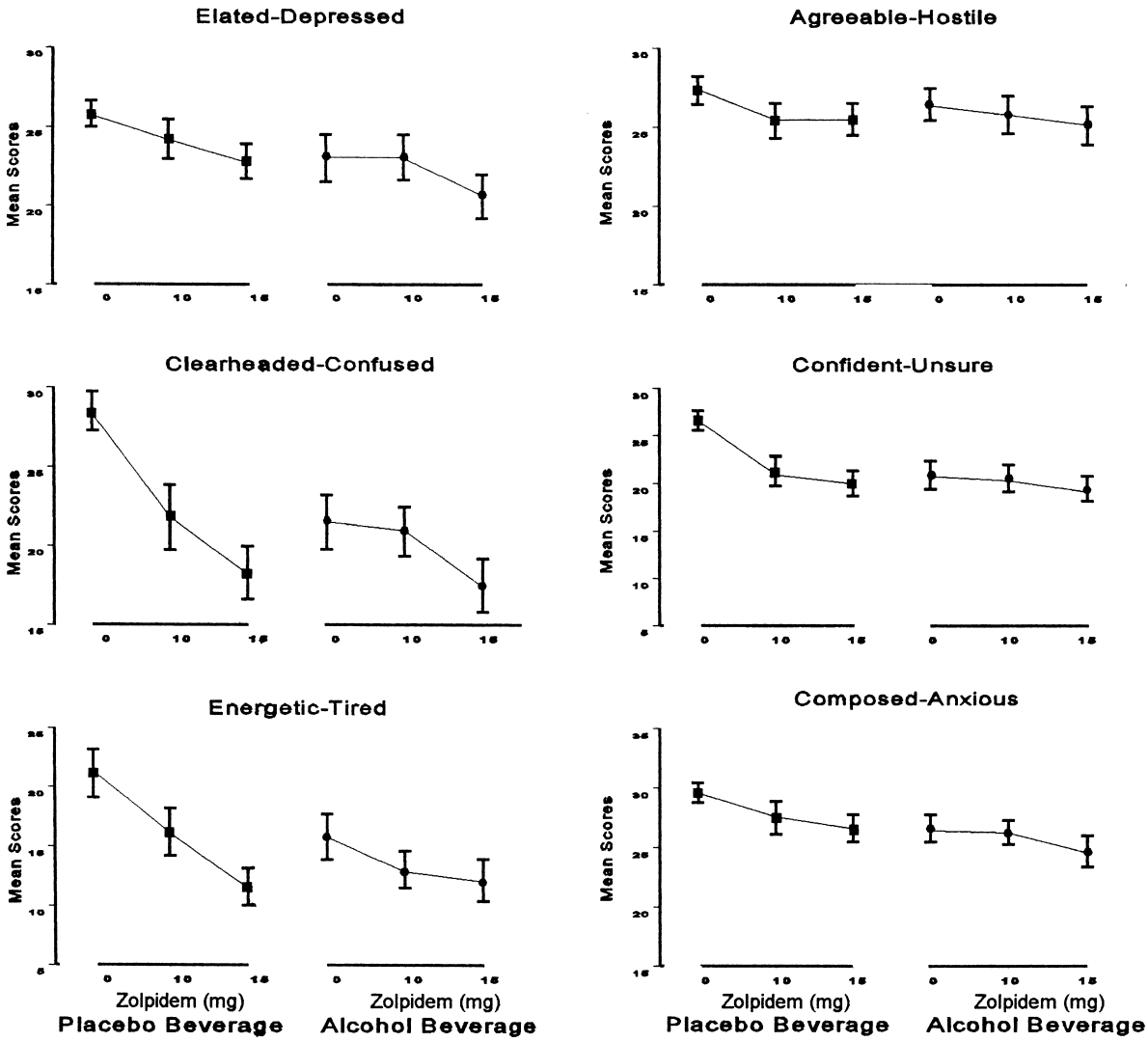


FIG. 4. Mean (± SEM) POMS subscales following zolpidem (0, 10, or 15 mg), with either placebo or alcohol beverage ($n$ = 24; POMS = profile of mood states—bipolar form; higher scores reflect more positive mood, i.e., first descriptor of each bipolar mood scale; maximum score = 36).

studies [cf. (9,27)]. Subjective ratings of peak effects, as reported in this article, were scheduled at two crucial time points: 1) to coincide with peak drug/alcohol blood concentrations at approximately + 1 h postdose, and 2) retrospectively (recalled peak effects) at approximately 5 h after peak effects.

The DEQ and ARCI-40 are validated questionnaires with empirically derived subjective rating scales (15,17,27). These instruments were designed for the assessment of drug abuse liability in confirmed drug abusers and previously have been used for the evaluation of zolpidem's abuse potential in such populations (10) as well as in documented "recreational" drug users (5). The POMS, which also is typically included in abuse liability studies, provides a profile of subjective changes produced by drugs (16,18,26). The present study extends the use of these standard abuse liability measures to evaluation of zolpidem in individuals without any history of drug abuse, but with some prior exposure to various social or "recreational" drugs including alcohol.

Significant alcohol-by-drug interactions obtained in the ANOVAs reflect differences in the zolpidem dose–response curves in the presence of placebo beverage and alcohol. The significant interactions result from less than additive effects and are not indicative of any potentiation or synergism. With placebo beverage, a progressive increase (or decrease) in scores was obtained as the dose of zolpidem was increased from 0 to 10 to 15 mg; with alcohol, the differences between zolpidem doses were less pronounced and mostly nonsignificant. This difference in the dose–effect relationship may be attributed primarily to the greater incremental effect of alcohol alone in the presence of placebo than in combination with the 10-mg or 15-mg doses of zolpidem.

The $t$-tests for additive effects of alcohol with zolpidem 10 or 15 mg typically were not significant. Three exceptions involved the lower 10-mg dose of zolpidem: significantly greater mean scores were obtained with zolpidem 10 mg and alcohol compared to zolpidem 10 mg alone for the DEQ drug-liking

TABLE 2

ADVERSE EVENTS IN 29 HEALTHY MEN OCCURRING WITHIN 24 HOURS FOLLOWING ZOLPIDEM (0, 10, OR 15 mg) WITH ALCOHOL OR PLACEBO BEVERAGE*

| | Number of Subjects (%) | | | | | |
|---|---|---|---|---|---|---|
| | Placebo Beverage | | | Alcohol Beverage | | |
| Adverse Event | Zolpidem 15 mg $n = 25$ | Zolpidem 10 mg $n = 26$ | Placebo $n = 25$ | Zolpidem 15 mg $n = 24$ | Zolpidem 10 mg $n = 26$ | Placebo $n = 27$ |
| Chest pain | 0 | 0 | 0 | 1 (4.2) | 0 | 0 |
| NEC sensation abdomen | 0 | 0 | 0 | 0 | 1 (3.8) | 0 |
| Ataxia | 7 (28.0) | 2 (7.7) | 0 | 7 (29.2) | 6 (23.1) | 0 |
| Dizziness | 5 (20.0) | 2 (7.7) | 1 (4.0) | 2 (8.3) | 4 (15.40) | 1 (3.7) |
| Headache | 2 (8.0) | 0 | 0 | 1 (4.2) | 2 (7.7) | 4 (14.8) |
| Lightheadedness | 0 | 1 (3.8) | 0 | 0 | 0 | 0 |
| Diarrhea | 0 | 0 | 0 | 0 | 0 | 1 (3.7) |
| Hiccup | 3 (12.0) | 0 | 0 | 2 (8.3) | 2 (7.7) | 0 |
| Nausea | 1 (4.0) | 1 (3.8) | 1 (4.0) | 2 (8.3) | 4 (15.4) | 2 (7.4) |
| Vomiting | 1 (4.0) | 0 | 0 | 2 (8.3) | 2 ((7.7) | 1 (3.7) |
| Dyspnea | 0 | 0 | 0 | 1 (4.2) | 0 | 0 |
| Upper respiratory infection | 0 | 0 | 0 | 1 (4.2) | 0 | 0 |
| Diplopia | 2 (8.0) | 2 (7.7) | 0 | 7 (29.2) | 5 (19.2) | 0 |
| Vision abnormal | 2 (8.0) | 1 (3.8) | 0 | 0 | 0 | 0 |
| Overall† | 14 (56.0) | 7 (26.9) | 2 (8.0) | 15 (62.5) | 14 (53.8) | 8 (29.6) |

NEC = not elsewhere classified.
*These 29 men reflect those subjects who were randomized and received at least one study dose.
†Total number (%) of subjects who experienced one or more adverse event in any body system.

scale, for the ARCI-40 PCAG scale (reflecting sedation and intoxication), and on the ARCI-40 LSD scale (a measure of dysphoria and fear). These significant results were not consistently obtained on similar subscale items in the different measures utilized. One might speculate that the absence of any interaction of the higher dose of zolpidem with alcohol constitutes a "ceiling effect." Such interpretation appears unlikely, however, because scores considerably higher than those reached in the present study have been recorded with higher doses of zolpidem or triazolam (9). In addition, no significant additive effects of alcohol were obtained with zolpidem 15 mg.

Based on ANOVAs and paired *t*-tests, zolpidem and alcohol (both alone and in combination) significantly increased subjective ratings on the DEQ and the ARCI-40. Relative to placebo on the DEQ, both zolpidem and alcohol increased ratings of drug liking and drug strength during the "right now" assessment at 60 min postdrug and during the retrospective "peak effects today" ratings at the end of the session. The ratings of "peak effects today" of zolpidem in the absence of alcohol are concordant with recently reported data (27). Subjects' order of ratings for drug liking was highest after the alcohol dosing, followed by zolpidem 15 mg, and then by zolpidem 10 mg. Subjects gave highest drug disliking and drug strength ratings to zolpidem 15 mg. Analyses also showed significant decreases in most of the scores on the POMS following either alcohol or zolpidem, reflecting negative effects of these treatments on mood states. In sum, both for zolpidem and for alcohol, subjects reported both positive and negative reactions to these treatments.

The ratings for drug liking following zolpidem or alcohol are consistent with some liability for abuse (14,15). Usually, however, drug-liking scores from the DEQ covary with ARCI-40 MBG scores (which reflect euphoria and well-being). In the present study, neither alcohol nor zolpidem had a significant effect on the MBG scores, whereas both treatments significantly increased drug liking. In other placebo-controlled abuse potential studies, this discrepancy also was reported with both zolpidem and triazolam (9) and zolpidem, triazolam, and temazepam (27). In a placebo-controlled study of lorazepam and methocarbamol, both agents yielded significantly greater drug strength and drug-liking scores than placebo; however, significantly elevated MBG scores were obtained with the benzodiazepine lorazepam, but not with the skeletal muscle relaxant methocarbamol (24). These conflicting findings may reflect the measurement of differing aspects of abuse potential by the MBG scale and the Drug Effect Questionnaire rating of drug liking.

In terms of negative drug effects, when alcohol and zolpidem were administered either alone or in combination, the significant scores on the ARCI-40 LSD scale (dysphoria and negative drug effects) were consistent with the drug-disliking scores on the DEQ. Moreover, POMS scales showed subjects' moods were significantly less positive during active treatment sessions. In general, the higher zolpidem dose (15 mg) appeared to have more negative effects than did alcohol alone: greater increases in LSD scores (dysphoria) and in the incidence of adverse events (e.g., ataxia, visual disturbance, and dizziness). Similar findings were obtained in a placebo-controlled comparative study of zolpidem and triazolam in which zolpidem produced a series of more "negative" subjective effects than did triazolam (9). In that study, zolpidem but not triazolam, for example, increased scores on the LSD (dysphoria) scale as well as on negative somatic symptoms (e.g., dizzy, anxious, queasy, and blurred vision).

In the present study, the types of most frequent adverse events are similar to those observed in previous clinical trials of zolpidem. The actual incidence rates, however, are somewhat higher, probably because this was a daytime study. Subjects were dosed in the morning and were expected to remain

awake during the testing session. In a similar study, it was concluded that adverse events that normally would go without notice during sleep may be reported in such a daytime study (2). The most clinically relevant information obtained from the present adverse event profile, however, is the increase (relative to placebo beverage sessions) in adverse event incidence rates when zolpidem and alcohol were combined. This increase with the addition of alcohol was greater with the 10-mg dose of zolpidem than with the 15-mg dose. Irrespective of a potential ceiling effect of zolpidem–alcohol interaction, this observation emphasizes the necessity for precautions when combining zolpidem with alcohol.

Overall, the drug effects rated by subjects in this study were negative and, therefore, do not appear to suggest a strong abuse liability for zolpidem alone or in combination with alcohol. Significantly higher DEQ ratings of drug liking with zolpidem in comparison to placebo, however, indicate that zolpidem has some potential to be abused. Taken in the proper perspective, these results have to be interpreted with caution because the subjects involved in this study, while not drug-naive, were healthy individuals who had only social experience with drugs including alcohol. As such, they are not necessarily representative of the typical potential drug abuser. Nonetheless, the current findings are significant in expanding our knowledge of the abuse potential of zolpidem, alone and with the widely used drug alcohol, in populations other than drug abusers. Although abuse liability experts have recommended first studying drug-abusing populations to differentiate the abuse potential of various sedative/anxiolytic agents, they also have noted findings indicating the value of also studying normal subjects with moderate social drinking (8), as was done in the present study. Interestingly, the present study's subjects showed a somewhat similar pattern of results to that reported for the drug abusing populations previously studied [cf. (9)], thus supporting the generalizability of the findings.

In summary, for this population and at the doses tested, the abuse potential of zolpidem appears to be modest and not increased to any appreciable extent by the addition of a moderately high dose of alcohol. The current report of the abuse liability measures, however, is admittedly limited by including only two assessment times. Although a prospective time course analysis of abuse potential is ideal, such repeated assessments at short time intervals was not feasible in this larger comprehensive study, which also required the subjects to perform a multidimensional performance test battery at three times during the 5-h session. Quite simply, repeated subjective ratings might have caused decreased motivation and increased task demands, fatigue, and response variability across all measures for the subjects.

Moreover, potential criticism that this study's reliance on the retrospective assessment of the "peak effects today" renders the abuse liability findings invalid is not completely sound. First, the direct subjective peak effects ("right now") for the DEQ also were assessed at +60 min postdrug and generally mirrored the findings obtained by the retrospective ratings of "peak effects today" at the end of the session. Second, despite the widely accepted reports (including from our prior study) of some zolpidem-induced memory impairment, the fact remains that future drug seeking and repeated drug use will largely be determined by whatever subjects actually can recall of their drug experience at the end of a drug-use episode. Indeed, experts in the field have acknowledged that ". . . retrospective ratings of [drug] liking may be better predictors of abuse liability than ratings obtained during the drug's effect because retrospective ratings more closely approximate the conditions for initiation of an episode of drug use" (8).

Notably, although not statistically signficant, this study found that the subjects' retrospective assessments of the drug effects actually were somewhat more negative than the direct assessment at +60 min postdose. Consequently, such recalled negative effects might mitigate abuse liability. On the other hand, this study only assessed abuse potential after acute drug doses. Because subjects may develop tolerance to the initial aversive effects of a drug but still continue to experience positive effects with repeated doses, an important future study will be to evaluate the effects of chronic use of zolpidem on abuse potential.

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