Pharmacology Biochemistry and Behavior, Vol. 61, No. 3, pp. 253–269, 1998

0091-3057/98 $19.00 + .00

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PII S0091-3057(98)00102-6

# Behavioral Pharmacology of Zolpidem Relative to Benzodiazepines: A Review

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Received 21 September 1997; Revised 3 March 1998; Accepted 25 March 1998

RUSH, C. R. *Behavioral pharmacology of zolpidem relative to benzodiazepines: A review.* PHARMACOL BIOCHEM BEHAV **61**(3) 253–269, 1998.—Zolpidem, an imidazopyridine that purportedly binds selectively to certain $GABA_A$ receptor subtypes, is the most commonly prescribed hypnotic. The present article critically reviewed the extant experimental literature to determine whether the behavioral pharmacologic profile of zolpidem also differs from that of benzodiazepines. Specific topics that are reviewed include: 1) reinforcing effects and abuse potential, 2) discriminative-stimulus effects, 3) subject-rated drug effects, 4) performance-impairing effects, 5) tolerance-producing effects, and 6) physiological dependence-producing effects. Studies that employed both nonhumans and humans are reviewed. Based on the available literature, the most parsimonious conclusion is that despite its unique neuropharmacological profile, the behavioral effects of zolpidem are generally similar to those of benzodiazepines. However, it is important to note the dearth of perspective, experimental studies that directly compared zolpidem and a benzodiazepine. Because of the clinical relevance and paucity of published studies, future research should focus explicitly on assessing the reinforcing effects, abuse potential, performance-impairing effects, tolerance-producing effects, and dependence-producing effects of zolpidem relative to a benzodiazepine. Important issues such as the selection of an appropriate comparison drug and subject population, and the doses tested needed to be considered in these future studies. © 1998 Elsevier Science Inc.

Abuse potential Drug discrimination Memory impairment Benzodiazepines Performance impairment Self-administration Humans Subjective effects Hypnotics Dependence Liability Imidazopyridines Zolpidem

ZOLPIDEM (AMBIEN®), an imidazopyridine hypnotic, was introduced into clinical practice in the United States in 1992 and is now the most commonly prescribed hypnotic (15). Zolpidem is clinically effective, safe, and well tolerated (67, 76,79,97,129). Zolpidem also has a favorable pharmacokinetic profile for use as a hypnotic in that it is rapidly absorbed and eliminated (34,70,118). These characteristics undoubtedly contribute to zolpidem's popularity.

The hypnotic actions of zolpidem, like benzodiazepine hypnotics, are mediated at the benzodiazepine recognition site of the $GABA_A$ receptor complex (52,128). However, the neuropharmacological profile of zolpidem is somewhat different from that of most benzodiazepines (1,5–7,9,11,21,56,74). For example, zolpidem binds with low affinity to $\alpha_5$-containing $GABA_A$-receptor subtypes (9). Triazolam and diazepam, two benzodiazepines, bind with high affinity to these $GABA_A$-receptor subtypes. Interestingly, $\alpha_5$-containing subtypes constitute a significant proportion of $GABA_A$ receptors in brain regions (i.e., hippocampus) thought to mediate complex behavioral processes such as learning and memory (78).

The functional significance of zolpidem's unique neuropharmacological profile is unclear. The present article critically reviewed the extant experimental literature to determine whether the behavioral pharmacologic profile of zolpidem differs from that of benzodiazepines. Specific topics that are reviewed include: 1) reinforcing effects and abuse potential, 2) discriminative-stimulus effects, 3) subject-rated drug effects, 4) performance-impairing effects, 5) tolerance, and 6) physiological dependence. Some of these topics have been reviewed separately (68,75,138). The present article differs from these previous reviews in that it integrates each of these topics in to a single manuscript and focuses on studies that compared zolpidem and a benzodiazepine. Finally, the present review identifies questions that remain unanswered, as well as areas that require additional research.

References were obtained from a MEDLINE (1976–1997) search that used the term "zolpidem," and from the citation lists of original research articles. Studies that used nonhumans and humans are reviewed. Where possible, this review focuses on prospective, laboratory, or clinical studies that compared

zolpidem and a benzodiazepine. Retrospective studies and case reports are not reviewed.

### REINFORCING EFFECTS AND ABUSE POTENTIAL

Commonly used benzodiazepine, nonbenzodiazepine and over-the-counter hypnotics have at least some abuse potential (4,50,85,100,152,153). Most notably, the nonmedical use of benzodiazepines at supratherapeutic doses is common among individuals with histories of ethanol, opioid, and sedative dependence (10,20,26,50,51,55,80,87,88,98,135,140).

The reinforcing effects of a drug may be the single most important determinant of its abuse potential. Preclinical studies with laboratory animals typically assess a drug's reinforcing effects by determining whether it maintains self-administration (12,13,46). In a typical self-administration experiment, animals receive administrations of drug or vehicle (i.e., placebo) contingent on emitting a response (e.g., lever press). Drugs that maintain rates of self-administration greater than those observed with vehicle are deemed to be reinforcers. Importantly, there is a high degree of concordance between drugs that function as reinforcers in laboratory animals and those that are abused by humans (32).

Self-administration procedures adapted for use with humans are sometimes used to determine the relative reinforcing effects of commonly prescribed hypnotics (4,50,100,101). More often, however, human laboratory studies indirectly assess the reinforcing effects of a drug using subject ratings (e.g., ratings of "drug liking"). Individuals with histories of ethanol or drug abuse are usually employed as subjects in these studies because they may be at increased risk to abuse anxiolytic/hypnotic compounds (24,29). Commonly abused sedatives generally increase ratings of "drug liking" as a function of dose in individuals with histories of ethanol or drug abuse, and there is a reasonably good correspondence between these ratings and the reinforcing effects of these drugs (24,29,99, 101,144).

Below, studies that compared the reinforcing effects and abuse potential of zolpidem are reviewed. Pharmacokinetic and physiochemical characteristics of zolpidem that may contribute to its reinforcing effects and abuse potential are then discussed.

#### *Studies Conducted With Laboratory Animals*

To the best of this author's knowledge, there is only one published study that compared rates of self-administration maintained by zolpidem and triazolam (49). In this experiment, separate groups of baboons initially trained to self-administer cocaine (0.32 mg/kg/injection) were allowed to self-administer a maximum of eight injections/day of zolpidem (0.01–1.0 mg/kg/injection) and triazolam (0.01–0.32 mg/kg/injection) ($n$ = 8 and 12 baboons/group, respectively). Zolpidem and triazolam maintained greater self-administration than vehicle at some dose (Fig. 1). The average number of injections/day across the last 5 days for the dose maintaining the greatest number of self-administrations was 6.9 for zolpidem (range = 3.0–7.8) and 5.5 for triazolam (range = 2.1–5.6).

#### *Studies Conducted With Humans*

To the best of this author's knowledge, the reinforcing effects of zolpidem have not been directly assessed in humans. There are, however, two reports that indirectly assessed zolpidem's reinforcing effects and abuse potential in individuals

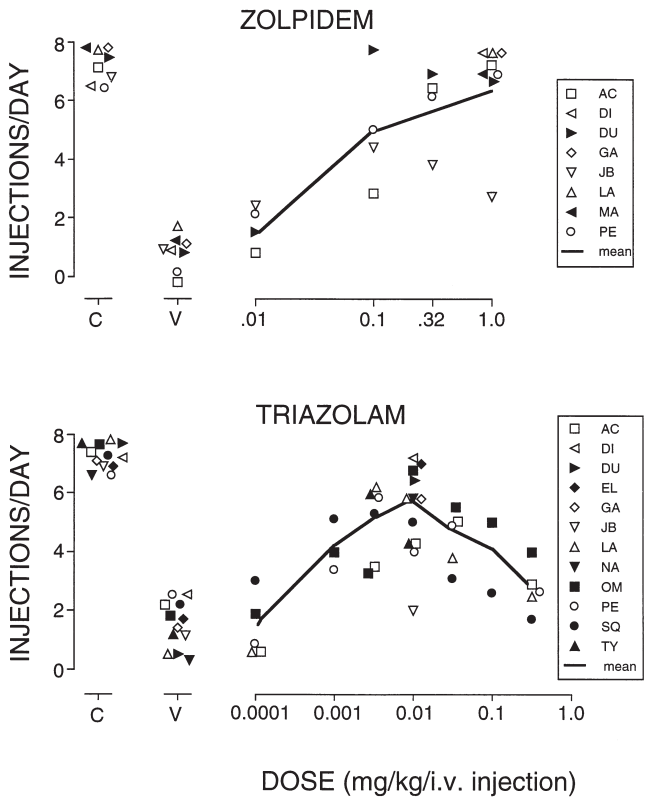


FIG. 1. Mean number of injections for zolpidem and triazolam. X-axes: dose (mg/kg/injection). Y-axes: injections per day. Data points above C indicate number of cocaine injections per day. Data points above V indicate number of vehicle injections per day. Symbols represent individual baboons. The line connects means for each dose tested. Redrawn from Griffiths et al. (49).

with histories of ethanol or drug abuse (28,108). In the first study, 15 volunteers with histories 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 (28). Across the range of doses tested, zolpidem and triazolam produced comparable dose-related increases in subject ratings of "drug liking" (Fig. 2).

A study recently completed in our laboratory was designed to replicate and extend these findings by indirectly assessing the reinforcing effects and abuse potential of zolpidem (15, 30, and 45 mg), triazolam (0.25, 0.5, and 0.75 mg), trazodone (100, 200, and 300 mg), and placebo in 10 volunteers with histories of ethanol and drug abuse (108). In this study, zolpidem and triazolam generally increased subject ratings of "drug liking" as a function of dose. The two highest doses of zolpidem and triazolam tested increased these ratings above placebo levels. Corresponding doses of zolpidem and triazolam produced comparable increases. Only the intermediate dose of trazodone tested, 200 mg, increased ratings of "drug liking" above placebo levels. These findings systematically replicate those described above, and suggest that the abuse potential of zolpidem is comparable to that of triazolam.

#### *Pharmacokinetics Factors*

Rate of onset is thought to be a critical determinant of a drug's reinforcing effects and abuse potential (14,31,57). Con-

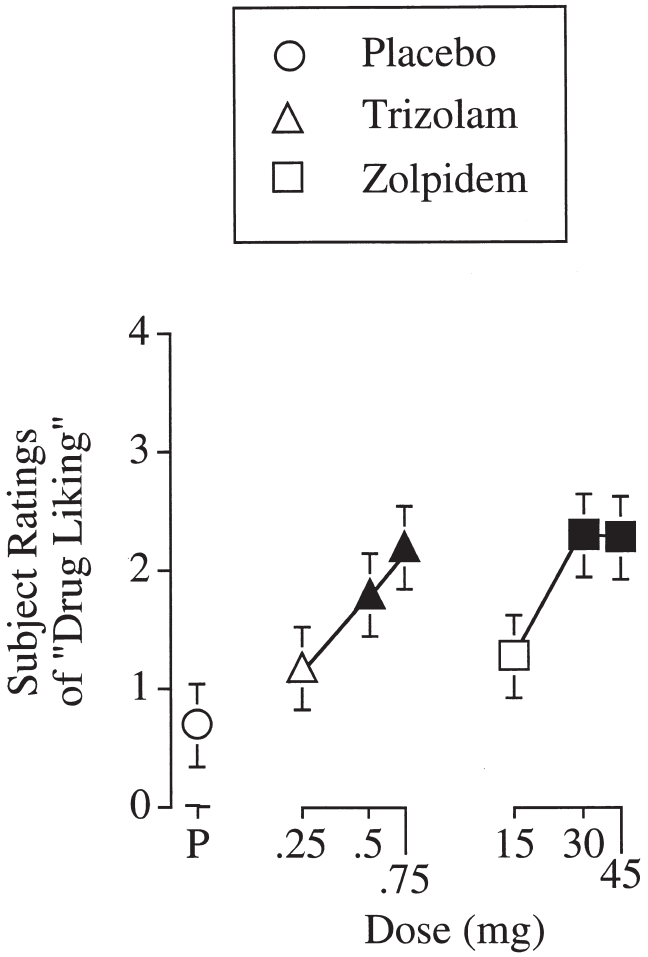


FIG. 2. Dose effects for subject ratings of "drug liking." Data are expressed as a peak effect; brackets show ±1 SEM. Data points show means of 15 subjects. X-axes: dose in mg; data points above "PL" designate placebo values. Y-axes: subject ratings of "drug liking." Filled symbols indicate those values which are significantly different from the placebo value. Redrawn from Evans et al. (28).

trolled laboratory studies that systematically manipulated the rate of onset of an anxiolytic/sedative compound (e.g., alprazolam, diazepam, and pentobarbital) generally support this notion in that subject ratings of "drug liking" or "euphoria" are significantly higher when peak drug plasma levels are attained rapidly (22,23,86).

Zolpidem is rapidly absorbed. The mean time-to-peak plasma concentration ($t_{max}$) following an acute oral dose of 20 mg zolpidem is approximately 0.8–2.6 h (34,70,118). The mean time-to-peak plasma concentration following an acute oral dose of 0.25 mg triazolam, 15 mg temazepam, or 4 mg estazolam is approximately 1, 1.5, and 2.3 h, respectively (40, 77). Based on these pharmacokinetic data, the reinforcing effects and abuse potential of zolpidem would not be expected to differ significantly from these benzodiazepines.

*Physiochemical Characteristics*

When drugs can be administered intravenously or intranasally their effects onset much faster, and the risk of abuse is probably greater (14,31,57). In the late 1980s, for example, there were several reports of intravenous temazepam abuse in the United Kingdom (50,141,154). These incidents of intravenous abuse were due, in part, to the fact that liquid temazepam was formulated in soft, penetrable capsules. The liquid temazepam could easily be drawn in to a syringe and injected. The manufacturers of temazepam subsequently reformulated temazepam in hard, impenetrable gel capsules or as tablets in an attempt to reduce parentral abuse (71).

Zolpidem tartrate is water soluble, while most available benzodiazepines are not (93). Thus, zolpidem could probably be injected more easily than most available benzodiazepines. However, to the best of this author's knowledge, there are no published reports of intravenous zolpidem abuse. Thus, whether parentrally administered zolpidem functions as a reinforcer and has abuse potential is unknown. Future studies that compare the reinforcing effects and abuse potential of intravenously administered zolpidem and a benzodiazepine would obviously be interesting and informative.

*Summary*

Zolpidem maintains rates of self-administration comparable to those observed with triazolam in nonhuman primates. Zolpidem and triazolam produced comparable increases in subject ratings of "drug liking" in human volunteers with histories of drug and ethanol abuse. The pharmacokinetic profile of zolpidem is similar to that of other commonly prescribed benzodiazepine hypnotics. Thus, the available literature suggests the reinforcing effects and abuse potential of zolpidem are probably not significantly different from those of most available benzodiazepine hypnotics. However, zolpidem, unlike most available benzodiazepines, is water soluble and may be more easily abused parentrally.

## DISCRIMINATIVE-STIMULUS EFFECTS

Preclinical laboratory studies characterize a drug's interoceptive or discriminative-stimulus effects using drug-discrimination procedures. In a typical drug-discrimination experiment, one response (e.g., press right lever) is reinforced following the injection of drug and a different response (e.g., press left lever) following the injection of vehicle. Following training, novel drugs are administered to determine if they share discriminative-stimulus effects with the training drug.

The drug-discrimination procedure has several advantages. First, drug discrimination is pharmacologically specific in that drugs from the same class as the training drug generally increase drug-appropriate responding as a function of dose, while drugs from different classes generally produce placebo-appropriate responding (37). Second, results from drug-discrimination studies are generally concordant with drug actions at the cellular level (54). Third, the discriminative-stimulus effects of drugs in laboratory animals are thought to be a model of the subject-rated effects of drugs in humans (96,133,134). Drugs that produce similar discriminative-stimulus effects in laboratory animals generally produce similar subject-rated effects in humans. Because of these advantages, drug-discrimination procedures have been used extensively in preclinical experiments to study sedative/hypnotic drugs.

Drug-discrimination procedures adapted for use with humans are being used more frequently to characterize the behavioral effects of commonly abused drugs, including sedative/hypnotic compounds (60,61,90,91,113). The results of these human drug-discrimination experiments are generally concordant with those from preclinical studies (63). Importantly, recently published studies conducted with humans sug-

gest that drugs that act at the $GABA_A$ receptor complex differ significantly in terms of their discriminative-stimulus effects (64). Below, studies that assessed the discriminative-stimulus effects of zolpidem are reviewed.

*Studies Conducted With Laboratory Animals*

Drug-discrimination studies conducted with rodents have consistently demonstrated that the discriminative-stimulus effects of zolpidem are distinguishable from those of benzodiazepines. First, in rats trained to discriminate between zolpidem (2 mg/kg) and vehicle, high doses of triazolam and chlordiazepoxide (0.3 and 20 mg/kg, respectively) only partially substituted for zolpidem (i.e., each drug occasioned approximately 70% zolpidem-appropriate responding) (120). Second, in rats trained to discriminate chlordiazepoxide (5 or 20 mg/kg) from vehicle, a high dose of zolpidem (3 mg/kg) only partially substituted for the training dose (i.e., approximately 55–70% drug-appropriate responding) (125). Third, in rats trained to discriminate pentobarbital (8 mg/kg) from vehicle, zolpidem (0.5–4 mg/kg) occasioned less than 50% drug-appropriate responding, while triazolam (0.1 and 0.2 mg/kg) occasioned ⩾80% drug-appropriate responding (107). Fourth, in rats trained to discriminate between 0.32 and 3.2 mg/kg midazolam from no drug, midazolam (0.032–10 mg/kg), triazolam (0.0032–3.2 mg/kg), and diazepam (0.032–18 mg/kg) produced similar effects (126). Each drug initially dose dependently increased low-dose (i.e., 0.32 mg/kg midazolam) lever responding and then dose dependently increased high-dose (3.2 mg/kg) lever responding. Zolpidem (0.032–3.2 mg/kg), by contrast, dose dependently increased responding only on the low-dose lever (i.e., 0.32 mg/kg midazolam). Fifth, Ro 16-6028 and Ro 17-1812, two mixed agonist–antagonist benzodiazepines, produced drug-appropriate responding in chlordiazepoxide-trained rats, but not zolpidem-trained rats (119). Sixth, CGS 9896, a pyrazoloquinoline, and ZK 91296, a β-carboline, antagonized the discriminative-stimulus effects of zolpidem, but not chlordiazepoxide (121). Finally, zolpidem did not occasion significant levels of drug-appropriate responding in rats trained to discriminate between 1.0 g/kg ethanol and saline (58). Benzodiazepines, by contrast, engender high levels of drug-appropriate responding in ethanol-trained rats (130).

Studies conducted with nonhuman primates suggest the discriminative-stimulus effects of zolpidem are similar to those of benzodiazepines. Zolpidem and triazolam completely substituted (i.e., >80 percent drug-appropriate responding) for the training drug in baboons and rhesus monkeys trained to discriminate between pentobarbital (10 mg/kg) and vehicle (49,107), and in baboons trained to discriminate between lorazepam (1.8 mg/kg) and vehicle (49).

*Studies Conducted With Humans*

There are at least five experiments that examined the discriminative-stimulus effects of zolpidem in humans (35,113, 115,117,137). The results of three of these studies suggest that the discriminative-stimulus effects of zolpidem may be distinguishable from those of triazolam. The first study used a three-way drug-discrimination procedure to determine if volunteers could discriminate between zolpidem (20 mg/70 kg), triazolam (0.5 mg/70 kg), and placebo (35). All volunteers acquired the active drug versus placebo discrimination, and five of seven acquired the zolpidem vs. triazolam discrimination. In the second study, the discriminative-stimulus effects of zolpidem (2.5–35 mg/70 kg), alprazolam (0.25–1.75 mg/70 kg), and caffeine (75–525 mg/70 kg) were examined in volunteers trained to discriminate between 0.35 mg/70 kg triazolam and placebo using a two-response and novel-response procedure (137). The novel-response procedure offers volunteers an alternative for drug effects that are unlike those of the training drug (i.e., triazolam) or placebo. Under the two-response procedure, zolpidem and alprazolam, but not caffeine, engendered dose-dependent increases in triazolam-appropriate responding. Under the novel-response procedure, zolpidem and alprazolam also engendered dose-dependent increases in triazolam-appropriate responding. However, intermediate doses of zolpidem also engendered some novel-appropriate responding. Caffeine engendered both novel- and placebo-appropriate responding. Finally, in an ongoing study in our laboratory, the discriminative-stimulus effects of zolpidem (2.5–15 mg), triazolam (0.0625–0.375 mg), pentobarbital (25–150 mg), and caffeine (100–600 mg) are being examined in volunteers trained to discriminate between 15 mg zolpidem and placebo (116). Preliminary results ($n = 2$) suggest that zolpidem and triazolam dose dependently increased drug-appropriate responding as a function of dose in both subjects. The two highest doses of pentobarbital tested occasioned 100% zolpidem-appropriate responding in one subject. In the other subject, by contrast, the doses of pentobarbital tested did not occasion any zolpidem-appropriate responding. Caffeine engendered low levels of drug-appropriate responding in both subjects.

The results of the other two human drug-discrimination studies suggest that the discriminative-stimulus effects of zolpidem are similar to those of pentobarbital and triazolam (113,115). In the first study, the discriminative-stimulus effects of zolpidem (2.5–20 mg), triazolam (0.0625–0.5 mg), pentobarbital (25–150 mg), and caffeine (50–400 mg) were assessed in four volunteers trained to discriminate between 100 mg pentobarbital and placebo (113). Zolpidem, triazolam, and pentobarbital, but not caffeine, generally increased pentobarbital-appropriate responding as a function of dose. On average, the three highest doses of zolpidem and triazolam, and the two highest doses of pentobarbital, occasioned ⩾75% drug-appropriate responding. In the second study, the discriminative-stimulus effects of zolpidem (2.5–20 mg/70 kg), triazolam (0.063–0.5 mg/70 kg), oxazepam (3.125, 6.25, 12.5, and 25 mg/70 kg), and caffeine (50, 100, 200, and 400 mg/70 kg) were assessed in five volunteers trained to discriminate between 0.25 mg/70 kg triazolam and placebo (115). Zolpidem and triazolam, and to a lesser extent oxazepam, but not caffeine, increased triazolam-appropriate responding as a function of dose.

*Summary*

The discriminative-stimulus effects of zolpidem are distinguishable from those of benzodiazepines and barbiturates in rodents, but not nonhuman primates. The reason for the discrepancy between studies conducted with rodents and nonhuman primates is unknown. However, the most parsimonious explanation is that the discriminative-stimulus effects of zolpidem have been studied under a more limited set of conditions in nonhuman primates.

Drug-discrimination studies conducted with humans are mixed regarding differences between zolpidem and benzodiazepines. The findings from three studies suggest the discriminative-stimulus effects of zolpidem are distinguishable from those of benzodiazepine hypnotics like triazolam. The findings from the other two studies, by contrast, suggest the discriminative-stimulus effects of zolpidem are similar to those of triazolam. The mixed results observed in studies conducted

with humans are likely attributable to the use of different methods, most notably the drug-discrimination procedures.

## SUBJECT-RATED DRUG EFFECTS

Human behavioral pharmacology studies often characterize the subject-rated effects of novel drugs relative to a standard compound (59). These studies usually administer a range of acute doses and subjects complete a battery of subject-rated drug-effect questionnaires before drug administration and periodically afterwards. Standardized mood questionnaires like the Addiction Research Center Inventory (ARCI) or Profile of Mood States (POMS) are often employed along with investigator-constructed instruments. The investigator-constructed instruments usually consist of 20–30 adjectives (e.g., sleepy, tired, nausea, stimulated, jittery) that are rated using a five-point ordinal scale (i.e., 0 = Not at All, 4 = Extremely) or a 100-mm visual-analog line (e.g., left-most extreme labeled "Not at All" and right-most extreme label "An Awful Lot") (109–114,117). Drug effects on these instruments are generally dose dependent and pharmacologically specific. Subject-rated drug effects are determined in individuals with and without histories of drug abuse. Below studies that compared the subject-rated effects of zolpidem and a benzodiazepine are reviewed.

### *Studies With Individuals With Histories of Drug or Ethanol Abuse*

To this authors' knowledge, there are two reports that examined the subject-rated effects of zolpidem in individuals with histories of drug abuse (28,108). In the first study, the acute subject-rated effects of zolpidem (15–45 mg), triazolam (0.25–0.75 mg), and placebo were examined in 15 volunteers with histories of drug abuse (28). Drug effects were measured with the ARCI, POMS, and several investigator-constructed instruments. Zolpidem and triazolam produced comparable dose-related increases in subject ratings of "drug effect," which suggests equivalent drug doses were tested. However, across several of the other subject-rated items, zolpidem and triazolam produced a different constellation of drug effects. Zolpidem, but not triazolam, increased subject ratings of somatic symptoms like dizziness, anxiousness, queasiness, and blurred vision. Moreover, on a pharmacological-class questionnaire, the highest zolpidem dose was identified as barbiturate-, benzodiazepine-, or alcohol-like about half as often as was the highest triazolam dose.

As noted above, a study recently completed in our laboratory was designed to replicate and extend these findings by assessing the acute behavioral effects of zolpidem (15, 30, and 45 mg), triazolam (0.25, 0.5, and 0.75 mg), trazodone (100, 200, and 300 mg) and placebo in 10 volunteers with histories of ethanol and drug abuse (108). Drug effects were measured with the ARCI and several investigator-constructed instruments. Zolpidem and triazolam produced comparable dose-related increases in subject ratings of "drug effect,) which suggests equivalent drug doses were tested. The highest dose of zolpidem and triazolam increased subject ratings of "dizzy" significantly above placebo levels, but these dose conditions did not differ from each other. The highest dose of triazolam, but none of the zolpidem doses tested, increased subject ratings of "nausea" significantly above placebo levels. Finally, across the range of doses tested, zolpidem and triazolam were identified as barbiturate- or benzodiazepine-like equally on a pharmacological-class questionnaire (i.e., 43 vs. 40%).

### *Studies With Individuals Without Histories of Drug or Ethanol Abuse*

To this author's knowledge there are at least six studies that comprehensively assessed the subject-rated effects of zolpidem and triazolam in healthy, nondrug abusing volunteers (8,44,110,113,117,150). Each of these studies compared the acute subject-rated effects of zolpidem to those of triazolam. The results of a majority of these studies suggest the subject-rated effects of zolpidem are qualitatively and quantitatively similar to those of triazolam (8,44,110,113,150). However, in the final study some differences between zolpidem and triazolam were observed (117). In this study, the acute subject-rated effects of zolpidem (7.5, 15, and 22.5 mg), triazolam (0.1875, 0.375, and 0.5625 mg), quazepam (15, 30, and 45 mg), and placebo were examined. Drug effects were measured with the ARCI, the Stanford Sleepiness Scale, and a 34-item Drug-Effect Questionnaire. Figure 3 shows some dose–response functions for zolpidem, triazolam, and quazepam from this experiment. This figure shows that zolpidem and triazolam generally produced comparable dose-related increases in PCAG scores on the ARCI, a putative measure of sedation, and subject ratings of "drug effect," which suggests equivalent drug doses were tested. By contrast, the highest dose of zolpidem tested increased ratings of "dizzy" and "confused" significantly above placebo levels while none of the triazolam doses tested did so. None of the doses of quazepam tested increased these ratings above levels observed with placebo.

### *Summary*

Two studies compared the acute subject-rated effects of zolpidem and triazolam in individuals with histories of drug abuse, and six studies compared these compounds in individuals without histories of drug abuse. The results of these studies are mixed. The reason for these mixed results is unknown, but may be due to the use of somewhat different subject-rated drug-effect questionnaires.

## PERFORMANCE-IMPAIRING EFFECTS

Acute administrations of benzodiazepines impair performance (27,36,73). In addition to its safety, tolerability, and favorable pharmacokinetic profile, some of zolpidem's popularity may be attributable to the belief that performance impairment occurs only at supratherapeutic doses (68). Below, studies that compared the performance-impairing effects of zolpidem and a benzodiazepine are reviewed. Special attention is given to those studies that compared 10-mg zolpidem, the recommended hypnotic dose in nonelderly patients, and the clinically recommended dose of a benzodiazepine (e.g., 0.25 mg triazolam or 30 mg temazepam) (93). Finally, because benzodiazepine hypnotics exacerbate the performance-impairing effects of ethanol, studies that assessed the combined effects of zolpidem and ethanol are also reviewed.

### *Studies Conducted With Laboratory Animals*

Preclinical laboratory studies use paradigms like scheduled-controlled responding, acquisition of a conditioned response, and passive avoidance to determine a drug's performance-impairing effects. Studies conducted with rodents have produced mixed results regarding differences between zolpidem and benzodiazepine (e.g., diazepam, lorazepam, and triazolam) (124,139,143). In the first study, doses of zolpidem (0, 0.25, 0.5, 1, and 2 mg/kg) that reduced locomotor activity did not significantly impair acquisition of a conditioned fear re-

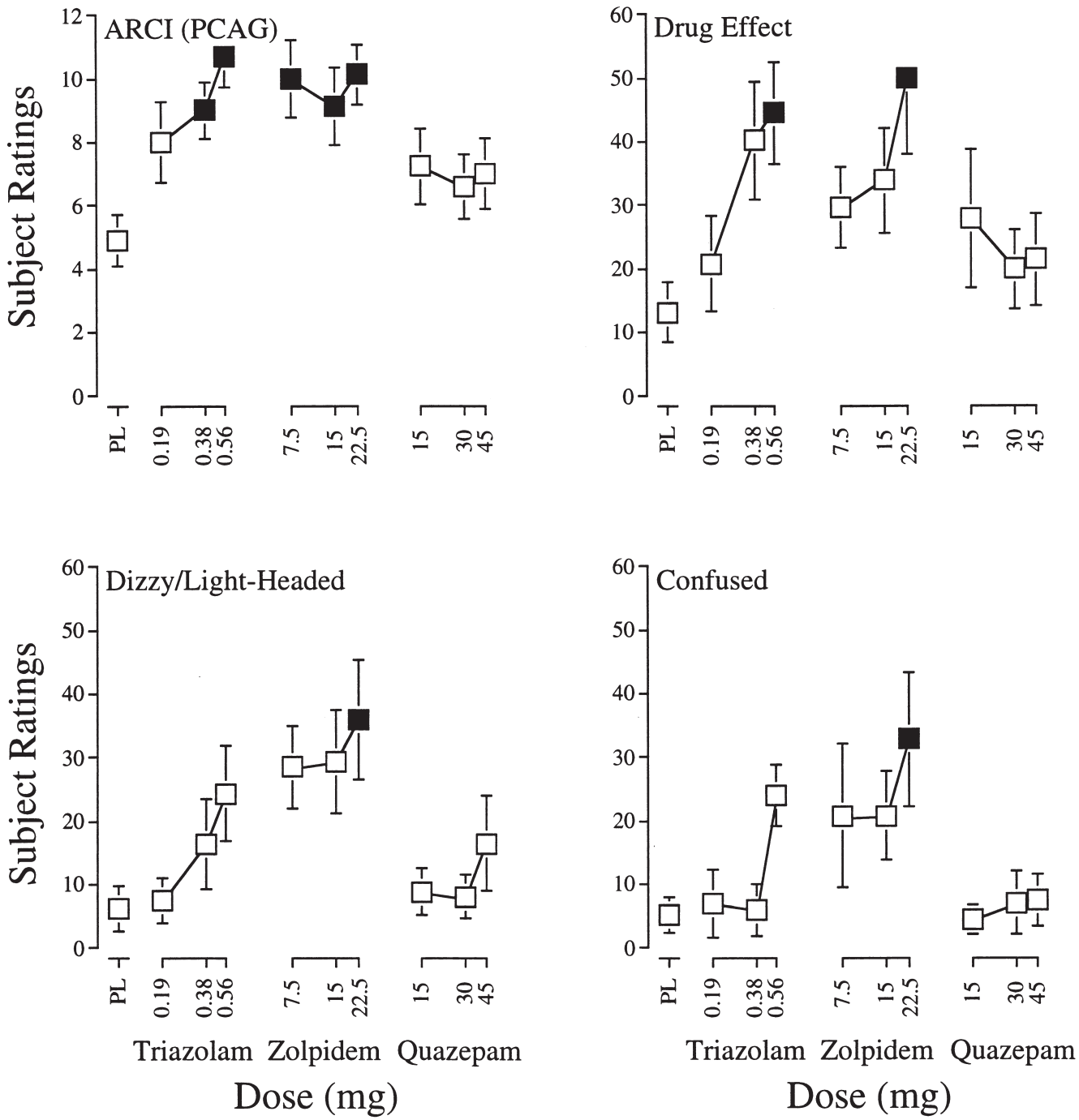


FIG. 3. Dose effects for triazolam, zolpidem, and quazepam for PCAG scores from the ARCI, and subject ratings of "drug effect," "dizzy/light-headed," and "confused." Data are expressed as peak effect. X-axes: dose in mg; data points above "PL" designate placebo values. Data points show means of nine subjects; brackets show ±1 SEM. Filled symbols indicate those values that are significantly different from the placebo value. Redrawn from Rush and Ali (117).

sponse, a measure thought to involve learning and memory (124). Triazolam (0, 0.0125, 0.025, 0.05, and 0.1 mg/kg), by contrast, significantly impaired acquisition of a conditioned fear response at doses lower than needed to significantly reduce locomotor activity. In the second study, the effects of zolpidem (0.33–10 mg/kg), lorazepam (0.1–0.5 mg/kg), and diazepam (0.1–10 mg/kg) on responding maintained by a differential reinforcement of low rate of responding (DRL) schedule were examined in rats (139). Diazepam and lorazepam, but not zolpidem, increased response rate and response bursting. Zolpidem, lorazepam, and diazepam dose dependently decreased reinforcement rate and shifted the distribution of interresponse times leftward. In the third study, the effects of zolpidem (0–30 mg/kg), triazolam (0–0.1 mg/kg), and diaz-

epam (0–10 mg/kg) were assessed in mice using a one-trial passive-avoidance task, a procedure also thought to involve memory (143). Each of the drugs generally impaired performance on this task as a function of dose, and the highest dose of each drug differed significantly from vehicle. To this author's knowledge, there are no published studies that compared the performance-impairing effects of zolpidem and a benzodiazepine in nonhuman primates.

*Studies Conducted With Humans*

There are at least 13 published studies that directly compared the acute performance-impairing effects of zolpidem to those of a benzodiazepine (2,8,28,44,81,95,102,108,110,113, 117,149,150). The results of these studies have been rather consistent despite the use of different methods, performance tasks, subject populations, and comparison compounds. Table 1 shows that the results of 11 studies suggest that the absolute magnitude of impairment produced by zolpidem and the comparison benzodiazepine (i.e., triazolam, temazepam, midazolam, and lorazepam) was comparable (8,28,44,81,95,102,108,110,113, 117,150)

Two studies found that zolpidem produced less impairment than triazolam (Table 1) (2,149). In the first study, zolpidem (20 mg) produced less impairment than triazolam (0.5 mg) on a simulated-escape task (2). In the second study, zolpidem (15 mg) produced less impairment than triazolam (0.5 mg) on a restricted-reminding test and paired-associates memory test (149). However, these doses are probably not clinically equivalent (i.e., zolpidem < triazolam). Testing relatively lower doses of zolpidem than triazolam obviously biases the outcome towards less impairment with the former.

Eight of the studies summarized in Table 1 tested the effects of the most commonly recommended clinical doses of zolpidem (i.e., 10 mg) and triazolam (i.e., 0.25 mg) or temazepam (i.e., 30 mg) (2,8,44,81,102,110,113,149). Six of these studies found significant impairment with 10 mg zolpidem vs. placebo (8,44,81,102,110,113). Significant impairment relative to placebo was also observed with 0.25 mg triazolam or 30 mg temazepam. For example, Figure 4 shows representative data from an experiment that compared the acute performance-impairing effects of zolpidem (5, 10, and 20 mg/70 kg), triazolam (0.125, 0.25, and 0.5 mg/70 kg), temazepam (15, 30, and 60 mg/70 kg), and placebo (110). This figure shows that zolpidem, triazolam, and temazepam impaired performance on a circular lights task as an orderly function of dose and time. The two highest doses of zolpidem, triazolam, and temazepam significantly impaired performance relative to placebo. The absolute magnitude of impairment was comparable across drugs, although the effects of zolpidem onset and offset more rapidly than those of triazolam and temazepam. Two studies failed to find significant impairment with 10 mg zolpidem (2,150).

A study recently completed in our laboratory found that even a subtherapeutic dose of zolpidem can significantly impair human performance (117). In this study, the acute performance-impairing effects of zolpidem (7.5, 15, and 22.5 mg), triazolam (0.1875, 0.375, and 0.5625 mg), quazepam (15, 30, and 45 mg), and placebo were compared in healthy volunteers (Table 1). A sheet of 18 pictures were presented to the volunteers 1.5 h after drug administration. Delayed recall of these pictures was tested 4 h later. Figure 5 shows that all of the doses of zolpidem tested, including 7.5 mg, which is a subtherapeutic dose in nonelderly patients, significantly impaired delayed picture recall relative to placebo. By contrast, only the supratherapeutic doses of triazolam tested, 0.375 and 0.5625 mg, significantly impaired delayed picture recall. None of the doses of quazepam tested impaired performance on this task.

*Interactions With Ethanol*

Combined use of hypnotics and ethanol is widespread and well documented (39). Moreover, hypnotics are often prescribed without adequate information concerning the patient's ethanol use (38). Combined use of hypnotics and ethanol pose increased risk to the individual and society because drug-induced impairment is greater when ethanol is also ingested (53,72). Because ethanol may also interact with the $GABA_A$ receptor (19,66,142), the purportedly unique binding profile of zolpidem suggests it may differentially interact with ethanol.

One study compared the effects of zolpidem and diazepam in combination with ethanol 7.5 ml/kg in mice (143). In this study, zolpidem and diazepam alone did not impair the traction and righting reflex up to doses of 30 mg/kg. When combined with 7.5 ml/kg ethanol, the $ED_{50}$ for zolpidem to impair the traction and righting reflex was 9 and 17 mg/kg, respectively. The $ED_{50}$ for diazepam to impair the traction and righting reflex in combination with ethanol was 0.5 and 1.1 mg/kg, respectively. Thus, both drugs were more toxic when combined with ethanol, although zolpidem was less potent than diazepam.

There is at least one study that examined the effects of zolpidem (10 and 15 mg), alone and in combination with ethanol (dose selected on individual basis to attain a peak blood ethanol concentration of 0.08%), in humans (151). Zolpidem alone (i.e., in combination with placebo ethanol) dose dependently impaired performance on a battery of tests that included a divided-attention, visual-backward masking, vigilance, and Sternberg task. Ethanol alone (i.e., in combination with placebo zolpidem) also significantly impaired performance on most of these tests. Combining zolpidem and ethanol produced greater impairment than observed with either drug alone. The combined effects of zolpidem and ethanol were approximately additive, which is similar to the effects of benzodiazepines in combination with ethanol (16,72).

*Summary*

Studies conducted with rodents have produced mixed results regarding differences between zolpidem and benzodiazepines in terms of performance-impairing effects. Most available studies conducted with humans suggest that zolpidem and benzodiazepines produce comparable performance impairment. Importantly, a majority of studies that tested the effects of 10 mg zolpidem, the clinically recommended hypnotic dose for nonelderly patients, found significant impairment relative to placebo. The magnitude of this impairment was generally comparable to that observed with the clinically recommended dose of a benzodiazepine (e.g., 0.25 mg triazolam or 30 mg temazepam). The results of a single study suggest that even a subtherapeutic dose of zolpidem can significantly impair human performance. This finding obviously needs to be replicated. Finally, the performance-impairing effects of zolpidem and ethanol are approximately additive, which is similar to the effects of benzodiazepines in combination with ethanol.

## TOLERANCE

Repeated administrations of benzodiazepine hypnotics often produce tolerance to their sleep-promoting effects. Toler-

TABLE 1

SUMMARY OF THE PERFORMANCE-IMPAIRING EFFECTS OF ZOLPIDEM VS. A BENZODIAZEPINE

| Authors | Reference Number | Drugs (Dose) | Dosing Regimen | Study Design | Subjects | Tasks | Results |
|---|---|---|---|---|---|---|---|
| Rush and Ali (1998) | 117 | Zolpidem (7.5, 15, 22.5 mg) Triazolam (0.1875, 0.375, 0.5625 mg) Quazepam (15, 30, 45 mg) Placebo | Acute | Within subject | Healthy Volunteers ($n$ = 9) | Picture recall, digit-entry and recall, DSST, repeated acquisition and circular lights task. | Zolpidem and triazolam produced comparable impairment on these tasks. Zolpidem and triazolam produced greated impairment than quazepam. |
| Rush et al. (1998) | 108 | Zolpidem (15, 30, 45 mg) Triazolam (0.25, 0.5, 0.75 mg) Trazodone (100, 200, 300 mg) | Acute | Within subject | Drug Abusers ($n$ = 10) | Picture recall, digit-enter and recall, DSST and balance. | Zolpidem and triazolam produced comparable dose-related impairment. |
| Rush et al. (1997) | 113 | Zolpidem (2.5, 5, 10, 20 mg) Triazolam (0.063, 0.125, 0.25, 0.5 mg) Placebo | Acute | Within subject | Healthy Volunteers ($n$ = 4) | Digit-enter and recall, and DSST. | Zolpidem and triazolam produced comparable dose-related impairment. |
| Mintzer et al. (1997) | 81 | Zolpidem (5, 10, 20 mg/70kg) Triazolam (0.125, 0.25, 0.5 mg/70 kg) Placebo | Acute | Within subject | Healthy Volunteers ($n$ = 11) | Word recall, digit-enter and recall, DSST, circular lights, time estimation, trails-making task, and balance task. | Zolpidem produced less impairment than triazolam on the time-estimation task, but zolpidem produced greater impairment than triazolam on the trails-making task. No other between-drug differences were observed. |
| Rush and Griffiths (1996) | 110 | Zolpidem (5, 10, 20 mg/70 kg) Triazolam (0,125, 0.25, 0.5 mg/70 kg) Temazepam (15, 30 60 mg/70 kg) Placebo | Acute | Within subject | Healthy Volunteers ($n$ = 11) | Picture recall, digit-entry and recall, DSST, repeated acquisition, circular lights and balance. | Zolpidem, triazolam, and temazepam produced comparable dose-related impairment. |
| Greenblatt et al. (1996) | 44 | Zolpidem (10 mg) Triazolam (0.25 mg) Placebo | Acute | Within subject | Healthy Volunteers ($n$ = 18) | Delayed word-list recall and DSST | Zolpidem and triazolam produced comparable impairment on both tasks. |
| Wesensten et al. (1995) | 150 | Zolpidem (20 mg) Triazolam (0.5 mg) Placebo | Acute | Between subject | Healthy Volunteers ($n$ = 30 [10/group]) | Restricted-reminding test, paired-associates test and simulated escape task. | Zolpidem and triazolam produced comparable impairment. |
| Wesensten et al. (1995) | 149 | Zolpidem (5, 10, 15 mg/70 kg) Triazolam (0.125, 0.25, 0.5 mg/70 kg) Placebo | Acute | Between subject | Healthy Volunteers ($n$ = 70 [10/group]) | Restricted-reminding test, paired-associates memory test and stimulated escape task. | Triazolam produced greater impairment than zolpidem. |

(*continued*)

TABLE 1
CONTINUED

| Authors | Reference Number | Drugs (Dose) | Dosing Regimen | Study Design | Subjects | Tasks | Results |
|---|---|---|---|---|---|---|---|
| Roehrs et al. (1994) | 102 | Zolpidem (10, 20 mg)<br>Triazolam (0.25, 0.5 mg)<br>Placebo | Acute | Within subject | Healthy Volunteers ($n$ = 23) | Digit-span and Buschke-selective-reminding-and-recognition task. | Zolpidem and triazolam produced comparable impairment. |
| Berlin et al. (1993) | 8 | Zolpidem (10 mg)<br>Triazolam (0.25 mg)<br>Placebo | Acute | Within subject | Healthy Volunteers ($n$ = 18) | Paired-associates-memory and picture-recall test. | Zolpidem and triazolam produced comparable impairment. |
| Balkin et al. (1992) | 2 | Zolpidem (5, 10, 20 mg)<br>Triazolam (0.5 mg)<br>Placebo | Acute | Between subject | Healthy volunteers ($n$ = 50 [10/group]) | Two-column addition, logical reasoning, and simulated-escape task. | Triazolam, but not zolpidem, impaired simulated-escape performance. |
| Evans et al. (1990) | 28 | Zolpidem (15, 30, 45 mg)<br>Triazolam (0.25, 0.5, 0.75 mg)<br>Placebo | Acute | Within subject | Drug abusers ($n$ = 15) | Picture recall, digit-entry and recall, circular lights, DSST, reaction time and balance. | Zolpidem and triazolam produced comparable dose-related impairment. |
| Praplan-Pahud et al. (1990) | 95 | Zolpidem (20 mg)<br>Midazolam (15 mg)<br>Placebo | Acute | Between subject | Preoperative patients ($n$ = 30–32/group) | Recall of a number and playing card. | Triazolam and midazolam produced comparable anterograde amnesia. |

ance may lead to dose escalation and increased risk of physiological dependence. Furthermore, dose escalation may lead to ingesting larger acute doses and, in turn, greater performance impairment. Hypnotic compounds that do not produce tolerance would obviously offer an advantage clinically. Below studies that compared the tolerance-producing effects of zolpidem and a benzodiazepine are reviewed.

### *Studies Conducted With Animals*

Four preclinical studies conducted with rodents suggest that tolerance does not develop to the behavioral effects of zolpidem (18,92,122,123). In two experiments, separate groups of rats received daily injections of 1 mg/kg zolpidem or 3 mg/kg midazolam for 10 days (122,123). In the third experiment, separate groups of mice received two daily injections of 30 mg/kg zolpidem or midazolam for 10 days (92). In the fourth study, separate groups of mice received injections of 1.5 mg/kg zolpidem or diazepam for 16 days (18). Tolerance developed to the anticonvulsant, behavioral and sedative effects of midazolam and diazepam. Tolerance to the effects of zolpidem was not evident or less pronounced than observed with midazolam and diazepam.

Two studies assessed whether rats chronically treated with a benzodiazepine became cross tolerant to the behavioral effects of zolpidem (17,105). The results of these studies are mixed. In the first study, rats received chronic infusions of triazolam (3 mg/kg/day) for 14 days (17). Chronic triazolam treatment produced cross tolerance to the depressant effects of lorazepam and zopiclone, but not zolpidem. In the second study, daily administrations of diazepam (5 mg/kg for 3 weeks) and flurazepam (20 mg/kg for 1 week) resulted in significant tolerance to anticonvulsant effects 12 and 48 h after the discontinuation of chronic drug treatment (105). Significant cross tolerance to the effects of zolpidem, bretazenil, and clonazepam were generally observed at these times.

The results of a study conducted with nonhuman primates suggest that repeated administrations of zolpidem produce tolerance (49). In this study, baboons received vehicle injections on days 1 and 10, and daily injections of zolpidem (3.2 or 5.6 mg/kg) on days 2–9. The initial administration of zolpidem produced significant ataxia. Ataxia progressively decreased with repeated administrations of zolpidem and returned to near vehicle levels by the fifth day. This effect was also observed with midazolam (5.6 mg/kg/day) under similar experimental conditions in the same laboratory (127).

### *Studies Conducted With Humans*

Several clinical trials that assessed the efficacy of zolpidem failed to find tolerance to its sleep-promoting effects following repeated administrations (30,94,104,129,131,136). However, to this author's knowledge, there is only one published report that directly compared zolpidem and triazolam in terms of their tolerance-producing effects (147). In this study, separate groups of patients with sleep complaints were treated with 10 mg zolpidem, 0.5 mg triazolam, or placebo for 28 nights. Active drug treatment was preceded by a 2-night placebo baseline period. Both zolpidem and triazolam were effective on nights 1 and 2, as evidenced by a significant decrease in latency to persistent sleep relative to baseline. The hypnotic efficacy of both drugs decreased across the 28-day treatment period, and on nights 27 and 28 neither drug significantly decreased latency to persistent sleep.

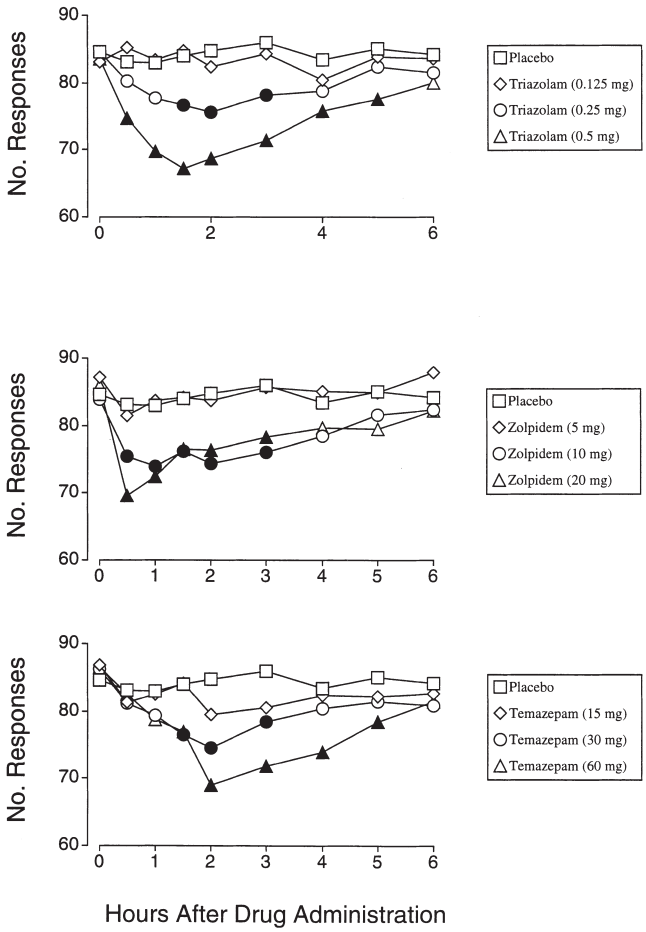


FIG. 4. Dose–effect and time-course functions for triazolam (top), zolpidem (middle), and temazepam (bottom) for number of responses on a circular lights task. X-axes: time after drug administration in hours; P indicates predrug. Data points show means of 11 subjects. Filled symbols indicate those values that are significantly different from the corresponding placebo value at the same time-point. Redrawn from Rush and Griffiths (110).

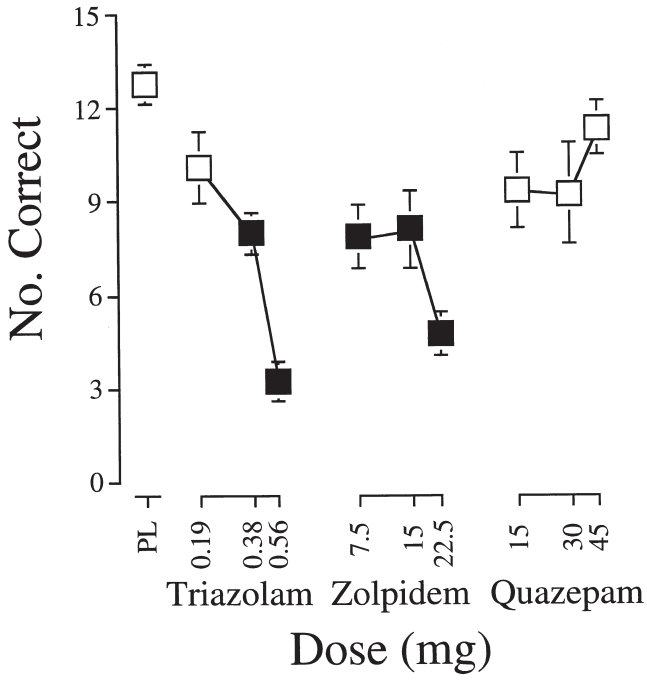


FIG. 5. Dose effects for triazolam, zolpidem, and quazepam for number correct on a delayed picture recall task. X-axes: dose in mg; data points above "PL" designate placebo values. Data points show means of nine subjects; brackets show ±1 SEM. Filled symbols indicate those values that are significantly different from the placebo value. Redrawn from Rush and Ali (117).

*Summary*

Studies conducted with rodents generally suggest that repeated administrations of zolpidem, unlike benzodiazepines, do not produce tolerance. Studies conducted with nonhuman primates, by contrast, suggest that tolerance develops to the behavioral effects of zolpidem with repeated administrations. The findings of the only published clinical study conducted with humans that directly compared zolpidem and a benzodiazepine suggest that tolerance develops to the hypnotic effects of both zolpidem and triazolam.

## PHYSIOLOGICAL DEPENDENCE

Repeated administrations of benzodiazepine hypnotics often produce physiological dependence, and discontinuing treatment results in a recognizable withdrawal syndrome. Preclinical studies determine whether a drug produces physiological dependence by chronically treating animals, and then abruptly terminating drug administration and observing the animal for symptoms of withdrawal, or by administrating an appropriate antagonist to determine if it precipitates withdrawal. Clinical studies determine whether a drug produces physiological dependence by observing patients for symptoms of withdrawal following the discontinuation of chronically administered drug. For example, following repeated administrations of benzodiazepine hypnotics, discontinuing treatment sometimes results in rebound insomnia, which is defined as a significant worsening of sleep difficulties relative to predrug levels (62). Studies that compared the withdrawal syndrome after discontinuing zolpidem or benzodiazepine treatment are reviewed below.

*Studies Conducted With Laboratory Animals*

There are at least four preclinical studies conducted with rodents that suggest repeated administrations of zolpidem generally do not produce dependence (92,132,143,145). In the first study, mice received daily injections of zolpidem (150 mg/kg), alprazolam (0.15–15 mg/kg/day), chlordiazepoxide (0.15–15 mg/kg/day), diazepam (1.5–15 mg/kg/day), flurazepam (1.5–15 mg/kg/day), midazolam (0.15–15 mg/kg/day), or triazolam (0.15–15 mg/kg/day) (145). Twenty-four hours after the last injection, mice received an intravenous injection of flumazenil (2.5 mg/kg), a benzodiazepine-receptor antagonist, and were then tested for electroshock seizure thresholds. Flumazenil-precipitated withdrawal, as evidenced by a lowering of the seizure threshold, was not evident in the zolpidem-treated mice. By contrast, flumazenil-precipitated withdrawal was observed in the benzodiazepine-treated mice. In the second

study, separate groups of mice were treated with zolpidem (30 mg/kg, b.i.d.), midazolam (30 mg/kg, b.i.d.), or vehicle for 10 consecutive days (93). Flumazenil (5 mg/kg) was administered 3 and 6 h after the last administration of zolpidem, midazolam, or vehicle to determine if a benzodiazepine-like withdrawal syndrome could be precipitated. Spontaneous withdrawal was measured for 67 h after the last drug administration. Neither precipitated or spontaneous withdrawal were observed in the zolpidem- or vehicle-treated mice. Precipitated withdrawal (e.g., decreased the latency to convulsions) was observed in the midazolam-treated mice and spontaneous withdrawal was observed 14 h after the last drug administration. In the third study, separate groups of mice were treated orally with zolpidem (100–300 mg/kg/day, b.i.d.), alprazolam (1-10 mg/kg/day, b.i.d.), bretazenil (30–300 mg/kg/day, b.i.d.), or vehicle for 17 days (132). Five hours after the last injection, the mice were injected with sarmazenil (3 mg/kg), a partial agonist, and observed for signs of withdrawal (e.g., tremor, wild running, seizures). Withdrawal was clearly evident in the alprazolam-treated mice, but much less so in the zolpidem- and bretazenil-treated mice. In the final study, separate groups of mice received daily injections of 150 mg/kg zolpidem, 300 mg/kg zolpidem, 30 mg/kg diazepam, or vehicle for 3 days (143). Twenty-four hours after the last injection, mice received an intravenous injection of flumazenil (2.5 mg/kg) and were then tested for electroshock seizure thresholds. Relative to the vehicle-treated group, the seizure threshold was significantly lower in mice treated with 300 mg/kg zolpidem and 30 mg/kg diazepam.

There are at least three preclinical studies conducted with nonhuman primates that examined whether repeated administrations of zolpidem produce physiological dependence (49,132,148). The results of two of these studies suggest that repeated administrations of zolpidem produce physiological dependence similar to that observed with repeated administrations of a benzodiazepine (49,148). In the first study, baboons were allowed to self-administer zolpidem (1 mg/kg/injection) for 2 weeks (49). Substitution of placebo resulted in a time-limited suppression of food intake, which suggests a withdrawal effect. This effect was similar to that observed with midazolam (5.6 mg/kg/day) under nearly identical experimental conditions in the same laboratory (127). In the second study, similar withdrawal signs were observed in baboons chronically treated with 32 mg/kg zolpidem for 17 days (148). In the final study, separate groups of squirrel monkeys were treated orally with zolpidem (10–20 mg/kg/day, t.i.d.), alprazolam (1 mg/kg/day, t.i.d.), bretazenil (1–3.3 mg/kg/day, t.i.d.), or vehicle for 11 days (132). The monkeys were injected with 0.25 mg/kg sarmazenil 5, 24, and 48 hours after the final oral treatment and observed for 2 h for signs of withdrawal (e.g., vomiting, tremors, and convulsions). Sarmazenil-precipitated withdrawal was also evident in the zolpidem- and bretazenil-treated monkeys, but it was much less striking than in the alprazolam-treated animals. Sarmazenil-precipitated withdrawal was more evident in those animals treated with high doses of zolpidem or bretazenil.

### *Studies Conducted With Humans*

To the best of this author's knowledge, there are only three reports that directly compared zolpidem and triazolam in terms of dependence-producing effects in humans (82, 104,147). In the first study, separate groups of patients suffering from moderate to severe chronic insomnia were treated with 10 mg zolpidem, 0.5 mg triazolam, or placebo for 27 nights (82). Placebo was substituted during a 3-night withdrawal phase. In the second study, separate groups of patients with sleep complaints were treated with 10 mg zolpidem, 0.5 mg triazolam, or placebo for 28 nights (147). Active drug treatment was preceded by a 2-night placebo baseline period. Placebo was substituted during a 3-night withdrawal period. In both of these studies, significant rebound insomnia was observed in the triazolam-treated group, but not the zolpidem- or placebo-treated groups, during the withdrawal period. In the third study, separate groups of hospitalized elderly insomniac patients (age = 58–98 years) were treated with 5 mg zolpidem, 10 mg zolpidem, or 0.25 mg triazolam at bedtime for 3 weeks (104). Active drug treatment was preceded by 3 days of placebo administration. When placebo was substituted during a 7-night withdrawal period, there was no evidence of rebound insomnia, agitation, or anxiety in any of the groups.

### *Summary*

Studies conducted with rodents suggest that repeated administrations of zolpidem generally do not produce physiological dependence. Studies conducted with nonhuman primates have produced mixed results regarding whether repeated administrations of zolpidem produce physiological dependence. The reason for the discrepancy between studies that employed nonhuman primates is unknown, but may be due to the methods used. Most notably, the one study that found less severe dependence with zolpidem than a benzodiazepine used sarmazenil, a partial agonist, to precipitate withdrawal. The studies that found comparable physiological dependence with zolpidem and a benzodiazepine, by contrast, precipitated withdrawal with flumazenil, a benzodiazepine antagonist, or discontinued chronic drug treatment and measured spontaneous withdrawal.

Studies conducted with humans suggest that repeated administrations of zolpidem do not produce physiological dependence. However, it is difficult to determine if zolpidem is significantly different from available benzodiazepines in terms of its dependence-producing effects because of the methods used in some of the available studies. As described above, rebound insomnia was observed in triazolam-treated patients, but not in zolpidem-treated patients (82,147). However, the doses of zolpidem (i.e., 10 mg) and triazolam (0.5 mg) compared in these studies are not clinically equivalent. The most commonly recommended hypnotic dose of zolpidem and triazolam is 10 and 0.25 mg, respectively (92). Testing relatively lower doses of zolpidem than triazolam obviously biases the outcome towards finding less severe dependence with the former.

## CONCLUSIONS AND DIRECTIONS OF FUTURE RESEARCH

Zolpidem, the most commonly prescribed hypnotic, is neuropharmacologically distinct from benzodiazepines. The present article reviewed the extant literature to determine if there are functionally significant differences between zolpidem and benzodiazepines. Based on the available literature, the most parsimonious conclusion is that despite its unique neuropharmacological profile the behavioral effects of zolpidem are generally similar to those of benzodiazepines. Studies conducted with nonhumans and humans suggest that the reinforcing effects, abuse potential, subject-rated effects, and performance-impairing effects of zolpidem are comparable to those of benzodiazepines. Studies that used drug-discrimination procedures suggest that the discriminative-stimulus effects of

zolpidem may differ from those of benzodiazepine, but the clinical significance of these findings remains to be determined. Studies conducted with rodents suggest tolerance and physiological dependence generally do not develop with repeated administrations of zolpidem. Studies that administered zolpidem repeatedly to nonhuman primates or humans found both tolerance and physiological dependence that was similar to that observed with benzodiazepines. Although the available studies suggest the behavioral pharmacologic profile of zolpidem is generally similar to that of benzodiazepines, it is important to note the dearth of perspective, experimental studies that explicitly addressed this issue. Additional studies that directly compare zolpidem and a benzodiazepine are clearly needed.

Future studies with nonhumans and humans need to focus on the relative reinforcing effects and abuse potential of zolpidem and benzodiazepines. Perhaps future studies that explicitly compare the relative reinforcing effects of zolpidem and a benzodiazepine will find differences, but this awaits confirmation. Before such studies can be conducted it is first necessary to refine the methods used to compare the reinforcing effects of drugs because preclinical drug self-administration studies may not accurately predict the relative abuse potential of drugs (65). For example, diazepam and alprazolam may have the greatest potential for abuse among drug abusers, yet in baboons these compounds maintain rates of self-administration similar to those observed with other benzodiazepines (3,47,48,51). The lack of adequate procedures to compare the relative reinforcing effects of a drug may explain the failure to detect differences between zolpidem and benzodiazepines.

Worth noting is that there are no published reports that directly assessed the reinforcing effects of zolpidem in humans. Instead, the reinforcing effects and abuse potential of zolpidem and triazolam have been compared using indirect methods like subject ratings of "drug liking." Although the reinforcing effects of drugs and subject ratings of "drug liking" generally covary, they are not isomorphic and can be dissociated (69,100,101). Future studies that directly compare the reinforcing effects of zolpidem and a benzodiazepine in humans are obviously needed.

Future studies that assess the reinforcing effects and abuse potential of zolpidem, either directly or indirectly, might include a comparison drug other than triazolam because reports of its abuse are relatively rare (3,33). The inclusion of an appropriate comparison compound is important in order to accurately assess the relative abuse potential of any drug (23,29). For example, the reinforcing effects and abuse potential of zolpidem might be assessed relative to alprazolam, diazepam, or flunitrazepam because these compounds may have greater abuse potential than other benzodiazepines (3,51). Supratherapeutic doses should be tested because high doses are often involved in abuse (23,29).

Future studies with humans that explicitly characterize the reinforcing effects and abuse potential of zolpidem relative to a benzodiazepine should employ different populations. Studying zolpidem's relative reinforcing effects in insomniac patients would be most clinically relevant. However, studying the relative reinforcing effects and abuse potential of zolpidem and a benzodiazepine hypnotic in individuals with histories of drug and ethanol abuse is also clinically relevant because these individuals may be at increased risk to abuse hypnotic medications. Studying the reinforcing effects and abuse potential of zolpidem and a benzodiazepine in elderly patients is also important because they are disproportionately represented among hypnotic users (25,84). Finally, it is important to study the relative reinforcing effects and abuse potential of hypnotics in healthy individuals because this population frequently uses hypnotics to manage transient sleep difficulties (e.g., promotion of sleep during extended travel or insomnia in rotating shift workers) (103,106,146).

Studies conducted with rodents have consistently demonstrated that the discriminative-stimulus effects of zolpidem are distinguishable from those of benzodiazepines. Studies conducted with nonhuman primates, by contrast, suggest the discriminative-stimulus effects of zolpidem are similar to those of triazolam. The reason for the discrepancy between rodent and primate studies is unknown, but may be because the discriminative-stimulus effects of zolpidem have been investigated under a more limited set of conditions in primates. For example, to the best of this author's knowledge, there are no published experiments that examined the effects of benzodiazepines or barbiturates in nonhuman primates trained to discriminate between zolpidem and placebo. Human drug-discrimination studies have produced mixed results, but a majority of these studies suggest the discriminative-stimulus effects of zolpidem are distinguishable from those of triazolam. The reason for the mixed results is unknown, but may be due to the use of different drug-discrimination procedures. Future studies with humans that assess the discriminative-stimulus effects of zolpidem in humans should use a standard set of drug-discrimination procedures. Future human-drug discrimination experiments should also compare the discriminative-stimulus effects of zolpidem and a benzodiazepine in a clinically relevant population such as insomniac patients, drug abusers or elderly patients.

The findings from a majority of the available studies suggest the subject-rated effects of zolpidem are qualitatively similar to those of benzodiazepines. However, there are a few studies in which differences between zolpidem and triazolam were noted, which is consistent with the human drug-discrimination experiments. The reason for these mixed results is unknown, but may be due to the use of somewhat different subject-rated drug-effect questionnaires. Future studies that compare the acute subject-rated effects of zolpidem and a benzodiazepine should use a standardized battery of questionnaires, or attempt to refine the questionnaires currently used. Future studies with individuals without histories of drug abuse might also test higher doses to determine putative differences between zolpidem and benzodiazepines.

The performance-impairing effects of zolpidem are indistinguishable from those of benzodiazepines. Future studies should continue to examine the performance-impairing effects of zolpidem relative to a benzodiazepine. These future studies need to test a wide range of doses. Testing subtherapeutic doses seems especially important because a recent study found that subtherapeutic doses of zolpidem, but not triazolam, significantly impaired performance. These future studies should attempt to develop tasks that are sensitive to subtle, but perhaps important, between-drug differences. Finally, future studies should compare the performance-impairing effects of zolpidem and a benzodiazepine in different populations. For example, the performance-impairing effects of zolpidem and a benzodiazepine have not been characterized across a wide range of doses in elderly volunteers. Determining differences between zolpidem and triazolam in the elderly is important because they are generally more sensitive to sedative drug effects (41–43,83,89).

As noted above, several clinical trials failed to find tolerance with repeated administrations of zolpidem. However, ex-

perimental studies that directly compared zolpidem and a benzodiazepine in terms of their tolerance-producing effects have produced mixed results. Studies conducted with rodents generally failed to find tolerance with repeated administrations of zolpidem. Studies conducted with nonhuman primates, by contrast, found tolerance with repeated administrations of zolpidem and midazolam. In the only published study that compared zolpidem and triazolam in humans, the hypnotic efficacy of both drugs decreased across the 28-day treatment period (147). Well-controlled studies that compare zolpidem and a benzodiazepine in terms of their tolerance-producing effects are obviously needed given the paucity of experimental studies that explicitly addressed this issue. As noted above, repeated administrations, if they produce tolerance, might lead to dose escalation and, as a consequence, greater performance impairment and increased risk of physiological dependence.

Several clinical trials also failed to find physiological dependence with repeated administrations of zolpidem. Studies conducted with rodents generally suggest that repeated administrations of zolpidem generally do not produce physiological dependence. A majority of studies conducted with nonhuman primates suggest that repeated administrations of zolpidem or a benzodiazepine results in physiological dependence. Studies conducted with humans suggest that following the discontinuation of chronic drug treatment, rebound insomnia occurs in triazolam-treated patients, but not zolpidem- or placebo-treated patients (82,147). However, these results must be viewed cautiously because it is unclear whether clinically equivalent doses of zolpidem and triazolam were tested. Future studies are obviously needed that compare groups of patients treated with clinically equivalent drug doses. Further studying the effects of repeated administrations of hypnotics is important because some estimates indicate that 80% of hypnotic drugs are consumed by people reporting daily use of 4 months or longer (45).

In conclusion, the available literature suggests that zolpidem is similar to benzodiazepines in terms of its reinforcing effects, abuse potential, subject-rated effects, and performance-impairing effects. The discriminative-stimulus of zolpidem may be distinguishable from those of benzodiazepines, although the clinical significance of this remains to be determined. While there is some evidence to suggest that the tolerance- and dependence-producing effects of zolpidem may be less than those of benzodiazepines, it is important to note the paucity of prospective, well-controlled studies that directly addressed this question. Because of the obvious clinical relevance, future well-controlled studies that compare the reinforcing effects, abuse potential, performance-impairing effects, tolerance-producing effects, and dependence-producing effects of zolpidem and a benzodiazepine would be especially useful. These studies should attempt to refine the methods currently used to compare the behavioral effects of drugs. Refining these methods may allow subtle, but important, differences between zolpidem and benzodiazepines to be more clearly elucidated.

ACKNOWLEDGEMENTS

Supported in part by NIDA grant DA 09841.

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