Published in final edited form as:

Eur J Pharmacol. 2008 November 19; 598(1-3): 64–67. doi:10.1016/j.ejphar.2008.09.011.

A therapeutic dose of zolpidem has limited abuse-like effects in drug-naïve females: A pilot study

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Abstract

Zolpidem has abuse potential, particularly among individuals with histories of drug abuse. This double-blind, placebo-controlled, cross over pilot study investigated the subjective effects of zolpidem (10 mg) in drug-naïve females. Over the course of a 5-h period vital signs were monitored and a series of computerized questionnaires were administered. Results indicate that zolpidem engendered subjective effects characteristic of hypnotic drugs, but reduced ratings of drug liking, willing to take again, and willing to pay for, relative to placebo. Thus, a therapeutic dose of zolpidem may have limited potential for misuse among females who have no experience with drugs of abuse.

Keywords

Zolpidem; Benzodiazepine; Subjective effects; Abuse liability; Human volunteer

1. Introduction

Over the past decade, abuse of the non-benzodiazepine hypnotic zolpidem (Ambien®) has risen dramatically. While zolpidem's popularity as the most commonly prescribed sleep-aid in the United States (Morlock et al., 2006) likely has contributed to the increased reports of misuse, a recent Drug Abuse Warning Network (DAWN) report indicating that emergency department visits involving zolpidem had increased from 2,400 per year between 1995-2002 to 11,000 per year in 2005 is impressive just the same (Substance Abuse and Mental Health Services Administration, 2007). Empirical studies have demonstrated that non-human primates will self-administer zolpidem to a greater extent than conventional benzodiazepines (Rowlett et al., 2005; Rowlett and Lelas, 2007) or barbiturates (Griffiths et al., 1992), while human study participants report more "drug liking" when comparing zolpidem to another hypnotic (Evans et al., 1990; Rush et al., 1999). Taken together, despite survey and epidemiological analyses suggesting that zolpidem has reduced abuse liability compared to benzodiazepines (Jaffe et al., 2004; Soyka et al., 2000), there is mounting evidence indicating that zolpidem does indeed have significant abuse potential.

Individuals most at risk for the inappropriate and non-medical use of benzodiazepine-type drugs such as zolpidem primarily are those with histories of drug and/or alcohol abuse. In fact,

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drug history has been shown to be a major determinant of the reinforcing effects of benzodiazepines in general (Griffiths and Weerts, 1997; Woods et al., 1992). Accordingly, studies demonstrating zolpidem's abuse-related effects in both human volunteers and laboratory animals have employed paradigms in which the subjects had extensive experience with drugs of abuse (Evans et al., 1990; Griffiths et al., 1992; Rowlett et al., 2005; Rowlett and Lelas, 2007; Rush et al., 1999). While the extent to which zolpidem has the potential to be abused among healthy drug-inexperienced individuals has received comparatively less attention, studies to date have suggested that zolpidem likely has less abuse potential in this population compared to drug-abusing individuals (Rush and Griffiths, 1996; Rush et al., 1997).

However, given that women have been shown to experience more sleep-related complaints than men (Krishnan and Collop, 2006), they are prescribed sleep-aids more frequently (e.g., de las Cuevas et al., 1999), and they metabolize zolpidem more slowly (Olubodun et al., 2003) which may make them more susceptible to abuse (Cubala et al., 2008), the present preliminary study investigated the abuse-related subjective effects of a therapeutic dose of the non-benzodiazepine zolpidem (10 mg) in healthy female volunteers.

2. Materials and Methods

2.1 Participants and procedures

Seven healthy female volunteers provided informed consent and were compensated for their participation. All participants were non-smokers, they reported ≤ 10 lifetime recreational drug experiences, no experience with zolpidem or any sedative/hypnotics, and only minimal weekly alcohol consumption (i.e., fewer than 5 drinks). Participants had no psychiatric disorders, nor were they taking psychotropic medications. This study was reviewed and approved by the McLean Hospital Institutional Review Board.

Participants came to the laboratory on two separate occasions, spaced several weeks apart. Following baseline physiologic and subjective measures, participants received a capsule containing either placebo or a therapeutic dose of zolpidem (10 mg, orally; Troy et al., 2000) under double-blind conditions. Throughout the 5-h session vital signs were monitored, and participants provided subjective ratings of drug effect at regular intervals using computerized questionnaires.

2.2 Measures

Physiologic measures included blood pressure, heart rate, and skin temperature, which were monitored continuously throughout the session. Data was collected on an Atlas™ patient monitor (Welch-Allyn Protocol, Inc.; Chicago, IL) and stored on an iMac computer using customized software.

Measures querying drug-induced subjective effects included the shortened version of the Addiction Research Center Inventory (ARCI; Jasinski, 1977) as well as an investigator-constructed visual analog scale (VAS). The ARCI is comprised of 49 true/false items intended to evaluate the subjective drug effects along five standardized scales: benzedrine group (stimulant-sensitive effects), morphine-benzedrine group (euphoria/well-being), amphetamine (*d*-amphetamine effects), pentobarbital-chlorpromazine-alcohol group (sedation/intoxication), and lysergic acid diethylamide (dysphoric/fear). Participants were administered the ARCI at 0-, 2-, and 5-h post-drug. These time points were chosen to capture the arc of drug effects since zolpidem peaks approximately 1-2 h after administration with a half-life of close to 2.5 h (Greenblatt et al., 1998). The VAS required participants to rate how they were feeling at that moment with respect to "anxious", "high", "sleepy", "dizzy", "nauseous", "confused", "loose",

“like”, “willing to take again”, and “willing to pay for”, by placing a mark on a 100-mm continuum that used “not at all” or “extremely” as anchors. Participants were administered the VAS every 15 min throughout the experimental session in order to capture a time course of a variety of zolpidem-induced subjective effects.

2.3 Data analysis

Drug effects were determined by separate repeated measures analyses of variance (ANOVAs) examining the within-subjects factors of treatment by time (SPSS 15.0 for Windows). Focused pair wise comparisons were made using Fisher’s LSD. Alpha was set at 0.05 for all statistical analyses.

3. Results

Of the seven healthy women who were recruited to participate, two did not return phone calls after the first visit, and five completed both visits of the study. Participants were 23-37 years old (Mean=27 ± 5), with 17 (± 0.5) years of education.

3.1 Physiologic measures

Physiologic measures were averaged across each individual hour of the 5-h experimental session. All blood pressure readings were in the normal range (i.e., below 120/80). Zolpidem had no effect on blood pressure relative to placebo, and blood pressure did not change over the course of the session (data not shown). Heart rate showed a treatment effect such that it was increased slightly by zolpidem [$F(1,4) = 11.11$, $P = 0.03$], while there was only a trend for an effect of time [$F(5, 20) = 2.47$, $P = 0.07$]. Despite no significant interaction between these variables, zolpidem increased heart rate by 8 beats per minute (bpm) relative to placebo during the 5th hour (76 ± 4 vs. 68 ± 2 bpm), an effect that was not biologically significant given that the normal range is 60-90 bpm. Skin temperature was unchanged by zolpidem relative to placebo, but within both experimental sessions, all participants’ skin temperature increased from 25°C to 31°C [$F(5,20) = 11.52$, $P < 0.001$]. Compared to baseline temperature readings, participants experienced an increase in temperature during the 2nd, 3rd, 4th, and 5th hours of each experimental session that most likely resulted from a normal diurnal increase (Mackowiak et al., 1992) combined with an increase in ambient room temperature.

3.2 Subjective effects

Analysis of the ARCI results failed to reveal significant effects of zolpidem on the pentobarbital-chlorpromazine-alcohol group, morphine-benzedrine group, benzedrine group, amphetamine, or lysergic acid diethylamide scales at either the 2- or 5-h time point following drug administration. However, based on our *a priori* hypotheses that any effects of zolpidem would become evident approximately 1.5-2 h following ingestion (Langtry and Benfield, 1990; Salva and Costa, 1995), focused pair wise comparisons were examined. These analyses revealed that zolpidem increased the pentobarbital-chlorpromazine-alcohol group score at both time points relative to baseline, and was different from placebo at the 5-h time point, while also increasing the amphetamine scores relative to placebo at the 5-h time point (Fig. 1; $P < 0.05$).

Responses on the VAS were averaged across each individual hour of the 5-h experimental session, and demonstrated several zolpidem-induced changes. Again, *a priori* hypotheses about the study design led to focused pair wise comparisons despite the lack of significant omnibus ANOVA. These analyses indicated that during the last hour of the session zolpidem increased ratings of “dizzy” (15.05 vs. 0.75), “nauseous” (5.45 vs. 0.00), “confused” (6.80 vs. 0.00) and “loose” (16.80 vs. 8.05). Zolpidem had the opposite effects on “like”, “willing to take again”, and “willing to pay for”. As the experimental session progressed, ratings of those items aimed

at addressing the abuse-related effects of zolpidem were decreased relative to placebo (Fig. 2). Analyses indicated that zolpidem reduced “like” to 22% and 27% of control levels during the 3rd and 4th hours, respectively. Similarly, “willing to take again” was reduced to 25% and 28% of control levels during those time points, while self-reported ratings of “willing to pay for” were decreased to a greater extent such that ratings during hours 2, 3, 4, and 5 were decreased to 3%, 4%, 10%, and 6% of control levels, respectively. In contrast, zolpidem had no effect on self-reported ratings of anxious, high, or sleepy (data not shown).

4. Discussion

These preliminary results demonstrate the effects of acute oral administration of a therapeutic dose of zolpidem in healthy, drug-inexperienced, female volunteers. This dose of zolpidem had little effect on vital signs, but it did increase ratings of the pentobarbital-chlorpromazine-alcohol group and amphetamine scales on the ARCI. Zolpidem increased feelings of “dizzy”, “nauseous”, “confused”, and “loose”, but did not have abuse-related effects in this sample. In fact, zolpidem decreased ratings of “like”, “willing to take again”, and “willing to pay for”, appearing to exhibit even fewer abuse-related effects than the non-drug condition.

Previous studies examining the subjective responses to this dose of zolpidem have demonstrated an increase in the lysergic acid diethylamide scale of the ARCI in volunteers with a history of social use of alcohol and drugs (Wilkinson, 1998), while in healthy volunteers it produced increases in the lysergic acid diethylamide and pentobarbital-chlorpromazine-alcohol group scales (Rush and Griffiths, 1996; Rush et al., 1997; Rush et al., 1998). The present results in healthy participants agree with those previous studies (Rush and Griffiths, 1996; Rush et al., 1997; 1998) in that the pentobarbital-chlorpromazine-alcohol group was increased, although the other scales were unchanged. These data also support the notion that this dose of zolpidem may engender variable subjective effects (Rush and Baker, 2001) because the VAS did not necessarily change in parallel with the ARCI. For example, the increase in the pentobarbital-chlorpromazine-alcohol group was not accompanied by an increase in self-reported ratings of “sleepy”. Similarly, the increase in a dysphoric-like item such as “nauseous” toward the end of the experimental session was not accompanied by a concomitant increase in lysergic acid diethylamide. However, the increase in ratings of “nauseous” as well as those of “dizzy”, “confused”, and feelings of “loose” agree with previous reports of zolpidem-induced nausea and/or emesis (Evans et al. 1990; Rush and Griffiths, 1996; Rush et al. 1999) as well as impaired concentration (Rush and Baker, 2001), although higher doses were used in those studies.

In contrast to those self-reported drug effects, over the course of the 5-h period, zolpidem decreased ratings of drug “liking”, “willing to take again”, and “willing to pay for”, relative to the non-drug condition. While in accordance with previous reports demonstrating that sedative/hypnotics such as benzodiazepine-type drugs (de Wit et al., 1984a; 1984b; 1985; Evans et al., 1995; Rush and Griffiths, 1996; Rush et al., 1997) or barbiturates (de Wit et al., 1989) are not particularly rewarding in drug-naïve volunteers, these results are striking in that they suggest that zolpidem may have been *aversive* in these female participants. While that hypothesis is speculative, as there were no direct measures of aversion in this study and ratings of “anxious” did not increase, healthy volunteers without significant drug experience may be less inclined to find benzodiazepine-like effects pleasant (de Wit et al., 1985).

Although other studies have examined the abuse-related effects of zolpidem in participants without histories of drug abuse, they have not restricted their investigation to female participants (e.g., Rush and Griffiths, 1996). While the results of this preliminary study are intriguing, they have to be interpreted with caution for several reasons. First, the sample size was small and direct comparisons to males were not made. Second, this study employed self-

report to assess zolpidem-induced subjective effects rather than a self-administration paradigm which would permit the direct measurement of reinforcing effects (see review by Griffiths et al., 2003). Third, only a single dose of drug was investigated in this study. Future studies should employ a higher dose of zolpidem since reports in the literature indicate that supra-therapeutic doses are those that are most often abused (Boulanger-Rostowsky et al., 2004; Liappas et al., 2003; Sethi and Khandelwal, 2005). However, not only was the present dose the recommended dose to treat insomnia, but a previous report has shown very little difference between the effects engendered by 10 mg and those engendered by 20 mg in healthy volunteers (Rush et al., 1997). With these caveats, the present study provides evidence to suggest that although zolpidem does have abuse liability among those individuals with a drug use and/or abuse history, a therapeutic dose of zolpidem may have limited potential to be abused in females who in the past have not abused sedatives, opiates, or alcohol.

Acknowledgements

This study was supported by grants from the National Institutes on Drug Abuse: T32 DA15036, K01 DA023659, and K05 DA00343. The authors wish to thank Dr. George Trksak for help with statistical analyses.

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Fig. 1.

Zolpidem-induced increases on the pentobarbital-chlorpromazine-alcohol group (PCAG; left) and amphetamine (AMPH; right) scales of the ARCI. Values are means $\pm$ S.E.M. The single asterisks represent significant differences at the 2nd and 5th hour relative to baseline, while double asterisks represent significant differences relative to placebo at the 5th hour ($P < 0.05$).

Fig. 2. Zolpidem-induced decreases in self-reported ratings of “like”, “willing to take again”, and “willing to pay for” over the course of a 5-h experimental session. Scale range that was available to the participants was 0 to 100. Values are means $\pm$ S.E.M. Asterisks represent significant differences from placebo ($P < 0.05$).