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Zolpidem does not serve as reinforcer in humans subjected to simulated shift work

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Abstract

Zolpidem attenuates shift-change-related sleep and performance disruptions. It is unknown whether these benefits alter the reinforcing effects of the drug during shift work. This study examined zolpidem-related reinforcing effects during simulated shift work. Eleven volunteers (3F, 8M) completed this 16-day within-participant, residential laboratory study. Each day participants were given an opportunity to self-administer oral zolpidem (10 mg) or receive a \$1 voucher immediately following a 9-hr work period and immediately before going to bed. Participants worked under two shift conditions: 1) during the night shift, participants completed computerized task batteries from 0030 to 0930 h and went to bed at 1600 h and 2) during the day shift, participants completed task batteries from 0830 to 1730 h and went to bed at 2400 h. Shift conditions alternated three times during the study. Despite the fact that sleep, psychomotor performance, and some ratings of mood were disrupted during night shift work, there was no significant effect of shift on choice to take zolpidem. Overall, participants selected markedly fewer zolpidem doses than monetary vouchers (17% versus 83%). Thus, zolpidem did not serve as a reinforcer even when sleep was disrupted. These data are consistent with previous reports indicating that sedatives produce limited reinforcing effects in individuals without a history of drug abuse.

Keywords

zolpidem self-administration; performance; subjective effects; sleep; shift work; humans

1. Introduction

Rotating shift work contributes to misalignment of the circadian sleep/wake cycle, which is associated with increased fatigue and impaired cognitive performance (Crowley et al., 2004;

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Eastman and Martin, 1999). Many shift workers take hypnotic medications prophylactically in an effort to improve the quality and quantity of daytime sleep, thus decreasing the likelihood of experiencing work-related performance decrements (e.g., Niedhammer et al., 1995). One such medication that has received increased experimental attention is the non-benzodiazepine hypnotic, zolpidem, the most widely prescribed sleep medication in the United States (Lamb, 2009). Recently, we investigated the effects of zolpidem during simulated shift work and found that it attenuated shift-change-related disruptions on measures of sleep, mood, and psychomotor task performance (Hart et al., 2003, 2005). Moreover, in a study of fatigue management in military personnel required to work irregular rotating shifts, individuals were given the opportunity to self-administer zolpidem in order to facilitate sleep during sleep periods (Van Camp 2009). The majority of individuals (63%) chose to take the medication. Presumably, zolpidem was being used to enhance sleep and to offset potential next-day work performance decrements.

Despite the fact that epidemiological and laboratory data suggest that the abuse liability of zolpidem is low (Licata et al., 2008; Soyka et al., 2000), the above observations suggest that, when subjected to abrupt changes in work shift schedules, an individual's propensity to self-administer zolpidem might be increased in an effort to attenuate shift-change-related disruptions in sleep, mood, and work performance. Consistent with this view is evidence indicating that the reinforcing effects of psychoactive drugs, including sedatives, may be influenced by non-pharmacological factors, such as work requirements, behavioral conditioning, or therapeutic necessity (e.g., Silverman et al., 1994; Alessi et al., 2002; Helmus et al., 2005). Thus, because zolpidem has been demonstrated to improve sleep and next-day performance of individuals subjected to abrupt changes in work-shift schedules, it is possible that the reinforcing effects of the drug will be enhanced under such conditions.

The present study examined zolpidem choice behavior of research participants during simulated day- and night-shift work. Under both conditions, participants were given the opportunity to self-administer oral zolpidem (10 mg) or receive a \$1 voucher at two time points each day: once before the recreation period and once before bedtime. We hypothesized 1) that participants would experience greater sleep, mood, and psychomotor performance disruptions during the night shift compared with the day shift and 2) that participants would choose to self-administer more zolpidem at bedtime during the night shift compared with the day shift in an effort to counteract these shift-related disruptions.

2. Methods and Materials

2.1. Participants

Eleven research volunteers (mean age 29.4 ± 6.1 [$\pm$ SD]) completed this 16-day inpatient study. Three participants were female (1 Black, 1 Hispanic, 1 White) and eight were male (1 Asian, 2 Black, 2 Hispanic, 3 White). On average, they had completed 12.5 ± 1.5 (mean $\pm$ SD) years of education. All passed comprehensive medical examinations and psychiatric interviews and were within normal weight ranges according to the 1983 Metropolitan Life Insurance Company height/weight table (body mass index: 23.0 ± 2.6 [mean $\pm$ SD]). Overall, participants reported infrequent drug use: four reported using amphetamines at least once, five reported using cocaine at least once, and four reported using MDMA at least once.

None reported current use of any of these substances. Eight participants reported current caffeine use (1–21 cups/week), eight reported current alcohol use (1–18 drinks/week), three reported current marijuana use (0.5–1.5 joints/week), and four smoked 4–20 tobacco cigarettes/day.

2.2. Pre-study Training

Before study commencement, participants completed two training sessions (3–4 hours each) on the computerized psychomotor tasks that would be used during the study. On two separate days they received zolpidem (10 mg) in order to provide them with experience with the study drug. On the first day, they received zolpidem in the afternoon and on the second day, they received the drug at night. Although they were not informed of the drug and dose at this time, participants were told that the same drug and dose would be available at the choice opportunities each day throughout the study.

2.3. Design

Across this 16-day study, participants completed computerized psychomotor task batteries during two different work shifts. During the day shift, they performed tasks from 0830 to 1730 h and went to bed at 2400 h; during the night shift, they performed tasks from 0030 to 0930 h and went to bed at 1600 h. Shifts alternated three times during the study. One group of participants (n=4) started on the night shift and two groups (n=7) started on the day shift. Participants were given the opportunity to self-administer zolpidem (10 mg) or receive a \$1 voucher twice daily: once before the social period and once before the sleep period (1500 h and 2300 h on the day shift; 0700 h and 1500 h on the night shift). Vouchers were redeemed for cash at the end of the study.

2.4. Procedure

Participants moved into the laboratory on the day before the study began and the first experimental day began the following morning at 0815 (0015) h [day shift (night shift)]. Fifteen minutes after awakening at 0830 (0030) h, participants completed a visual analog sleep questionnaire and the baseline task battery, which was composed of the psychomotor tasks and the subjective-effects questionnaire (described below), and were given time to eat breakfast. Following breakfast, participants completed four task batteries from 1015 (0215) to 1300 (0500) h, took a 1.5-h lunch break period, and completed four additional task batteries from 1445 (0645) to 1730 (0930) h. At 1500 (0700) h, participants were given the opportunity to choose between drug or monetary voucher. Beginning at 1730 (0930) h, participants had access to the social area, where they could interact with other study participants and engage in recreational activities. At 2300 (1500) h, each participant was again presented with a choice between the two available options. Lights were turned out at 2400 (1600) h for an 8.25-h sleep period.

2.5. Subjective-Effects and Psychomotor Battery

The computerized visual analog questionnaire consisted of 50 lines labeled ‘not at all’ at one end and ‘extremely’ at the other end (Hart et al., 2003). The 100-mm lines were labeled with adjectives describing a mood (e.g., ‘I feel Unmotivated’), a drug effect (e.g., ‘I feel a Good

Drug Effect'), or a physical symptom ('I have a Headache'). The computerized psychomotor task battery consisted of five tasks: 1) the Digit Recall Task, designed to assess changes in immediate and delayed recall (Hart et al., 2001); 2) the Digit-Symbol Substitution Task, designed to assess changes in visuospatial processing (McLeod et al., 1982); 3) the Divided Attention Task, designed to assess changes in vigilance and inhibitory control (Miller et al., 1988); 4) the Rapid Information Task, designed to assess changes in sustained concentration and inhibitory control (Wesnes and Warburton, 1983); and 5) the Repeated Acquisition Task, designed to assess changes in learning and memory (Kelly et al., 1993).

2.6. Sleep questionnaire

Subjective sleep experience from the immediately preceding sleep period was measured by a visual analog questionnaire completed shortly after waking. The questionnaire consisted of a series of 100-mm lines labeled 'not at all' at one end and 'extremely' at the other end. The lines were labeled: 'I slept well last night,' 'I woke up early this morning,' 'I fell asleep easily last night,' 'I feel clear-headed this morning,' 'I woke up often last night,' 'I am satisfied with my sleep last night,' and a fill-in question in which participants were asked to estimate the number of hours they slept the previous night (Haney et al., 2001).

2.7. Drug

Zolpidem hydrochloride (5 mg; Ambien, G.D. Searle and Company, Chicago, IL) was repackaged by the Pharmacy Department of the New York State Psychiatric Institute by placing two tablets into a white no. 00 opaque capsule and adding lactose filler.

2.8. Data Analysis

Choice, psychomotor performance, sleep measures, and subjective-effects data were analyzed using a two-factor repeated-measures analyses of variance (ANOVA): the first factor was shift condition (day, night) and the second factor was day within condition (1, 2, 3). For all analyses, ANOVAs provided the error terms needed to calculate planned comparisons that were designed to answer two questions: 1) did participants choose more capsules during the night shift compared with the day shift and 2) were psychomotor task performance, subjective-effect ratings, and sleep disrupted during the night shift? To evaluate whether participants chose more zolpidem during the night shift, choice data from each night shift night were compared with the corresponding day shift day data. To evaluate night shift-related disruptions, data from the task batteries preceding the first zolpidem choice were analyzed and each day shift day was compared with the corresponding night shift night (e.g., the first day shift versus the first night shift). The area under the curve (AUC) for the subjective-effects and psychomotor battery was determined using the trapezoidal method (Tallarida and Murray, 1981). *P* values were considered statistically significant at less than 0.05, using Huynh-Feldt corrections when appropriate.

3. Results

3.1. Zolpidem choice

Figure 1 (left panel) displays the proportion of zolpidem capsules chosen before the social and sleep periods, collapsed across all 8 days, as a function of work shift condition.

Zolpidem choice did not vary as a function of shift condition (i.e., day shift vs. night shift) or choice opportunity (i.e., before the social period vs. before the sleep period). Overall, participants selected zolpidem only 17% of the time.

3.2. Psychomotor Performance and Subjective-Effects

On Day 1, participants completed fewer trials on the repeated acquisition task during the night shift compared to the day shift (179.36 ± 18.37 versus 195.50 ± 23.52 , $p < 0.05$). On Day 2, maximum speed on the DAT was reduced during the night shift compared with the day shift (38.36 ± 2.44 versus 42.09 ± 1.99 , $p < 0.05$). There were no other significant performance effects observed.

Figure 1 (middle panel) illustrates that ratings of 'Sleepy' were significantly increased during the night shift compared with the day shift on Days 1–2 ($p < 0.01$ for both comparisons). Table 1 shows that several other subjective-effects measures were significantly altered during the night-shift condition. Notably, on Day 1 ratings of 'Alert,' 'Can't concentrate,' and 'Energetic' were significantly decreased during the night shift.

3.3. Sleep

Figure 1 (right panel) shows that estimates of the number of hours slept were significantly decreased on Day 1 of the night shift compared with the day shift ($p < 0.0001$). Table 1 shows other sleep measures that were disrupted during the first two nights of night shift work.

3.4. Correlations of zolpidem choice and subjective and performance effects

Correlations conducted between choice and several measures of performance, subjective effect ratings, and sleep revealed no significant effects.

4. Discussion

We hypothesized that participants would choose to self-administer zolpidem during the night shift in order to counteract shift-related disruptions. This hypothesis was not borne out, even though measures of sleep, mood, and performance were disrupted during the night shift. Participants overwhelmingly chose the monetary voucher over zolpidem (83% versus 17%) regardless of shift condition. One possible reason for these findings is that participants had a limited psychoactive drug use history and none reported current drug use. As a result, they may have been disinclined to take a psychoactive substance when presented with a choice under most conditions. Nonetheless, the observation that zolpidem capsules were infrequently selected is in agreement with data suggesting that the drug has limited abuse liability (e.g., Licata et al., 2008; Soyka et al., 2000).

Sleep, psychomotor performance, and mood were disrupted on the first two nights of the night shift. The majority of these decrements occurred on Night 1 but had resolved on subsequent nights. These findings are consistent with earlier laboratory investigations of the effects of rotating shift work (e.g., Muehlbach and Walsh, 1995; Sharkey et al., 2001), which have shown that shift-related sleep, mood, and performance disruptions are most prominent

during the first night (e.g., Reid and Dawson, 2001; Kirkpatrick et al., 2009). One possible limitation of the current study is that an “off-day” (i.e., a day during which participants were not required to work) was not interspersed between shift conditions. Thus, it is possible that the amount participants slept during the first sleep period of night shift work was influenced by this design choice.

In conclusion, these data show that individuals subjected to abrupt shift schedule changes did not choose to self-administer a therapeutic oral dose of zolpidem. In general, these data are consistent with previous reports indicating that zolpidem, like other sedatives (Woods et al., 1987, 1992), produces limited reinforcing effects in non-drug abusers.

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Figure 1.

Left panel: Proportion of zolpidem capsules chosen before the social and sleep periods, collapsed across all 8 days, as a function of work shift condition. *Middle panel:* Ratings of 'Sleepy' as a function of shift condition and day within condition. *Right panel:* Subjective estimate of the number of hours slept during the previous sleep period as a function of shift condition and day within condition. Error bars represent one SEM. An * indicates Night Shift significantly different from Day Shift ($p < 0.05$). Overlapping error bars were omitted for clarity.

Subjective-effect ratings (AUC) and subjective sleep questionnaire measures during the day- and night-shift conditions on Day 1 and Day 2

Table 1

Measure	Shift Conditions					
	Day 1			Day 2		
	Day shift Mean (SEM)	Night Shift Mean (SEM)	F Value	Day Shift Mean (SEM)	Night Shift Mean (SEM)	F Value
<i>Subjective-effect ratings</i>						
Alert	267.0 (25.1)	182.0 (24.5)	11.30 [*]	241.2 (22.8)	218.4 (23.3)	0.82
Can't Concentrate	83.4 (23.6)	138.5 (27.3)	8.88 [*]	72.0 (21.7)	107.3 (27.6)	3.63
Content	212.6 (27.7)	150.3 (24.6)	16.94 [*]	210.9 (22.9)	159.0 (23.4)	11.75 [*]
Energetic	206.1 (30.5)	107.6 (22.3)	26.46 [*]	183.1 (28.7)	139.2 (24.9)	5.25 [*]
Friendly	217.5 (22.0)	151.7 (25.8)	10.06 [*]	204.1 (23.3)	199.4 (20.9)	0.05
Irritable	35.0 (14.3)	100.2 (30.6)	15.96 [*]	20.7 (8.1)	44.1 (18.1)	2.06
Social	201.5 (25.8)	117.2 (20.5)	41.19 [*]	182.8 (23.4)	156.9 (19.2)	3.91
Tired	110.0 (21.7)	212.5 (41.1)	12.65 [*]	78.6 (15.4)	166.5 (25.5)	9.27 [*]
Trouble Sleeping	102.7 (34.8)	155.8 (43.7)	3.40	60.3 (19.2)	144.6 (42.3)	8.60 [*]
<i>Sleep questionnaire</i>						
Fell Asleep Easily	56.9 (6.6)	38.5 (7.0)	4.99 [*]	62.3 (6.0)	63.7 (6.2)	0.01
Satisfied with Sleep	61.4 (6.9)	32.0 (6.6)	7.95 [*]	60.8 (6.4)	39.2 (5.8)	4.31

* $p < .05$, Night Shift significantly different from Day Shift