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Pharmacology, Biochemistry and Behavior 79 (2004) 17–24
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Therapeutic doses of diazepam do not alter impulsive behavior in humans

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Received 22 December 2003; received in revised form 3 March 2004; accepted 7 June 2004
Available online 12 August 2004

Abstract

This study examined the effects of low, therapeutic doses of diazepam on several measures of impulsive behavior in healthy volunteers. Volunteers (N=35) participated in a three-session double-blind randomized design in which they received diazepam (5 or 10 mg) or placebo. The volunteers were classified as high and low impulsive based on the Barratt Impulsiveness Scale-11 (BIS-11). One hour after ingesting the capsule on each session, participants completed mood questionnaires and five impulsivity tasks: go/no-go task, delay discounting task, time estimation task, stop task, and the balloon analogue risk task (BART). Diazepam (5 and 10 mg) produced its prototypic sedative-like mood effects. However, the drug did not affect performance on any of the measures of impulsive behavior in either the high or low BIS participants. These results suggest that low doses of diazepam, including doses that are used therapeutically, do not increase impulsive behavior. Whether higher doses would increase impulsivity remains to be determined.

Keywords: Diazepam; Valium; Impulsivity; Inhibit; Behavioral task measures; Humans; Delay discounting

1. Introduction

Diazepam and other benzodiazepines are widely used therapeutically as anxiolytics, muscle relaxants, and anticonvulsants and, at higher doses, they are occasionally abused (e.g., Woods et al., 1987; Gelkopf et al., 1999). Despite their widespread use, little is known about the effects of these drugs on measures of decision making and impulsivity. From the point of view of drug safety, it is important to determine whether these commonly used drugs impair cognitive or decision-making abilities that might affect daily activities, such as driving. Recent evidence suggests that other types of mood-altering drugs, such as alcohol and cannabis, increase certain indices of impulsive behavior (de Wit et al., 2000; McDonald et al., 2003). Thus, the primary goal of this study was to determine whether low, therapeutic doses of the prototypic benzodiazepine, diazepam, affect performance on any of a number of impulsive behaviors.

Several behavioral tasks have been developed to assess different dimensions of impulsivity. These tasks include measures of the ability to inhibit behavior, tolerance for delay to a reward, time perception, and risk taking (e.g., Evenden, 1999; Lejuez et al., 2002; Mischel et al., 1989; Richards et al., 1999). The specific measures used in this study included the stop task (Logan et al., 1997) and the go/no-go task (Newman et al., 1985) as measures of behavioral inhibition. Children with attention deficit hyperactivity disorder (ADHD), who are known to be more impulsive than healthy children, perform more poorly on tasks that measures inhibition than controls (e.g., Nigg et al., 2002), and methylphenidate reverses this impairment (Schacher et al., 1993). We have shown that both alcohol and Δ^{-9} tetrahyrocannabinol impair inhibitory capacity on the stop and go/no-go tasks, in healthy volunteers (de Wit et al., 2000; McDonald et al., 2003). Another task used to measure impulsive behavior in the present study was delay discounting (Rachlin et al., 1991; Richards et al., 1999), which assesses the value of delayed rewards. Populations believed to be more impulsive, including heavy drinkers, smokers, gamblers, and patients with substance use disorders,

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doi:10.1016/j.pbb.2004.06.011

perform more impulsively on discounting procedures (Vuchinich and Simpson, 1998; Mitchell, 1999; Reynolds et al., 2004; Allen et al., 1998; Crean et al., 2000; Madden et al., 1997; Petry and Casarella, 1999). We also utilized measures of time perception and risk taking, which have also been hypothesized to be indicators of impulsive behavior (Barkley et al., 2001; Lejuez et al., 2002).

There is evidence that benzodiazepines may increase certain forms of impulsive behavior. In humans, there are occasional clinical reports that certain benzodiazepines, such as flunitrazepam, increase impulsivity or aggression, resulting in violent or criminal behavior (Daderman et al., 2002). In addition, benzodiazepines have been reported to induce behavioral disinhibition and increase aggression in therapeutic contexts (Fava, 1997). In a laboratory-based study with healthy volunteers, a relatively low dose of diazepam (10 mg) increased aggressive responding on a behavioral task of aggression (Weisman et al., 1998). Recently, Deakin et al. (2004) reported that diazepam (20 mg, and to a lesser extent with 10 mg) produced disinhibitory effects on two speeded reaction time tasks and on tasks that involved planning and decision making. In nonhumans, diazepam has been tested on tasks involving impulsive behavior, including delay discounting and conflict procedures. The studies with delay discounting have found conflicting results, with both increases and no effect (Thiebot et al., 1986; Evenden and Ryan, 1996). In conflict procedures, diazepam and other benzodiazepines reliably increase, or "release", responding suppressed by punishment (Davidson and Cook, 1969; Carlton et al., 1981). This "anticonflict" effect is often viewed as a form of disinhibition. Together, these findings suggest that diazepam may reduce response inhibition.

The present study also investigated the possibility that diazepam increases impulsive behavior only in at-risk individuals, who are high on a trait measure of impulsivity. To examine this possibility, we recruited participants who scored within the normal range and above average on the Barratt Impulsiveness Scale-11 (BIS-11; Patton et al., 1995), a standardized self-report measure of the personality trait of impulsiveness. Thus, the study investigated the effects of low doses of diazepam (5 and 10 mg) on several behavioral measures of impulsivity, and examined these effects in individuals high and low on a trait measure of impulsivity.

2. Method

2.1. Participants

Healthy men (n=19) and women (n=16) aged 18 to 45 years participated. Participants were recruited by means of posters, advertisements in newspapers, and word-of-mouth referrals. After a brief telephone interview, participants attended an in-person clinical assessment, including a psychiatric interview and physical examination including an electrocardiogram. Volunteers were excluded if they met criteria for major Axis I DSM-IV diagnoses, had less than high school education, had a body mass index outside of the range 1926 kg/m^2, and smoking more than five tobacco cigarettes per day. During the phone screening or the interview, participants completed the BIS-11 (Patton et al., 1995) to identify individuals who scored more than 1 standard deviation above the mean (73 for women, 75 for men). Half of the men and half of the women scored over this criterion.

Before participating in the study, participants attended an orientation session where they provided written informed consent, were familiarized with the experimental procedures, and completed personality questionnaires. The consent form stated that the study was an investigation of the effects of commonly used drugs on mood and performance. For blinding purposes, participants were advised that they might receive any of several classes of drugs and their associated side effects were listed. Participants were instructed to abstain from use of alcohol and other drugs except their normal amounts of caffeine and nicotine for 24 h before and 6 h after each session. Their compliance was verified by testing breath alcohol levels (BAL) and urine samples for D-amphetamine, cocaine, phencyclidine, and opiates. Participants were instructed not to eat for 2 h before the session. Female participants provided urine samples for pregnancy tests before each session.

2.2. Design

This study utilized a three-session, double-blind, placebo-controlled, within-subject design. Placebo, or 5 or 10 mg diazepam were administered in random order on the three test sessions. Sessions were conducted from 10 a.m. to 2 p.m. and were scheduled a minimum of 72 h apart, with an average interdose interval of 168 h.

2.3. Procedure

This experimental protocol was approved by the University of Chicago Hospital's Institutional Review Committee for the use of human participants. Volunteers were tested individually in comfortably furnished rooms with a television/VCR, magazines, and a computer for administering questionnaires and tasks. When no dependent measures were being obtained, participants were allowed to watch television, movies, or read, but they were not allowed to work or study.

Upon arrival for each session at 10 a.m., a urine sample was obtained for drug and pregnancy screening and BAS was checked. Participants completed precapsule subjective effects questionnaires (described in detail below), measures of performance (Digit Symbol Substitution Test and Digit Span; see below), and vital signs were recorded. Then, they ingested a capsule containing diazepam (5 or 10 mg) or placebo under double-blind conditions. Forty-five minutes

later, participants repeated the subjective effects questionnaires, DSST, and Digit Span, and vital signs were recorded. The behavioral tasks were administered between 60 and 105 min after capsule ingestion, coinciding with the peak time of effects (Johanson and Uhlenhuth, 1980; Griffiths et al., 1984). They completed the delay discounting, balloon analogue risk task (BART), time test, go/no-go, and stop tasks (see descriptions below). All tasks were completed via computer, in the same order. After finishing the tasks (about 105 min after capsule ingestion), they again completed the subjective effects questionnaires, DSST, and Digit Span. Finally, they completed an end-of-session questionnaire and were transported home. After completing all three sessions, participants attended a debriefing session at which time they were paid for their participation.

2.4. Drugs

Diazepam (Valium, 5 or 10 mg; Roche) was administered in opaque gelatin capsules (size 00) with dextrose filler. Placebo capsules contained only dextrose. Low doses were selected to minimize the chance of nonspecific motor or cognitive impairment (Kelly et al., 1993). Doses of diazepam as low as 5 mg significantly increase subjective ratings of fatigue and confusion (Johanson and Uhlenhuth, 1980; de Wit and Griffiths, 1991).

2.5. Dependent measures

2.5.1. Behavioral measures of impulsivity

2.5.1.1. Delay discounting task (Richards et al., 1999). Delay discounting provides an index of the relative value of immediate vs. delayed rewards. On this computerized version of the procedure, participants choose between US$10 available after some delay and a smaller amount available immediately (e.g., "would you rather have US$10 in 30 days or US$2 right now?"). The task uses an adjusting amount procedure (Richards et al., 1999) to derive an indifference point at which the delayed and immediate options are judged to be equivalent. The indifference points obtained at each of the delays are plotted and discount functions are derived through curve-fitting analyses, yielding a parameter k. Higher values of k indicate greater impulsivity. At the end each session, participants rolled a die. If they rolled a 1 or 6, one of their answers was randomly selected and the participant was rewarded accordingly.

2.5.1.2. Balloon analogue risk task (Lejuez et al., 2002). In this task, participants were required to "pump up" a series of 30 balloons on a computer screen. Each pump was worth 1/2, 1, or 5 cents, which accumulated during a trial. Participants could stop pumping at any time and bank their accumulated money. However, if they continued to pump, the balloon would occasionally "explode", resulting in the loss of the money accumulated on that trial. Thus, more pumps on a trial were taken to be an indicator of greater risk taking. At the end of each session, participants were rewarded for part of their winnings, based on a random drawing.

2.5.1.3. Time test (Barkley, 2002). The time test assesses participant's ability to reproduce varying intervals of time. Duting the test, light bulbs appear on the left or right of a computer screen. First, the bulb on the left is illuminated for 2, 4, 8, 16, or 32 s. Then, participants depress the spacebar to illuminate the bulb on the right for the same amount of time. They are instructed not to count time, and they are required to count distracter figures that appear irregularly on the screen.

2.5.1.4. Go/no-go task (Newman et al., 1985). The go/no-go task is a learning task designed to assess participants' ability to inhibit inappropriate responses. It consists of repeated presentations of eight numbers, of which four are designated "correct" and four "incorrect". A different list of numbers was used for each session. Participants were required to respond to correct numbers, and withhold responses to incorrect numbers. They were rewarded for correct responses (+10 cents) and penalized for incorrect responses (−10 cents). Errors of omission (withholding a response when a "correct" stimulus is presented) and errors of commission/false alarms (responding to an "incorrect" stimulus) were recorded, and participants received money they earned at the end of the session.

2.5.1.5. Stop task (Logan et al., 1997). The stop task is designed to assess the ability to inhibit a prepotent motoric response. Participants are instructed to respond as quickly as possible when a certain letter (go signal) appears on a computer screen, and to inhibit their responses when a tone is heard (stop signal). The tone is presented on random trials and at different delays following the letter presentation. The delays to the stop signal are adjusted until the participant inhibits his or her responses on approximately 50% of trials. At this 50% criterion, the stop reaction time (SRT) can be calculated by subtracting the final mean delay at which the tone is presented from the mean go reaction time (GRT). Both GRT and SRT are measured in milliseconds.

2.5.2. Measures of subjective effects

2.5.2.1. Addiction Research Center Inventory (ARCI; Haertzen and Hickey, 1987). The ARCI is a standardized questionnaire consisting of 53 true/false statements. The ARCI was specifically designed to measure subjective effects of certain classes of abused drugs. This version of the ARCI consists of six empirically derived scales, which measure drug-induced euphoria (Morphine–Benzedrine Group; MBG), stimulant-like effects (Amphetamine; A,

and Benzedrine Group; BG), sedation (Pentobarbital–Chlorpromazine; PCAG), and dysphoria and somatic effects (Lysergic Acid; LSD).

2.5.2.2. Profile of Mood States (POMS; McNair et al., 1971). The POMS consists of 72 adjectives commonly used to describe mood states. Participants indicate how they feel at that moment in relation to each of the adjectives using a five-point scale ranging from *not at all* (0) to *extremely* (4). The POMS consists of eight scales: friendliness, anxiety, depression, fatigue, anger, elation, confusion, and vigor, and two derived scales: arousal and positive mood (Johanson and Uhlenhuth, 1980).

2.5.2.3. Drug Effects Questionnaire (DEQ; Johanson and Uhlenhuth, 1980). The DEQ consists of four questions concerning drug effects. On a 100-mm line, participants indicate the extent to which they feel the drug, how high they feel, if they like the drug, and if they want more of the drug. The 100-mm line has *not at all* on the extreme left end and *extremely* on the extreme right.

2.5.3. General measures of performance

2.5.3.1. Digit Symbol Substitution Test (DSST; Wechsler, 1958). The DSST was used to assess psychomotor performance. Participants are required to transpose symbols for numbers as quickly and accurately as possible. The number of correct responses in 90 s was recorded. Forty versions of the DSST were used to avoid learning effects.

2.5.3.2. Digit Span (Wechsler, 1958). The Digit Span is a memory task in which participants are read progressively longer series of numbers ranging from two to nine digits and then asked to repeat the series, forwards and backwards. A trial ends when the participant misses both trials at one sequence length. Six versions of the Digit Span were used to reduce learning across trials.

2.5.3.3. Vital signs. Blood pressure and heart rate measures were recorded before and 45 min after ingesting the capsule using a Digital Blood Pressure Monitor Dinamap 1846SX (Critikon, Tampa, FL).

2.6. Personality questionnaire

2.6.1. Barratt Impulsiveness Scale-11 (Patton et al., 1995)

The BIS-11 assesses impulsivity as a personality trait. The questionnaire consists of 30 statements to which participants respond by choosing one of the following responses: rarely/never, occasionally, often, and almost always. In addition to a total score, each participant receives scores on six scales: attention, motor impulsivity, self-control, cognitive complexity, perseverance, and cognitive instability. The total score was used for grouping the participants.

2.7. Primary data analyses

Data analyses were conducted using SPSS version 10. For analyses of vital signs, subjective measures, and the general measures of performance, two-way repeated-measures analyses of variance (ANOVAs; factors drug dose and time) were used. The k values derived from the delay discounting task were normalized using a log-10 transformation because the data were skewed. Past research has log transformed these values as well to create a more normal distribution of scores (e.g., Richards et al., 1999). For analysis of the drug on task performance, a one-way repeated-measures ANOVA was used. Matched-samples t tests were used for post hoc analyses when significant main effects or interactions were obtained. For analyses of sex and level of impulsivity (high or low BIS) on the tasks, two-way ANOVAs were used. The significance level for all of the statistical analyses was $P<.05$.

3. Results

3.1. Participants

Participant demographic and drug use history data are summarized in Table 1. Most participants were in their early 20s, had some college education, and were full-time

Table 1
Participant demographics and drug use summaries (N=35)

	Low BIS		High BIS	
	Female	Male	Female	Male
n	9	10	7	9
Age (mean±S.E. years)	21.3±1	22.4±1	22.4±2	25.4±3
BMI (mean±S.E.)	21.3±1	23.3±1	22.0±1	22.4±1
Education (*n*)				
High school/partial college	1	2	0	4
College degree/advanced degree	2	2	4	2
Full-time student	6	6	3	4
Current drug use (mean±S.E.)				
Alcohol (drinks/week)	4.4±1	7.5±2	5.6±2	8±2
Caffeine (drinks/week)	7±2	8.6±2	11.7±3	12.6±3
Cigarettes (number who smoke more than 10/day)	2	2	3	5
Marijuana (number who smoke 1 or more a week)	2	4	2	5
Lifetime drug use				
Stimulants (*n*; ever used)	2	5	4	6
Tranquilizers (*n*; ever used)	0	2	1	1
Hallucinogens (*n*; ever used)	3	8	4	7
Opiates (*n*; ever used)	1	3	0	2
Marijuana				
Never (*n*)	3	4	2	2
Used 1–10 times (*n*)	0	1	1	2
Used 11–50 times (*n*)	2	1	1	0
Used>100 times (*n*)	3	4	2	5
Inhalants (*n*; ever used)	3	3	2	4

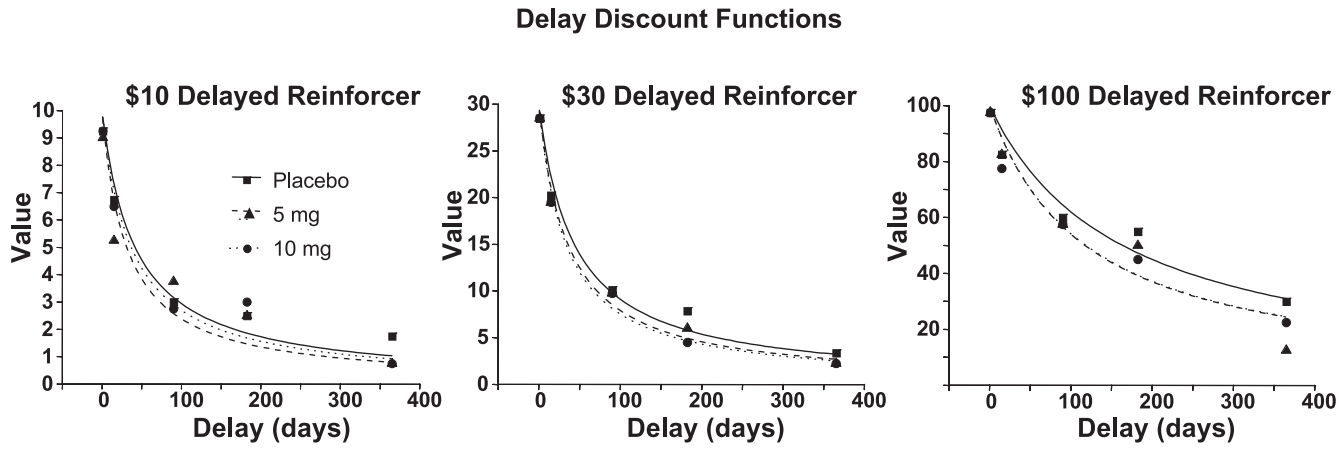

Fig. 1. Median indifference points and best-fit functions for a delayed US$10 reward (left panel), a delayed US$30 reward (middle panel), and a delayed US$100 reward (right panel). Participants completed placebo, and 5- and 10-mg sessions for each delayed reward.

students. The mean BIS-11 total score for the high-impulsive group (H-BIS; n=15; 7 females) was 83.4 (S.D.=6.4), and the mean for the low-impulsive group (L-BIS; n=20, 9 females) was 63.3 (S.D.=9.9).

3.2. Behavioral task measures of impulsivity

Diazepam did not affect performance on any of the behavioral task measures of impulsivity, including k values on the discounting task, SRT on the stop task, false alarms on the go/no-go task, and time estimation or number of pumps on the BART. There also were no interactions with sex or BIS scores. The primary results for the delay discounting task are shown in Fig. 1. Table 2 shows the k and R^2 values for three reward magnitudes on the delay discounting task, which shows that the curves fit the discounting model well, and that the discount functions were, as expected, sensitive to changes in magnitude of reward.

3.3. Subjective effects

Diazepam (5 and 10 mg) produced its prototypic effects (see Fig. 2). It increased subjective ratings on the DEQ scales of "feel drug", "feel high", and "want more"; it decreased measures of stimulation (ARCI BG) and increased measures of sedation (decreased POMS Vigor and Arousal and increased POMS Fatigue; ARCI PCAG; Fig. 2). Most of these effects were observed at 45 and 105 min after drug ingestion. Diazepam (5 and 10 mg) also increased ARCI LSD scores at 45 min, but not 105 min.

There were no interactions between sex and subjective responses, and only one interaction with BIS level. The H-BIS group report significantly more intense subjective experiences on the DEQ feel-drug and feel-high subscales, but this occurred on both active drug and placebo sessions, suggesting that it was a nonpharmacological effect.

Table 2
R^2 and k values for delay discount functions of three different delayed reward amounts

Delayed amount (US$)	Drug condition	R^2 value	k Value
10	Placebo	.96	.012
	5 mg	.87	.016
	10 mg	.95	.014
30	Placebo	.98	.011
	5 mg	.99	.014
	10 mg	.99	.015
100	Placebo	.94	.003
	5 mg	.92	.004
	10 mg	.95	.004

R^2 and k values are based on median indifference point values for each drug condition.

3.4. General measures of performance and vital signs

Diazepam (10 mg) impaired DSST performance 45 and 105 min postdrug administration. However, the drug did not affect performance on the Digit Span task nor did it alter heart rate, systolic, or diastolic blood pressure.

3.5. Correlations between personality and behavioral tasks

Performance on the behavioral tasks was not correlated with BIS-11 total scores, but they were related to scores on certain BIS-11 subscales. For example, there was a significant correlation between logged k values for the US$10 delayed reward and the cognitive complexity subscale of the BIS-11, $r(28)=-.39$, $P<.05$. Participants who discounted most scored lowest in cognitively complexity (e.g., "I save regularly" and "I am more interested in the present than the future"). Stop task SRT values were correlated with the perseverance, $r(34)=-.49$, $P<.05$, and cognitive instability subscales, $r(34)=-.38$, $P<.05$, such that those with the fastest SRTs scored highest in perseverance and cognitive stability. Finally, scores on the time reproduction task (all delays) were correlated with the motor impulsivity subscale, $r(33)=-.48$, $P<.05$. Participants who overestimated on the times, meaning that they tended to

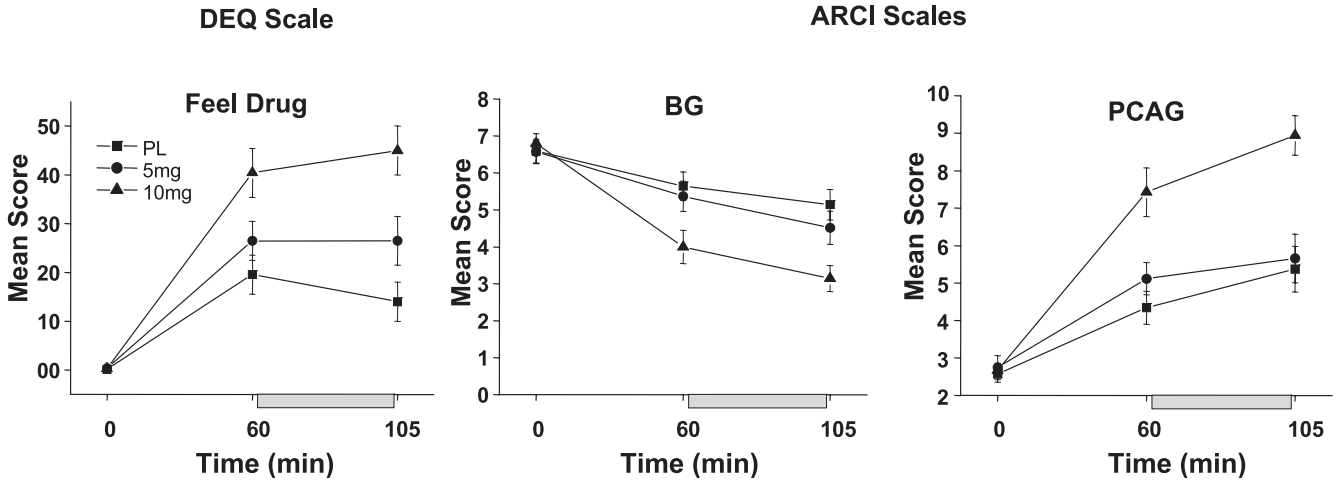

Fig. 2. Mean (±S.E.M.) for DEQ "feel drug" scale and for the BG and PCAG scales of the ARCI at three different doses: placebo, and 5 and 10 mg. The three time points along the *x* axis shows measurement times: before drug administration, and 60 and 105 min after capsule ingestion. The shaped regions along the *x* axis indicate when the behavioral tasks were performed.

perceive time as passing more slowly than it actually was, had lower motor impulsivity scores.

4. Discussion

Diazepam, at doses that significantly increased subjective ratings of sedation, did not affect performance on any of the five behavioral measures of impulsivity. Diazepam produced dose-dependent, prototypic subjective feelings of sedation, including decreased vigor and arousal and increased fatigue. Yet, despite these changes in subjective state and impairment on DSST performance, the drug did not affect performance on standardized tasks measuring delay discounting, inhibition, risk taking, or time perception. These results indicate that the drug does not produce a robust effect on impulsive behavior, as measured by several validated, but operationally distinct, tasks.

An important feature of the present study was the use of a relatively low dose of diazepam. The 10-mg dose was selected because it reliably produces subjective, sedative-like effects in healthy volunteers (Johanson and Uhlenhuth, 1980), effects that were observed in this study, as well. At higher doses, diazepam produces impairments in memory and psychomotor performance that could interfere with the participants' ability to perform the impulsivity tasks, masking the more specific effects of the drug on measures of decision making and inhibition. Indeed, in the present study, even the 10-mg dose impaired performance on the DSST, a measure of nonspecific psychomotor performance, suggesting that higher doses would produce even greater impairments. Nevertheless, it would be valuable to test the effects of higher doses, especially in light of a recent report that 20 mg diazepam produced disinhibitory cognitive effects in human volunteers (Deakin et al., 2004). Another methodological consideration is the interval that elapsed between sessions. Although the average interdose interval in the present study was 168 h, the half-life of diazepam can be as long as 24 to 48 h, with an active metabolite for up to 60 h. This raises the possibility that there were carryover effects. However, there were no significant effects of order on any measures, and it is unlikely that carryover effects masked an effect of the drug on task performance.

The present findings are apparently inconsistent with two other recent studies on behavioral effects of diazepam. Weisman et al. (1998) reported that diazepam (10 mg) increased aggression on a laboratory task procedure, and impulsive and aggressive behaviors are often linked. In another study, Deakin et al. (2004) reported that diazepam (20 mg) impaired performance on several executive tasks, including a measure of attentional vigilance, a go/no-go task, a risk-taking task, and the Tower of London, a measure of planning. An analysis of covariance suggested that these impairments were not secondary to subjective sedation. Lower doses of diazepam (5 and 10 mg) produced marginal effects on these tasks, as they did in the present study, but 10 mg did increase latency to respond on certain measures.

The lack of effect of diazepam on the stop task in the present study has implications for the interpretation of our previous findings with alcohol on this task (de Wit et al., 2000). In the previous study, alcohol impaired SRT at a dose (0.4 g/kg) that did not affect GRT, suggesting a specific effect on inhibition. However, at the 0.4-g/kg dose, participants reported significant increases in sedation, raising the possibility that the increase in SRT could have been mediated by an increase in the subjective state of sedation. However, the increase in sedation (ARCI PCAG) observed after diazepam (10 mg) in the present study was substantially higher than that produced by 0.4 or 0.8 g/kg ethanol in the alcohol study (Holdstock and de Wit, 1999), and yet performance on the task was unaffected. In the previous study, 0.8 g/kg ethanol impaired both GRT and SRT. These findings indicate that the effects of alcohol on the measure of behavioral inhibition occurred independently

of its effects on subjective state. Although it is always difficult to compare across drugs and studies, this comparison suggests that diazepam, unlike alcohol, does not have pronounced effects on impulsive behavior.

An important question is whether the tasks used in this study were sensitive to the effects of drugs. Although the tasks have effectively been used to distinguish impulsive from nonimpulsive individuals, i.e., as a measure of a stable behavioral pattern, only some of the measures are known to be sensitive to the effects of acute behavioral changes. The stop task is known to be sensitive to both increases and decreases in inhibition after D-amphetamine, ethanol, and Δ^{-9} tetrahyrocannabinol (de Wit et al., 2000, 2002; McDonald et al., 2003), and the go/no-go task detected an improvement in performance after D-amphetamine (de Wit et al., 2002). However, several studies have failed to find acute drug-induced changes in the delay discounting task (Crean et al., 2000; Richards et al., 1999). Although this task differentiates impulsive and nonimpulsive participant samples (e.g., Madden et al., 1997; Mitchell, 1999; Reynolds et al., 2004), it has been relatively insensitive to pharmacological manipulations expected to increase impulsive behavior (e.g., Richards et al., 1999; de Wit et al., 2002; McDonald et al., 2003). Thus, it is possible that the lack of effect of diazepam on discounting was related to insensitivity of the task. The BART also differentiates between-subject differences in risk taking (Lejuez et al., 2003), but its sensitivity to alterations after drug administration has not been tested. Similarly, there is little information about the effects of drugs on the particular measure of time perception used here. However, several previous studies with humans and nonhumans have also failed to detect effects of diazepam on timing behavior using other time reproduction and time estimation tasks (Gourevitch and Yanev, 1979; Unrug-Neervoort et al., 1992; Ferguson and Paule, 1996).

Although the effects of diazepam were not, as predicted, related to BIS level, there were some modest, nondrug-related correlations between the BIS-11 factor scores and performance on the tasks. Participants who scored high on the cognitive complexity scale of the BIS exhibited less discounting on the delay discounting task on the placebo session. Furthermore, participants who scored high on perseverance and low on cognitive instability had shorter SRTs on the stop task. These modest correlations between personality and behavioral measures are consistent with previous findings. Although some studies have reported significant correlations between self-report, personality measures of impulsivity, and behavioral tasks (Kirby et al., 1999; Richards et al., 1999), others have not (Crean et al., 2000; Lane et al., 2003; Mitchell, 1999; Reynolds et al., 2004). It is likely that self-report questionnaires measure different aspects of "impulsivity" from the behavioral tasks, and further research on the factor structure of impulsive behavior and self-report measures of impulsive personality is needed to resolve these discrepancies.

In summary, the present findings extend previous findings on the effects of benzodiazepines on impulsive behavior by examining low, behaviorally active doses in a carefully conducted, double-blind, placebo-controlled study with healthy volunteers. The results add to a body of evidence and extensive clinical experience indicating that benzodiazepines are generally well tolerated and safe (Woods et al., 1987).

Acknowledgements

This research was supported by grants from NIDA (DA09133, DA10588 and T32DA07255). The authors acknowledge the expert assistance of Elizabeth Young and April Adams.

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