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Reinforcing and Subjective Effects of Diazepam in Nondrug-Abusing Volunteers

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DEWIT, H., J. PIERRI AND C. E. JOHANSON. *Reinforcing and subjective effects of diazepam in nondrug-abusing volunteers.* PHARMACOL BIOCHEM BEHAV **33**(1) 205–213, 1989.—Preference for diazepam was assessed in 18 light and 12 moderate social drinkers using a cumulative dosing procedure. The 7-session procedure consisted of: 1) four sampling sessions, during which participants ingested color-coded capsules containing either diazepam (five 4-mg capsules administered at 30-min intervals; total dose 20 mg) or placebo, and 2) three choice sessions, during which they could ingest up to 7 capsules of their preferred color of capsule, each separated by 30 min. Subjective (mood) and behavioral (performance) measures were obtained throughout the 4-hour sessions. The light social drinkers chose diazepam over placebo on 66% of the choice sessions, and ingested a mean dose per session of about 16 mg. The moderate drinkers chose diazepam on 100% of the choice sessions, and ingested an average dose of 25 mg per session. Diazepam produced sedation in both groups, but in the moderate drinkers it also increased measures of subjective effects suggestive of "euphoria." The results indicate that diazepam can serve as a positive reinforcer under laboratory conditions in nondrug-abusing individuals who are moderate users of alcohol and other drugs. Greater reinforcing efficacy may be indicative of higher risk of abuse. The results illustrate the usefulness of the cumulative dosing procedure to measure both drug preference and dose preference.

Benzodiazepines Diazepam Human Drug preference Cumulative dosing Normal volunteers

BENZODIAZEPINES are among the most widely prescribed drugs in the United States. In a national household survey (27) over 11% of respondents reported having used an antianxiety agent, usually a benzodiazepine, at least once during the preceding year. Despite the large number of individuals exposed to these drugs through therapeutic use, however, relatively few people develop problems with excessive use or abuse (16, 27, 32). Even among drug abusers, benzodiazepines are rarely the sole drug of abuse (30).

Perhaps because of the relative rarity of benzodiazepine abuse, neither the environmental conditions under which they are likely to be abused, nor the characteristics of individuals who are likely to abuse them are well understood. One way to study the variables associated with abuse of a drug is to study its positive reinforcing properties, or its tendency to maintain drug-seeking behavior under laboratory conditions (23,25). A good concordance has been found between drugs that are abused and those that serve as positive reinforcers in laboratory tests of drug self-administration. These laboratory tests can be used not only to identify drugs that might have potential for abuse, but they are also useful for studying both the environmental conditions and the individual subject-related variables that influence drug-taking behavior.

The reinforcing properties of benzodiazepines have been tested in both laboratory animals and human volunteers (3, 12, 19, 22). While in general these drugs drugs have been found to be relatively ineffective reinforcers compared to other abused drugs, one factor which appears to increase their efficacy as positive reinforcers is prior drug exposure. For example, monkeys which are given experience self-administering a depressant drug such as pentobarbital are more likely to self-administer diazepam than animals with an immediate history of self-administering a stimulant drug (4). Analogously, humans who already have a history of abusing sedative drugs such as barbiturates prefer diazepam over a placebo in choice tests (17–19), whereas normal volunteers without a history of extensive drug use do not (10–12, 24). Whether this apparent facilitatory effect of prior drug experience reflects a selection effect of individuals predisposed to self-administer drugs, or whether the drug history or related behavioral history in itself influences the reinforcing efficacy of drugs is not clear.

Epidemiological data indicate that therapeutic use of benzodiazepines is greater among alcoholics than in the general population (13,32), and the incidence of abuse has been estimated to be higher among alcoholics than among other benzodiazepine users (2,5). How drinking history affects the subjective or behavioral responses to diazepam has not been well studied. In one laboratory

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study (21), the subjective effects of diazepam were evaluated in recently detoxified alcoholics. These subjects rated the drug as euphorigenic, similar to subjects with histories of sedative abuse.

The present study explored the relationship between alcohol use and response to diazepam in normal social drinkers. The subjective and behavioral responses to diazepam were evaluated in individuals who were regular, moderate users of alcohol and in individuals who reported only light consumption of alcohol. None of the participants had any history of drug- or alcohol-related problems, and they reported either light (i.e., an average of less than 5 drinks per week; Study I) or moderate (i.e., an average of 11 drinks per week; Study II) use of alcohol. Using similar definitions of light and moderate drinking (6), it has been estimated that 70% of 20–40-year-olds are light drinkers or less (i.e., light drinkers, infrequent drinkers or abstainers). Thirteen percent are estimated to be moderate drinkers, and the remaining 17% can be classified as heavier drinkers. The light drinkers in the present study reported a level of alcohol consumption that is similar to the level reported by a comparable subject sample of first year medical students (7).

STUDY I: LIGHT SOCIAL DRINKERS

METHOD

Participants

Eighteen normal healthy volunteers aged 21 to 35 participated in the first study. Volunteers were recruited from the university and local community through advertisements in the university newspaper, by posters, and by word-of-mouth referrals. Candidates completed medical and drug use histories, a psychiatric interview, a commonly-used psychiatric symptom checklist [Hopkins Symptom Checklist; HSCL; (8)], an electrocardiogram and a physical examination by a cardiologist. Individuals were accepted if they had completed high school, if they had no current medical or psychiatric problems, and no history of an Axis I psychiatric problems, and no history of an Axis I psychiatric disorder (1). In addition, they were not accepted if they reported being totally abstinent from alcohol, or if they reported any history of drug- or alcohol-related problems. Alcohol-related problems included such items as difficulty stopping drinking, problems with the law or with their job related to drinking, blackouts, or being told by a health professional to limit drinking.

Prior to participating in the study, participants signed a consent form which outlined the procedures to be used and listed possible side effects of any drugs they might receive. As part of this consent, participants agreed not to take any drugs (other than their normal amounts of caffeine or tobacco) or medication for 12 hours prior to, and 6 hours following each session. Volunteers were paid for their participation, and the study was approved by the local Institutional Review Board.

Procedure

The experiment consisted of seven 4-hour weekly sessions conducted from 7 to 11 p.m. The testing environment consisted of two comfortably furnished rooms. One room had a couch and upholstered chairs, and contained a television with a VCR. The other room contained a bar with bar stools, and a table for board games. Playing cards, a variety of board games, and a radio/cassette player were available. Participants could engage in leisure activities of their choice but they were not allowed to work or study. They were tested in groups of three or four individuals who were acquainted with one another prior to the study in order to simulate a relaxed and naturalistic setting.

The first four experimental sessions were sampling sessions, and the last three were choice sessions. On each sampling session, participants ingested, at regular intervals, a series of five color-coded capsules (see below) containing either drug or placebo. The capsules were colored so that for each individual the same color of capsule always contained either drug or placebo, but across individuals the colors were varied. Diazepam capsules and placebo capsules were administered double-blind, on an alternating basis during the first four (sampling) sessions. All individuals in a group received drug or placebo on the same sampling session. Three testing groups received diazepam capsules on sessions 1 and 3 and placebo on sessions 2 and 4, while the other two groups received drug and placebo in the reverse order. Participants were told that they might receive a stimulant, a minor tranquilizer, alcohol, or a placebo, and that the same color of capsule would always contain the same substance. They were told that other members of the group may or may not be receiving the same drugs. On sampling sessions, participants ingested one capsule every 30 min between 7 p.m. and 9 p.m. The five capsules contained either diazepam (4 mg per capsule; 20 mg total) or placebo. This divided dosing procedure allowed participants to experience the effects of low as well as higher doses of the drug during the sampling phase. On choice sessions, participants first indicated which of the two colors of capsule (i.e., the color containing diazepam or placebo) they wished to take on that session, and they were required to ingest one unit dose of the color they chose. For the remainder of the session, they were given options every 30 min to take up to six additional unit doses of the *same* substance. Thus, they could take up to 28 mg of diazepam. Paticipants indicated all their capsule choices individually and privately with the technician. The number of sessions (out of three) on which participants chose diazepam over placebo was the measure of drug preference. The number of unit doses of diazepam they ingested within a session was the measure of dose preference. The number of placebo capsules selected on placebo choice sessions served as a comparison to the number of drug capsules taken, indicating how many "doses" of an inactive substance participants would choose.

Diazepam (4 mg) was prepared in colored capsules (size 00) with dextrose powder as filler. Placebo capsules were identical but contained dextrose powder only. Participants drank 90 ml of water with each ingestion.

On each session, participants reported to the laboratory shortly before 7 p.m., at which time they filled out predrug (hour 0) self-report mood or subjective effects questionnaires (see below). At this time they also completed a test of psychomotor performance, the Digit Symbol Substitution Test [DSST; (31)], and presession breath alcohol determinations were obtained to ensure that the participants were alcohol-free. Capsules were administered at the beginning of the session and again at 30-min intervals as described above. On both the sampling and the choice sessions, subjective effects questionnaires were administered every 30 minutes (except at 10:30 p.m.). The DSST was administered shortly before the first drug ingestion, and again at 8 and 9:30 p.m. A technician present during the sessions rated the presence or absence of 10 drug-related behaviors (e.g., slurred speech, loquacity, trouble filling out forms) at each hour.

At 11 p.m. participants completed an additional questionnaire on which they indicated what they thought they had received (stimulant, tranquilizer, alcohol or placebo), and how much they liked the drug's effects. Liking was measured on a 100 mm line labelled "not at all" at one end and "extremely" at the other. After completion of this questionnaire they were escorted to a clinical research ward where they spent the night. Upon awakening in the morning, they completed a final set of subjective effects questionnaires, as well as the Leeds Sleep Evaluation Questionnaire [LSEQ; (28)]. The LSEQ consists of 10 questions concerning the latency and quality of subjects' sleep and their alertness

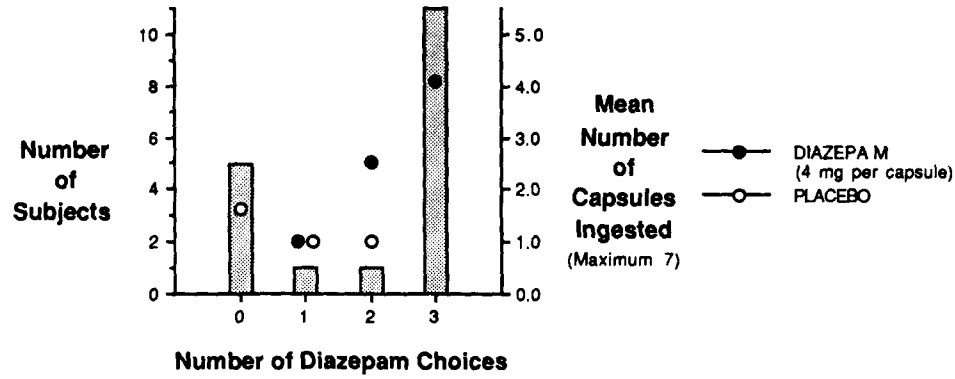

FIG. 1. Bars indicate the number of participants in Study I who chose diazepam on 0 through 3 of the choice sessions. Circles indicate the mean number of drug (closed symbols) and placebo (open symbols) capsules ingested, out of a maximum of 7, for participants who chose drug on 0 through 3 sessions.

upon awakening. The 10 questions are separated into four subscales, corresponding to measures of Getting to Sleep (GTS), Quality of Sleep (QOS), Awakening from Sleep (AFS) and Behavior following Wakefulness (BFW). Higher scores on these scales indicate shorter latency, better quality of sleep, easier awakening, and greater alertness upon awakening.

Subjective effects measures: the scale used to assess subjective drug effects was an experimental version of the Profile of Mood States [POMS; (26)]. This version consists of 72 adjectives commonly used to describe momentary mood states. Participants indicate how they feel at the moment in relation to each of the adjectives on a 5-point scale ranging from "not at all" (0) to "extremely" (4). Eight clusters of items have been empirically derived using factor analysis. These clusters, which form the eight scales of the questionnaire, have been given names that best describe the clustered adjectives: Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness and Elation. Two additional subscales (unvalidated) were derived on an intuitive basis from other scales [Arousal = (Anxiety + Vigor) − (Fatigue + Confusion), and Positive Mood = Elation − Depression].

During the debriefing interview which followed the experiment, participants completed a battery of personality and attitude tests. They included the Sensation Seeking Scale [SSS; (33)], the Rotter Internal/External Locus of Control Scale [IE; (29)], the Eysenck Personality Inventory [EPI; (14)], the Psychopathic State Inventory [PSI; (20)] and the Drug Attitudes Scale [DAS; (15)]. These tests were selected because of their purported relationships to drug use.

Data Analysis

Choice data were analyzed using log linear methods for nonparametric data. The POMS data were analyzed using separate, two- or three-way repeated measures analyses of variance for each scale. Only data from the sampling sessions were used in most of these analyses because of variability in doses self-administered during the choice sessions. Fisher's least significant difference post hoc tests were used when significant ($p<0.05$) main effects or interactions were obtained.

RESULTS

Most (61%) of the 18 light-drinking participants chose the diazepam-containing capsule over the placebo capsule on all three of the choice sessions, while a smaller number (28%) consistently chose the placebo (Fig. 1). The distribution of frequencies of choice (0–3) exhibited significant linear ($z=3.17$, $p<0.005$) and quadratic ($z=3.21$, $p<0.05$) trends (log linear analysis). On sessions when they chose the diazepam capsules, participants ingested an average dose of 15.6 mg, or a mean of 3.9 capsules. When they chose the placebo, participants took on average only 1.6 capsules. Figure 1 shows the average number of drug or placebo capsules ingested within choice sessions. It can be seen that individuals who took diazepam on all three sessions tended also to take more doses of the drug within sessions than those who chose the drug only one or two times.

Because of the apparently bimodal distribution of individuals choosing the placebo or diazepam capsules, participants were categorized post hoc into two groups based on the amount of drug they ingested during the choice sessions. For each individual, the average dose of diazepam per choice session was calculated, and individuals falling below the median unit doses (i.e., 10 mg or 2.5 doses per session) formed the Low Choice (LC) group while those falling above the median formed the High Choice (HC) group. Thus formed, the LC group ($N=9$) chose diazepam over placebo on average on 1 out of 3 sessions, taking an average dose per choice session of 4.9 mg (or 1.23 capsules), whereas members of the HC group ($N=9$) chose the diazepam on all three choice sessions and ingested an average dose of 18.8 mg per session (or 4.7 capsules). The LC group chose about as many "doses" of placebo as they took of diazepam (means 1.4 and 1.23). To explore variables that might be associated with greater or less drug choice, data from most of the remaining dependent measures will be presented separately for the LC and HC groups.

Demographic Characteristics

The LC and HC groups did not differ in age, gender, drug use history, or the proportion who were students (Table 1). Participants in both groups were typically students in their early 20's who were light alcohol drinkers (less than 5 drinks per week) and very occasional users of other recreational drugs.

Liking Scores

Liking scores, obtained from the end-of-session questionnaires (hour 4), were averaged for the two drug and the two placebo sampling sessions, and a liking difference score was calculated by subtracting the mean placebo score from the mean drug score. The overall drug-minus-placebo difference score for the entire group was 6.5 (sem 3.6). For the LC group alone the mean difference score was −3.1 (sem 5) and for the HC group alone it was 16.1 (sem 2.7) (two-sample, $t=2.36$, $p<0.05$).

TABLE 1

CHARACTERISTICS OF PARTICIPANTS IN STUDY I: LOW CHOICE INDIVIDUALS (LC) VERSUS HIGH CHOICE (HC) INDIVIDUALS

	LC		HC	
N	9		9	
Mean age (sem)	22.0	(0.5)	22.7	(1.4)
Full-time student	7		5	
Current caffeine use				
Mean (sem) drinks per week	10.7	(1.6)	13.0	(2.1)
Current alcohol use				
Mean (sem) drinks per week	4.4	(1.2)	5.2	(0.9)
Current tobacco use				
Nonuser	8		7	
<10 cigarettes/day	0		2	
10+ cigarettes/day	1		0	
Lifetime nonprescription drug use:				
Marijuana: Never	0		2	
1–50 times	8		4	
50+ times	1		3	
Tranquilizers: Ever used	1		1	
Stimulants: Ever used	7		5	
Hallucinogens: Ever used	2		2	
Opiates: Ever used	1		1	

TABLE 2

DRUG LABELS

	Received Diazepam				Received Placebo			
Label:	T	A	S	P	T	A	S	P
Study I:								
LC group	11	7	0	0	2	1	6	8
HC group	7	10	1	0	4	1	4	9
Study II:	16	5	2	1	3	0	7	14

Frequencies of labels of diazepam and placebo as Tranquilizer (T), Alcohol (A), Stimulant (S) and Placebo (P) in Study I and Study II.

Data based on the two diazepam and two placebo sampling sessions for each of the nine individuals in the LC and HC groups in Study I, and the twelve participants in Study II.

Drug Identification

Individuals in both the LC and HC groups labelled the diazepam-containing capsule about equally often as either a tranquilizer or alcohol during sampling sessions (Table 2). Both groups identified the placebo correctly on about 50% of the sampling sessions.

On choice sessions, the HC group again labelled the diazepam equally often as either tranquilizer or alcohol: 14 'tranquilizer' labels and 11 'alcohol' labels out of a total of 27 sessions (9 individuals, 3 choice sessions). The LC group labelled diazepam correctly on 6 out of 9 diazepam choice sessions, and labelled placebo correctly on 15 out of 18 placebo choice sessions.

DSST

Diazepam significantly impaired performance on the DSST, and did so to a similar degree in both the LC and HC subjects (ANOVA; drug-by-hour interaction, $p<0.01$). On diazepam sampling sessions, at hour 0 the mean DSST score for all 18 subjects was 57.6; at hours 1 and 2.5 the mean scores fell to 56.1 and 52.5, respectively. On placebo sessions scores at 1 and 2.5 hours postdrug did not differ from predrug scores. The LC and HC groups did not differ either in DSST scores in the absence of drug (i.e., hour 0 or placebo sessions), or in impairment after diazepam.

Observer Ratings

The mean number of behaviors observed at each hour (8, 9, 10 and 11 p.m.) on the 10-item checklist on diazepam sampling sessions were 1.0, 3.9, 3.3 and 3.2 items in the LC group, and 0.7, 2.3, 2.4 and 2.0 items in the HC group. The two groups differed only at 9 p.m., when the LC group showed more signs than the HC group (ANOVA, drug-by-hour-by-group interaction, $p<0.02$; Fishers LSD post hoc test). Less than 0.2 behavioral signs were observed at any hour on placebo sessions.

Sleep Questionnaire

When all 18 subjects were considered together, diazepam significantly decreased the time taken to get to sleep (GTS scale; mean drug-minus-placebo difference score 28.02; sem 3.1; $t=9.0$, $p<0.001$) and improved the quality of sleep (QOS scale; mean drug-minus-placebo difference score 25.83, sem 3.9; $t=6.5$, $p<0.001$). When the LC and HC groups were compared, the LC group reported feeling more tired after awakening than the HC group (BFS scale; LC difference score: −7.4; HC difference score: 8.8; $t=2.3$, $p<0.05$).

Subjective Effects (Sampling)

When data from all 18 subjects were considered together, diazepam produced typical tranquilizer-like effects, including decreased Vigor and Arousal at hours 1 to 3, and increased Fatigue and Confusion at hours 1 to 4 (drug-by-hour interactions, $p<0.05$). The drug also significantly decreased Positive Mood and Elation scores at the hour 1 determination (drug-by-hour interaction, $p<0.05$). The hourly mean scores for several of these scales are presented in Fig. 2.

Diazepam did not affect the LC and HC groups differentially on the POMS. The POMS data for the LC and HC groups were analyzed in a three-way ANOVA (group, drug, hour), and the only effects involving the group factor that approached statistical significance were main effects on the Friendliness and Vigor scales. On these scales, the LC group scored slightly higher than the HC group, regardless of drug (i.e., on drug and placebo sessions) or hour (main effects of group, $p<0.07$). There were no differences in the two groups' POMS scores after diazepam administration.

Subjective Effects (Choice)

For the 13 subjects who chose diazepam on at least one of the choice sessions, the POMS scores on diazepam choice sessions were compared to data from diazepam sampling sessions. The POMS scores from choice sessions were averaged across the sessions on which diazepam was chosen regardless of the dose of diazepam self-administered. (The average dose of diazepam taken by these 13 participants was 14.8 mg, and doses ranged from 4 mg to 28 mg. The timing of the doses within the choice sessions also varied from individual to individual.) The data from diazepam sampling sessions and diazepam choice sessions were compared

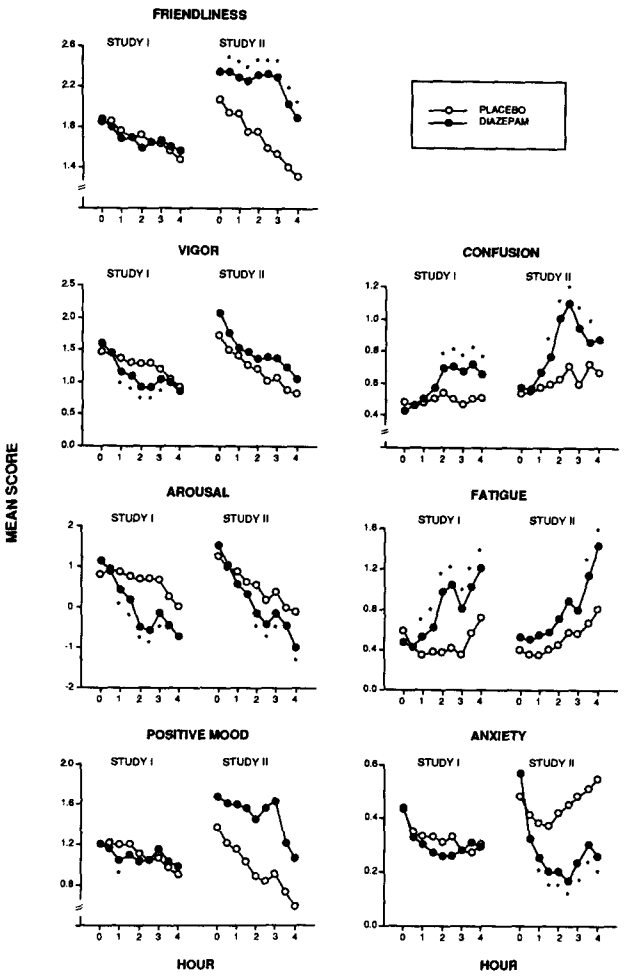

FIG. 2. Hourly mean POMS scores for diazepam and placebo sessions for Study I (left portion of each panel) and Study II (right portion of each panel). Data are from sampling sessions only. Asterisks indicate significant differences (post hoc tests, $p<0.05$) between drug and placebo means at each hour, for scales on which significant drug-by-hour interactions were obtained.

using a two-way ANOVA (sampling versus choice and hour). Diazepam produced less pronounced subjective effects during the choice phase than during the sampling phase: The drug increased Confusion scores to a greater degree during sampling than during choice sessions, and it produced a more marked decrease in Arousal scores. These differences in subjective effects occurred between 2 and 3.5 hours after ingestion of the first capsule, and are consistent with the differences in pattern of doses ingested during sampling and choice: During sampling participants ingested 20 mg over the first two hours of the session, whereas during choice they ingested a lower total dose over a longer interval.

STUDY II: MODERATE SOCIAL DRINKERS

METHOD

Participants

The participants in this study were twelve healthy men and women (aged 21 to 35) who met two of the following criteria for alcohol use: 1) consumes at least 7 drinks per week, 2) consumes at least three drinks on a single occasion at least once a week, and 3) consumes alcohol on at least four days of the week. As in Study I, individuals with any history of drug- or alcohol-related problems were not accepted. All other acceptance criteria and screening procedures were the same as in Study I, and, as in Study I, participants wre recruited in groups of four individuals who were acquainted with one another prior to the study. Recruitment efforts for this study extended beyond the university community into the greater metropolitan area, by advertising in a city-wide newspaper.

TABLE 3

CHARACTERISTICS OF PARTICIPANTS IN STUDIES I AND II

	Study I		Study II		p*
N	18		12		
Age	22.4	(0.3)†	25.3	(9.9)	<0.02
Gender (M/F)	13/5		5/7		n.s.
HSCL Anxiety	0.15	(0.16)	0.13	(0.14)	n.s.
HSCL Depression	0.16	(0.20)	0.26	(0.23)	n.s.
Education					
Partial college	2		5		
College degree	16		7		n.s.
Full-time student	12		1		<0.01
Current drug use (last 30 days):					
Caffeine (cups/week)	11.8	(1.4)	9.2	(1.7)	n.s.
Alcohol (drinks/week)	4.8	(1.4)	11.8	(1.5)	<0.001
Tobacco					
Nonuser	15		5		
<10 cigarettes/day	3		4		
10+ cigarettes/day	0		3		<0.05
Marijuana					
Nonuser	15		2		
<1 joint/week	1		4		
>1 joint/week	2		6		<0.01
Lifetime nonprescription drug use:					
Marijuana					
Never used	2		0		
1–50 times	12		0		
50+ times	4		12		<0.01
Tranquilizers					
Ever used	2		3		n.s.
Stimulants					
Ever used	12		11		n.s.
Hallucinogens					
Ever used	4		8		<0.05
Opiates					
Ever used	2		7		<0.01

*Quantitative data tested with t-tests, frequency data with chi-square.
†Mean (standard error).

Procedure

The experimental protocol used in Study II was identical to that described for Study I.

RESULTS

Demographic Characteristics

Study II participants were similar to Study I participants in

gender, education, current caffeine use, and lifetime nonprescription use of tranquilizers and stimulants but differed from Study I participants in the use of several other classes of drugs (Table 3). Their weekly alcohol use was, as intended, significantly higher than that of Study I participants, but Study II participants also reported greater current use of marijuana and tobacco, and a higher proportion reported having ever used hallucinogens and opiates. Study II participants were also slightly older and fewer were students than in Study I.

Choice

All twelve participants in Study II chose the diazepam-containing capsule on all three choice sessions. They chose an average dose of 25.2 mg per choice session (or 6.3 out of the seven available unit doses).

Drug Liking

Study II participants rated their liking of diazepam significantly higher than their liking of placebo. The mean drug-minus-placebo difference score was 24.9 (sem 3.7; $t=6.84$, $p<0.001$). This liking difference score was significantly higher than the mean difference score for participants in Study I ($t=3.59$, $p<0.002$).

Drug Identification

Drug and placebo identifications by participants in Study II were similar to those in Study I (Table 2). They correctly identified the diazepam as a tranquilizer on 66% (16 out of 24) of the sampling sessions and the most common incorrect label was alcohol (n=5). The placebo was correctly identified on 14 out of 24 occasions, and the most common incorrect label was stimulant (n=7).

DSST

Diazepam significantly decreased DSST scores at both 1 and 2.5 hours after drug ingestion (ANOVA; drug-by-hour interaction, $p<0.01$). On diazepam sampling sessions the mean DSST scores at hours 0, 1 and 2.5 on diazepam sampling sessions were 53.3, 50.6 and 46.1, while on placebo sampling sessions scores did not change over the session. Diazepam's effects on DSST performance were similar in Studies I and II.

Observer Ratings

Diazepam significantly increased the number of drug-related signs (ANOVA; drug-by-hour interaction, $p<0.02$). The mean number of signs at 8, 9, 10 and 11 p.m. on diazepam sampling sessions were 0.6, 2.3, 2.6 and 2.6, while on placebo sessions the hourly mean did not exceed 0.2. Diazepam produced similar effects on observer ratings in Study II participants as in Study I.

Sleep Questionnaire

As in study I, diazepam significantly facilitated getting to sleep (GTS scale, mean drug-minus-placebo difference scores 28.3) and improved the quality of sleep (QOS scale, mean difference score 27.4).

Subjective Effects (Sampling)

Diazepam significantly increased scores on Friendliness, Confusion and Fatigue scales, and decreased scores on Arousal and Anxiety (drug-by-hour interactions, $p<0.05$). Figure 2 shows that the diazepam-placebo differences on most of these scales peaked between 2 and 4 hours, although the increase in Fatigue occurred relatively late in the session (hour 3.5 to 4). The drug effects on the Anxiety and Confusion scales showed the clearest time course, with a relatively fast onset early in the session (hour 1 to 1.5) and an apparent return to placebo levels toward the latter part of the session (hours 3 to 4).

On diazepam compared to placebo sampling sessions, participants also scored higher on Vigor, Elation and Positive Mood scales (main effects of drug, $p<0.05$). However, predrug (hour 0) differences between drug and placebo sessions on these scales scores complicate the interpretation of these apparent drug effects. A separate analysis was conducted to determine whether the hour 0 drug/placebo differences were present on the first pair of sampling sessions (i.e., on sampling sessions 1 and 2) or whether they appeared only after the first experience with the capsules (i.e., on sampling sessions 3 and 4). This analysis revealed that the hour 0 differences occurred only during the second pair of sessions suggesting that expectancy or anticipatory drug effects may have placed a role in the predrug differences on sessions 3 and 4.

TABLE 4

DIAZEPAM AND PLACEBO SESSION MEANS ON POMS SCALES WITH DRUG × GROUP INTERACTIONS

	Study I		Study II		
	Placebo	Diazepam	Placebo	Diazepam	
	a	b	c	d	$p<0.05$
Anger	0.03	0.07	0.18	0.07	ac; cd
Vigor	1.24	1.10	1.19	1.46	cd
Friendliness	1.67	1.66	1.68	2.23	cd
Elation	1.10	1.29	1.01	1.52	cd

Subjective Effects (Choice)

As in Study I, POMS scores from diazepam choice sessions were compared to those from diazepam sampling sessions. Sampling and choice scores were different only at occasional hours on the Anxiety, Fatigue and Confusion scales (phase-by-hour interactions) and across the entire session on the Elation scale (main effect of phase). On the Anxiety scale, hour 0 scores were higher on sampling sessions than on choice sessions. However, by hour 1, Anxiety scores on sampling sessions had decreased to a level lower than that reported for the same hour on choice sessions. Fatigue scores were higher at hour 0.5 and at hour 4 on sampling sessions compared to choice sessions, and Confusion scores were lower on choice sessions at 2 and 2.5 hours. Mean Elation scores across all hours were significantly higher on sampling compared to choice sessions.

Study I and II Comparisons

Study I participants' POMS scores were also compared to Study II participants' scores (three-way ANOVA; group, drug, hour). Sampling session data only were used for this analysis. The groups differed significantly in their responses to diazepam on the Anxiety and Fatigue scales (drug-by-hour-by-group interactions, $p<0.05$). On the Anxiety scale, Study II participants scored higher on placebo sessions and showed a more marked decline after diazepam. On the Fatigue scale, the increase in Fatigue scores occurred earlier in the session in Study I participants (hour 1) compared to Study II (hour 3.5).

Study I and II participants also differed in their overall session mean scores on the Anger, Friendliness, Vigor and Elation scales (drug-by-group interactions, $p<0.05$; Table 4). On the Anger scale, Study II participants' scores were higher on placebo sessions relative to their own scores after diazepam and relative to Study I participants' scores after diazepam or placebo. On the Friendliness, Vigor and Elation scales, Study II participants' scores were higher on diazepam sessions compared to placebo sessions.

Personality Tests

Within Study I, the LC and HC subjects did not differ on any of the personality scales. However, when participants from Studies I and II were compared, Study II participants scored higher than Study I participants on two scales of the DAS and on one SSS scale. Study II participants scored significantly higher on the "attitudes towards cannabis" scale of the DAS (mean score 23.4; sem 0.9 compared to mean in Study I of 16.3; sem 0.8; $t=5.6$, $p<0.001$) and on the "attitudes towards hallucinogens" scale (Study II mean: 22.1, sem 1.4; Study I mean: 15.0, sem 1.2; $t=3.8$, $p<0.001$). This indicates that Study II participants had more positive attitudes toward these drug classes. Study II participants also scored higher on the SSS Experience Seeking scale (Study II mean score 8.3, sem 0.5; Study I mean score 5.9, sem 0.4; $t=4.3$, $p<0.001$), indicating a greater tendency to seek novel experiences.

DISCUSSION

Study I

In Study I two-thirds of a sample of normal healthy volunteers with no history of drug abuse consistently chose capsules containing diazepam over placebo capsules, taking an average diazepam dose of 15.6 mg on each choice session. This level of diazepam choice was substantially higher than that observed in previous studies, when, under various different testing conditions, normal volunteers seldom chose a diazepam-containing capsule over placebo (9, 11, 24). In one series of studies (11,24), capsules containing either diazepam (2, 5 or 10 mg) or placebo were administered in the mornings, and participants experienced the drug's effects in their normal daily environments. Under these conditions, few participants preferred the diazepam over the placebo, perhaps because the drug's sedative effects interfered with their daily activities. In another study (9), a single dose capsule containing diazepam (20 mg) or placebo was administered in the evening in a recreational environment similar to the one used here. In that study, participants had only one opportunity to choose their preferred capsule (diazepam or placebo), and only three of the eleven subjects chose the drug capsule. Thus, most participants did not prefer a fixed dose of diazepam over a placebo, whether the drug's effects were experienced in their daytime environment or in a comfortable recreational environment.

A major difference between this and previous studies was in the dosing regimen by which diazepam was administered. Whereas in previous studies the total dose was administered in a single capsule (and participants chose either that dose or the placebo), the total dose in the present experiment was divided into a number of unit doses administered at regular, spaced intervals. This cumulative dosing procedure was followed during the sampling phase to provide participants with experience with several doses of the drug. Doses were also administered cumulatively during the choice phase, but in addition participants were given the opportunity to regulate their own doses. Thus, two major differences between this and previous studies were the dosing regimen by which the drug was administered and the control given to participants over their dose of drug during the choice phase. Either of these factors may have influenced participants' choice behavior.

Two features of the testing milieu may also have influenced the participants' choice behavior. In order to create a naturalistic social environment and to minimize social variables that might inhibit drug choice, the testing groups were comprised of volunteers who were acquainted with one another prior to their participation. It was assumed that this would create a more social and relaxed atmosphere than would have existed if four previously unacquainted individuals had been tested together. In addition, all individuals in a group received drug capsules or placebo capsules on the same sampling sessions. This was designed to approximate a naturalistic drug-taking environment. Whether either of these aspects of the testing environment influenced the participants' choice behavior will be addressed in future studies.

Despite the high overall level of diazepam choice in Study I, relative to previous studies, participants in this study varied widely both in their drug choices and in their selection of doses. Whereas some individuals never chose the drug, others always selected the drug over the placebo, and doses ingested ranged from 4 to 28 mg. These individual differences were examined more closely by comparing data from the participants who ingested the most and the fewest diazepam doses across the three choice sessions. The level of drug choice among Study I participants was not related to their demographic, prior drug use, personality characteristics, their identifications of the drug, or their impairment in DSST performance within the study. Drug choice was, not surprisingly, related to ratings of drug liking during the sampling phase. Less frequent drug choice was also associated with more overt behavioral signs of drug effects during sampling, and with reports of being sleepier the mornings after drug administration. Any of these factors may have influenced individuals' choice behavior.

Despite the positive relationship between drug liking and choice, diazepam did not increase POMS measures that might be associated with drug-induced "euphoria," such as Friendliness, Positive Mood or Elation. This lack of euphorigenic effect is consistent with previous findings in this laboratory (9–11, 24). However, the fact that diazepam was consistently chosen by some individuals (HC group) without producing any correlated changes in subjective effects (e.g., euphoria) is paradoxical and not consistent with previous findings showing that behavioral preference is usually associated with certain subjective drug effects. These data suggest that the two measures (choice behavior and mood effects) do not always covary, and that organismic or environmental factors other than the acute effects of the drug may have influenced drug preference in this study.

Study II

In marked contrast to Study I, participants in Study II exhibited behavioral and subjective responses to diazepam that were suggestive of some risk for abuse of the drug. First, these individuals chose diazepam on every available choice session, and they ingested close to the maximum number of doses available. Second, the subjective effects reported by these individuals included not only the typical sedative-like effects (e.g., decreased Arousal and increased Confusion), but also increases in Friendliness and Positive Mood, mood states which might be associated with drug-induced "euphoria." Consistent with their behavioral preference and their subjective responses as measured by the POMS, these individuals' ratings of drug liking were also high (relative to their own ratings of placebo liking and relative to Study I subjects' ratings of drug liking).

Increases in positive mood states such as Elation and Friend-

liness after diazepam have not previously been observed in individuals without a history of drug abuse. These findings suggest that even moderate users of alcohol and other drugs may be likely to experience euphoric effects from diazepam. Moreover, both the relatively greater frequency of these individuals' choice of diazepam over placebo, and the higher doses ingested on choice sessions indicate that the drug serves as an effective positive reinforcer. Thus, both the positive subjective responses to the drug during the sampling phase and subjects' drug-taking behavior during the choice phase were indicative of relatively greater liability for abuse.

It is interesting to note that participants did not report greater or more positive subjective effects after diazepam during the choice sessions compared to during the sampling sessions, despite the fact that they ingested higher doses of the drug on choice sessions, and they ingested these doses according to their own, self-selected schedule. This lack of increase in response (and in some cases decrease in subjective effects) may reflect the development of tolerance to the drug's pharmacological effects, or it may be a consequence of repeated behavioral testing that is unrelated to pharmacological tolerance (e.g., boredom).

Apart from the apparent differences in positive mood, Study II participants differed from Study I participants on several other measures of subjective drug response. For example, Study II participants reported higher levels of Anxiety on placebo sessions than Study I participants. However, the fact that they did not score higher either on the Anxiety scale of the HSCL during screening nor at the predrug (hour 0) POMS determinations suggests that there were not stable group differences in level of anxiety. The sharp decline in Anxiety scores after diazepam in Study II is consistent with the drug's known anxiolytic effect, but whether it was related to participants' choice behavior is not clear. A previous study (10) showed that anxiety reduction, even in highly anxious individuals, was not in itself a sufficient condition for diazepam to be preferred.

Study II participants differed from Study I participants extra-experimental as well as intra-experimental variables. They were on average slightly older and fewer were students. With respect to their drug use, Study II participants differed not only on the intended experimental variable, alcohol consumption, but also on their current and lifetime use of other drugs such as marijuana, tobacco, hallucinogens and opiates. In addition, Study II participants reported more positive attitudes towards two recreationally-used drugs, cannabis and hallucinogens. Which particular demographic or drug use variables (if any) were related to choice behavior will be a subject for future research.

The important findings in this study were that within the nondrug-abusing population there are some individuals who, under the appropriate environmental conditions, show positive reinforcing effects from diazepam and report experiencing positive mood effects from the drug. The results suggest that regular but moderate use of some drugs, perhaps alcohol, is related to the mood-altering and behavioral (i.e., reinforcing) effects of another drug, such as diazepam. How this interaction between prior drug use and acute behavioral and subjective responses to a new drug occurs is not clear. It may be related either to the pharmacological or behavioral history of the individual, or to some other preexisting characteristics of the individual (e.g., personality or constitutional factors). Finally, although this pattern of responses in the laboratory environment is associated with elevated risk for abuse, other facilitatory factors (e.g., psychosocial factors) may be necessary for the emergence of problems with excessive drug use.

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