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Self-Administration of Pentobarbital in Light and Moderate Alcohol Drinkers

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COLE-HARDING, S. AND H. DE WIT. *Self-administration of pentobarbital in light and moderate alcohol drinkers.* PHARMACOL BIOCHEM BEHAV **43**(2) 563–569, 1992.—Preference for a moderate dose of pentobarbital was assessed in light and moderate alcohol drinkers using a double-blind, placebo-controlled laboratory choice procedure. Sixteen light drinkers (less than six alcoholic drinks per week) and 13 moderate drinkers (six or more drinks per week) participated in a seven-session study in which they first sampled capsules containing pentobarbital (150 mg) or placebo and then chose and ingested the capsule they preferred. Subjective and behavioral measures were obtained at regular intervals during each session to characterize the drug's effects. Both groups chose pentobarbital *less* often than placebo: Mean pentobarbital choice in light drinkers was 20.8% and in moderate drinkers was 38.5%. Pentobarbital choice and drug liking ratings were highest among male moderate drinkers but still did not exceed placebo levels. The drug did not increase scores on standardized measures of drug euphoria, even among the most frequent choosers or the heaviest alcohol consumers. The results extend previous reports showing that individuals without histories of drug abuse, even those who are moderate consumers of alcohol, do not self-administer sedative/anxiolytic drugs or experience their effects as euphorigenic.

Pentobarbital Drug preference Humans Alcohol Self-administration Individual differences Subjective drug effects Abuse liability

THE use of alcohol and other drugs is often thought to covary, and there is a high incidence of comorbidity of alcoholism and drug abuse (19). A possible reason for this association is that heavy use of alcohol alters the subjective or behavioral effects of drugs. Animal studies have shown that previous exposure to certain drugs increases the reinforcing effects of other drugs (22). In humans, prior exposure to drugs or alcohol may alter the subjective effects of other drugs (e.g., increasing the euphorigenic effects). Alternatively, use of one drug (e.g., alcohol) may lead to cross-tolerance to other drugs (e.g., sedative/hypnotics and anxiolytics), which may decrease aversive effects such as sleepiness and thus increase overall liking of the drug (3). Another possible reason for the associations between alcohol and other drug use may be that the behaviors share the same predisposing factors, such as the desire for novel experiences or changes in mood. Finally, the level of use of all drugs, including alcohol, may be influenced by genetic factors, perhaps interacting with environmental factors outlined above (15).

Consistent with the observed associations between alcohol and drug use in clinical settings, it has been found that drug preferences in human subjects, as tested in laboratory studies, depend upon the subjects' drug use histories. For example, diazepam is preferred over a placebo in double-blind choice tests by individuals with histories of sedative abuse (11) but generally not by normal, healthy volunteers (8,12). Recently, it was demonstrated that even modest differences in habitual alcohol use can affect preferences for diazepam (7): Normal (i.e., nonproblem) moderate social drinkers who consumed an average of 12 drinks per week were compared to lighter drinkers who consumed on average 5 drinks per week. It was found that the moderate drinkers chose diazepam substantially more often than the lighter drinkers and reported experiencing more positive subjective effects from the drug. The present study was designed in part to test the generality of this finding to another sedative drug, pentobarbital.

Pentobarbital is a sedative/hypnotic drug thought to have a relatively high potential for abuse. The illicit use of this drug is confirmed by epidemiological data (18) and clinical research reports (1,13). Moreover, pentobarbital is readily self-administered by laboratory animals in studies designed to measure abuse potential (21). Like diazepam, however, self-administration of pentobarbital in humans depends upon the population studied, in particular on the subjects' drug use histories: Whereas individuals with histories of sedative abuse reliably self-administer pentobarbital (11), healthy volunteers without drug abuse histories do not (6,9).

In the present study, we examined the relationship between drinking history and pentobarbital preference among normal social drinkers. Moderate drinkers who consumed six or more drinks per week were compared to lighter drinkers who consumed one to five drinks per week. They participated in a

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seven-session double-blind choice procedure, in which they first sampled capsules containing drug or placebo and were then given three opportunities to choose the capsule they preferred. It was hypothesized that heavier users of alcohol would choose the pentobarbital more often. Higher drug choice in laboratory tests such as this are considered indicative of a higher risk for abuse.

METHOD

Subjects

Twenty-nine male and female volunteers aged 21–35 years were recruited through newspaper ads and posters at several universities in the Chicago area. Two groups of subjects were formed based upon their self-reported habitual alcohol intake. One group consisted of light drinkers (LD group), subjects who drank less than six drinks per week. The other group consisted of moderate nonproblem drinkers (MD group), individuals who drank six or more drinks per week. A "drink" was defined as 1.5 oz. of 70-proof liquor, one can of beer, or one glass of wine. These categories of light and moderate alcohol use correspond roughly with U.S. standards of ethanol consumption, as described by Cahalan et al. (2), and are within the typical range of social drinking for university/medical student populations (4). At a screening interview, subjects completed a psychiatric symptom checklist, the SCL-90 (10), and a health questionnaire that included questions regarding quantity and frequency of recreational drug use. They were interviewed by professional staff and examined by a physician. Subjects were carefully screened to exclude anyone with a history of alcohol problems, for example 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. Other exclusion criteria included histories of drug abuse, current alcohol consumption of less than one drink per week, serious mental disorders within the past year, heart problems and high blood pressure, or, in women, pregnancy. Before participation, subjects signed an informed consent form, which described procedures in the study. Subjects were paid for their participation in the study. This project was approved by the local Institutional Review Board.

Procedure

The experiment consisted of seven sessions conducted at least 2 days and not more than 1 week apart. Sessions 1–4 were sampling sessions, in which capsules containing pentobarbital or placebo were given on alternate days. Half the subjects received pentobarbital in Sessions 1 and 3 and placebo in sessions 2 and 4 and the order was reversed for the other subjects. Sessions 5–7 were choice sessions, in which subjects could choose either of the capsules they had sampled in sessions 1–4. The choice of the drug or placebo capsule was the primary dependent measure.

To reduce the influence of expectancies, subjects were told they would be given drugs from any of the following classes: tranquilizers/sedatives, alcohol, antihistamines, stimulants/appetite suppressant, or placebo. Pentobarbital (150 mg) and placebo (dextrose) were administered in color-coded size 00 capsules. The colors were assigned randomly to different subjects, but for each individual the colors for drug and placebo were constant. Thus, subjects could choose the preferred drug based upon the color of the capsule. The experimenters who had contact with subjects were blind to the identity of the drugs being administered.

Subjects arrived at the laboratory at 6:45 p.m. They had been told not to consume any drugs (other than usual amounts of caffeine or nicotine) for 12 h prior to and 12 h following the experimental session. Breathalyzer measurements were taken to verify 0.0% blood alcohol levels, and subjects completed predrug mood questionnaires and psychomotor tests described below. Capsules were ingested at 7:00 p.m. In sampling sessions, capsules were given to subjects in the test room to be taken with 100 ml water. In choice sessions, subjects indicated their preference privately with the experimenter and ingested the capsule before returning to the test room. They completed additional (postdrug) questionnaires measuring mood and drug effects at 7:30, 8:00, 9:00, 10:00, and 11:00 p.m., and performed the psychomotor test at 8:00 and 9:30 p.m. At 11:00 p.m., they also completed a questionnaire rating their overall liking of the drug. At hourly intervals, the experimenter conducting the session completed a checklist of behavioral signs of drug effects (see below). At 11:00 p.m., after subjects completed questionnaires and a final psychomotor task they were provided with transportation home. They took with them questionnaires to be completed the following morning. These questionnaires assessed the quality of sleep after the session and their mood state the next day.

Subjects were tested in groups of three or four in a room with comfortable furniture, colorful posters on the walls, and a television set, magazines, and games available for entertainment. Between test rounds, subjects were allowed to watch videotaped movies, play board games or cards, or read material that was not work or school related.

After the last experimental session, subjects were debriefed regarding their choices of drugs and experiences during the sessions.

Dependent Measures

The primary dependent variable was drug choice. The measure was defined as the number of times, of the three choice sessions, each subject chose the drug-containing capsule.

The Profile of Mood States (POMS) is an adjective checklist that has been used to measure changes in mood after drug administration (16). The 72 questions have been factor analyzed into eight scales: Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness, and Elation. Additional scales are composites of some of the basic scales: Arousal = (Anxiety + Vigor) − (Fatigue + Confusion) and Positive Mood = Elation − Depression. Subjects respond to adjectives by marking a number from 0 (not at all) to 4 (extremely). The dependent variables are the mean scores for items comprising the scales.

The 49-question form of the Addiction Research Center Inventory (ARCI 49) is a widely used questionnaire developed to measure differential reactions to drugs (14). The Benzedrine Group scale (BG) and Amphetamine scale (A) measure the effects typical of those stimulants, the Pentobarbital, Chlorpromazine, and Alcohol Group scale (PCAG) measures sedative responses, the Lysergic Acid (LSD) scale measures dysphoric or psychotomimetic effects, and the Morphine-Benzedrine Group (MBG) scale measures euphoric effects.

The Drug Liking Questionnaire (LQ) consists of four questions regarding whether the subjects feel a drug effect (FEEL), how much they like the effects (LIKE), whether they feel "high" (HIGH), and whether they would like more (MORE) of the drug. The subjects record their responses on a 100-mm visual analog scale (VAS), with "not at all" at 0 and "extremely" at 100. The dependent variable is the distance (in mm) between the left end of the line and the subject's mark.

The Digit Symbol Substitution Test (DSST) is a test of cognitive/psychomotor performance (20) consisting of symbols that must be substituted for numbers. The number of symbols completed in 60 s is the dependent variable for this test. Five different forms of the test, with different symbols, were used to minimize learning effects.

The Observer Rating Form (ORF) is a questionnaire completed by the experimenter conducting the session, on which the observer rates subjects' apparent drug responses such as slurred speech, glazed or bloodshot eyes, trouble walking or filling out forms, increased loquacity, flushed face, drowsiness, sleeping, yawning, agitation, or restlessness.

The End-of-Session Questionnaire (EOS) consists of a VAS concerning subjects' liking of the drug effect overall. It also contains questions regarding whether subjects thought they had received an appetite suppressant/stimulant, a sedative/tranquilizer, alcohol, or placebo, and whether they would take the drug again.

The Leeds Sleep Evaluation Questionnaire (LSEQ) (17) is a 10-item self-rated questionnaire measuring quality of sleep. Dependent variables are average VAS scores for items included in the following scales: getting to sleep, quality of sleep, awakening from sleep, and behavior following wakefulness.

Data Analysis

Student's *t*-test, analysis of variance (ANOVA), and χ^2 tests were used to compare the LD and MD groups on demographic variables and on the number of times pentobarbital was chosen over placebo. Separate repeated-measures ANOVAs (group, drug, hour) were used with dependent measures obtained after drug administration to compare LD and MD subjects' response to pentobarbital and placebo. Data from the sampling sessions only were used in the analysis of direct drug effects: These analyses were conducted using data averaged across the two placebo sessions and the two drug sessions.

RESULTS

Subject Characteristics

Table 1 shows the demographic characteristics of the LD and MD subjects, as well as their current and lifetime patterns of drug use. MD subjects were slightly younger than LD subjects, and they reported consuming more alcohol and more caffeine than the LD group.

Choice

Subjects in neither the LD nor the MD group consistently preferred pentobarbital over the placebo (Fig. 1): Those in the LD group chose the drug on 10 of 48 possible opportunities (20.8%, or an average of 0.62 of three sessions). Subjects in the MD group chose the drug on 15 of 39 possible opportunities (38.5%, or an average of 1.07 sessions). The mean number of choices were not significantly different between the two groups (*t*-test, n.s.). Taken together, the LD and MD groups chose pentobarbital significantly less often than placebo ($t = 4.2$, $p < 0.01$). When gender was included in an ANOVA of choice data, there was a marginally significant ($p < 0.10$) interaction between gender and group: MD males chose drug more often than the other groups (mean drug choice frequency: MD females 0.4, LD females 0.7, LD males 0.5, MD males 1.5; see Fig. 1). Gender alone was not related to drug choice when all 29 subjects were considered (females mean choice frequency 0.6, males 1.07, ANOVA gender, n.s.). No other demographic variables (i.e., age, race, status as student, SCL-Anxiety scale, SCL-Depression scale, current and life-

TABLE 1

DEMOGRAPHIC CHARACTERISTICS OF SUBJECTS

	LD Group	MD Group	Significance
n	16	13	
Age (mean)	25.6	22.7	$p < 0.01$
Gender (F/M)	10/6	5/8	n.s.
Race (W/B/O)	8/5/3	13/0/0	
Marital status (S/M or D)	13/3	13/0	
Education (*n*)			
Partial college	6	5	n.s.
College degree	9	8	n.s.
Advanced degree	1	0	n.s.
Full-time student (yes)	8	7	n.s.
Current drug use			
Alcohol (mean drinks per week)	2.3	13.8	$p < 0.01$
Alcohol (mean drinks per occasion)	1.8	4.6	$p < 0.01$
Caffeine (mean drinks per week)	8.7	17.5	$p < 0.05$
Tobacco (number of smokers)	3	6	n.s.
Lifetime recreational drug use (*n*, ever used)			
Stimulants	7	5	n.s.
Tranquilizers	3	2	n.s.
Hallucinogens	4	6	n.s.
Opiates	7	2	n.s.
Marijuana	10	11	n.s.

n.s., not significant.

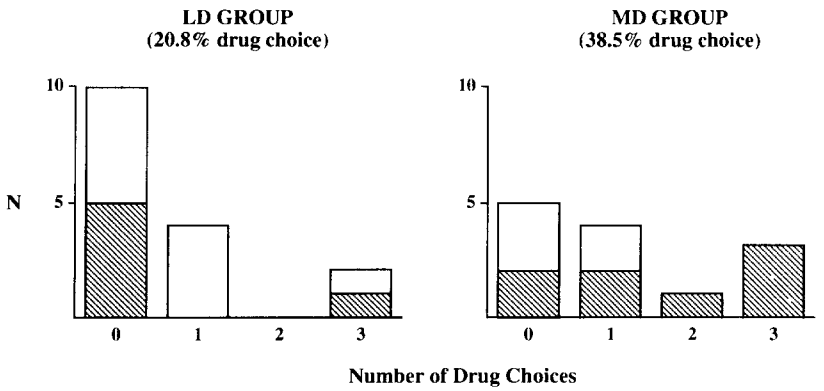

FIG. 1. Number of LD and MD subjects who chose the pentobarbital-containing capsule on 0, 1, 2, or 3 of the choice sessions. Male subjects are indicated by ▨, female subjects by □.

time drug use; t-tests or χ^2) were related to pentobarbital choice.

POMS

Pentobarbital increased Confusion and Fatigue scores and decreased Vigor and Arousal scores (ANOVA; main effects of drug, for Confusion, $p < 0.01$; for Fatigue, $p < 0.001$; for Vigor $p < 0.05$; for Arousal $p < 0.01$; and drug × hour interactions, for Fatigue, $p < 0.001$; for Arousal, $p < 0.01$). These effects began to appear at hour 0.5 or 1.0 and continued to increase throughout the session (Fig. 2). The LD group scored higher than the MD group on Depression (MD mean: 0.013, SD 0.05; LD mean: 0.073, SD 0.12, ANOVA; main effects, $p < 0.05$), but there were no interactions between drinking group and drug. Main effects of time were observed on most POMS scales (all but Anger and Anxiety), in the direction of increasing fatigue and dysphoria over the session (ANOVA; main effects, $p < 0.001$). POMS scores were also analyzed by gender and by drug choices [nonchoosers (0 drug choices) vs. choosers (1-3 drug choices)]. No significant interactions between drug and gender were observed. In the comparison of choosers vs. nonchoosers, nonchoosers overall scored higher on Anxiety (ANOVA; main effect of group, $p < 0.05$) and showed larger drug-induced increases in Fatigue (ANOVA; group × drug × hour interaction, $p < 0.06$).

On the POMS measures obtained the morning following the session, significant drug effects on Fatigue, Vigor, and Arousal scales were still apparent (ANOVA; main effects, for Fatigue, $p < 0.01$, for Vigor, $p < 0.05$, for Arousal, $p < 0.01$), but there were again no interactions with drinking history group.

ARCI

Pentobarbital increased PCAG and LSD scores and decreased scores on the BG scale (ANOVA; drug × hour interactions, for PCAG, $p < 0.0001$; for LSD, $p < 0.04$; for BG, $p < 0.01$). These effects peaked at 0.5-1 h. No interactions with drinking group were obtained. Significant effects of time were obtained on the A, BG, MBG, and PCAG scales, with the first three declining across hours and PCAG increasing (ANOVA; main effects of time, for all, $p < 0.0001$).

Liking VAS

Liking VAS scores were analyzed by subtracting placebo session scores from drug session scores. Relative to placebo scores, the two groups showed elevations in ratings of FEEL and HIGH after pentobarbital administration (ANOVA; main effects of hour). These effects peaked between 0.5 and 1 h, and began to decline after 2 h. Further, the LD and MD groups also differed significantly on the MORE scale (i.e., main effect of group, $p < 0.02$): The MD group scored higher overall than the LD group.

DSST

Overall, the MD group scored higher on the DSST than the LD group (ANOVA; main effect of group, $p < 0.05$). As shown in Fig. 3, the drug decreased scores to a similar extent in both groups at 1 and 2.5 h (ANOVA; main effects of drug, $p < 0.001$, and time, $p < 0.001$; interaction of drug × hour, $p < 0.01$).

Observer Ratings

Pentobarbital increased scores on the observer ratings (ANOVA; drug × hour interaction, $p < 0.01$). The increases were most marked at 0.5-1 h, and were gone by the end of the session (ANOVA; main effect of hour, $p < 0.001$; interaction of drug × hour, $p < 0.01$). A three-way interaction (ANOVA; group × drug × hour, $p < 0.05$) was obtained on the observer ratings: The LD group showed more signs of intoxication after ingestion of the drug than the MD group.

End-of-Session Liking and Drug Identification

Liking difference scores were calculated by subtracting each subject's placebo liking score (sampling session data only) from his or her pentobarbital liking score. The mean liking score for the LD and MD groups did not differ significantly (LD mean score −11.27 and MD mean score −3.12; ANOVA group, n.s.). Liking scores were, however, positively correlated with drug choice ($r = 0.65$, $p < 0.001$). Although liking ratings were not significantly different for males and females (female mean score −10.77, male mean score −3.57, $t < 1$, n.s.), there was a significant gender × group interaction: MD males rated their liking of the drug significantly higher than LD males (means male LD −21.7, male MD

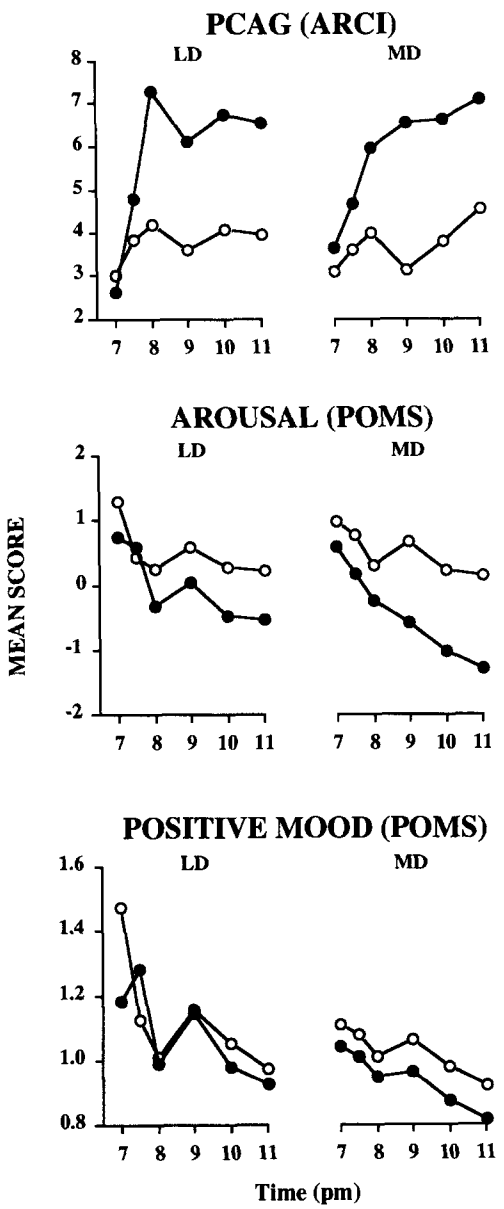

FIG. 2. Mean scores on representative ARCI and POMS scales showing effects of pentobarbital (●) and placebo (○) across hours in LD and MD subjects. Typical sedative effects were observed on the PCAG (ARCI) scale and the Arousal (POMS) scale. Positive Mood scores are shown to illustrate the absence of positive or euphoria-like effects in this subject population.

10.06; ANOVA, $p < 0.005$) or either female group (means female LD −5.8, female MD −20.7; ANOVA; gender × drinking history interaction, $p < 0.01$).

Subjects in the MD group were better at identifying the pentobarbital effects as those of a sedative/tranquilizer (LD: correct 13, incorrect 18; MD: correct 19, incorrect 7; $\chi^2 = 4.38, p < 0.05$).

Sleep Questionnaire

Pentobarbital had significant effects on all four sleep scales (ANOVA; main effects of drug, for getting to sleep, $p <$ 0.001; for quality of sleep, $p < 0.01$; for awakening, $p <$ 0.001; for behavior following awakening, $p < 0.0001$), consistent with its effects as a hypnotic. However, the two groups did not differ in their response to the drug.

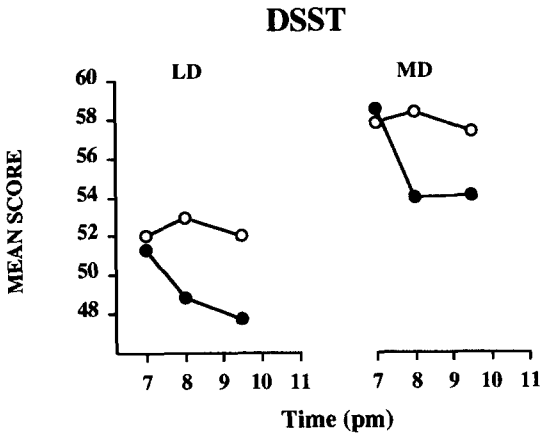

FIG. 3. Mean scores on DSST after pentobarbital (●) and placebo (○) in LD and MD groups. The groups differed in overall DSST scores but not in their responses to the drug: Pentobarbital impaired performance in both groups.

Gender and Weight Effects

The effects of gender and body weight were examined with each of the dependent measures. Males and females did not differ significantly on most drug-related measures, other than CHOICE and end-of-session liking, as described above. Body weight was not correlated with either drug choice or drug liking ratings. However, heavier subjects reported feeling less drug effect on the FEEL drug VAS (ANOVA; drug × hour × weight interaction, $p < 0.01$) and were less impaired by the drug on the DSST (ANOVA; drug × hour × weight interaction, $p < 0.05$).

DISCUSSION

The hypothesis that moderate alcohol users (defined as more than six drinks per week) would show a greater preference for pentobarbital than lighter drinkers was only partially confirmed. Most subjects, in both the LD and MD groups, chose pentobarbital less often than placebo (20.8% and 38.5%, respectively). The difference in choice between the two groups was not significant, and neither group reported experiencing euphorigenic drug effects or "liking" the drug more than placebo. Nevertheless, when subjects' gender was taken into account it was found that males in the MD group chose the drug marginally more often and reported higher levels of drug liking than males in the LD group, suggesting that drinking history did influence responses to pentobarbital among male subjects. However, the level of preference and liking for pentobarbital even among MD males was low: Their level of drug choice was about 50% and their liking ratings of pentobarbital did not exceed their liking ratings of placebo. Neither the LD nor the MD group (including the subgroup of male MDs) reported any euphoria-like effects (e.g., increases on the MBG scale of the ARCI or on the Positive Mood scale of the POMS).

Due to sampling error, the LD and MD groups were not matched on several demographic characteristics other than

drinking history. Subjects in the MD group were slightly younger and reported heavier caffeine use. Furthermore, 50% of the LD group were nonwhite, while all subjects in the MD group were white. Whether, or how, these differences may have influenced the outcome of the study is not known. The age differences were relatively small and unlikely to have masked a true difference between LD and MD groups. Little is known about the relationship between race and responses to psychoactive drugs. Most of the subjects in our previous studies have been white, and in those studies that included nonwhites we found no systematic relationship between race and drug preferences (5). Although these extraneous differences between the groups limit the interpretation of this study, it seems unlikely that any of these variables would have completely obscured an interaction between drinking history on pentobarbital preference.

Pentobarbital produced typical, sedative-like effects in most subjects, similar to the effects reported in previous studies (6,9). The drug increased scores on the ARCI sedative scale (PCAG) and on POMS scales reflecting sedative effects (e.g., Fatigue). It also impaired performance on the DSST and produced typical sedative-like effects on observer ratings and ratings of sleep quality. Although subjects varied in their liking ratings of the drug's effects, most subjects either were neutral or disliked the drug. Pentobarbital produced similar effects in the LD and MD groups, indicating that MD subjects were neither more tolerant to its effects nor more susceptible to its euphorigenic effects.

Interactions between gender and drug choice have not been observed in previous studies in this laboratory with either pentobarbital or diazepam (6,7). It is possible that the single, fixed dose of pentobarbital used in the present study was excessively high for female subjects. Females in general weighed less than the males, and it was found that body weight was negatively correlated with several measures of drug response, including DSST and FEEL drug. However, body weight was not correlated with either drug preference or drug liking ratings, suggesting that differences in weight alone did not account for the observed gender differences on these measures. Other factors, such as relatively greater social inhibition, may have limited drug choice among MD females as compared to MD males.

The present results with pentobarbital can be compared to the results of two previous pentobarbital preference studies (6,9) with relatively light alcohol users. In one study (6), subjects whose average alcohol consumption was 8.0 drinks per week sampled pentobarbital in five cumulating doses (30 mg per dose ingested at 30-min intervals; total dose 150 mg). On choice sessions, they chose between pentobarbital and placebo capsules and were permitted to ingest from one to seven capsules of either. Under these conditions, pentobarbital was chosen more often than in the present study (52 vs. 29% of sessions). The slightly higher level of drug choice in the former study may have been related to subjects' opportunity to self-regulate their dose during choice sessions. In another, earlier study (9), subjects whose average alcohol consumption was 6.1 drinks per week sampled pentobarbital in a single dose (160 mg) and were then given a single choice session in which to choose between drug and placebo. Six of the 11 subjects chose drug over placebo. Thus, the present results are consistent with two previous studies in which pentobarbital was not reliably preferred over placebo in individuals without histories of excessive drug or alcohol use. The present findings extend this general conclusion to a group of individuals with heavier use of alcohol.

The present results stand in contrast to a previous study (7) in which it was found that preference for another sedative-like drug, diazepam, was related to habitual alcohol consumption. Using subjects whose drinking histories were similar to those in the present study, it was found that moderate drinkers consistently chose diazepam over placebo and reported more positive subjective effects from the diazepam than lighter drinkers. Why moderate drinkers did not prefer pentobarbital in the present study is surprising in light of the previous diazepam results, particularly in view of the fact that pentobarbital is considered to have even higher abuse liability than diazepam (11). Although it is possible that the differences indicate a real difference between diazepam and pentobarbital, it seems more likely that methodological differences (e.g., sampling or procedural) account for the differences. For example, the diazepam study was conducted using the cumulative dosing procedure described above, which may have increased overall drug choice. Further, subjects in the diazepam study were tested in groups of four friends, while in the present study subjects were tested in previously unacquainted groups. Drug preferences are clearly the result of complex interactions between many subject-related and environmental variables. It is hoped that studies such as this, which explore the determinants of drug preferences in the laboratory, will both improve the sensitivity of laboratory models of drug abuse and also suggest factors that influence drug taking outside the laboratory.

In conclusion, the present results indicate that pentobarbital is neither highly preferred nor euphorigenic in individuals without histories of substance abuse. Even in individuals who are regular consumers of alcohol, and even when the drug is consumed in a comfortable and safe recreational setting, the drug produces primarily sedative-like, noneuphorigenic effects, and it is chosen less often than a placebo. These findings support previous evidence that the risk of abuse of this class of drugs is low in individuals without histories of drug abuse.

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