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# Lack of Effect of Social Context on the Reinforcing Effects of Diazepam in Humans

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JOHANSON, C.-E. AND H. DE WIT. *Lack of effect of social context on the reinforcing effects of diazepam in humans.* PHARMACOL BIOCHEM BEHAV 43(2) 463–469, 1992.—The reinforcing effects of diazepam (DZP) were compared under two conditions in human volunteers using a cumulative dose procedure. Under the social (SOC) condition, groups of two to four subjects participated concurrently whereas in the solitary (SOL) condition subjects participated individually. During the first four sessions of each condition, subjects received 20 mg DZP in five divided doses (4 mg) in two of the sessions and placebo (PL) in the other two sessions. Each drug (DZP or PL) was administered in a distinctively colored capsule and labeled by letter code. During the last three choice sessions, subjects chose which capsule they wished to self-administer and were allowed to choose up to a maximum of seven capsules (28 mg DZP) during each session. Subjects also filled out questionnaires that assessed momentary mood. Overall, DZP was chosen on 33% of choice sessions and there were no differences across conditions. There was a tendency for choice to be correlated with levels of weekly alcohol consumption and liking scores, and as well the latter two measures were correlated. DZP produced sedative-like subjective effects that did not appear to be related to setting, choice of drug in the study, or alcohol drinking history. These results partially confirm previous reports of a relationship between DZP preference and alcohol consumption, but differ from previously reported studies in the overall lower level of DZP choice.

Diazepam Reinforcing effects Self-administration Choice Humans Social context

THE reinforcing effects of diazepam (DZP) have been extensively evaluated under laboratory conditions in both nonhumans and humans. In rats and nonhuman primates, intravenous DZP maintains relatively low rates of responding, indicating low reinforcing efficacy (15). On the other hand, DZP maintains higher rates of self-administration in rhesus monkeys with a history of pentobarbital self-administration (1). The reinforcing effects of DZP have also been evaluated in experimental studies in humans (2). For instance, in volunteers with a history of sedative abuse evaluated in a residential laboratory, oral DZP was self-administered more than placebo but was not preferred to pentobarbital (6,7). However, in volunteers without a history of sedative or drug abuse, DZP was not self-administered (4,9). The studies with nondrug abusers were conducted on an outpatient basis (i.e., subjects did not remain in the laboratory after drug was self-administered) using relatively low doses (5 and 10 mg). When DZP preference was assessed in normal volunteers with a laboratory that simulated a recreational environment, preference for DZP over placebo increased to approximately 60% (3). Further, when subjects with a history of higher levels of daily alcohol consumption were tested preference increased to 100% (3). However, these latter laboratory-based studies differed from the outpatient studies in several respects. They were conducted using a cumulative dose procedure in which self-administration of doses of DZP up to 28 mg was allowed. In addition, self-administration took place under conditions where subjects were interacting with several of their friends who were also allowed to self-administer DZP (8).

Several studies have shown that the euphorigenic and reinforcing effects of alcohol and tetrahydrocannabinol (THC) are greater in a social setting (5,10,11,13,14). Similarly, the effects of DZP may be greater in a social setting and this may account for the differences in DZP's effects across studies. Therefore, the present studies were designed to assess the effect of social condition on DZP preference in subjects without a history of sedative or drug abuse by comparing the subjective and reinforcing effects of DZP in a social setting to its effects in a solitary setting.

## METHOD

### *Design*

Two choice studies were conducted independently at two sites using different subject samples but using almost identical procedures [cumulative dose choice procedure described origi-

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nally by de Wit et al. (3)]. Study A was conducted at the Uniformed Services University of the Health Sciences under the direction of C.-E.J. and study B was conducted at The University of Chicago under the direction of H.d.W. Study A utilized a within-subjects design in which subjects participated sequentially (in mixed order) in two conditions, the solitary (SOL) condition and the social (SOC) condition. Study B utilized a group design in which subjects were tested under only one condition; approximately half the subjects were tested under the SOL condition and the other half under SOC conditions. Most of the same dependent measures were obtained in both studies.

*Subjects*

Eighteen normal, healthy adults participated in Study A and 25 participated in Study B. These subjects ranged in age from 21–38. Subjects were recruited using advertisements posted in the university and surrounding community area, published in the local area newspapers, and through word-of-mouth referrals. Study A was also advertised by the normal volunteer recruiting office of the National Institutes of Health. After an initial telephone screening, eligible candidates were scheduled for an interview. At the interview, subjects were given information about the nature of the study and completed a medical history questionnaire, a psychiatric rating scale, and a questionnaire that assessed quantity and frequency of past and present drug use. Subjects were also interviewed by a psychiatrist in Study A and a psychiatric social worker in Study B. These interviews were semistructured and designed to verify psychiatric and drug use status. Subjects also underwent a physical examination, and subjects in Study A received a complete blood count and blood and urine chemistry evaluation. Exclusion criteria included: a) significant medical or psychiatric problems that would place a subject at risk if he/she participated; b) presence of any current or past DSM-III-R Axis I psychiatric disorder other than tobacco dependence, adjustment disorder occurring more than 1 year before the interview, or a single episode of major depression occurring more than 2 years before the time of the interview; and 3) history of drug- or alcohol-related problems. Females were not allowed to participate if they were breast-feeding, pregnant as determined by a urine test, or planning to become pregnant in the near future.

Prior to participation in the study, subjects read and signed a consent form that outlined the procedures of the study. The stated purpose was to assess the behavioral and subjective effects of drugs. Subjects were informed that they might receive a stimulant, tranquilizer, ethanol, or placebo, and the consent form listed potential effects from all drugs they might receive. Subjects were paid for their participation and the protocols were approved by the respective institutional review boards.

*Procedure*

Drug preference was evaluated under two conditions, a SOC condition and a SOL condition. In the SOC condition, subjects were tested in groups of two to four subjects, whereas in the SOL condition they were tested alone. In Study A (but not B) the groups of subjects in the SOC condition were friends before participating in the study. Each condition consisted of seven sessions occurring one or two evenings per week. Sessions were conducted in comfortably furnished rooms located in a hospital. The rooms contained couches, upholstered chairs, and tables, and were designed to simulate a living room/dining room atmosphere. Television/VCRs, radio/cassette recorders, and a variety of board games were available. Apple IIe or Macintosh computers were used for administration of the mood questionnaires. Subjects were free to engage in recreational activities of their choice but were not allowed to work or study. In the SOC condition, subjects were encouraged to interact with one another (e.g., to play board games) whereas in the SOL condition they were alone except for brief visits from the technician.

The seven sessions of each condition were comprised of four sampling sessions followed by three choice sessions. In sampling sessions, subjects were given either DZP (total dose 20 mg) or placebo (PL). On choice sessions, they were instructed to choose the substance (DZP or PL) they preferred and were also allowed to choose the number of capsules they wished to take.

*Sampling Sessions*

Subjects ingested five capsules on each sampling session, one every 30 min from the start of the session. On two of the sampling sessions (i.e., sessions 1 and 3 or 2 and 4), each capsule contained 4 mg DZP (total dose 20 mg over 2 h). On the two remaining sampling sessions (sessions 2 and 4 or 1 and 3), the capsules contained PL. Capsules were color-coded for each subject so that the same color always contained the same substance (i.e., DZP or PL). In Study A, all subjects received the same capsule during each sampling session (i.e., DZP or PL) whereas in Study B half the subjects received DZP and half PL during each sampling session.

*Choice Sessions*

At the beginning of each choice session, subjects indicated which color of capsule they preferred to take on that evening. In the SOC condition, choices were made privately with only the technician present. Subjects were required to ingest at least one dose of their chosen substance at the beginning of the session and could only take additional capsules of the same color for the remainder of the session. They could take one additional dose every 30 min, up to a maximum of seven doses total (i.e., a total cumulative dose of 28 mg DZP). Thus, after the first, required dose, subjects could accept or decline doses every 30 min in any pattern they wished over the remainder of the session.

*Session Protocol*

Subjects reported to the laboratory at the same time for each session (between 5:00 and 7:00 p.m.), at which time they filled out predrug (hour 0) self-report mood questionnaires (see below). A breath alcohol sample was obtained to ensure that they were alcohol free. In Study A, urine samples were also collected and randomly analyzed for illicit drugs. For the remainder of the session, subjects completed questionnaires at hourly or half hourly intervals. In Studies A and B, they remained in the laboratory for 6 and 4 h, respectively.

At the end of each session, subjects completed a drug liking and identification questionnaire, on which they indicated how much they liked the drug's effects and what class of drug they thought they had received. In Study A, the possible identification classes were "stimulant," "sedative," or "placebo" whereas in Study B "alcohol" and "other" were also included. Liking was rated on a 100-mm line labeled "disliked a lot" at one end and "liked a lot" on the other. Following all sessions in Study

A and the sampling sessions in Study B, subjects were transported to their homes by taxi. Following choice sessions in Study B, subjects remained overnight in the Clinical Research Center.

*Measuring Instruments*

The questionnaire used to assess subjective drug effects in both studies was an experimental version of the Profile of Mood States [POMS; (12)]. This version of the POMS consists of 72 adjectives commonly used to describe momentary mood states. Subjects indicated whether each adjective described how they felt at the moment, from "not at all" (0) to "extremely" (4). Eight clusters of items have been 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 scales (unvalidated) were derived on an intuitive basis from other scales [Arousal = (Anxiety + Vigor) − (Fatigue + Confusion); Positive Mood = Elation − Depression].

*Data Analysis*

The primary dependent variable was the number of choice sessions under each condition during which DZP was chosen. Choice was compared across the two conditions for each site and across studies using Student's *t*-tests (paired and unpaired). The relationship between average alcohol weekly alcohol consumption and DZP choice was examined using a correlation (Pearson product moment) between drinks per week and DZP choice (because no differences were obtained between SOC and SOL conditions, we used data from all subjects in Study B, while for Study A we arbitrarily used choice data from the SOC condition only). Demographic differences across studies were analyzed using *t*-tests and $\chi^2$ tests. Drug liking scores were compared across condition (SOC vs. SOL separately for each study) using *t*-tests. The relationships between liking and choice and between liking and alcohol drinking history were assessed using correlations. For all *t*-tests and $\chi^2$ analyses, two-tailed tests were used whereas one-tailed tests were used for the correlations.

The POMS was analyzed using repeated-measures analyses of variance (ANOVAs). Separate analyses were performed for each POMS scale. Data from the sampling sessions only were used because all subjects received the same dose of DZP on these sessions. Tukey posthoc tests were used when significant ($p < 0.05$) main effects or interactions were obtained.

Three sets of ANOVAs were performed on the POMS results. The first included factors of condition (SOC vs. SOL), drug (DZP vs. PL), and hour (0, 1, 2, 3, 4) and was done separately for each study. The second set included the factors of drug (DZP vs. PL), and hour (0, 1, 2, 3, 4) plus a between-group factor of choice (chooser vs. nonchooser). Chooser was defined as any subject that chose DZP on one or more choice sessions during the SOC condition. Only results obtained from the SOC condition were used and results were collapsed across studies. Finally, the third set included the factors of alcohol drinking history (low vs. high average weekly intake), drug (DZP vs. PL), and hour (0, 1, 2, 3, 4). Again, only results from the SOC condition were included and results were collapsed across studies.

*Drugs*

DZP tablets (two 2-mg tablets) were placed in opaque, colored capsules (size 00) with dextrose filler. In Study A, Valium (Hoffman La Roche, Inc., Nutley, NJ) was used and in Study B generic diazepam (Warner Chilcott, Morris Plains, NJ) was used. PL capsules contained dextrose alone.

TABLE 1

SUBJECT CHARACTERISTICS IN STUDIES A AND B

| Variable | Study A | Study B |
|---|---|---|
| Gender (% males) | 17 | 56* |
| Age (mean) | 27.7 | 23.8† |
| Students (%) | 28 | 72† |
| Married (%) | 44 | 12* |
| Education (%) | | |
| HS/college | 33 | 33 |
| Degree/advanced | 67 | 67 |
| Alcohol drinks/Week (mean) | 3.0 | 9.6* |
| Tobacco (% using) | 44 | 32 |
| Tranquilizers (% ever used) | 38 | 20 |

*$p < 0.05$.
†$p < 0.01$.

## RESULTS

*Demographics*

Table 1 shows the characteristics of the two subject populations. As can be seen, there were significant differences across the populations of Studies A and B in terms of male/female ratio, age, student status, and marital status with no differences in education, current tobacco use, and lifetime tranquilizer use. The mean number of alcohol drinks consumed weekly by subjects in Study A was significantly lower than the number consumed by Study B subjects ($t = -3.8$, $p < 0.0005$). There were no differences between the two subpopulations of Study B in any of these variables (data not shown) except subjects that participated in the SOL condition had higher levels of education ($\chi = 4.688$, $p < 0.04$).

*Choice*

The number of sessions in which subjects chose the DZP capsule was similar in the SOL and SOC conditions in both studies (study A, $t < 1$, n.s.; study B, $t < 1$, n.s.) and ranged between 0.7–1.5 drug choices of a maximum of 3 (Fig. 1). DZP choice was higher in Study B relative to Study A although this difference only reached significance in the SOL condition ($t = 2.46$, $p < 0.01$). DZP choice was positively correlated with subjects' average weekly alcohol consumption (drinks per week; $r = 0.30$, $p < 0.05$). Given the tendency for males to drink more than females and the small number of males in Study A, it is important to note that choice was not related to gender ($t = 1.85$, n.s.). Although average number of DZP doses did not differ across conditions in either study, subjects chose significantly more DZP capsules than placebo capsules (overall mean PL doses 2.9, overall mean DZP doses 4.5; two-sample $t = 3.4$, $p < 0.05$).

*Drug Liking*

For each subject, a liking difference score was calculated by averaging the end-of-session liking scores (0–100 mm) from the two PL and two DZP sampling sessions and subtracting the PL mean from the DZP mean. Positive scores indicated

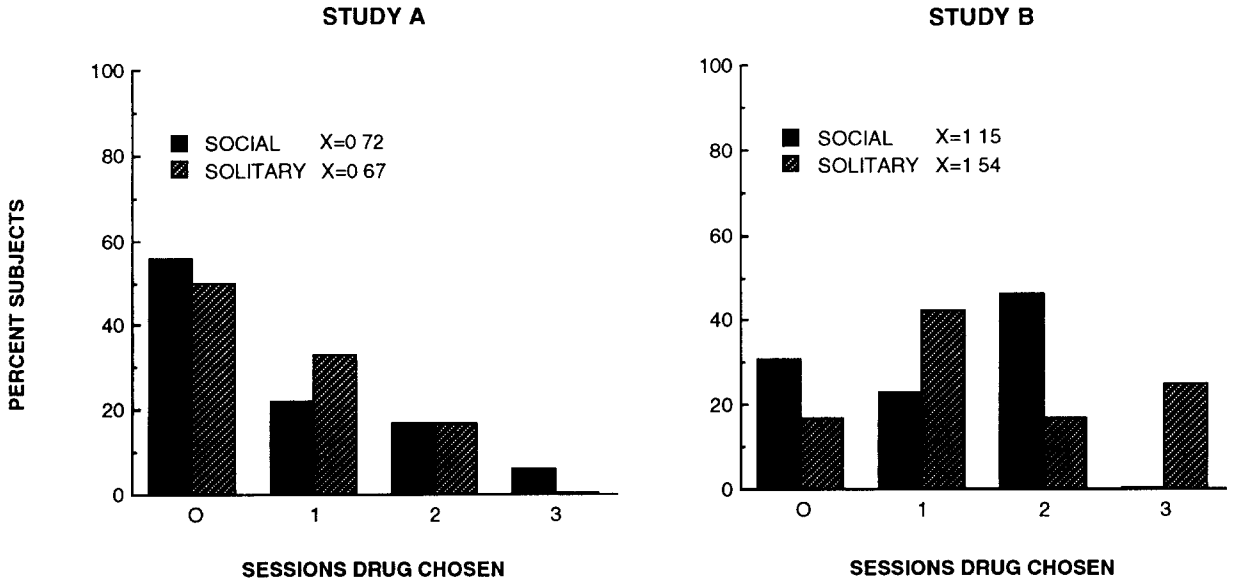


FIG. 1. Percent of subjects who chose DZP on 0, 1, 2, or 3 of the choice sessions during the SOC and SOL conditions across both Studies A and B.

DZP was liked more than PL and negative scores showed the opposite. The liking difference scores were not different in the SOL and SOC condition in either study (Study A: SOC difference = 15.3, SOL difference = −15.2, $t = -0.017$, n.s.; study B: SOC difference = −6.5, SOL difference = 5.0, $t = -1.55$, n.s.). There was a tendency for liking difference scores to be more negative in Study A than Study B (−15.2 vs. −2.3) but the difference did not reach statistical significance ($t = -1.67$, $p < 0.1$). The liking difference scores were correlated with the number of times DZP was chosen ($r = 0.41$, $p < 0.01$) and with the subjects' weekly alcohol consumption ($r = 0.29$, $p < 0.05$). There was also a significant difference between the liking difference scores of nonchoosers and choosers (−24.10 vs. 0.86; $t = 3.43$, $p = 0.001$) and for the nonchoosers there was also a significant difference between the raw liking scores for DZP and PL ($t = 5.76$, $p < 0.0001$) whereas liking scores were almost identical in choosers ($t = -0.16$, n.s.).

*Drug Identification*

In both studies and in both the SOL and SOC conditions, DZP was labeled correctly by most subjects as a sedative. PL was usually identified correctly except in the SOC condition of Study A, where subjects were as likely to label PL as a "stimulant" or "sedative" as placebo. Overall across the two studies, DZP was labeled correctly on 82% of occasions in the SOC condition and 73% of occasions in the SOL condition, and the placebo labels were 37 and 63% correct in the SOC and SOL conditions, respectively.

*Subjective Effects*

In the analysis of the POMS to assess the effects of condition, drug, and hour, separate analyses were performed on each scale, separately for the two studies. With two exceptions, there were no main effects or interactions involving the condition factor, that is, the effects of DZP and PL were largely the same under both SOC and SOL conditions in both studies. In Study A, there was a significant condition × drug effect on anxiety ($p < 0.03$). Inspection of the results indicated that this interaction was attributable to differences pres-

TABLE 2

SIGNIFICANT ANOVA EFFECTS ON POMS FOR STUDIES A AND B. CONDITION, DRUG, AND HOUR AS FACTORS

| Study | Scale | Drug | Drug × Hour |
|---|---|---|---|
| A | Arousal | 0.001 ⇓ | 0.001 ⇓ |
| B | | 0.001 ⇓ | 0.011 ⇓ |
| A | Confusion | 0.002 ⇑ | 0.0001 ⇑ |
| B | | 0 003 ⇑ | 0.002 ⇑ |
| A | Depression | | 0 036 ⇑ |
| B | | | |
| A | Elation | 0.035 ⇓ | 0.0003 ⇓ |
| B | | | |
| A | Fatigue | 0.005 ⇑ | 0.0001 ⇑ |
| B | | 0.002 ⇑ | 0.030 ⇑ |
| A | Friendliness | | 0 022 ⇓ |
| B | | | |
| A | Positive Mood | 0.046 ⇓ | 0.0002 ⇓ |
| B | | | |
| A | Vigor | 0.003 ⇓ | 0.0001 ⇓ |
| B | | | |

For main effects, scores were higher (⇑) or lower (⇓) for DZP than PL. For interaction, scores were significantly higher (⇑) or lower (⇓) for DZP than PL except hour 0.

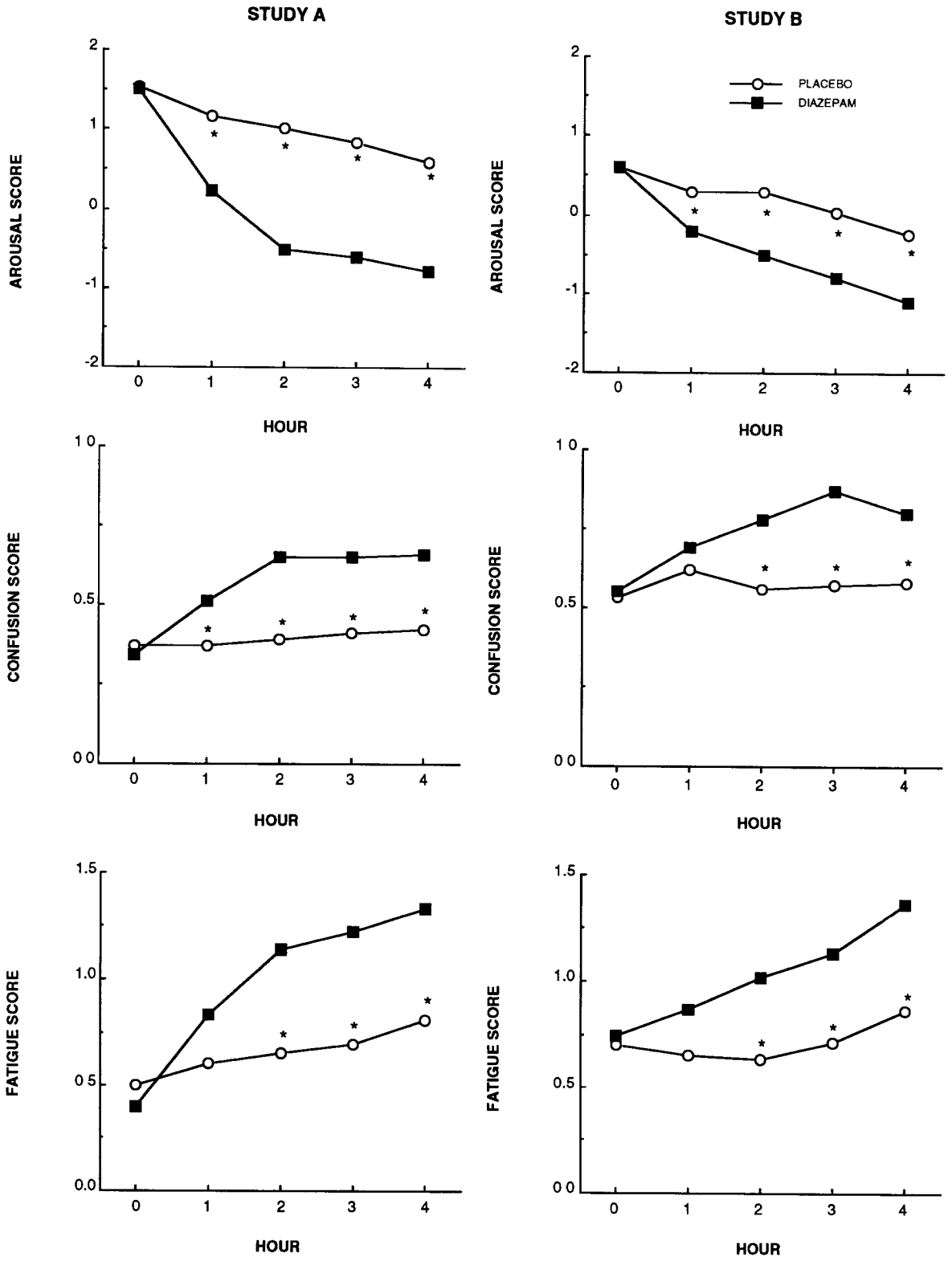


FIG. 2. Representative examples of the subjective effects of DZP (■) and PL (○) on the POMS in Studies A and B. There was a significant drug × hour interaction ($p < 0.05$) on all three scales in both studies. Asterisks (*) indicate significant differences across hours (Tukey's HSD).

TABLE 3

SIGNIFICANT EFFECTS ON POMS: DRINKING HISTORY, DRUG, AND HOUR AS FACTORS

| Scale | Drug | Drug × Hour | Drug × History |
|---|---|---|---|
| Arousal | 0.006 ⇓ | 0.0001 ⇓ | |
| Confusion | 0.005 ⇑ | 0.0002 ⇑ | |
| Elation | | 0.046 ⇓ | |
| Fatigue | 0.035 ⇑ | 0.0002 ⇑ | |
| Friendliness | | | 0.017 |
| Vigor | | 0.0018 ⇓ | |

For main effects, scores were higher ( ⇑ ) or lower ( ⇓ ) for DZP than PL. For drug × hour interaction, scores were significantly higher ( ⇑ ) or lower ( ⇓ ) for DZP than PL at all hours except hour 0.

ent even prior to drug administration (hour 0). In Study B, there was a significant drug × hour × condition interaction ($p < 0.008$) on the Anxiety scale but this was due to a decrease following DZP relative to PL under the SOL condition but not under the SOC condition.

There were significant main effects for drug and several significant drug × hour interactions (Table 2). Relative to PL, DZP decreased Arousal and increased Confusion and Fatigue. In Study A, DZP also decreased Elation, Positive Mood, and Vigor. Significant drug × hour interactions were found for Arousal, Confusion, and Fatigue for both studies (Table 2 and Fig. 2) with additional significant interactions found in Study A for Depression, Elation, Friendliness, Positive Mood, and Vigor. In all cases, there were no significant differences between DZP and PL scores at hour 0 with differences emerging on most scales at hour 1 and continuing throughout hour 4.

Because condition had little effect on the subjective effects of DZP and PL across hours, further analyses could have collapsed across this factor. However, because Study A was a within-subjects design but Study B used different groups for the SOC and SOL condition further POMS analyses were conducted using only data obtained during the SOC condition. Data were also collapsed across studies. Two sets of analyses were performed, with both sets including drug and hour as within-subject factors and one additional between-groups factor. For the first set, this factor was alcohol drinking history (two levels based upon a median value of drinks/ week) and the second set included choice as the between-groups factor. Choosers were defined as those participants who chose DZP on at least one choice session whereas nonchoosers were participants that never chose DZP.

Table 3 shows the results of the first set of analysis. There was only one significant effect involving drinking history, namely, a significant drug × history interaction on the Friendliness scale. Subjects classified as low-rate drinkers showed a decrease in Friendliness following DZP. Although Friendliness scores were higher on DZP sessions compared to PL sessions for the high-rate drinkers, this difference is difficult to interpret because these scores were higher even before drug administration (hour 0). Again, significant drug and/or drug × hour interaction effects indicated that DZP decreased Arousal, Elation, and Vigor and increased Confusion and Fatigue relative to PL.

Table 4 shows the results of the second set of analysis (choice × drug × hour). There was only one significant effect involving the choice factor, a choice × drug × hour interaction on the Fatigue scale. Subjects who chose DZP showed the usual increase in Fatigue across hours whereas nonchoosers showed no drug effect on this measure. Significant drug and/or drug × hour interaction effects indicated that DZP decreased Anxiety, Arousal, Elation, Positive Mood, and Vigor and increased Confusion and Fatigue relative to PL.

TABLE 4

SIGNIFICANT EFFECTS ON POMS. CHOICE, DRUG, AND HOUR AS FACTORS

| Scale | Drug | Drug × Hour | Drug × Hour × Choice |
|---|---|---|---|
| Anxiety | 0.047 ⇓ | | |
| Arousal | 0.006 ⇓ | 0.0001 ⇓ | |
| Confusion | 0.004 ⇑ | 0.0001 ⇑ | |
| Elation | | 0.034 ⇓ | |
| Fatigue | 0.038 ⇑ | 0.0001 ⇑ | 0.046 |
| Positive Mood | | 0.033 ⇓ | |
| Vigor | | 0.001 ⇓ | |

For main effect, scores were higher ( ⇑ ) or lower ( ⇓ ) for DZP than PL. For drug × hour interaction, scores were significantly higher ( ⇑ ) or lower ( ⇓ ) for DZP than PL at all hours except hour 0.

## DISCUSSION

The importance of social facilitation in increasing reinforcing effects has been demonstrated in previous studies with alcohol, marijuana, and THC. These studies have shown that euphorigenic effects are enhanced by social settings, and furthermore that subjects self-administer more drug in the presence of others (10,11,13,14). Therefore, two separate studies were conducted where subjects were given an opportunity to choose DZP or PL either in a situation where other subjects were also present (social condition) or when alone (solitary condition). The two studies differed in several respects, including the use of within- vs. between-subjects design and the demographic characteristics of the participants. Subjects in Study A were older, were more likely married and female, and in particular drank less alcohol on a weekly basis than subjects in Study B. Despite these differences, both studies found that DZP preference was unaffected by the presence or absence of other individuals. Nevertheless, there was a modest correlation between choice and drinking history, similar to the finding by de Wit et al. (3). In that same study, overall preference even in light drinkers was higher than in the present study. However, the preponderance of previous studies with normal volunteers have consistently found a low preference for DZP similar in magnitude to that found in the present study (8).

The subjective effects of DZP assessed using the POMS were similar across settings and were also similar to those that have been reported previously (8). These effects can be characterized as sedative like (e.g., increases in Fatigue and decreases in Vigor on the POMS) with no indication of effects that could be considered indicative of abuse potential (e.g., increases in Elation). In addition, consistent with the low levels of choice, liking scores for DZP were either similar to those for PL or lower. However, liking difference scores were correlated with drinking history and choice: Subjects reporting higher levels of weekly drinking disliked DZP less and chose it more relative to light drinkers. On the other hand,

the subjective effects of DZP relative to PL assessed using the POMS were similar in choosers and nonchoosers as well as individuals with low and high levels of drinking.

In summary, the present studies demonstrate that social setting does not influence drug choice when the drug being tested is one with minimal reinforcing effects. This is in contrast to other studies with alcohol, marijuana, and THC demonstrating a facilitative effect (10,11,13,14). This result should not be interpreted to indicate that DZP's reinforcing effects are not susceptible to facilitation. Augmentation by social setting may nevertheless occur when reinforcing effects are greater in the absence of social influences. That is, it may be possible to more adequately assess the influence of social conditions by only testing individuals who drink significant amounts of alcohol.

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