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Reinforcing Effects of Triazolam in Sedative Abusers: Correlation of Drug Liking and Self-Administration Measures

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ROACHE, J. D., R. A. MEISCH, J. E. HENNINGFIELD, J. H. JAFFE, S. KLEIN AND A. SAMPSON. *Reinforcing effects of triazolam in sedative abusers: Correlation of drug liking and self-administration measures.* PHARMACOL BIOCHEM BEHAV **50**(2) 171-179, 1995.—Six male subjects with histories of sedative abuse were allowed to orally self-administer a maximum of 18 color-coded triazolam and placebo capsules during daily 3-h sessions. The schedule of reinforcement was a signaled fixed-interval 10-min schedule in which triazolam and placebo were concurrently available as mutually exclusive choices. Triazolam was shown to be a reinforcer in four of the six subjects. The two subjects who did not self-administer triazolam in preference to placebo also had lesser histories of drug dependence. Self-administration of triazolam (0.125 or 0.25 mg per capsule) was generally stable over 7-10 days. Manipulations of triazolam dose (0.0312-0.25 mg) per capsule in two subjects showed that the number of capsules self-administered was inversely related to capsule dose. Subject ratings of drug liking obtained from experimenter-administered doses of triazolam were correlated with self-administration behavior occurring 1-7 days later. Of the subject ratings, next day ratings obtained on the day after dosing resulted in significant correlations whereas same day ratings obtained while subjects were under the influence of triazolam did not. These results have important implications for abuse liability prediction and suggest that next day ratings have greater predictive validity than measures collected while subjects are under the influence of benzodiazepines.

Triazolam Drug abuse Benzodiazepines Drug self-administration Humans Abuse liability

MANY studies have assessed the abuse potential of benzodiazepines by examining the subject ratings of drug liking, positive mood, or euphoria induced by drugs in subjects with a history of sedative use/abuse (19,24,25). These assessments assume that euphoria or other positive subjective effects (2,9) are correlated with abuse potential. In general, there appears to be a reasonable correspondence between the results of such abuse liability studies and actual indicies of abuse (8,19,24). However, the validity of subject ratings to predict abuse potential can be and has been questioned (24,25).

Laboratory measures of drug self-administration are considered the most valid predictors of abuse potential (19,20, 24,25). Several recent reviews show that benzodiazepines can function as reinforcers and maintain self-administration behavior in animals and humans (1,19,24,25). In humans, reinforcing effects of benzodiazepines have been demonstrated reliably in sedative abusers (5,18,19). Studies in nondrug users generally have reported a lack of reinforcing effects (3,11). However, in social drinkers, the reinforcing effects of diazepam may be positively related to the amounts of alcohol these drinkers normally consume (4). Previous reports have shown that triazolam is self-administered and has an abuse potential similar to that of other benzodiazepines, including diazepam (5,9,17-19).

Self-administration studies in both sedative abusers (18,19) and normal volunteers (3) have suggested that there is some predictive correlation between ratings of drug liking and subsequent self-administration behavior. However, the corre-

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spondence is not complete (18), and several authors have emphasized the lack of correspondence between these measures (12,24,25). The relationship between subject ratings of drug effects and self-administration behavior needs to be better defined in empirical studies directly examining these issues.

The present study examined the reinforcing effects of the benzodiazepine triazolam in human subjects with histories of sedative abuse. Because the methods of the present study obtained a good quantitative range of self-administration behavior and subject ratings of drug liking, we were able to examine the correlation between these measures. The data reported herein are from the first part of a two-phase study. The second phase involved pretreatment with various doses of yohimbine to determine whether chemically induced anxiety would increase self-administration behavior. However, those data are not included in this report so as to not dilute the focus on triazolam-induced drug liking and self-administration. Preliminary data from this study have been published in abstract form (21).

METHOD

Subjects

Six male subjects participated 5 days per week (M–F) while living on a closed residential research ward for a 4–8-week period. Each subject participated on separate occasions with no overlap. Subjects were not permitted to eat solid food or drink milk between 0200 and 1245 h. Caffeine use was prohibited at all times. Cigarette smoking was unrestricted; however, for safety reasons, sedative-intoxicated subjects were permitted to smoke only under staff supervision and when seated in a designated observation chair. Subjects ranged in age from 25 to 44 years, weighed between 59 and 84 kg (mean = 72.6 kg), and had from 9 to 15 years of education (mean = 12.5 years). All subjects were tobacco dependent and smoked 1–2 packs/day (mean = 1.6 pks/day). All subjects reported moderate to heavy alcohol drinking patterns ranging from 16 to 125 drinks (median = 34 drinks) consumed on 2 to 9 days (mean = 5 days) over the 2-week period immediately preceding the study. All subjects had histories of sedative abuse meeting DSM III-R criteria and reported using a variety of drugs including alcohol, prescription sedatives, hallucinogens, marijuana, and stimulants. The prescription sedatives included barbiturates for all subjects except S-JC and S-MT and benzodiazepines for all but S-JM. All subjects except S-BW and S-JC had past histories of intravenous (IV) drug use and physical dependence on a substance other than tobacco. No subject was physically dependent on drugs at the time of the study and all subjects provided drug free urine samples before beginning the study. All subjects were medically healthy as determined by physical and laboratory examination. Other than histories of substance abuse/dependence disorders, no subject currently had significant psychiatric disturbances as determined by the Diagnosic Interview Schedule (DIS) and by personal interview. This study was approved by a local Institutional Review Board and all subjects signed a written informed consent before participating.

Study Design

This study involved an Initial Acclimation Period, followed by a Sample Period, followed by the Self-Administration Period as described below. After the first three subjects (S-WW, S-LK, and S-JM) completed the study, several procedural modifications were instituted to improve subject safety and abbreviate the study duration. Material below describes the original self-administration procedure and then the modified procedure.

Initial Acclimation Period

All subjects began with an Initial Acclimation Period (4–8 days) in which they were familiarized with the procedures and triazolam dose-response functions were assessed. On each day, subjects received eight experimenter-administered white capsules at the rate of one every 10 min beginning at 0900 h. Triazolam dose-response was evaluated by administering 0.125 mg triazolam per capsule (a total dose of 1.0 mg) on one day and 0.25 mg per capsule (2.0 mg total dose) on another day. Triazolam doses were administered in an ascending series with a placebo dose intervening between the two. This intervening placebo was used as the "placebo" for all statistical analyses of Initial Acclimation Period data. Placebo doses were administered on all other days but were not included in any analyses.

Sampling Period

The Sampling Period allowed subjects to associate capsule color with the effects of the drugs (triazolam and placebo), which subsequently would be available for self-administration. All subjects received eight colored capsules containing either triazolam or placebo on different (consecutive) sessions. These capsules were given according to the experimenter-administered dosing procedure of the Initial Acclimation Period. Subjects received eight capsules of one drug/color combination on the first day and the other drug/color combination on the second day. For all subjects, one capsule color was placebo and the other was triazolam. The triazolam dose was 0.125 mg/capsule for most subjects; however, for S-LK2 and S-BW, the triazolam dose was 0.25 mg/capsule. The dose was changed for these two subjects for reasons described below (see Dose Variation). Drug order and capsule color varied across subjects in a counterbalanced fashion. After the first 2 days of sampling, the original procedure provided subjects with repeated exposure to each capsule color again on a third and fourth day. On these days, subjects were allowed to self-administer extra capsules beyond the experimenter-administered minimum number of eight capsules. All subjects tested with this procedure self-administered additional triazolam capsules (two–seven additional capsules), and one subject (S-WW) also self-administered one additional placebo capsule. Data from these additional days of sampling exposure were not used in any subsequent data analyses.

Self-Administration Period

After the Sample Period, all subjects began the Self-Administration Period in which a maximum of 18 color-coded placebo and triazolam capsules were available for self-administration from 0900 to 1205 h daily. For each subject, the triazolam dose per capsule available was the same as that administered in the Sample Period. The schedule of reinforcement was a signaled fixed-interval 10-min schedule in which triazolam and placebo capsules were concurrently available as a mutually exclusive choice. At the end of each 10-min interval, a stimulus light was turned on to signal capsule availability. The stimulus light was a desk lamp visable to the subject. Upon the subject's verbal request for a particular capsule color, research staff administered a single capsule and turned the stimulus light off, initiating the next 10-min interval. If

subjects did not request a capsule, the stimulus light remained on until the end of the session at 1205 h. After completing 10 days of the Self-Administration Period, the triazolam dose per capsule was varied for two subjects (S-LK and S-JM) as described below (see Dose Variation).

Procedure Variation

After the first three subjects completed the study according to the original procedure described above, several modifications were instituted to improve subject safety and to abbreviate the length of time required for protocol completion. Subject S-LK participated initially under the original procedure and then returned 6 months later to participate a second time (S-LK2) under the modified procedure. The modified procedure differed from the original procedure in three ways. First, the original procedure permitted subjects to remain in the research ward dayroom area throughout the day except for the 3-h self-administration session, which occurred in an isolated laboratory area. To minimize risks to sedative-intoxicated subjects, the modified procedure required subjects to remain seated in a lounge chair within the isolated laboratory for the entire day, from 0845 to 1600 h. Subjects in either procedure were permitted to read, sleep, watch TV, etc., when the other protocol activities permitted. The second modification involved only 2 days of exposure during the Sampling Period. These were equivalent to the first 2 days of the original procedure (described above). The third modification involved the administration of five capsules of placebo pretreatment at 0815 h daily, throughout a subject's study participation. This modification was introduced to allow for the examination of drug pretreatment effects in the later (i.e., yohimbine) phase of the study—the data from which are not presented herein.

Dose Variation

To assess the dose-related effects of triazolam on self-administration, the triazolam dose per capsule was varied for two subjects under double-blind conditions. After self-administering triazolam (0.125 mg/capsule) for 10 days in the Self-Administration Period, the dose was switched to 0.03125 mg/capsule for S-JM or to 0.125 and then to 0.25 mg/capsule for S-LK. The number of days that these doses were available to each subject was variable (5–12 days) to insure that there were no increasing or decreasing trends in the self-administration behavior. We also attempted to vary dose between subjects. Because S-LK had received 0.125 mg/capsule during his initial participation, he received 0.25 mg/capsule when he returned to the study under the modified procedure (i.e., S-LK2). The next subject enrolled in the study (S-BW) also received 0.25 mg/capsule of triazolam. However, this dose did not function as a reinforcer for this subject. After this failure and because of the small sample size of the study, we abandoned the effort to vary dose between subjects and the remaining subjects received only the 0.125 mg/capsule dose.

Blind Drug Administration

All drugs were administered orally in size 0 opaque gelatin capsules. Triazolam capsules were prepared by filling each capsule with a specified amount (0.0312–0.25 mg) of crushed or broken tablets of 0.25 mg Halcion (The UpJohn Co.) mixed with cornstarch. All placebo capsules contained only cornstarch. Subjects were completely blind as to capsule contents and were informed only that they might receive placebo or one of several different sedatives (including triazolam) and stimulants listed on the consent form. The research staff were blind to the extent that they knew only that yohimbine or placebo might be administered as a pretreatment and that triazolam or placebo might be available for self-administration.

Subject Instructions

Subjects received written instructions describing the procedures of the experiment. Briefly, instructions regarding the Initial Acclimation Period stated that subjects would " . . . receive eight white capsules at the rate of one every ten minutes." Instructions for the Sample Period stated that subjects should " . . . associate the effects of the drug with the color of the capsule because in the future you will have the opportunity to choose which of these capsules you want to receive." The instructions presented at the beginning of the Self-Administration Period contained the following information:

1. Over a 3-h session, subjects would have the " . . . opportunity to take as many as 18 capsules."
2. "After taking a capsule, at least 10 minutes must pass before you can take another capsule. To let you know when 10 minutes have passed, a desk light will be turned on."
3. "You do not have to take any capsules when the light comes on. It is completely up to you whether you receive any capsules. You may receive all, some, or none of the capsules; it is completely your decision."
4. " . . . if you do wish to take a capsule, you will always be given a choice of taking a yellow capsule or a blue capsule."
5. "You will be required to remain in your chair for the entire three hours, regardless of whether you take capsules or not."

Subject Ratings

Subjects completed two sets of visual analog rating scales by marking a position on a 100-mm line (labeled "not at all" to "extremely") to rate several items. Subjects completed the "Same Day" ratings at repeated time points throughout the experimental day and completed the "Next Day" ratings on the morning of the next day. Same Day rating items were:

1. "How strong of a drug effect do you feel?"
2. "To what degree do you like the way the drug makes you feel?"
3. "To what degree do you dislike the way the drug makes you feel?"
4. "Do you feel calm or relaxed?"
5. "Do you feel anxious or nervous?"

These ratings were completed before (at 0855 h), at four time points during (at 15, 45, 75, 120, and 180 min), and at three time points following (2, 3, and 4 h) the self-administration session. Subjects completed the Next Day ratings at 0815 h in the morning and answered questions referring to the drug effect experienced on the previous day. The next-day items were:

1. "How strong of a drug effect did the drug you took yesterday produce?"
2. "To what degree did you like the drug you took yesterday?"
3. "To what degree did you dislike the drug you took yesterday?"

These rating scales are slightly modified versions of questionnaires previously reported (17,18).

Other Measures

Each time that subjects completed ratings, the research assistant separately recorded staff observer ratings of drug effect magnitude on a 100-mm visual analog scale. At repeated time points before and after drug administration, several other measures were collected, including two objective performance tasks. The digit-symbol-substitution (DSST) was a computerized perceptual-motor task where subjects typed positions on a keypad to reproduce symbol patterns. The data were the number of symbols correctly substituted in 90 s (postdrug observations were expressed as a percentage of the predrug observation). The Picture Recognition task was a measure of long-term memory and involved memorization of six pictures at three times (0, 1, and 3 h) following the period of drug administration. Recognition testing was conducted at the end of the day, 5 h after the end of drug administration. Data were the total number of pictures correctly recognized out of 18 possible. Each of these measures have been described previously (17,18).

Data Analysis

Dependent measures of self-administration behavior observed on each day of the Self-Administration Period included: 1) the number of placebo capsules ingested; 2) the number of triazolam capsules ingested; 3) the total milligram amount of triazolam consumed (i.e., accounting for the mg/capsule amount); and 4) the triazolam preference ratio (i.e., number triazolam capsules/number triazolam + number placebo capsules). Self-administration data were analyzed by visual inspection and by descriptive statistics. Reinforcing effects of triazolam were inferred when the number of triazolam capsules self-administered consistently exceeded the number of placebo capsules.

The effects of experimenter-administered triazolam and placebo doses were compared by examining data from the staff and subject ratings and performance measures collected during the Initial Acclimation and Sample Periods. For the staff and subject ratings and the DSST task measure, peak drug effects were determined as the maximal rating or the minimal task performance observed following drug administration. For the memory task, data were the total number of pictures recognized (summing across the three postdrug observations). These data were analyzed by a one-way ANOVA containing five levels (i.e., placebo, 1.0, and 2.0 mg triazolam of the Initial Acclimation Period plus placebo and drug of the Sample Period). Post hoc comparisons were made using Tukey's procedure.

Correlational analyses (Pearson's Product Moment Correlations) were used to determine whether subject ratings of drug liking predicted subsequent self-administration behavior. Liking ratings were obtained following triazolam and placebo doses administered by the experimenter during the Initial Acclimation and Sample Periods and included both Next Day liking ratings as well as the peak degree of liking observed from the Same Day ratings. Self-administration behavior measures included data from the first day of the Self-Administration Period as a measure of initial drug taking, and average data across all days of the Self-Administration Period as an overall composite of drug taking.

RESULTS

Initial and Sample Day Effects of Triazolam

Table 1 shows the effects of triazolam observed during the Initial Acclimation and Sample Periods. For all measures, one-way ANOVAs coupled with post hoc testing showed all doses of triazolam were significantly ($p < 0.001$) different than either placebo dose. Thus, triazolam impaired DSST and picture recognition performance, increased staff ratings of drug effect, and increased subject ratings of drug effects, liking, and disliking. Triazolam effects were reasonably dose related except for the Same Day subject ratings. It is important to note that the 1.0-mg dose was more disliked and resulted in lower liking ratings on the Next Day Questionnaire than did the 2.0-mg dose. Also note that placebo liking ratings were negligible.

Triazolam and Placebo Self-Administration

Figure 1 shows the number of triazolam and placebo capsules self-administered by individual subjects. Under the original procedure, the first three subjects (S-WW, S-LK, and S-JM) clearly self-administered triazolam at greater levels than placebo. With S-LK2 and the latter three subjects under the modified procedure (S-BW, S-JC, and S-MT), placebo levels of self-administration clearly were elevated. For two subjects (S-JC and S-BW) placebo self-administration was equal to or greater than the number of triazolam capsules, suggesting a lack of drug reinforcement. With S-LK2, triazolam self-administration always exceeded that of placebo. With S-MT, triazolam self-administration exceeded placebo on most occassions (i.e., 5 out of 7 days). There were no increasing or decreasing trends in the level of triazolam self-administration observed for each subject; however, there was variability. Three subjects (S-WW, S-JM, and S-MT) self-administered zero triazolam capsules on at least 1 day but resumed self-administering triazolam on subsequent days. Across subjects, the mean number of triazolam capsules self-administered ranged from 2.0 (S-BW) to 15.3 (S-LK) and the mean total amount of triazolam ingested ranged from 0.33 mg (S-WW) to 2.82 mg (S-LK2).

Triazolam Dose-Response

The triazolam doses within each capsule were varied for two subjects, as shown in Fig. 2. For both individuals, consistent dose-related effects were observed. Higher triazolam doses were associated with fewer capsules self-administered but greater total milligrams triazolam consumed. Note also that S-LK averaged 12.8 capsules per day with the 0.25-mg dose tested during his first participation (Fig. 2) and he maintained a similar average (11.3 capsules per day) at the same dose on his repeat participation (see S-LK2 shown in Fig. 1). This suggests within-subject stability of the dose-effect function.

Predictive Correlations of Drug Liking With Self-Administration

None of the Same Day liking ratings obtained in the Initial Acclimation and Sample Periods showed any correlation with the various measures of self-administration behavior. In contrast, the Next Day ratings did show a number of significant correlations. Table 2 shows the correlations between the various measures of self-administration behavior and the Next Day liking scores observed following placebo and triazolam doses administered during the Initial Acclimation and Sample Periods. The first thing to note is that greater triazolam-induced drug liking was associated with fewer placebo capsules self-administered (i.e., all negative correlations with number of placebo capsules) and with greater triazolam intake

TABLE 1

EFFECTS OBSERVED IN THE EXPERIMENTER-ADMINISTERED DOSING PERIODS

	Initial Period			Sample Period	
Measure	Placebo	1.0 mg	2.0 mg	Placebo	Triazolam
DSST	92.8	49.1	26.5	93.9	40.9
(% correct)	(0.8)	(15.0)	(3.4)	(1.5)	(13.3)
Pictures Memory	13.5	4.7	2.8	14.2	3.3
(no. recognized)	(0.8)	(1.1)	(0.7)	(1.0)	(0.8)
Staff–effect	2.1	44.6	68.0	0.3	40.7
(mm scores)	(1.3)	(9.5)	(8.5)	(0.3)	(8.7)
Same day–effect	4.3	35.7	34.3	4.0	42.0
(mm scores)	(2.2)	(7.5)	(5.4)	(2.6)	(7.7)
Same day–liking	4.9	35.4	36.9	2.6	43.1
(mm scores)	(3.0)	(9.0)	(8.4)	(2.1)	(7.1)
Next day–effect	3.0	38.6	63	4.7	49.7
(mm scores)	(1.6)	(9.9)	(5.8)	(3.1)	(6.8)
Next day–liking	2.0	24.7	42.6	1.7	47.0
(mm scores)	(1.0)	(9.8)	(7.7)	(0.8)	(12.8)
Next day–disliking	1.4	21.0	11.0	0.1	6.57
(mm scores)	(1.4)	(10.3)	(7.3)	(0.1)	(4.8)

Data are means (SEM) of seven subjects. DSST scores are the peak degree of task impairment observed. Pictures Memory represents the total number of picture items recognized. Staff–Effect refers to the maximal drug effect magnitude rated by staff observers on a visual analog scale. The Same Day and Next Day ratings are the maximal ratings completed by subjects on these two visual analog questionnaires.

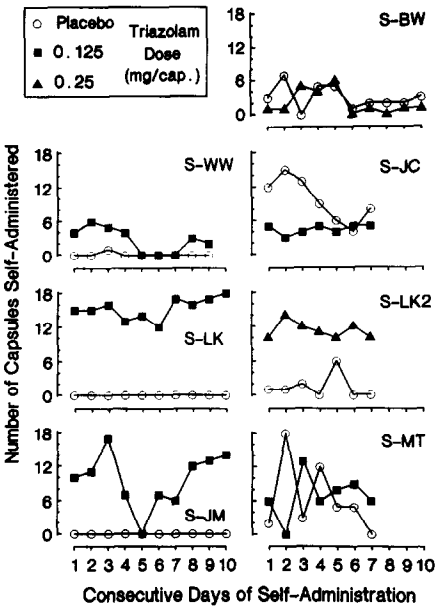

FIG. 1. Triazolam and placebo capsule self-administration observed during the 7–10 days of the self-administration period. Subjects varied in the number of days and the triazolam dose per capsule as identified in the upper panel of the figure. Data points show the number of capsules self-administered by each subject on each day; a maximum of 18 capsules were available on each day.

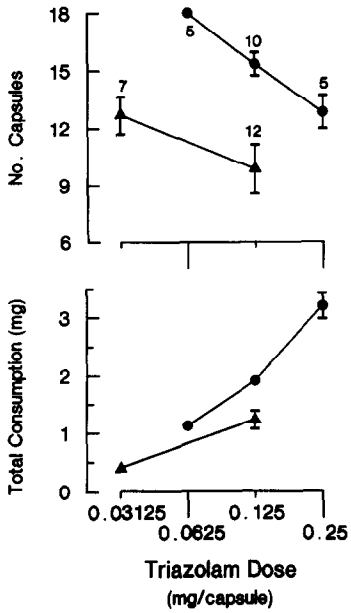

FIG. 2. Effects of varying triazolam dose per capsule in two subjects (circles = S-LK and triangles = S-JM). Data points show means ± SEM of the number of triazolam capsules self-administered and the total amount of triazolam consumed on each day as a function of the triazolam dose contained in each capsule. The numbers associated with each data point show the number of sessions tested at that dose. The number of observations varied from 5–12 to ensure that there were no upward or downward trends in the data. The sequence with which doses were tested was as follows: 0.125, 0.0625, and 0.25 for S-LK; and 0.125 and 0.03125 for S-JM.

TABLE 2
DRUG LIKING CORRELATIONS WITH SELF-ADMINISTRATION MEASURES

	Next-Day Liking Scores						
	Initial Acclimation			Sample		TZ – Pl Difference	
Self-Administration Measure	Pl	1.0	2.0	Pl	TZ	Initial	Sample
No. Placebo Capsules							
First day	–	–	−0.85*	–	−0.71	−0.90*	−0.70
All days	–	–	−0.78*	–	−0.69	−0.81*	−0.68
No. Triazolam capsules							
First day	–	–	–	−0.81*	0.77*	–	0.78*
All days	–	–	–	−0.83*	0.74	–	0.75*
Triazolam consumption (mg)							
First day	–	–	0.72	−0.74	0.71	0.68	0.71
All days	–	–	0.75	−0.76	–	0.71	0.68
Triazolam preference ratio							
First day	–	–	0.78	−0.77	0.91*	0.84*	0.91*
All days	–	–	0.85*	−0.88*	0.93*	0.88*	0.93*

Pearson Product Moment Correlation Coefficients that were significant at $p < 0.10$; asterisks indicate those correlations significant at $p < 0.05$. Correlations are between various measures of self-administration behavior and subject-rated liking scores for placebo (Pl) and triazolam (TZ: 1.0 or 2.0 mg) observed during the Initial Acclimation Period and the Sample Period. The last two columns show correlations with triazolam liking after adjustment for placebo liking (TZ liking minus Pl liking difference score) on data from the Sample Period and the 2.0-mg dose of the Initial Acclimation Period.

on all three measures of triazolam self-administration. Liking ratings obtained in the Inital Acclimation Period following placebo and 1.0-mg triazolam did not predictively correlate with any self-administration measures. Also shown are the self-administration behavior correlations with triazolam liking after adjustment for the placebo liking ratings (i.e., the TZ minus PL difference scores). There were no substantial differences in the correlations based upon the use of difference scores and those observed with triazolam liking uncorrected for placebo liking.

To further examine the correlations of self-administration and drug liking, Fig. 3 shows xy coordinate plots of triazolam consumption and preference as a function of the Next Day and Same Day liking ratings obtained from the first sampling exposure to triazolam. Next Day liking ratings showed correlations that were significant at probability levels below $p < 0.10$; among these, the preference ratio measures showed the strongest correlations ($p < 0.005$). In contrast, the Same Day liking ratings showed no correlation (all $p > 0.5$) with any measure of self-administration behavior. The greatest outliers from the overall linear regression were S-WW, who showed low consumption associated with moderate liking, and S-LK2, who showed the greatest consumption but not the greatest liking. Whereas the three subjects under the original self-administration procedure all showed high preference ratios (regardless of liking score), they showed more graded degrees of consumption that were roughly related to Next Day liking. Attesting to the strength of these correlations, they were still present even when examining only the four subjects tested under the modified self-administration procedure. Those correlations were significant ($p < 0.05$) both for measures of preference ratio and for mean consumption (all days). However, the first day consumption correlation was marginal ($p < 0.11$) when using data only from these four subjects.

DISCUSSION

Under blind experimental conditions, four of six subjects with histories of sedative abuse self-administered triazolam at levels exceeding that of placebo. These data indicate that triazolam functioned as a reinforcer in four of the six subjects tested. In two subjects, triazolam dose manipulations showed evidence of a dose-response relationship such that higher doses resulted in fewer capsules ingested but greater cumulative total milligram intakes. There have been a number of studies that have shown benzodiazepines will function as modest reinforcers in animals (1,10,24,25). Our results are consistent with human studies showing that benzodiazepines (4, 6–8,14), including triazolam (18), maintain drug self-administration above placebo levels under blind experimental conditions.

Two subjects (S-BW and S-JC) self-administered triazolam but not at levels exceeding the concurrently available placebo. Thus, triazolam was not demonstrated to be a reinforcer for these two subjects. Unfortunately, experimental parameters (e.g., dose, reinforcement schedule) were not varied to determine if triazolam may have functioned as a reinforcer for these individuals under a different set of conditions. It is not clear why these two subjects failed to show reinforcing effects of triazolam. Except for reduced next day ratings of drug liking, these subjects did not seem to differ from the other subjects in their behavioral or subjective response to triazolam. As with the other subjects, these individuals had a history of abusing a variety of substances including benzodiazepines. However, these subjects differed from the others on two dimensions. They did not have any history of IV drug use and they reported no experience of physical dependence on any substance other than tobacco. These data are consistent with literature suggesting an influence of drug history in determining the reinforcing effects of drugs (1,10,11,15).

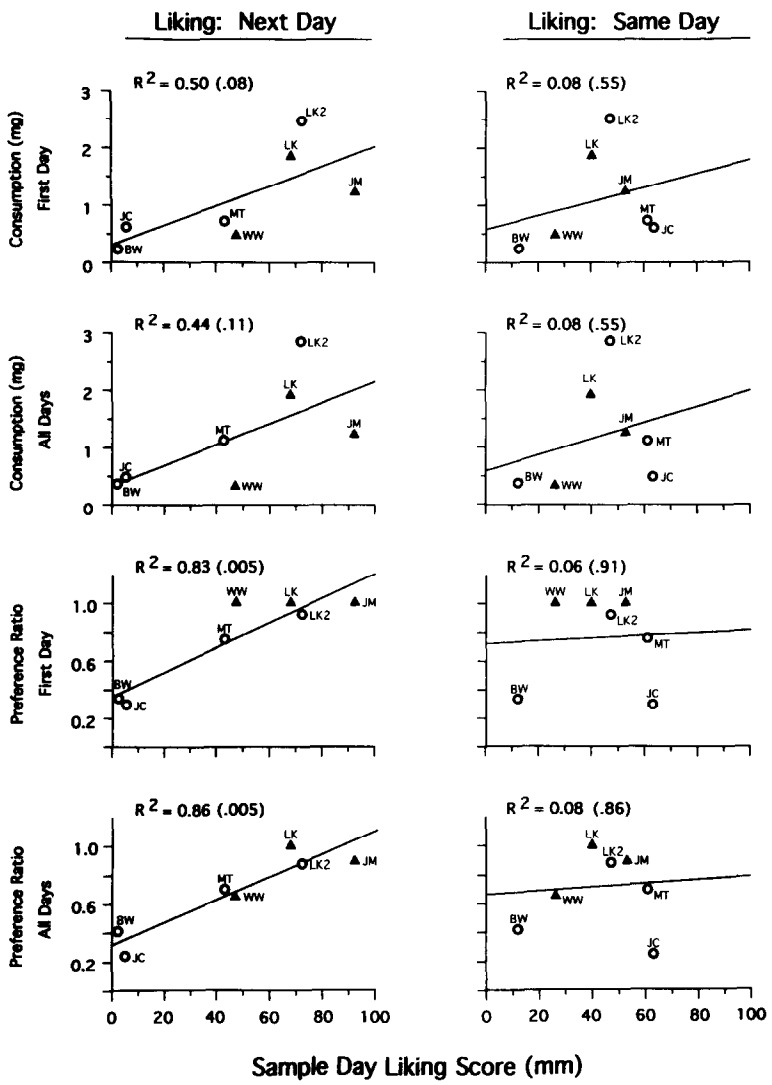

FIG. 3. Correlation between measures of self-administration behavior and measures of drug liking. Drug liking scores (mm) were obtained from the Same Day and Next Day questionnaires associated with the experimenter-administered dose of triazolam given on the first drug day of the Sample Period. Self-administration data include measures of triazolam consumption (mg ingested) and triazolam preference ratio obtained on the "First Day" of the self-administration period or mean data for each subject averaged across "All Days" of the self-administration period. R^2 values and their probabilities (in parentheses) are shown above each panel. Within each panel, data points are labeled to identify individual subjects; triangles represent subjects tested under the original procedure and circles represent subjects tested under the modified procedure.

Although the present study was not designed to systematically examine different self-administration procedures, two slightly different procedures (the original and a modified procedure) were used in the present study. Subjects under the modified procedure tended to have higher rates of placebo self-administration, and the two subjects for whom triazolam was not a reinforcer were tested under these conditions. Due to the small number of subjects in each group, it is not clear whether these represent true differences between the two procedures or whether it is random variation. There were two potentially important differences in these procedures. First, subjects in the original procedure were given two sampling exposures to each capsule color whereas subjects in the modified procedure received only one. It is possible that the enhanced sampling exposure of the original procedure served to more clearly distinguish the drug and placebo capsules. The second major difference between procedures was that the modified procedure required subjects to remain seated in the laboratory all day long. However, recent data (23) have suggested that such a sedentary environment would be expected to increase, not decrease, the reinforcing effects of triazolam.

Dose-response functions for drug reinforcement in laboratory animals usually have an "inverted U" shape (13,15,20). Only a few studies of human sedative self-administration have experimentally varied dose. The usual finding has been that increases in drug dose resulted in increased self-administration behavior (6-8). Only one human study with pentobarbital (16) described an inverted U-shaped dose-response curve. The present results, showing an inverse relationship between triazolam dose and the number of capsules self-administered, suggest that these doses were on the descending limb of an inverted U-shaped dose-response function.

Because the self-adminstration procedure permitted subjects to consume 0–18 capsules daily, there was a good quantitative range in the amount of behavior observed. There was substantial between-subject and some within-subject variability in self-administration. However, there were no consistent upward or downward trends and triazolam self-administration persisted over a 7–10 day period. This is in contrast to previous studies in which decreasing trends in self-administration were observed (6,18). Numerous procedural differences between this and previous studies preclude a definitive explanation of the difference. However, previous studies employed bicycle-riding work requirements whereas the present study involved a minimal response requirement (i.e., a verbal request), which may have allowed the maintenance of behavior over longer time periods.

An important finding of the present study relates to the ability of drug liking ratings produced by experimenter-administered doses of triazolam to predict subsequent self-administration behavior. Significant correlations of drug liking with different measures of self-administration behavior were observed, including a negative correlation between triazolam liking and placebo self-administration. Significant correlations were observed with liking ratings measured on the next day following drug ingestion but not with ratings obtained on the same day while subjects were under the influence. These results confirm and extend a similar finding observed in a study of diazepam and triazolam self-administration (18) and suggest that the way subjects feel the next day after benzodiazepine intoxication may best predict their future behavior. Mechanisms for the reduced correlation with same day ratings could be related to impaired recognition or awareness of benzodiazepine intoxication, a finding that has been reported in earlier studies (17,19,22). Other studies conducted with normal volunteers (3) also have reported that individual differences in diazepam self-administration may be predicted by subject drug liking ratings. Overall, these data indicate that subject ratings of drug liking may correlate with drug self-administration behavior under certain conditions. However, the correlations are imperfect. Self-administration may be maintained in instances in which drug liking is absent (12) or when tolerance to drug-induced liking has developed (18). Also, in the present study, the first active dose administered during the Initial Acclimation Period (i.e., 1.0 mg triazolam) did not correlate with subsequent self-administration behavior, even though there was a significant amount of drug liking observed. Reasons for the lack of correlation in that case could be due to the significant extent of drug disliking also measured for this dose. Alternatively, it has been suggested previously that repeated dose effects are more predictive of subsequent self-administration behavior (18) than are the acute effects of an initial dose exposure.

In summary, the present report shows stable patterns of triazolam self-administration and evidence of drug reinforcement in four of six subjects having histories of sedative abuse. Of great importance are the findings that subject ratings of drug liking obtained following experimenter-administered conditions correlated with subsequent subject self-administration behavior. However, these correlations are imperfect, indicating that subject-rated drug liking is related to, but not completely predictive of, drug-taking behavior. Whereas additional research is required to better define the relationship between verbal self-reports and actual self-administration behavior, there is now one finding of central importance to human abuse liability studies. Namely, benzodiazepine-induced subject ratings obtained in the morning of the next day after drug intoxication are more predictive of future self-administration behavior than are ratings obtained while subjects are under the influence of the drug.

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