JOURNAL OF THE EXPERIMENTAL ANALYSIS OF BEHAVIOR 1995, 63, 277–294 NUMBER 3 (MAY)

DISCRIMINATIVE STIMULUS EFFECTS OF DIAZEPAM AND BUSPIRONE IN NORMAL VOLUNTEERS

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A within-subject design was used to characterize the effects of dose manipulations on discriminative and self-reported effects of oral diazepam and buspirone. Subjects were trained to discriminate diazepam (10 mg) versus placebo (n = 10), or buspirone (10 or 15 mg) versus placebo (n = 9). The compounds were identified to subjects by letter code before discrimination training began. In later sessions, correct identifications at 2 hr after the oral administration of drug earned money. All subjects showed accurate discrimination performance during the test-of-acquisition phase. In a low-dose generalization phase, diazepam and buspirone produced dose-related increases in drug identifications across a four-fold range of doses. In a subsequent low-dose training phase, in which subjects were trained to discriminate progressively lower drug doses, the median lowest discriminable dose of diazepam and buspirone was 2.5 and 7.5 mg, respectively. Dose–response functions for drug identifications were shifted leftward in the low-dose training phase relative to the low-dose generalization phase, suggesting that reinforcement of progressively lower doses enhances drug discriminability. The self-reported effects of diazepam and buspirone were similar (e.g., both drugs increased ratings of drug strength and clumsy/uncoordinated) and different (e.g., diazepam but not buspirone increased ratings of drowsy/sleepy; buspirone but not diazepam increased ratings of tense/nervous). This study demonstrates discriminative and self-reported effects of diazepam and buspirone at doses lower than previously shown to be behaviorally active, and suggests that at commonly used clinical doses, diazepam is relatively more discriminable than buspirone.

Key words: diazepam, buspirone, anxiolytics, drug discrimination, self-reported effects, behavioral pharmacology, humans

Buspirone, a pyrimidinylpiperazine derivative commonly used in the treatment of anxiety, is pharmacologically distinct from the benzodiazepines in that it acts primarily at the 5-HT_{1A} subtype of the serotonin receptor rather than at the gamma-aminobutyric acid (GABA) receptor complex (Eison & Temple, 1986; Riblet, Taylor, Eison, & Stanton, 1982; Taylor, Eison, Riblet, & Vandermaelen, 1985). Buspirone is also behaviorally distinct from the benzodiazepines. Across a wide range of doses, buspirone produces less behavioral impairment than do the benzodiazepines (Barbee, Black, & Todorov, 1992; Mattila, Aranko, & Seppala, 1982; Mattila, Seppala, & Mattila, 1986; Sellers, Schneiderman, Romach, Kaplan, & Somer, 1992; Troisi, Critchfield, & Griffiths, 1993) and does not potentiate the disruptive behavioral impairment caused by alcohol (Mattila et al., 1982; Seppala, Aranko, Mattila, & Shrorriya, 1982).

Buspirone also appears to differ qualitatively and quantitatively from the benzodiazepines in terms of the self-reported (i.e., subjective) effects it produces (Cole, Orzack, Beake, Bird, & Bar-Tal, 1982; Griffith, Jasinski, Casten, & McKinney, 1986; Sellers et al., 1992; Troisi et al., 1993). A prior study in our laboratory, for example, found that across an eight-fold dose range, lorazepam and buspirone produced comparable dose-related increases in subject ratings of drug strength in individuals with a history of recreational sedative use (Troisi et al., 1993). Lorazepam, however, produced largely positive mood effects (e.g., increased ratings of drug liking), whereas buspirone produced largely negative mood effects (e.g., increased ratings of drug disliking, bad effects, tension and anxiety).

A number of preclinical studies suggest that the discriminative stimulus effects of buspirone differ from those of benzodiazepines. Buspirone does not occasion significant drug-appropriate responding in nonhumans that have been trained to discriminate between a benzodiazepine and no drug (Ator & Grif-

This work was supported by the National Institute on Drug Abuse Grant R01 DA 03889. The authors thank John H. Texter for his expert data management and figure preparation.

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fiths, 1986; Evans & Johanson, 1989; Hendry, Balster, & Rosecrans, 1983; Spealman, 1985), nor do benzodiazepines occasion significant drug-appropriate responding in nonhumans that have been trained to discriminate between buspirone and no drug (Hendry et al., 1983; Mansbach & Barrett, 1987).

To date, eight studies have examined the discriminative stimulus effects of benzodiazepines or buspirone in human subjects (Altman, Albert, Milstein, & Greenberg, 1977; Bickel, Oliveto, Kamien, Higgins, & Hughes, 1993; Johanson, 1991a, 1991b, 1993; Kamien et al., 1994; Oliveto, Bickel, Hughes, Higgins, & Fenwick, 1992; Oliveto, Bickel, Kamien, Hughes, & Higgins, 1994). The present study was designed to examine further the discriminative stimulus effects of benzodiazepines and buspirone in humans. In contrast to previous studies that have generally presented averaged group data, the use of an intensive within-subject design allowed statistical analyses of individual-subject data for both discrimination responding and self-reported mood effects. One group of subjects was trained to discriminate between diazepam and placebo, and a second group of subjects was trained to discriminate between buspirone and placebo. After the test-of-acquisition phase, a range of doses of the training drug was repeatedly administered to determine whether they shared discriminative stimulus effects with the training dose. In a final phase, subjects were trained to discriminate progressively lower doses, and the lowest discriminable dose of diazepam and buspirone was established.

METHOD

Subjects

Nineteen healthy adults were recruited to participate via advertisements in newspapers and on bulletin boards. Subjects were interviewed and a brief physical examination was given before beginning the study. All subjects were in good health (i.e., normal electrocardiogram, heart rate, and blood pressure), were within ±20% of their ideal body weight (Metropolitan Life tables), and were without contraindications to anxiolytic medications. Volunteers were excluded if they had not completed high school or if they had histories of drug- or alcohol-related problems or major psychiatric disorders. Female subjects were excluded if they were currently pregnant, nursing, or were not using an effective method of birth control. Urine samples were gathered throughout the study and were analyzed to ensure that females did not continue in the study if pregnant. Modest use of alcohol, caffeine, nicotine, and over-the-counter analgesics containing only aspirin, ibuprofen, or acetaminophen was allowed. Subjects agreed not to drive for 6 hr after drug administration. The research protocol was approved by the local Institutional Review Board for human research, and subjects gave their informed written consent prior to beginning the study.

Twelve female and 7 male subjects participated in the study. On average, subjects were 32 years old (range, 25 to 46), weighed 68 kg (range, 50 to 95), consumed two alcoholic drinks per week (range, 0 to 5), consumed 164 mg of caffeine per day (range, 0 to 492), and had completed 15 years of education (range, 12 to 21). Eight subjects reported smoking an average of 16 cigarettes per day (range, 2 to 30). These subjects were allowed to smoke ad libitum. Two additional subjects were enrolled in the study but were released due to scheduling conflicts.

Procedure

Instructions to subjects. Subjects were told that the purpose of the study was to examine the effects of low to moderate doses of commonly prescribed therapeutic agents on mood and behavior; 12 drugs including diazepam and buspirone were listed on the consent form. Subjects were told that throughout the study they would receive only two of the drugs listed on the consent form or one of the drugs and an inactive placebo, but they were not told specifically which drug(s) they would receive. Instead, the two drugs were identified by letter codes (e.g., Drug A or B) that were unique for each subject. Subjects were told that they would receive only one of the two drugs each experimental day, but the drugs could be randomly changed across days. To discourage communication between subjects about their drugs and drug effects, they were told that different subjects might receive different drugs.

General procedures. Subjects participated as

outpatients at the Behavioral Pharmacology Research Unit of the Johns Hopkins University School of Medicine. Subjects reported to the research laboratory 3 to 5 days per week (Monday through Friday). Subjects were asked to report to the laboratory at approximately the same time each day throughout the experiment. On experimental days, subjects reported to the laboratory and completed the self-report mood questionnaire (requiring approximately 5 to 10 min), orally ingested a capsule under double-blind conditions, and then left the laboratory. Thus, subjects remained at the laboratory approximately 10 to 15 min. Subjects were instructed to complete the drug-identification and self-report mood questionnaire 1 and 2 hr after drug ingestion, and were instructed to return the completed questionnaires to the laboratory at their next scheduled session. Approximately 2 hr after drug ingestion, subjects telephoned the laboratory and reported their drug identification by letter code. Subjects were then told immediately whether their identification was correct or incorrect.

Before drug-discrimination training, each subject received a single administration of their training drug (i.e., either 10 mg of diazepam or 15 mg of buspirone) to screen for possible adverse effects that would contraindicate research participation. One subject (B08) experienced nausea following the administration of 15 mg of buspirone. That subject was subsequently given 10 mg of buspirone and did not experience any further adverse effects. That dose of buspirone was used in the subsequent drug-discrimination procedures for that subject.

Drug-Discrimination Procedures

Sampling phase. All subjects received four sampling sessions (two sessions of active drug and two sessions of placebo). Active drug and placebo were administered in mixed order. Subjects reported to the laboratory and completed a self-report mood questionnaire (described below). Subjects then ingested a capsule that was identified to them by letter code (e.g., Drug A or B) at the time of ingestion and then left the laboratory. During this phase, subjects were instructed to pay attention to the way the capsules made them feel and to associate this with the letter code, because, in subsequent sessions, they would be paid for correctly identifying the drugs. Subjects were instructed to complete the self-report mood questionnaire 1 and 2 hr after drug administration. Separate groups of subjects were exposed to diazepam and placebo or buspirone and placebo. Subjects were assigned to the two groups (i.e., diazepam or buspirone) sequentially.

Test-of-acquisition phase. Following the sampling sessions, a test-of-acquisition phase was conducted. The test-of-acquisition phase consisted of 10 sessions for all subjects except D09, who completed only nine sessions. On the test-of-acquisition days, subjects ingested a capsule under double-blind conditions but were not told which drug they had received. During this phase, subjects were instructed to complete the drug-identification questionnaire 1 and 2 hr after drug administration. Subjects were first asked to identify which drug they had received by letter code. Subjects were instructed that they could change their identification between Hour 1 and Hour 2 based on what they believed at the time. Subjects were instructed to telephone the laboratory immediately after completing the drug-identification questionnaire at the 2-hr observation, identify themselves, and report their final drug identification by letter code (no monetary consequences were attached to completion of the written questionnaire). Subjects were told whether each verbal drug identification was correct or incorrect, and for each correct identification $10.00 was credited towards a bonus. The criterion for having acquired the discrimination was at least 80% correct identifications. Order of administration of drug and placebo was quasi-random, and all subjects received active drug on five or six occasions.

Low-dose generalization phase. Six subjects in the diazepam group (D01, D03, D06, D08, D09, D10) and 6 subjects in the buspirone group (B01, B03, B04, B07, B08, B09) participated in a low-dose generalization phase to determine whether other doses of the training drug shared discriminative stimulus effects with the training dose. The low-dose generalization phase consisted of test days interspersed with test-of-acquisition days. Approximately half the days were test days, and the other half were test-of-acquisition days. Before beginning the low-dose generalization

phase, subjects were instructed that there would be days on which they would not be given any feedback concerning the accuracy of their drug identification, and that these days would be designated as test days. Subjects were also instructed that on these days they would be credited with $10.00 independent of their identification. Thus, test days were identical to test-of-acquisition days except that subjects did not receive any feedback as to which drug they had ingested and they always received the monetary bonus independent of their drug identification. Subjects were not told the purpose of test days, nor did they know when test days were scheduled until after their verbal drug identification. On test days, subjects in the diazepam group received 0, 2.5, 5.0, or 10.0 mg, and subjects in the buspirone group received 0, 3.75, 7.5, or 15 mg (Subject B08 received 0, 2.5, 5.0, or 10 mg of buspirone). Placebo and the training dose of diazepam or buspirone were included as test conditions to insure that subjects did not learn that they would always receive something other than the two training drugs on test days and also to evaluate the two training drugs under conditions identical to those of the test doses. Test doses were administered four to seven times each in quasi-random order.

In order to determine whether subjects maintained the discrimination throughout the testing phase, test-of-acquisition days were intermixed among test days in a quasi-random sequence. These test-of-acquisition days were identical to those in the test-of-acquisition phase (i.e., subjects received their training drug or placebo, were informed whether their verbal drug identification was correct, and received bonus money contingent on correct identifications). If a subject responded incorrectly on a test-of-acquisition day, the subject received additional test-of-acquisition days. Additional test-of-acquisition days continued until the subject correctly identified both conditions (i.e., the training dose and placebo). In general, no more than two additional test-of-acquisition days were required. These additional test-of-acquisition days were omitted from all analyses.

Low-dose training phase. Seven subjects in the diazepam group (D01, D02, D03, D04, D05, D06, D07) and 6 subjects in the buspirone group (B01, B02, B03, B04, B05, B06) participated in the low-dose training phase in which the training dose was progressively decreased until discrimination accuracy fell below the criterion. Each subject was exposed to each dose for 10 to 30 sessions. During the first 10 sessions at each dose, significant discrimination was defined as making the correct verbal identification on at least 8 of 10 (i.e., 80%) occasions. If discrimination accuracy was $\geq$80%, the dose was decreased by half. If discrimination accuracy was $<$80%, the number of sessions was extended in blocks of 10 sessions up to a maximum of 30 sessions. When the number of sessions was extended, significant discrimination was defined as at least 15 correct identifications during the last 20 sessions. If the criterion was not met by 30 sessions, the subject was considered to have completed the experiment. One subject (B01) in the buspirone group met the criterion after 20 sessions at 1.87 mg but was unable to complete additional sessions for reasons unrelated to the study. To help to maintain continued subject participation during the low-dose training phase, the bonus payment for correct drug identifications was increased to $15.00 when doses $\leq$2.5 mg of diazepam and $\leq$3.75 mg of buspirone were tested.

Self-Report Mood Questionnaire

The self-report mood questionnaire consisted of two parts, and was used to assess subject-rated drug effects. The first part was comprised of two questions. Subjects were asked to rate the strength of drug effect on a 5-point scale (0 = *I feel no effect from the drug at all,* 4 = *I feel a very strong drug effect*). Subjects were then asked to rate liking of the drug effect on a 9-point scale (0 = *I dislike the drug effect very much,* 4 = *I neither dislike nor like the drug effect* [neutral], 8 = *I like the drug effect very much*). The second part consisted of six items that assessed current mood and behavior. Subjects rated each item on a 5-point scale (0 = *not at all,* 1 = *a little,* 2 = *moderately,* 3 = *quite a bit,* 4 = *extremely*). The questionnaire items were drowsy/sleepy; tense/nervous; feel like talking; able to concentrate; clumsy/uncoordinated; and calm/relaxed. Subjects completed both parts of the questionnaire immediately before ingesting the drug and were instructed

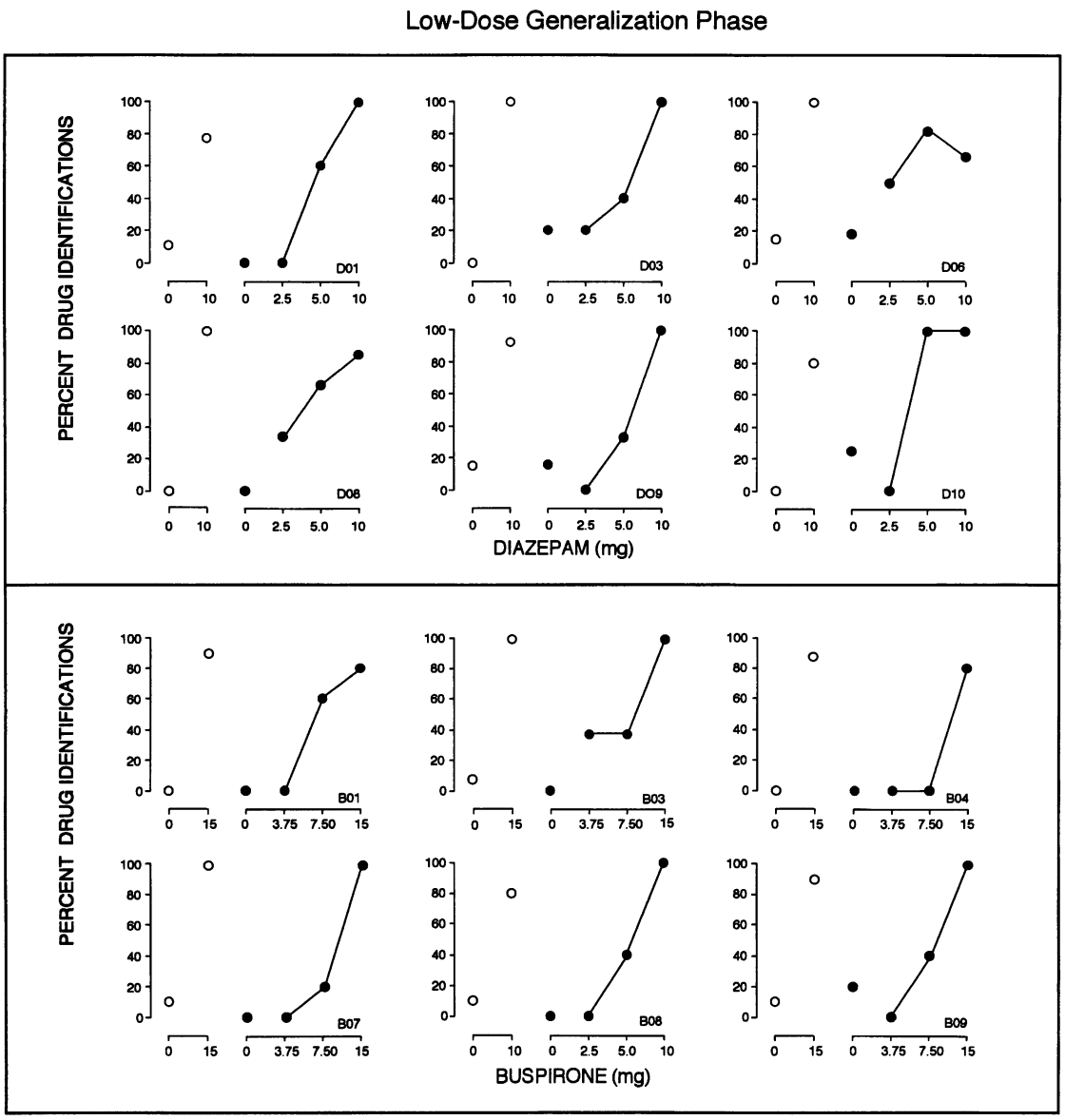
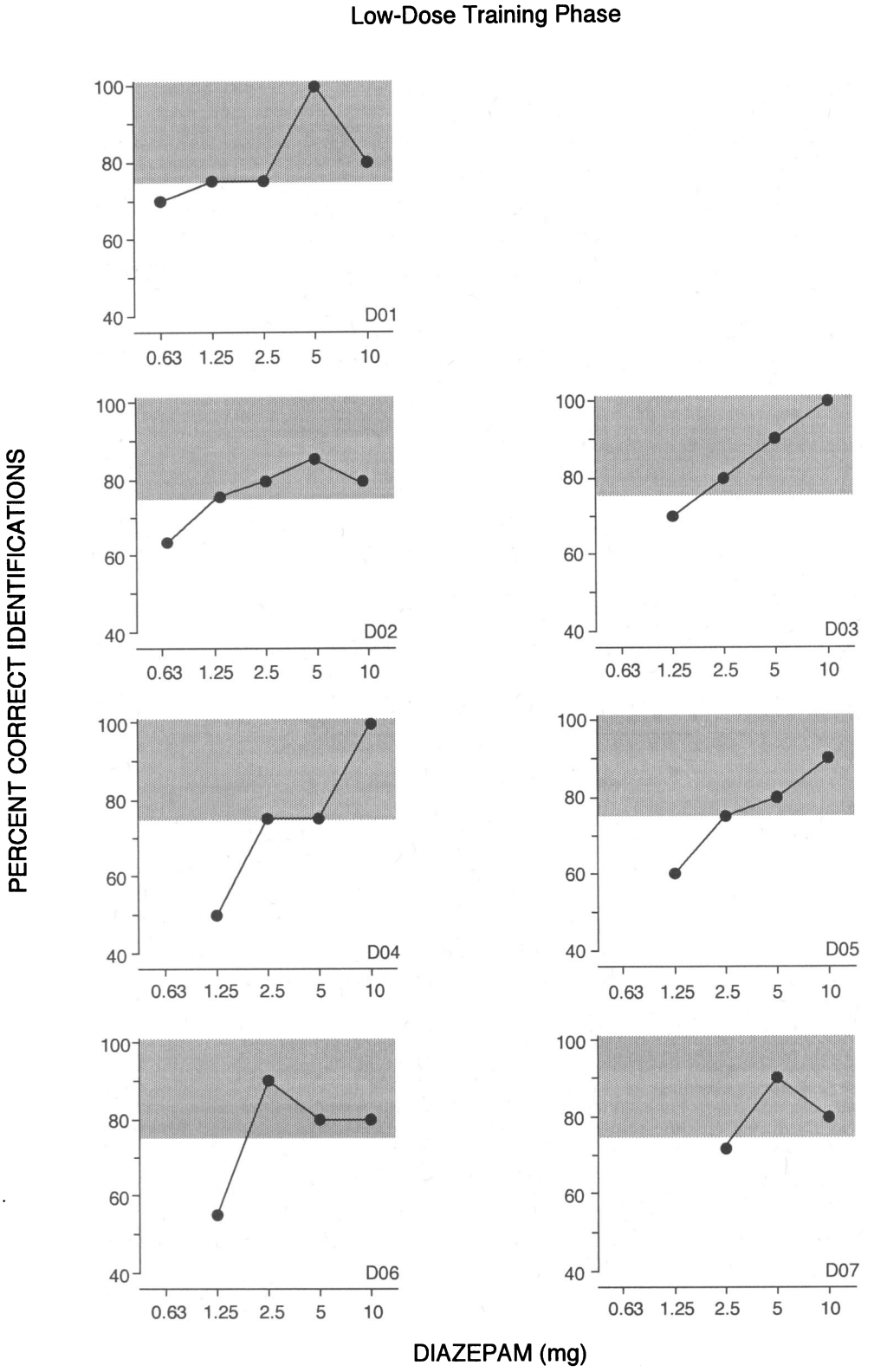


Fig. 1. Percentage drug identification as a function of training condition and test dose in each of the 6 subjects in the diazepam group and the 6 subjects in the buspirone group who participated in the low-dose generalization phase. Vertical axes: percentage of drug identifications reported by telephone 2 hr after capsule administration; horizontal axes: dose (mg). For each individual subject panel, open symbols show mean data for all training sessions (n = 18 to 27) during the dose–response testing phase (i.e., placebo data are plotted above 0/drug; drug data are plotted above the training dose). Filled symbols show the percentage of drug identifications at each dose during the low-dose generalization phase; each dose was tested four to seven times in each subject.

to complete them again 1 and 2 hr after drug ingestion. At the 2-hr observation, subjects were instructed to complete the questionnaire immediately before telephoning the research unit to report their verbal drug identification.

Payments

Subjects were paid for their participation. Each subject earned a base pay of $6.00 per session. As described above, subjects received bonus payments for correct verbal drug iden-


Low-Dose Training Phase
PERCENT CORRECT IDENTIFICATIONS
100
80
60
40
D01
D02
D03
D04
D05
D06
D07
0.63 1.25 2.5 5 10
DIAZEPAM (mg)

tifications on test-of-acquisition days and for all drug identifications on test days. The base pay was paid weekly, and the bonus payment for correct verbal drug identifications was paid after each subject completed participation in the experiment. Subjects also earned a $50.00 bonus for completing the experiment and complying with all the requirements.

Capsule Preparation and Administration Procedures

During each session, subjects orally ingested a capsule under staff supervision. Each capsule was taken with 150 ml of water. Drug-administration procedures were designed to ensure that subjects swallowed the capsules and did not open them in their mouths and taste the contents. To accomplish this the research assistant (a) watched the subject to ensure that he or she swallowed and did not remove the capsule from his or her mouth and (b) spoke with the subject in order to determine if the subject had anything in his or her mouth. Subjects were instructed not to ingest food for 1 hr before and after capsule administration.

Data Analysis

Drug discrimination. Written and verbal drug identifications were generally similar at 1 and 2 hr. For purposes of data analysis, the 2-hr verbal drug identification was used because the written identification was obtained under unsupervised conditions. For each subject, discrimination accuracy was analyzed using the binomial probability distribution. Significant discrimination was defined as making the correct letter identification on at least 8 of the first 10 sessions or on at least 15 of the last 20 sessions. These criteria were chosen because they represent the threshold for statistical significance.

Self-report mood questionnaire. Self-report mood questionnaire data were analyzed for each subject. In the low-dose generalization phase, peak effect (i.e., the postdrug value representing the greatest change from predrug value) was determined and analyzed with analyis of variance (ANOVA), with dose (placebo, 2.5, 5.0, and 10 mg of diazepam or placebo, 3.75, 7.5, and 15 mg of buspirone) as a between-session factor. Another ANOVA was conducted on peak-effect data from the training days during the low-dose generalization phase, with dose (placebo or active drug) as the between-session factor. Finally, two sets of ANOVAs with dose (placebo versus active drug) as the between-session factor were conducted on peak-effect data from the training and low-dose training phases.

Analyses of the group data were conducted to further examine drug effects on the self-report mood questionnaire. In the low-dose generalization phase, for each subject, average peak-effect data were calculated for all exposures to a dose (i.e., placebo, 2.5, 5.0, and 10 mg of diazepam or placebo, 3.75, 7.5, and 15 mg of buspirone). Group data were analyzed with a repeated measures ANOVA, with dose (placebo, 2.5, 5.0, and 10 mg of diazepam or placebo, 3.75, 7.5, and 15 mg of buspirone) as the factor. Post hoc comparisons were then conducted using Dunnett's test to determine which doses of active drug (2.5, 5.0, and 10 mg of diazepam or 3.75, 7.5, and 15 mg of buspirone) differed significantly from placebo. Another ANOVA was conducted on peak-effect data from the training days during the low-dose generalization phase, with dose (placebo or active drug) as the between-session factor. Finally, two sets of ANOVAs with dose (placebo versus active drug) as the between-session factor were conducted on peak-effect data from the training and low-dose training phases. For all statistical analyses, effects were considered significant for $p \leq .05$. For repeated measures ANOVAs, Huynh-Feldt corrected p values were used.

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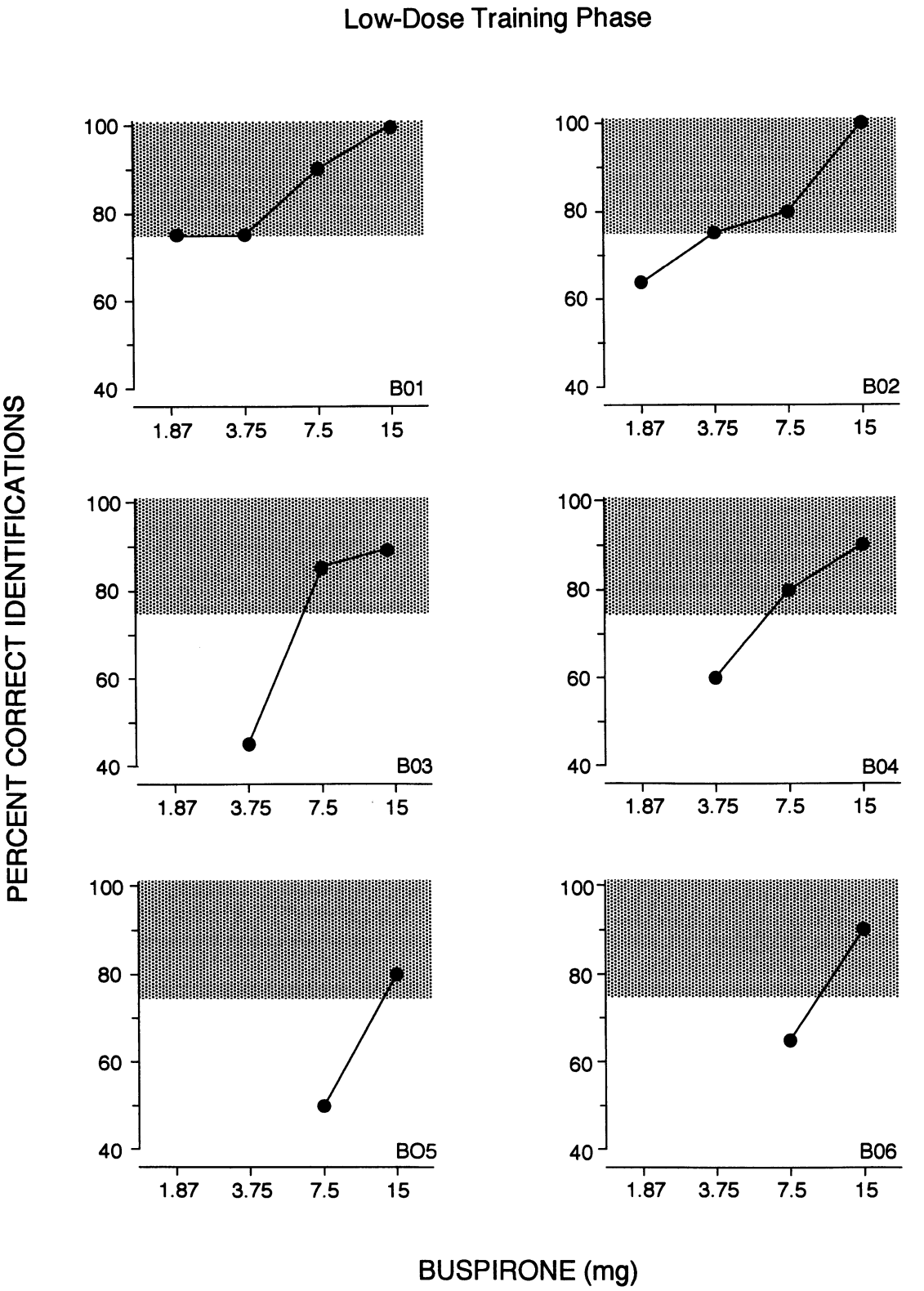
Fig. 2. Diazepam versus placebo discrimination accuracy as a function of dose in each of the 7 subjects who participated in the low-dose training phase. Vertical axes: percentage of correct identifications; horizontal axes: dose (mg), log scale. Data are based on drug identifications reported by telephone 2 hr after capsule administration for either the first 10 sessions (i.e., occasions on which accuracy was ≥80%) or the last 20 sessions. Data points overlapping the shaded area indicate statistically significant discrimination performance ($p \leq .05$). Doses were studied in decreasing order. Data from the 10-mg condition represent discrimination accuracy from the 10 sessions in the initial test-of-acquisition condition.


Low-Dose Training Phase
PERCENT CORRECT IDENTIFICATIONS
100
80
60
40
B01
B02
B03
B04
BO5
B06
1.87
3.75
7.5
15
BUSPIRONE (mg)

RESULTS

Drug Discrimination

Test-of-acquisition phase. All subjects in both groups showed significant discrimination performance (i.e., ≥80% correct identifications) during the first 10 sessions of the test-of-acquisition phase. Overall mean discrimination accuracy was 91% (range, 80 to 100%) for the diazepam group and 91% (range, 80 to 100%) for the buspirone group.

Low-dose generalization phase. Accurate discrimination performance was maintained on the test-of-acquisition days that were interspersed among the test days in the low-dose generalization phase in both groups. Placebo and drug were correctly identified on >90% of the training days (Figure 1, open symbols: Placebo occasioned the drug identification on <10% of the days in contrast to the active drug, which occasioned the drug identification on >90% of the test-of-acquisition days).

Percentage of drug identifications generally increased as a function of dose in all subjects in the diazepam and buspirone groups (Figure 1). Placebo, 2.5, 5, and 10 mg of diazepam produced a mean of 13, 17, 64, and 92% diazepam identifications, respectively. Placebo, 3.75, 7.5, and 15 mg of buspirone produced a mean of 0, 7, 33, and 93% buspirone identifications, respectively. For Subject B08, placebo, 2.5, 5, and 10 mg of buspirone produced 0, 0, 40, and 100% buspirone identifications, respectively.

Low-dose training phase. Subjects in the diazepam group varied in the lowest dose at which significant discrimination was maintained, but all subjects were able to discriminate at least one dose lower than that used in the test-of-acquisition phase (Figure 2). Two subjects (D01, D02) discriminated 1.25 mg of diazepam, 4 subjects (D03, D04, D05, D06) discriminated 2.5 mg of diazepam, and 1 subject (D07) discriminated 5 mg of diazepam. Subjects in the buspirone group also varied in the lowest dose at which statistically significant discrimination was maintained (Figure 3). One subject (B01) discriminated 1.87 mg of buspirone, but, as noted above, was unable to complete additional sessions for reasons unrelated to the study. One subject (B02) discriminated 3.75 mg of buspirone, 2 subjects (B03, B04) discriminated 7.5 mg of buspirone, and 2 subjects (B05, B06) discriminated 15 mg of buspirone.

Comparison of low-dose generalization phase and low-dose training phase. Figure 4 shows data from the 3 subjects in the diazepam group (D01, D03, D06) and the 3 subjects in the buspirone group (B01, B03, B04) who completed both the low-dose generalization phase and the low-dose training phase. For each subject, the dose–response function for percentage of drug identifications was shifted leftward in the low-dose training phase relative to the low-dose generalization phase. Moreover, for each subject, there was at least one dose that consistently occasioned drug identifications (i.e., ≥75% drug identifications) in the low-dose training phase but not in the low-dose generalization phase.

Self-Report Mood Questionnaire

Low-dose generalization phase. Figure 5 shows results from the analysis of group data on the self-report mood questionnaire. Both diazepam and buspirone produced increases in ratings of drug strength and clumsy/uncoordinated. Dose-related differences also emerged between the two drugs. Diazepam, but not buspirone, significantly increased ratings of drowsy/sleepy and decreased ratings of able to concentrate. By contrast, buspirone, but not diazepam, significantly increased ratings of tense/nervous and decreased ratings of calm/relaxed. Table 1 shows the results from the individual-subject analyses. These data show differences across subjects with respect to the number of items significantly affected. For example, D06 in the diazepam group and B03 in the buspirone group showed no statistically significant effects, whereas D01 and D03 in the diazepam group and B01 and B04 in the buspi-

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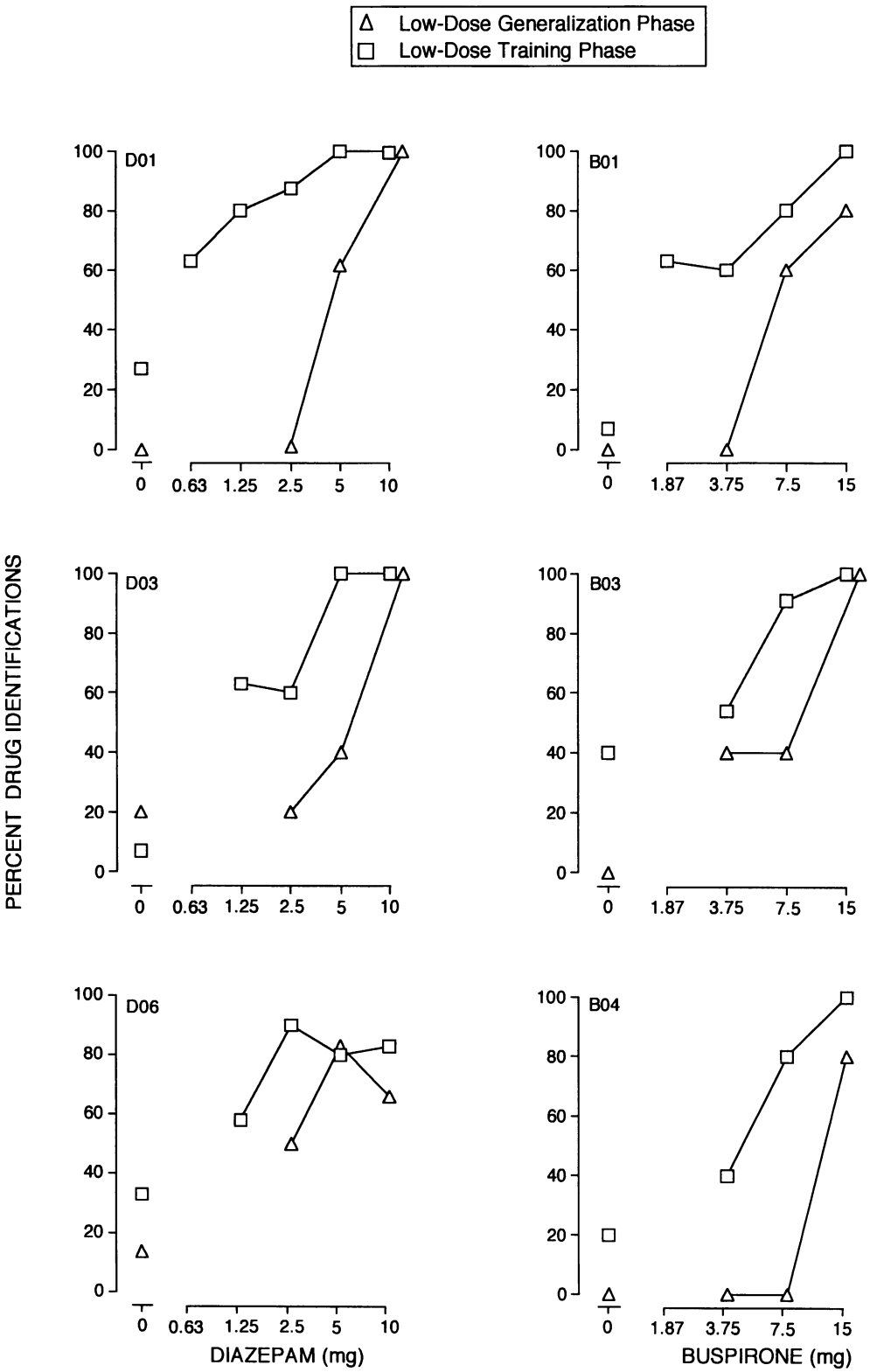
Fig. 3. Buspirone versus placebo discrimination accuracy as a function of dose in each of the 6 subjects who participated in the low-dose training phase. Data from the 15-mg condition represent discrimination accuracy from the 10 sessions in the initial training condition. Other details are the same as in Figure 2.


Low-Dose Generalization Phase
Low-Dose Training Phase
PERCENT DRUG IDENTIFICATIONS
D01
B01
D03
B03
D06
B04
100
80
60
40
20
0
0
0.63
1.25
2.5
5
10
1.87
3.75
7.5
15
DIAZEPAM (mg)
BUSPIRONE (mg)

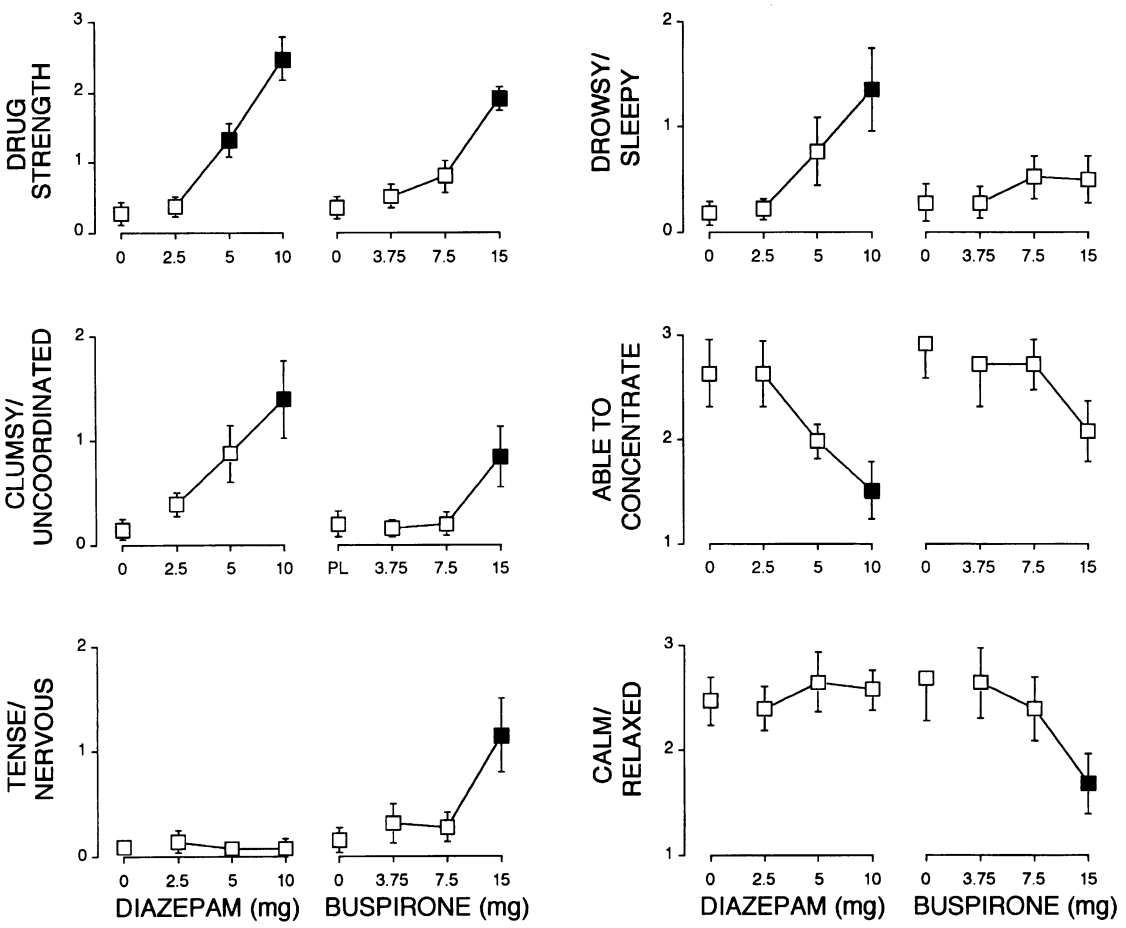


Fig. 5. Peak effects on subject ratings of drug strength, drowsy/sleepy, clumsy/uncoordinated, able to concentrate, tense/nervous, and calm/relaxed are shown for the group of 6 subjects tested at placebo, 2.5, 5, and 10 mg of diazepam and the 5 subjects tested at placebo, 3.75, 7.5, and 15 mg of buspirone in the low-dose generalization phase. Vertical axes: peak effect subject rating; horizontal axes: dose of diazepam (mg) and buspirone (mg). Data points are means; brackets show ±1 *SEM*; upper bracket has sometimes been deleted for clarity; absence of brackets indicates 1 *SEM* fell within the area of the symbol. Filled symbols are significantly different from placebo (Dunnett's test, $p \leq .05$). Subject ratings of drug liking and feel like talking are not presented, because analyses of the group data showed no significant effects of either drug.

rone group showed significant effects on at least six of the eight items. Despite these differences, inspection of Table 1 shows that the individual analyses were generally consistent with the results from the group analyses. The results on the self-report mood questionnaire from the low-dose generalization phase were qualitatively similar to those observed during

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Fig. 4. Percentage of drug identifications as a function of drug dose for diazepam (left column) and buspirone (right column) in each of the 6 subjects who participated in both the low-dose generalization and the low-dose training phases. Vertical axes: percentage of drug identifications reported by telephone 2 hr after capsule administration; horizontal axes: dose (mg), log scale. Triangles represent data from the low-dose generalization phase (replotted from Figure 2). Squares represent data from the low-dose training phase. Drug data points are means from drug days only; placebo (i.e., 0 mg) data points are means collapsed across all dose conditions.

Table 1

Summary of statistical results on the self-report mood questionnaire during the low-dose generalization phase. Column 2 presents group data. Columns 3 to 8 display individual-subject data; subject codes are indicated at the top of each column. Arrows indicate a statistically significant effect of drug dose, and dashes indicate no significant effect. Direction of the drug effect relative to placebo is indicated by the direction of the arrows. Data are from the test days.

Diazepam							
	Group	D01	D03	D06	D08	D09	D10
Drug strength	↑	↑	↑	—	↑	↑	↑
Drug liking	—	↓	↓	—	—	↓	↑
Drowsy/sleepy	↑	↑	↑	—	—	↑	—
Clumsy/uncoordinated	↑	↑	↑	—	—	—	—
Able to concentrate	↓	↓	↓	—	↓	—	↓
Tense/nervous	—	—	—	—	—	—	—
Calm/relaxed	—	—	—	—	↑	—	—
Feel like talking	—	↓	↓	—	—	—	—
Buspirone							
		B01	B03	B04	B07	B08	B09
Drug strength	↑	↑	—	↑	—	↑	↑
Drug liking	—	—	—	↓	↓	—	↓
Drowsy/sleepy	—	↑	—	—	—	—	—
Clumsy/uncoordinated	↑	↑	—	↑	—	—	↑
Able to concentrate	—	↓	—	↓	↓	—	—
Tense/nervous	↑	↑	—	↑	—	—	↑
Calm/relaxed	↓	↓	—	↓	—	—	↓
Feel like talking	—	—	—	↓	—	—	—

the test-of-acquisition phase and on the training days interspersed among the test days during the low-dose generalization phase (data not shown).

Low-dose training phase. Analysis of data from the self-report mood questionnaire revealed that the lowest discriminable dose of diazepam significantly increased subject ratings of drug strength for the group and for 5 of 7 subjects (D01, D02, D03, D04, D07) and produced a small but significant decrease in another (D06). Similarly, the lowest discriminable dose of buspirone significantly increased subject ratings of drug strength for the group and for 4 of 6 subjects (B01, B02, B04, B05). The only other significant effect for the group was that buspirone decreased ratings of feel like talking.

Comparison of low-dose generalization phase and low-dose training phase. Figure 6 shows drug-strength ratings from the 3 subjects in the diazepam group (D01, D03, D06) and the 3 subjects in the buspirone group (B01, B03, B04) who completed both the low-dose generalization and the low-dose training phases. The dose–response function for ratings of drug strength tended to be shifted leftward in the low-dose training phase relative to the low-dose generalization phase. However, this shift was of smaller magnitude than that observed with discrimination performance (cf. Figures 4 and 6).

DISCUSSION

The present study trained and tested the discriminative stimulus effects of diazepam

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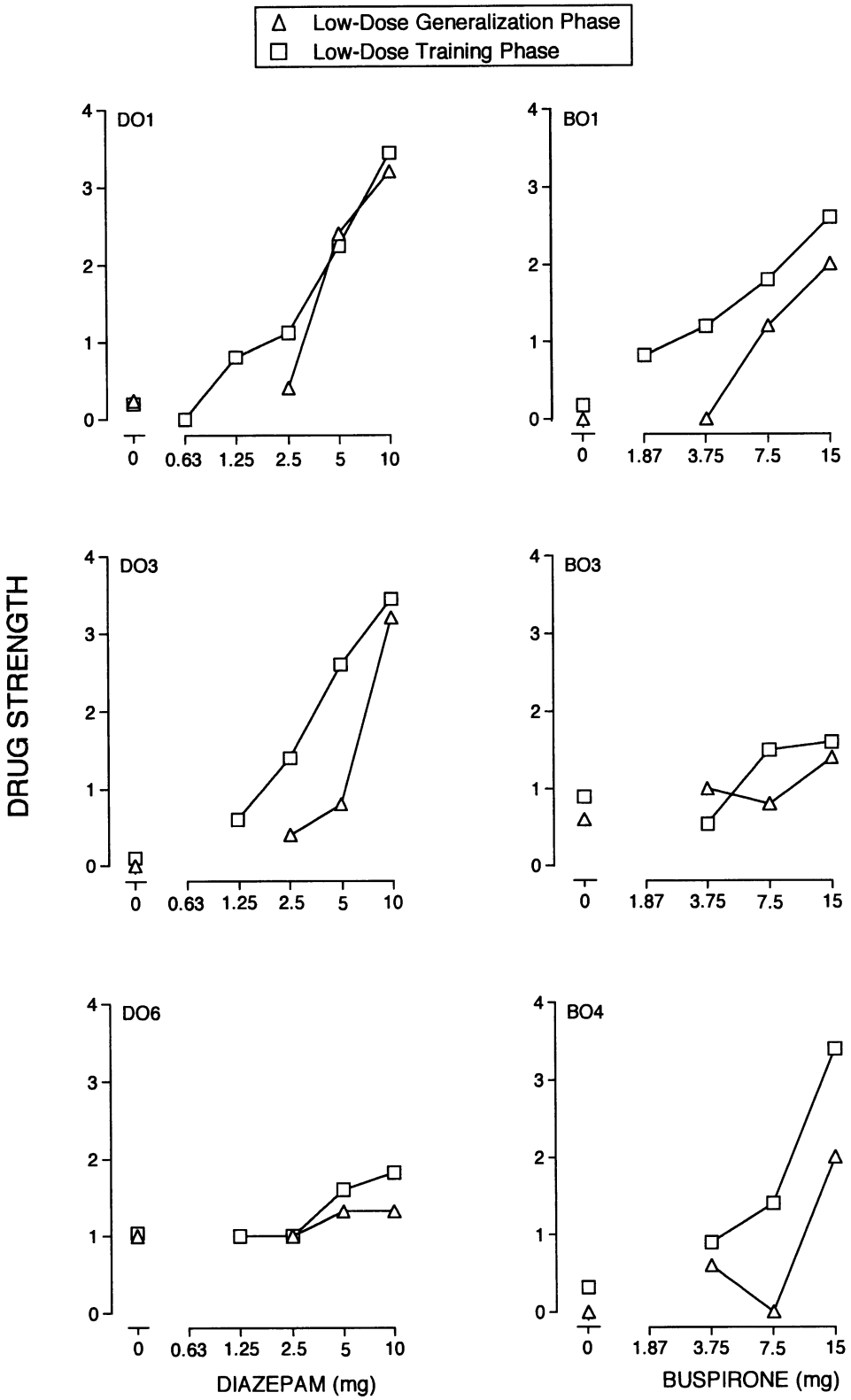
Fig. 6. Subject ratings of drug strength as a function of drug dose for diazepam (left column) and buspirone (right column) in each of the 6 subjects who participated in both the low-dose generalization and the low-dose training phase. Vertical axes: peak effect on subject ratings of drug strength; horizontal axes: dose (mg), log scale. Other details are the same as in Figure 4.


Low-Dose Generalization Phase
Low-Dose Training Phase
DO1
BO1
DO3
BO3
DO6
BO4
DRUG STRENGTH
0
1
2
3
4
0 0.63 1.25 2.5 5 10
0 1.87 3.75 7.5 15
DIAZEPAM (mg)
BUSPIRONE (mg)

and buspirone in separate groups of human subjects. The discriminations of diazepam versus placebo and buspirone versus placebo were acquired by all subjects. A subsequent low-dose generalization phase showed that across a four-fold range of doses, both diazepam and buspirone produced dose-related increases in drug identifications. The interspersing of test-of-acquisition days between test days in the low-dose generalization phase showed that the drug versus placebo discrimination was maintained in all subjects. In a final phase, the discriminative stimulus effects of progressively lower doses of diazepam and buspirone were examined. The median lowest discriminable dose of diazepam was 2.5 mg (range, 1.25 to 5 mg), and the median lowest discriminable dose of buspirone was 7.5 (range, 1.87 to 15 mg) in the low-dose training phase.

The present study demonstrated that the discriminative stimulus effects of both diazepam and buspirone are readily trained. In previous studies that specifically examined the discriminative stimulus effects of diazepam and buspirone, approximately 70 to 90% of the subjects were able to discriminate 10 mg of diazepam versus placebo (Johanson, 1991a, 1991b), and approximately 50% of the subjects were able to discriminate 15 mg of buspirone versus placebo (Johanson, 1993). In the present study, all of the subjects in both the diazepam and the buspirone groups were able to discriminate between drug and placebo. The reason that more subjects were able to discriminate between drug and placebo in the present study is unknown, but may be due to different methods. Subjects completed self-reported mood questionnaires and recorded their drug identifications at various times after drug administration in both the prior and the present studies, but only the 6-hr drug identification in the prior studies and the 2-hr drug identification in the present study were differentially reinforced. The peak behavioral effects of diazepam and buspirone typically occur approximately 1 to 2 hr after oral administration and abate by 4 to 5 hr after oral administration (Griffiths, McLeod, Bigelow, Liebson, & Roache, 1984; Johanson & Uhlenhuth, 1980; Patat, Klein, Hucher, & Granier, 1988; Troisi et al., 1993). Thus, subjects in the prior studies likely made their discrimination based on a recollection of the drug effect. By contrast, subjects in the present study likely made their discrimination while they were still experiencing a significant drug effect. The relationship between the acquisition of discrimination of a drug versus placebo and the proximity of the drug identification to the peak effect of the drug should be examined experimentally.

Data from the low-dose training phase demonstrated behavioral activity of diazepam and buspirone at oral doses lower than those previously shown to affect the behavior of normal volunteers. The median lowest discriminable dose of diazepam was 2.5 mg (range, 1.25 to 5 mg), and the median lowest discriminable dose of buspirone was 7.5 (range, 1.87 to 15 mg). In contrast, the results from the low-dose generalization phase as well as from previous investigations of the behavioral activity of diazepam in normal volunteers have often failed to find significant effects of diazepam doses $\leq$5 mg (e.g., de Wit, Uhlenhuth, & Johanson, 1985; Higgins, Bickel, O'Leary, & Yingling, 1987; Higgins & Stitzer, 1990; Rodrigo & Lusiardo, 1988) and buspirone doses $\leq$10 mg (e.g., Barbee et al., 1992; Lader, 1982; Mattila et al., 1986).

The present study used an intensive within-subject design with individual-subject data analysis, whereas most previous human drug-discrimination studies have relied on analyses of group data. Group designs offer the advantage of reducing the number of drug exposures for an individual subject, but data from these studies often imply homogeneous drug effects. In the present study, the use of a within-subject design with repeated observations obtained at each drug condition allowed both homogeneous and heterogeneous drug effects to be observed. Homogeneous drug effects were observed in the test-of-acquisition phase, in that all subjects showed significant discrimination performance during the first 10 sessions. Similarly, in the low-dose generalization phase, the dose–response functions were similar across individual subjects. By contrast, heterogeneous drug effects were observed in the low-dose training phase, in that individual subjects varied in terms of the lowest dose of drug that they could discriminate (i.e., range of 1.25 to 5 mg diazepam; range of 1.87 to 15 mg buspirone). Individual differences in the lowest discrim-

inable dose have been reported previously with caffeine and theobromine (Griffiths et al., 1990; Mumford et al., 1994; Silverman & Griffiths, 1992). The homogeneous and heterogeneous drug effects observed in the present study argue for the use of within-subject designs in future drug-discrimination studies with humans.

The present study provides provocative data suggesting that the behavioral contingencies influence the discriminability of low to intermediate drug doses. As illustrated in Figure 4, for each of 6 subjects who participated in both the low-dose generalization phase and the low-dose training phase, the dose–response function for percentage of drug identifications was shifted leftward in the low-dose training phase relative to the low-dose generalization phase. This shift could be attributable to the increased monetary bonus that was used when low doses (i.e., ≤2.5 mg diazepam and ≤3.75 mg of buspirone) were tested in the low-dose training phase. However, inspection of the data shows that the shift included 5 mg of diazepam and 7.5 mg of buspirone, doses at which the monetary bonus was the same in both the low-dose generalization and low-dose training phases. Alternatively, this shift could be due to a practice effect, because the low-dose training phase always followed the low-dose generalization phase. However, inspection of data from the low-dose generalization phase indicated that there was not an increasing trend in drug identifications across the sequential exposures to the test doses. Consistent with this lack of a practice effect, a previous study with caffeine provided no evidence for increasing sensitivity across a 5- to 9-month study period (Evans & Griffiths, 1991). The most parsimonious interpretation is that the shift observed in Figure 4 was due to procedural differences between the low-dose training phase and low-dose generalization phase. In the low-dose training phase, correct identifications with lower doses were explicitly reinforced, whereas in the low-dose generalization phase, responses to lower doses were not explicitly reinforced.

A leftward shift in the dose–response function was also observed with subject ratings of drug strength in the low-dose training phase versus the low-dose generalization phase. However, this shift was of a smaller magnitude than that observed with discrimination performance, and was rather unconvincing in half the subjects. These findings suggest that the shift in the dose–response function observed with discrimination performance in the low-dose training phase relative to the low-dose generalization phase was not due entirely to an overall increased sensitivity to the drug effects. This further suggests that the explicit reinforcement of progressively lower drug doses in the low-dose training phase accounts for the shift in the dose–response functions.

The demonstration of a covariation of subject ratings and discrimination performance after explicit reinforcement of the discrimination performance but not the subject ratings suggests a possible functional relationship between subject ratings and discrimination performance. Previous studies with human subjects have generally shown a rather good relationship between subject ratings and discriminative effects (Griffiths & Mumford, in press; Preston & Bigelow, 1991), but to our knowledge no previous study has examined subject-rated effects after experimentally manipulating discriminative performance. Thus, the present findings provide the clearest experimental demonstration to date that discriminative stimulus and subject-rated effects of drugs overlap. However, it should be noted that the leftward shift observed with subject ratings of drug strength was generally smaller in magnitude than that observed with discrimination performance (cf. Figures 4 and 6). This observation suggests that the discriminative stimulus and subject-rated effects of drugs are not completely isomorphic.

The leftward shift of the diazepam and buspirone dose–response functions in the low-dose training versus the low-dose generalization phase is consistent with preclinical pharmacology studies that trained rats to discriminate between saline and progressively lower doses of the training drug (Colpaert, Niemegeers, & Janssen, 1980; Overton, 1979; Zenick & Goldsmith, 1981). In one experiment, for example, rats were trained to discriminate between fentanyl (0.04 mg/kg) and saline (Colpaert et al., 1980). Following the acquisition of this discrimination, the rats were trained to discriminate progressively lower doses of fentanyl. The median lowest

discriminable dose of fentanyl was 0.004 mg/kg (range, 0.04 to 0.00125). Low-dose generalization testing indicated that the fentanyl dose response for the percentage of animals selecting the drug lever was shifted progressively leftward as the training dose was systematically decreased. These findings suggest that doses of drug not previously discriminable may come to function as discriminative stimuli when explicit behavioral contingencies are imposed.

The data from the low-dose training phase have implications for the relative discriminability of diazepam and buspirone during clinical treatment. A recent review of clinical studies comparing the efficacy of diazepam and buspirone in the treatment of anxiety suggests that the two compounds are approximately equally potent (Hollister, Muller-Oerlinghausen, Rickels, & Shader, 1993). The present data showing a three-fold potency difference between diazepam and buspirone in the median lowest discriminable dose (i.e., 2.5 mg of diazepam vs. 7.5 mg of buspirone) suggest that, at commonly used clinical doses, patients may be able to more readily detect the acute effects of diazepam than those of buspirone.

The present findings showed that despite some similar effects (e.g., increases in ratings of drug strength and clumsy/uncoordinated), diazepam and buspirone produced some clearly different self-reported effects. Diazepam, but not buspirone, significantly increased ratings of drowsy/sleepy and decreased ratings of ability to concentrate; this difference is consistent with previous reports (for a review, see Goa & Ward, 1986). Buspirone, but not diazepam, significantly increased subject ratings of tense/nervous and decreased ratings of calm/relaxed. These findings are consistent with clinical studies that reported nervousness to be a side effect of buspirone (Newton, Marunycaz, Alderdice, & Napoliello, 1986; Rickels, Amsterdam, Clary, Puzzuoli, & Schweizer, 1991), and with several clinical case reports suggesting that buspirone induced jitteriness, mania, or sleep disruption (Liegghio & Yeragani, 1988; Liegghio, Yeragani, & Moore, 1988; McDaniel, Ninan, & Magnuson, 1990; McIvor & Sinanan, 1991; Price & Bielefield, 1989; Troisi et al., 1993). To the extent that self-reported drug effects and discriminative stimulus effects covary (for a review, see Preston & Bigelow, 1991), the present findings are consistent with the assumption that diazepam and buspirone might not share discriminative stimulus effects. The present study, unfortunately, did not test buspirone in diazepam-trained subjects, nor did it test diazepam in buspirone-trained subjects. Thus, it is not known whether buspirone would have been identified as diazepam in diazepam-trained subjects, or whether diazepam would have been identified as buspirone in buspirone-trained subjects. In support of the position that diazepam and buspirone might not share discriminative stimulus effects are findings from the preclinical laboratory showing that buspirone does not occasion significant drug-appropriate responding in nonhumans trained to discriminate between a benzodiazepine and no drug (Ator & Griffiths, 1986; Evans & Johanson, 1989; Hendry et al., 1983; Spealman, 1985), nor do benzodiazepines occasion significant drug-appropriate responding in nonhumans trained to discriminate between buspirone and no drug (Hendry et al., 1983; Mansbach & Barrett, 1987).

Curiously, in the two published studies with human subjects that trained diazepam and buspirone as discriminative stimuli and then tested the other drug, diazepam and buspirone were found to share discriminative stimulus effects (Johanson, 1991a, 1993). The reasons for the differences between the Johanson studies and preclinical results are not known. Johanson (1993) speculated that the discrimination in nonhumans might be mediated via a specific receptor mechanism, but the discrimination in humans may be related to the general therapeutic action of the drugs. However, a more parsimonious explanation may be that the methods used by Johanson were not sufficiently sensitive to differentiate diazepam and buspirone. For example, when more sensitive drug-discrimination procedures (e.g., the novel-response procedure of Bickel et al., 1993) are used, differences between benzodiazepines and buspirone emerge. In subjects trained to discriminate between triazolam (0.32 mg/70 kg), a triazolobenzodiazepine, and placebo, buspirone (0 to 30 mg/70 kg) occasioned novel responding in a dose-dependent fashion (Kamien et al., 1994). These findings suggest that under these conditions, the discrim-

inative stimulus effects of buspirone are not like triazolam, nor are they like placebo.

In summary, then, the present study replicates and extends previous human drug-discrimination research with diazepam and buspirone. All subjects were able to discriminate diazepam versus placebo and buspirone versus placebo with minimal training. Across a four-fold range of doses, both diazepam and buspirone produced dose-related increases in drug identifications. However, across this range of doses, diazepam and buspirone produced some different self-reported drug effects. By training progressively lower drug doses, the present study also demonstrated behavioral activity of diazepam and buspirone at oral doses lower than those previously shown to affect the behavior of normal volunteers. Finally, the present study showed that lower doses of diazepam tended to be more discriminable than lower doses of buspirone, suggesting that at commonly used clinical doses, patients may more readily detect the acute effects of diazepam than those of buspirone.

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Received April 11, 1994
Final acceptance January 9, 1995