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Drug Preference and Mood in Humans: Diazepam*

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Abstract. A group of ten normal human volunteers participated in choice experiments comparing *d*-amphetamine or diazepam with placebo and with each other. Although amphetamine was preferred to placebo by most subjects, 2 mg diazepam and placebo were chosen equally. However, placebo was chosen over higher doses (5 and 10 mg) of diazepam and 5 mg *d*-amphetamine was preferred to 2 mg diazepam. Subjective effects were assessed using the Profile of Mood States (POMS) before drug was taken and 1, 3, and 6 h later. Compared to placebo, amphetamine produced changes in mood on the POMS including increases in Vigor and Arousal. Doses of 5 and 10 mg diazepam produced decreases in Vigor and Arousal and increases in Fatigue and Confusion. The effects of diazepam were most pronounced 1 h after ingestion and appeared dose-dependent. For one subject who consistently chose diazepam, its subjective effects were similar to placebo and he stated that he could not distinguish them. These results are discussed in terms of the abuse liability of diazepam.

Key words: Amphetamine – Diazepam – Drug preference – Subjective effects – POMS – Humans – Abuse liability

The abuse liability of the minor tranquilizers is a matter of great concern and controversy. Although there are many who believe that the extraordinary amounts of diazepam (Valium) and chlordiazepoxide (Librium) manufactured and prescribed each year in the United States indicate their abuse, there are others who claim that the level of use is simply due to the drugs' ability to alleviate some highly prevalent psychological disorders (Marks 1978).

Controlled laboratory studies directly addressing the question of the abuse liability of these compounds have been conducted using both animals and humans. Many of these studies have assessed abuse liability by viewing these drugs as positive reinforcers capable of maintaining behavior. Although some studies have shown that animals self-administer IV tranquilizers (Findley et al. 1972; Yanagita and Takahashi 1973), other studies have shown these compounds do not maintain behavior above saline or placebo levels (Gotestam 1973; Hackett and Hall 1976).

In humans, the abuse potential of diazepam has been assessed by allowing subjects to ingest this drug voluntarily under a variety of experimental circumstances. These studies have shown that humans readily self-administer diazepam; the dose increases over a period of time and decreases with increase in the minimum time between ingestions and in the work required per ingestion (Bigelow et al. 1976; Griffiths et al. 1976, 1979). However, all these studies were conducted with inpatients who had an extensive history of sedative abuse including minor tranquilizers and barbiturates. In the present study conducted on an outpatient basis, subjects with minimal psychotropic drug experience were given a choice between diazepam and placebo, and between diazepam and amphetamine. In addition, the subjective effects of these drugs were concurrently evaluated to determine the relationship between preference and mood.

Materials and Methods

Subjects. The subjects in these experiments were ten normal human volunteers (three female and seven male) between the ages of 21 and

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Table 1. The number of subjects participating in six choice experiments comparing drug 1 and drug 2[a]

Drug 2	Drug 1			
	5 mg *d*-amphetamine	2 mg diazepam	5 mg diazepam	10 mg diazepam
Placebo	10	9	10	9
2 mg diazepam	8	–	2	–

[a] One additional experiment was conducted: 10 mg *d*-amphetamine versus 5 mg diazepam in subject No. 17 (see text)

32. They were recruited using advertisements in the local student newspaper, notices posted on the University campus, and word-of-mouth referral. Prior to acceptance, each subject was given a brief interview during which: (1) the nature of the experiments was explained in detail; (2) a psychological evaluation was conducted, and (3) a drug history was taken. Subjects were accepted if they were considered normal on the basis of this interview and a subsequent physical examination which included ECG, blood chemistry screen, complete blood count, differential and routine urinalysis. Most subjects had some experience with psychotropic drugs but none had a history of any type of drug abuse.

Subjects signed a consent form prior to participation which outlined the study in detail and indicated all possible side effects of any drug they might be given. They were informed that they would not be told what drug they ingested at the time, except that it would be either a psychomotor stimulant, minor tranquilizer or placebo, and that the dose would be within the daily therapeutic range. Each subject also agreed not to take other drugs, except their normal amounts of coffee and cigarettes, 12 h before and 6 h after receiving drug. Except for the actual drug ingested, subjects were completely informed of all other procedural details as outlined below.

Each subject participated in the experiments independently, i.e., subjects did not participate either simultaneously or sequentially although there was usually overlap.

Procedure. Of the subjects nine participated in five separate choice experiments and the tenth subject participated in four. The procedure for each experiment was identical except for the two drugs available, which included three doses of diazepam (2, 5, and 10 mg), two doses of *d*-amphetamine (5 and 10 mg) and placebo. Table 1 shows the seven combinations tested and the number of subjects in each experiment.

Every experiment consisted of three sessions per week over a 3-week period, resulting in a total of nine sessions. During the first four sessions, the subject reported to the experimental room between 9 and 11 a.m. At that time, he/she filled out a mood form (see below) and received a colored capsule (i.e., drug 1 or 2) for immediate ingestion. Approximately half of the subjects received drug 1 during sessions 1 and 3 and drug 2 during sessions 2 and 4. The order was reversed for the other half. For each subject, each drug was dispensed in a capsule of a consistent and distinctive color in order to facilitate identification. Capsule colors were assigned randomly across subjects to avoid the influence of color preference. Each subject was instructed during the initial four sessions to note the capsule colors and to try to associate each of the two colors with the effects of the substances contained in them. After ingesting the capsule, subjects were free to leave. They took three additional mood forms with them, which they were to fill out 1, 3, and 6 h later.

During the last five sessions, the procedure was identical in every respect except that the subjects were given a choice of two colored capsules to ingest, i.e., a choice between drug 1 and 2.

Sequence of Experiments. For all ten subjects, the first two experiments conducted compared 5 mg *d*-amphetamine (drug 1) and placebo (drug 2), and 5 mg diazepam (drug 1) and placebo (drug 2). For five of the subjects, the amphetamine experiment was done first and the diazepam experiment second; for the other five subjects, the order was reversed. The remaining experiments were done in a mixed order and to some extent depended on the results of previous experiments. The experiments were completely independent, except that it was made clear to the subjects that the color of the capsule associated with a certain drug at a certain dose would remain constant throughout the entire series. This was done to facilitate identification.

Subjective Effects. The scale used to assess mood was an experimental version of the Profile of Mood States (POMS) which has been shown to be sensitive to the effects of psychotropic drugs (McNair et al. 1971; Johanson and Uhlenhuth 1980). The scale consisted of 72 adjectives commonly used to describe momentary mood states. Subjects indicated how they felt at the moment in relation to each of the 72 adjectives on a 5-point scale ranging from "not at all" (0) to "extremely" (4). There are eight clusters of items (subscales) which have been separated empirically using factor analysis (Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness, and Elation). The value of each subscale is determined by adding the numbers checked for each adjective in the cluster and dividing the total by the number of adjectives. Two additional subscales, Arousal and Positive Mood, were derived from the other subscales as follows: Arousal = (Anxiety + Vigor) − (Fatigue + Confusion); Positive Mood = Elation − Depression.

The ten POMS scores were averaged across sessions for each subject separately for drugs 1 and 2 at each of the four time periods. A two-way analysis of variance (drug × hour) was performed separately for each factor. If a significant ($P < 0.05$) drug × hour interaction was found, further statistical tests were conducted to determine at which hours the scores for the two drugs were significantly different[1].

Drug Preparation. Drug tablets of the required dose were placed in opaque gelatin capsules (size 00) which then were filled with dextrose powder. Placebo capsules were identical in size and contained dextrose powder alone.

Results

The present group of experiments are part of a larger series of studies designed to compare a variety of drugs on several dimensions. Every subject, however, was given a standard comparison between 5 mg *d*-amphetamine and placebo, and these results have been presented elsewhere (Johanson and Uhlenhuth 1980). The results for the experiment comparing 5 mg *d*-amphetamine and placebo will therefore be presented here only briefly to demonstrate that the present subsample of ten subjects is representative of the larger

1 Because of the exploratory nature of this work, a relatively powerful post hoc test, Fisher's LSD was employed for contrasting cell means (Fisher 1951; Winer 1971). The drawback to this procedure is that because of the non-independence of the individual tests performed, the overall probability of at least one Type I error is greater than that set for each comparison taken separately. In the current study, a 0.05 significance level was considered the maximum acceptable. In most of the actual cases, a much smaller probability was computed

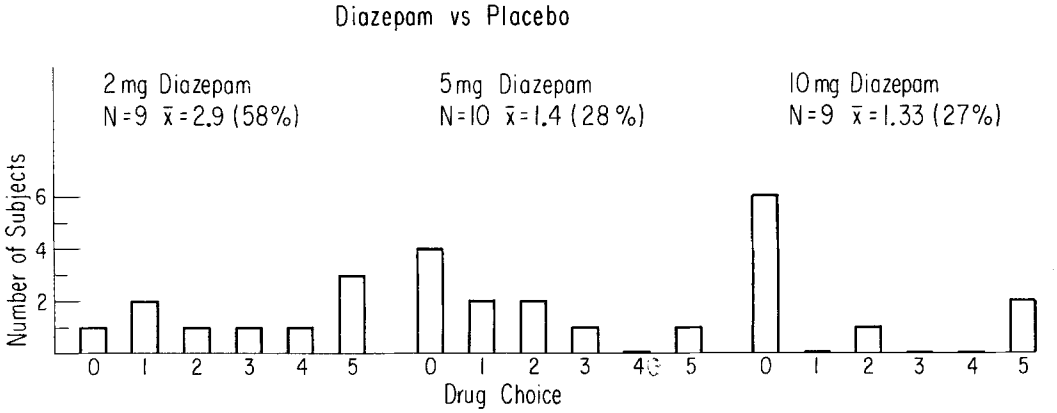

Fig. 1. The number of subjects (ordinate) who chose 2, 5, or 10 mg diazepam 0 to five times (abscissa) during the five choice sessions. The mean and percent of diazepam choices are also shown

group. On average the subjects chose amphetamine 3.8 times (76%) out of 5 ($P < 0.005$)[2]. Compared with placebo, amphetamine produced significant increases ($P < 0.05$) in the Vigor and Arousal subscales of the POMS. Both the preference results and subjective effects are similar to those found with the larger group of 31 subjects (Johanson and Uhlenhuth 1980).

Figure 1 presents the choice data for all three doses of diazepam versus placebo. As can be seen, placebo and 2 mg diazepam were chosen about equally. The higher doses of 5 and 10 mg diazepam, however, were chosen only 1.4 (28%) and 1.33 (27%) times respectively (both $P < 0.05$). For the eight subjects given a choice between 5 mg *d*-amphetamine and 2 mg diazepam, the amphetamine was chosen 3.75 times (75%) out of 5 ($P < 0.05$).

In the comparison between 5 mg diazepam and placebo only two subjects chose the drug at most sessions. Subject 19 chose diazepam three times and subject 17 chose diazepam all five times. These subjects were then tested additionally in a comparison between this dose of diazepam and 5 mg *d*-amphetamine. Subject 19 chose amphetamine on all five occasions but subject 17 chose diazepam four out of five times. This same subject (No. 17) also chose 5 mg diazepam in preference to a higher dose of *d*-amphetamine (10 mg) four out of five times. In addition, he chose 10 mg diazepam over placebo at every opportunity (Fig. 1).

The effects of diazepam on mood as assessed by the POMS are shown in Fig. 2. In the experiment comparing 2 mg diazepam versus placebo, there were no significant main effects and no drug × hour interactions on any of the factors. However, in the experiments comparing the two higher doses of diazepam to placebo, four subscales (Vigor, Fatigue, Confusion and Arousal) showed significant drug × hour interactions. Compared with placebo, diazepam produced dose-dependent decreases in Vigor and Arousal and increases in Confusion and Fatigue (Fig. 2). These effects were most pronounced after 1 h and had disappeared after 3 h for the 5 mg dose and after 6 h for the 10 mg dose.

As previously noted, subject 17 consistently chose diazepam over both placebo and amphetamine. However, during his debriefing interview, he stated that he had thought that both 5 and 10 mg of diazepam were placebo. Furthermore, the mood changes he reported on the POMS were not similar to those experienced by the other subjects. Table 2 shows that his mood scores on Vigor, Arousal, Confusion and Fatigue were similar for drug and placebo and that many of the hour 1 and 3 scores fell beyond the 95% confidence limits of the averages shown in Fig. 2.

Discussion

The present study indicated that diazepam at doses which produced changes in mood was not preferred over placebo by normal human volunteers. Although in the experiment comparing 2 mg diazepam and placebo, both were equally preferred, there were no significant differences in their subjective effects. This may indicate that this dose of diazepam was too low to be discriminated from placebo. The higher doses of diazepam, however, were significantly different from placebo in their subjective effects, producing increases in Fatigue and Confusion and decreases in Vigor and Arousal. The differences were dose-dependent and were greatest 1 h after drug ingestion, but had disappeared after 6 h.

2 The statistic used for testing the significance of all choice results was a two-tailed *t*-test with a log $(x + 1)$ transformation applied to the data. A log transformation was used because of outlyers and log $(x + 1)$ was used because of the 0 score (Edwards 1972)

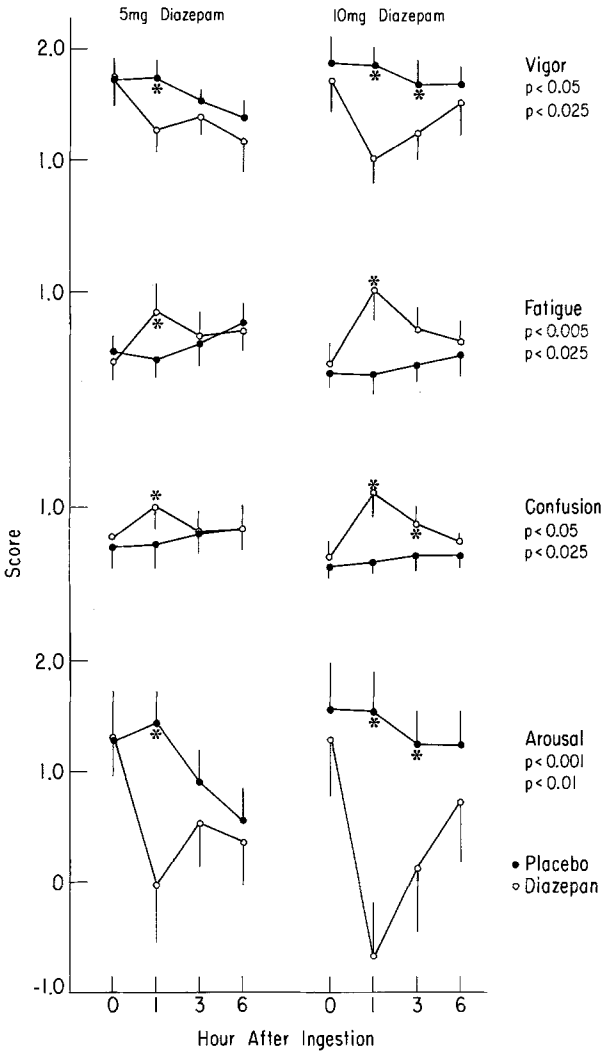

Fig. 2. The effects of 5 mg (left side) and 10 mg (right side) diazepam (open circles) compared to placebo (closed circles) at 0, 1, 3, and 6 h after ingestion on the scores of four subscales of the POMS of nine or ten subjects during all sessions when drug or placebo respectively was ingested. Subscales which did not show a significant drug × hour interaction ($P < 0.05$) are not shown. The P values for the drug × hour interaction are shown under the name of each scale for both the 5 mg (top P value) and 10 mg (bottom P value) dose. The asterisks (*) indiate a significant difference ($P < 0.05$) between drug and placebo at that hour specifically

In contrast, the same subjects preferred 5 mg *d*-amphetamine over placebo. A similar result has been shown previously (Johanson and Uhlenhuth 1980). In addition, 5 mg *d*-amphetamine was preferred over 2 mg diazepam. This latter finding is not surprising since it is unlikely that 2 mg diazepam is easily discriminated from placebo. Interestingly, many of the subjective effects of amphetamine in the present study and in a previous one were the opposite of those produced by diazepam. For instance, amphetamine produced increases in Vigor and Arousal whereas diazepam produced decreases. In addition, amphetamine has been shown in a more extensive study (Johanson and Uhlenhuth 1980) to produce decreases in Confusion whereas diazepam, as shown here, produced increases.

Table 2. Subject No. 17: Selected POMS scores from diazepam vs placebo experiments

Hour	Subscale							
	Vigor		Fatigue		Confusion		Arousal	
	5[a]	P[b]	5[a]	P[b]	5[a]	P[b]	5[a]	P[b]
0	2.0	2.1	0.4	0.1	0.6	0.4	1.3	2.1
1	1.7	2.2	0.3[c]	0.1	0.7	0.5	1.1	1.9
3	1.8[c]	1.7	0.4	0.4	0.7	1.0	1.0	0.6
6	1.6[c]	1.4	0.3	0.6	0.6	1.1	0.9	0.1
	10[a]	P[b]	10[a]	P[b]	10[a]	P[b]	10[a]	P[b]
0	1.8	2.0	0.1	0.1	0.5	0.5	1.6	1.8
1	1.8[c]	1.8	0.1[c]	0.2	0.4[c]	0.5	1.5[c]	1.4
3	1.7	1.7	0.3	0.4	0.6	0.5	1.2	1.2
6	1.9	1.9	0.1[c]	0.1	0.5	0.7	1.6	1.5

[a] mg dose of Diazepam
[b] Placebo
[c] Beyond 95% confidence limits (see text)

The results with diazepam appear to be in disagreement with those found by others indicating that human volunteers choose to ingest diazepam (Bigelow et al. 1976; Griffiths et al. 1976, 1979). However, these studies differ from the present one in two possibly important respects. First of all, their subjects were inpatients with few demands made upon their performance. In contrast, the subjects in the present study were free to leave the experimental situation following drug ingestion. These subjects either were students or were employed full-time. During their initial intake interview, many of them had expressed concerns about participating in the experiment if the drug was going to interfere with their normal functioning. Since diazepam produced increases in Confusion and Fatigue but decreases in Vigor and Arousal, it is likely that this type of subject at this time of day (i.e., in the morning before classes and work) preferred to avoid these effects. In contrast, amphetamine produced opposite effects and even may have been perceived as an aid to functioning.

A second difference between these studies was that the subjects in the Bigelow et al. (1976) and Griffiths et al. (1976, 1979) studies had an extensive history of sedative abuse which included the use of barbiturates as well as minor tranquilizers. Harris et al. (1968) have shown that rats initially given a choice between water and oral chlordiazepoxide almost exclusively preferred water. However, after a 25-day period of forced

exposure to the tranquilizer (the delivery of food was contingent upon drinking chlordiazepoxide), these rats increased their intake of the minor tranquilizer. It may be that prior exposure to sedative agents alters the reinforcing properties of minor tranquilizers. If so, humans with prior drug experience, as in the Bigelow and Griffiths studies, would prefer diazepam, whereas less experienced subjects, as in the present study, would not.

Unfortunately, it is not possible, given the present data, to determine unequivocally the relevance of past drug history on drug preference. Discrepancies noted in animal studies (Hackett and Hall 1976 versus Yanagita and Takahashi 1973) may also be a function of drug history. Since it is not clear that this is the case, experiments addressing this question directly need to be performed. Animal studies of drug self-administration seem particularly suitable for this purpose for both practical and ethical reasons. However, in the absence of such data, the discrepancies in the results from the various studies in both humans and animals suggest the importance of environmental variables in determining the valence of the reinforcing properties of certain drugs.

In contrast, although environmental factors can alter the extent of their reinforcing properties (Johanson 1978) most studies with humans and animals demonstrate that *d*-amphetamine as well as other psychomotor stimulant drugs are positive reinforcers (Balster and Schuster 1973; Pickens and Harris 1968; Johanson and Uhlenhuth 1980). However, even this conclusion may be premature, since Wise et al. (1976) have shown that *d*-amphetamine has both positive and negative properties. Although rats self-administer amphetamine, they also avoid drinking solutions previously paired with amphetamine administration. Clearly more research is needed to describe the range of conditions affecting the reinforcing properties of drugs. This seems particularly relevant for minor tranquilizers where differences in results in laboratory studies with both humans and animals as well as the clinical controversy regarding their abuse potential indicate their interaction with a variety of pharmacological and environmental variables.

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