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Effects of Response Requirement Upon Human Sedative Self-Administration and Drug-Seeking Behavior[1]

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BIGELOW, G. E., R. R. GRIFFITHS AND I. A. LIEBSON. *Effects of response requirement upon human sedative self-administration and drug-seeking behavior.* PHARMAC. BIOCHEM. BEHAV. 5(6) 681–685, 1976. – Five male volunteers with histories of sedative drug abuse were given the opportunity to self-administer up to 20 oral doses per day of either diazepam (10 mg per dose) or sodium pentobarbital (30 mg per dose). Each dose was purchased with tokens earned by exercising on a stationary exercise bicycle. Each two minutes of exercise earned one token. In a mixed order across days the number of tokens required to purchase each dose was varied among 1, 3, 5, 8 and 10. Drug intake decreased as a function of increased response requirement for purchasing the drug. Response output for drug tended to be an inverted-U shaped function of the response requirement. Thus, the cost of drug doses acts as a powerful environmental influence upon both of these aspects of drug abuse behavior – amount of drug consumed and amount of drug-seeking behavior.

Drug self-administration Drug abuse Response cost Diazepam Pentobarbital Human

IN AN earlier report [3], we have described a methodology for conducting experimental analyses of determinants of human sedative abuse by permitting optional self-administration of sedative compounds by human volunteers within a controlled experimental context. We report here the results of one such analysis which assesses the influence upon drug self-administration and drug-seeking behavior of variations in the cost (in terms of effort required) of individual doses of either sodium pentobarbital or diazepam.

Essig [8] noted the general similarity of the clinical effects of chronic high doses of the barbiturates and the minor tranquilizers – sedation, intoxication, tolerance, cross-tolerance, and physical dependence – and suggested that caution be taken with all of these compounds to minimize their abuse. Abuse of both classes of compounds has been reported clinically [8, 19, 25].

A report by the Committee on Problems of Drug Dependence [7] has pointed to the need to develop human experimental procedures for assessing abuse liability of sedative compounds. Schuster and Thompson [23] have suggested that the abuse liability issue is best addressed by investigating the range of controlling variables which influence drug self-administration, and have noted that compounds with the highest abuse potential are those which are self-administered under the widest variety of conditions.

The present approach to analyzing the controlling influence of environmental variables upon human sedative self-administration is derived from procedures originally developed for the analysis of human ethanol self-administration [4,15]. Experimental human drug self-administration procedures have also been utilized in the study of tobacco [10], marihuana [1, 16, 18], heroin [2,17] and dilaudid [13]. Experimental human sedative self-administration has been reported to be influenced by the time interval required between successive dose availabilities, and by the dose of drug made available [11].

METHOD

Subjects

Five white male volunteers participated. Subjects were referred by treatment or service agencies and gave their

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sober informed consent in writing prior to research participation. Volunteers were medically and psychiatrically screened. On the basis of examination, history, routine laboratory chemistries, and chest x-ray they were found to be without significant medical or psychiatric disturbance other than their drug abuse. A documented history of prior sedative drug abuse was a prerequisite to participation. Subjects were interviewed about their drug abuse history (types and quantities of drugs, and patterns of abuse), and the general accuracy of the interview information was corroborated by treatment personnel who had worked directly with the subject and who had access to relevant information from various other sources (e.g., arrest records, urinalysis data, personal observation, etc.). During research participation subjects were allowed to self-administer only drugs and maximum dosages for which they reported a history of prior abuse. Subject characteristics are summarized in Table 1.

Subject WN2 had previously participated in a number of behavioral pharmacology experiments in this laboratory. Other subjects were participating in their first experiment.

Procedure

General. Subjects were observed in the hospital for at least two days prior to the initiation of the experiment. None showed evidence of significant physical dependence on sedative drugs. Subjects were then given the opportunity under experimental conditions to self-administer orally a sedative drug which they had previously abused. Subjects JM1 and WN2 were given access to diazepam (10 mg dose). Subjects AJ3, LG4 and LB5 were given access to sodium pentobarbital (30 mg dose). Drug assignment was not random but was based upon subjects' reports of their previous major sedative abuse. Subjects were informed of both the drug and the dosage used. Each subject participated in an experiment in which the cost of individual doses of drug was varied in a mixed order across days. For two days preceding the beginning of the experiment the number of doses available for self-administration was gradually increased, reaching 20 on day three. The experiment began on day three and was conducted throughout with a maximum of 20 doses available per session. The subjects participated sequentially in independent experiments, not concurrently in a single experiment.

Setting. Subjects participated while residing on an eight-bed behavioral pharmacology research ward. Other subjects on the research ward participated concurrently in a variety of other experiments involving ethanol, diazepam or sodium pentobarbital ingestion. Various recreational materials, including a pool table, television, cards, games, crafts, reading material, etc., were continually available to subjects.

Conditions of drug availability. Drugs were available for self-administration during a 7-hr daily session (2:00 p.m.–9:30 p.m. for Subject LB5, and 8:00 a.m.–3:00 p.m. for other subjects). A maximum of 20 doses was available per session (200 mg diazepam or 600 mg sodium pentobarbital). A minimum interval of 15 min was required between successive doses as a precaution against acute overdosage. Individual doses were purchased with tokens earned by exercising on a stationary exercise bicycle. Each subject had a bicycle which was available only to him for the 7½ hr interval beginning one-half hour prior to the beginning of the drug availability session. Subjects earned one token for each two minutes of bicycle operation. Exercising occurred under continuous staff observation and subjects were required to keep the bicycle wheel in continual rotation; there was no speed requirement. Staff started a mechanical timer when subjects began exercising and dispensed the proper number of tokens when subjects stopped. Tokens not expended for drugs were available for exchange within the general research ward token economy for minor ward privileges (e.g., use of recreational equipment, or day-time access to the bedroom). At the end of each day all remaining tokens were converted to monetary credit (one token equal to one cent); money was received at the end of research participation. No tokens could be saved from one day to the next. Tokens were color-coded to

TABLE 1

SUBJECT CHARACTERISTICS

Subject	Assigned Drug	Age	Weight (kg)	Drug Abuse History	Concurrent Drug Use
JM1	Diazepam	23	90.9	narcotics, benzodiazepines	methadone 60 mg daily
WN2	Diazepam	34	90.9	alcohol, benzodiazepines	none
AJ3	Sodium Pentobarbital	20	67.3	barbiturates, benzodiazepines, amphetamines, narcotics	none
LG4	Sodium Pentobarbital	25	94.5	narcotics, barbiturates, amphetamines, benzodiazepines	methadone 20 mg daily
LB5	Sodium Pentobarbital	22	81.0	barbiturates, benzodiazepines, narcotics	none

prevent exchange among subjects. The number of tokens required to earn a single dose of drug was varied across days in a mixed order among 1, 3, 5, 8 or 10 tokens per dose. Each subject was exposed to at least three cost values for a minimum of two sessions each. The first experimental day was always at a cost of 1 token. The number and value of different token costs used with individual subjects was determined in part by the durations of subjects' research participation and in part by subjects' drug self-administration data: some effort was made to include cost values which would result in an intermediate level of drug intake. Subjects were informed daily of the token cost for that session within the half-hour preceding the onset of exercise bicycle availability. Care was taken throughout the experiment to provide no instructions to subjects concerning what they were "supposed" to do or of what outcomes were expected.

Drug administration. Diazepam was dispensed as a 10 mg dose. Sodium pentobarbital was dispensed as a 30 mg dose. Doses were dispensed by the ward nursing staff at the subject's request and upon his presentation of the proper number of tokens. To insure that drugs were ingested when dispensed, for both drugs tablets were crushed at the time of dispensing and dispensed in suspension with water. Oral consumption was carefully monitored by the nursing staff. Only a single dose was dispensed at each ingestion.

The two patients who were concurrently maintained on methadone received their daily methadone doses orally within the half-hour following termination of their daily session.

RESULTS

Drug intake. Variation of the response cost per dose had a similar effect upon the sedative self-administration of all subjects; as cost increased, drug intake decreased. Figure 1 shows, for each subject, drug intake as a function of cost per dose.

At the lowest cost level (1 token per dose) subjects consumed all or nearly all of the available doses. However, at increasing cost levels drug intake progressively declined. Drug intake occasionally fell to zero in all subjects except WN2, whose intake fell only to 50 percent of the maximal level.

Response output. Figure 2 shows the number of tokens paid for drug as a function of cost per dose. All subjects initially increased their mean token expenditures for drug as the cost per dose increased above one token. As cost per dose increased to higher values subjects AJ3, LG4 and LB5 showed decreases in mean token expenditures, whereas token expenditures for subjects JM1 and WN2 leveled off at the higher token cost values but did not show a significant decrease. The data in Fig. 2 also provide a description of the absolute amount of subjects' drug-seeking behavior. Since each token spent represents two minutes of exercising, these data are readily converted to total time spent working for drug. The maximum durations of exercising in single sessions was 6.3, 4.3, 3.5, 2.0 and 2.0 hr for each of the five subjects, respectively. All subjects tended to provide a maximum of 2–4 hr of work for drug on those sessions when drug was self-administered at costs greater than one token per dose, except for subject LG4 whose response output was always 2 hr or less.

Pattern of drug intake. For each subject the temporal pattern of drug ingestion was examined for sessions in

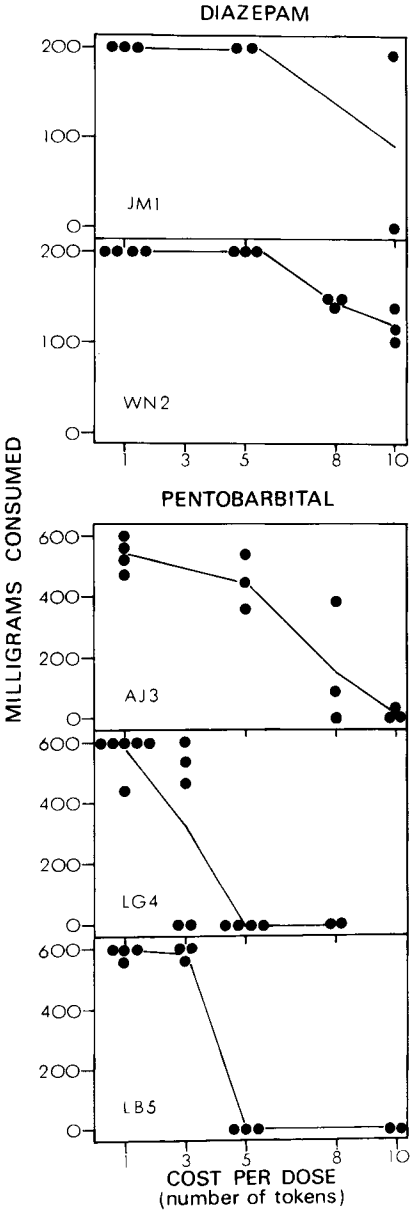

FIG. 1. The total milligrams of drug consumed per session is shown for each subject as a function of cost per dose. Each point represents a single daily session; means are connected. Diazepam was dispensed as a 10 mg dose; sodium pentobarbital as a 30 mg dose.

which doses were available at a cost of one token. All subjects tended to ingest doses shortly after the experimentally-imposed 15 min inter-ingestion interval had elapsed: 82.8% of inter-ingestion intervals were less than 20 min (the range across subjects was 69.1% to 85.5%). Long inter-ingestion intervals were infrequent (only 3.6% were greater than 30 minutes), and were more likely to occur after many doses had already been ingested.

Drug intoxication. Subjects displayed considerable tolerance to the general depressant effects of the drugs. They remained ambulatory and frequently engaged in social and recreational activities even after having ingested 15–20

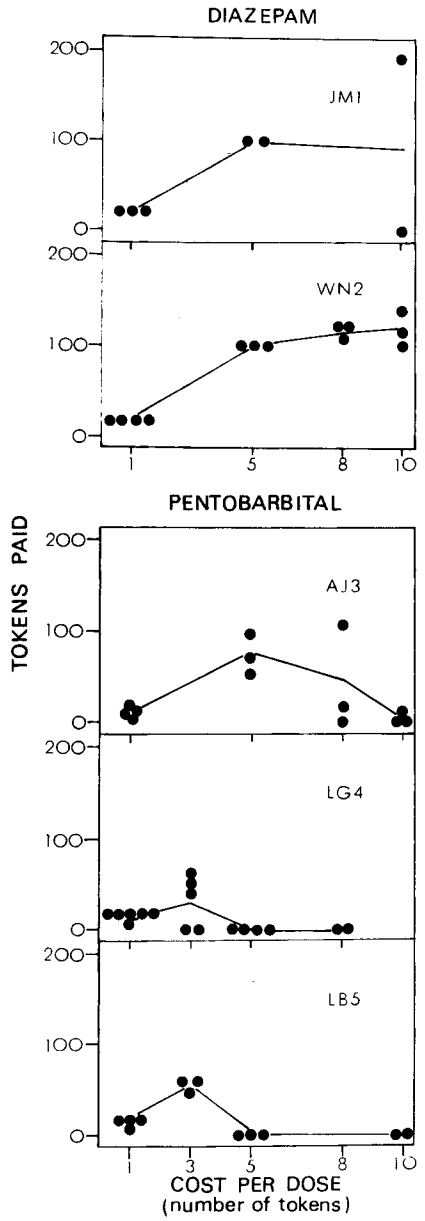

FIG. 2. The total tokens paid fro drug per session is shown for each subject as a function of cost per dose. Each point represents a single daily session; means are connected. Diazepam was dispensed as a 10 mg dose; sodium pentobarbital as a 30 mg dose.

doses of drug (150–200 mg of diazepam or 450–600 mg of sodium pentobarbital). Signs and symptoms of central nervous system depression were, however, frequently apparent – ataxia, slurred speech, drooping eyelids, tiredness and sleep occurred.

DISCUSSION

These data indicate that a model of sedative abuse can be established within the laboratory, in which human sedative abusers are given access to sedatives under experimental conditions and in which environmental conditions are manipulated so as to reveal environmental determinants of sedative self-administration. In the present case, cost of drug doses in terms of the response requirement to obtain doses, was found to bear a significant controlling relationship over drug intake and drug-seeking behavior (response output). The fact that drug-seeking behavior declined at the higher cost values when little or no drug was being consumed indicates that the decline was not due to a drug-produced decrement in performance capability. A similar relationship between cost, drug intake and response output has been observed in the study of ethanol self-administration by alcoholics using a simple switch-closure operant [5]. Laboratory animal drug self-administration studies have also observed that response output increases and drug intake decreases as cost per dose increases for pentobarbital [9], secobarbital [6], ethanol [14] and morphine [24]. Several animal self-administration studies have failed to observe any suppressive effect of increased response requirements upon drug intake with several CNS stimulant drugs – cocaine [9,22], d-amphetamine [20] and methylamphetamine [21]. However, Brady and Griffiths [6] have shown that self-administration of both cocaine and methylpheidate declines as response requirement increases in a progressive-ratio procedure. Studies of CNS stimulant self-administration by humans have not been reported.

Several infrahuman drug self-administration procedures have been utilized to provide measures of a drug's relative reinforcing efficacy, which may relate to its abuse liability [6]. One of the more promising procedures is the progressive-ratio paradigm in which the resistance of drug self-administration to suppression by increasing response costs is assumed to provide a measure of the drug's reinforcement strength or abuse liability [12]. The present study suggests that the assessment of response-cost effects may also provide a useful strategy for human experimental assessment of abuse liability.

The present study clearly demonstrates that the response cost for individual drug doses can be a powerful determinant of the sedative self-administration (i.e., doses consumed) of human sedative abusers. Similarly, the cost of individual doses of drug is shown to be a determinant of the amount of drug-seeking behavior emitted (i.e., bicycle riding). Interestingly, the effect of cost variations on these two outcome measures is not identical. Since these two outcome measures might each be used as indicators of the abuse liability of a drug, it follows that the abuse liability of the drug is not solely a characteristic of the pharmacological compound and its dose, but is substantially influenced by the environmental conditions of drug availability. Furthermore, the two indicators of abuse liability (amount of drug-seeking behavior versus amount of drug consumed) do not yield parallel results as a function of this environmental cost manipulation.

In the present experiment the 10 mg dose of diazepam maintained drug self-administration behavior under a somewhat broader range of cost conditions than did the 30 mg dose of pentobarbital. However, these differences cannot properly be attributed to pharmacological differences between the two compounds since each drug was tested at a single dose level and in subjects with unique histories. However, the study does illustrate how human drug self-administration procedures might be used to assess relative abuse liability by assessing the robustness of drug-reinforced behavior under a variety of conditions.

Development of profiles of how drug intake and drug-seeking behavior are influenced by various drugs, doses and environmental conditions can provide a framework within which to compare and evaluate drugs as well as a framework within which to assess the influence of manipulable environmental conditions upon drug abuse and drug self-administration behaviors.

The effects of drug cost variations upon drug intake and drug-seeking behavior may be relevant to the practical issue of efforts of control drug abuse by restricting the availability (i.e., increasing the cost) of drugs. The present data illustrate both the strength and the weakness of these efforts. The strength is that at sufficiently high cost drug-taking and drug-seeking behavior may be reduced or eliminated. The weakness is that increases in drug cost can lead to a corresponding increase in the amount of drug-seeking behavior.

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