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Experimental Human Drug Self-Administration: Methodology and Application to the Study of Sedative Abuse*

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THE development of procedures for studying self-administration of drugs in animals has provided laboratory experimental models of drug abuse. One can also establish such laboratory experimental models in man. While for ethical reasons one certainly can not achieve the same degree of rigorous experimental control with people which is possible with laboratory animals, one can achieve a degree of control adequate to permit the successful conduct of experiments involving manipulation of environmental variables and the observation of consequent covariations in drug self-administration behaviors. A substantial literature exists concerning experimental studies of human ethanol self-administration (1, 16), and several reports of human experimental marihuana self-administration have appeared (20, 21). The methodology of human experimental drug self-administration is now being applied to the study of other varieties of drug abuse also.

The abuse of sedative compounds constitutes a significant social, medical, and behavioral problem. Sedative abuse is thought to be more widespread than opiate abuse, presents the greater medical risk, and is becoming increasingly common (11, 24). Chronic barbiturate intoxication in man has occasionally been established within the laboratory for purposes of experimental study (9, 10, 13). However, to date these studies have involved programmed schedules of drug ingestion rather than self-administration, and the focus of these studies has been upon description and analysis of the correlates and consequences of chronic drug ingestion rather than upon analysis of the determinants of drug intake. Consequently, knowledge about the actual behavior of abusive sedative self-administration and its determinants is derived primarily from the retrospective self-reports of abusers, and from uncontrolled clinical observation. A controlled experimental context in which human volunteers are permitted optional self-administration of sedative compounds can permit experimental analysis of the determinants of human sedative abuse.

Methodological Considerations

The methods which we have adopted for the study of human sedative self-administration represent systematic extensions of those previously developed and used in the experimental study of determinants of human ethanol self-administration. We have assumed that the same general methodological procedures would be appropriate for the experimental study of other varieties of drug self-administration, and that the study of sedative self-administration could benefit from the considerable history of procedural development which has occurred in the study of ethanol self-

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administration. The procedural evolution which has occurred over the past decade in the experimental study of the determinants of ethanol self-administration has been reviewed previously (1). During this decade studies of experimental ethanol consumption have progressed from the phase of observation and description of the correlates and consequences of ethanol intake to the phase of experimental modification of ethanol self-administration behavior.

Historically, the body of human drug self-administration research derives from the pioneering experimental study of chronic ethanol consumption by human alcoholics reported by Mendelson and colleagues (19). In that initial study ethanol was not available for optional self-administration, but was dispensed on a temporally programmed schedule. The essential methodological alterations which have permitted experimental study of the *determinants* rather than the consequences of ethanol intake are 1) the introduction of optional ethanol self-administration (17); 2) the introduction of experimental manipulations during ethanol self-administration periods (23); and 3) the development of stable and sensitive patterns of ethanol self-administration against which to assess the effects of experimentally manipulated variables (4).

Thus, the basic methodology which has evolved for investigating the determinants of human drug self-administration involves making available to volunteer substance abusers a substantial quantity of their drug of abuse for optional self-administration within a residential research ward while experimental conditions are systematically manipulated. The residential research ward allows a considerable degree of experimental control over the conditions of drug availability, as well as over the array of and conditions of availability of alternative behavioral options. The result is an experimentally-controlled yet complex residential research environment for the study of human drug self-administration. Summarized below are what seem to be important practical and procedural considerations relevant to the efficient and successful conduct of human drug self-administration experimentation.

Stability and Sensitivity

In order to proceed successfully with an experimental analysis of human drug self-administration one must first achieve two requirements with the dependent variable: stability and sensitivity. Stability refers to the establishment of conditions under which variability is sufficiently reduced to allow adequate replication of observed effects. Sensitivity refers to the establishment of a set of parameters under which drug self-administration is measurably influenced by manipulation of other variables.

Restricting drug availability. By restricting the amount and conditions of drug availability one may enhance the stability of drug self-administration behavior. In studies of ethanol self-administration, conditions of relatively unrestricted ethanol availability have not produced stable patterns of self-administration; instead wide spontaneous variability is observed (18, 22). This variability is likely to occur with unrestricted access to other drugs also. Appropriate restrictions on drug availability (*e.g.*, dose, session length, inter-dose interval, response requirement, *etc.*) should permit the establishing of parameters within which the drug is self-administered, yet which prevent subjects from ingesting toxic quantities. The stabilizing effect of restricting drug availability has also been recognized in animal studies of drug self-administration. Under conditions of unrestricted drug availability instability has been observed in monkeys' self-administration of ethanol (27) and of cocaine and amphetamine (5). However, under conditions of restricted drug availability, stable self-administration of these compounds can occur (6, 27).

Restrictions on drug availability can serve also as a powerful tool for increasing

the sensitivity of drug self-administration behavior to the effects of experimental manipulations. For example, Bigelow *et al.* (3) evaluated the suppressive effect upon alcoholic drinking of scheduling 10 min of physical and social isolation as an immediate consequence to the taking of each alcoholic drink. Drinking was more sensitive to this manipulation when ethanol availability was restricted by requiring that at least 1 hr elapse between successive unit doses, than when no minimum interdose interval restriction was imposed.

Restricting environmental alternatives. By restricting the range and conditions of availability of behavioral alternatives which might compete with drug self-administration one can often adjust the sensitivity of drug self-administration behavior to the effects of experimental maniuplations. This has been illustrated in a study involving ethanol self-administration reported by Griffiths, *et al.* (8). That study evaluated the effect of scheduling a brief loss of social interaction opportunities as an immediate consequence to the taking of each alcoholic drink, and found that ethanol self-administration was more sensitive to this contingent loss procedure during sessions when watching TV and/or reading were not possible than during sessions when they were possible. Thus, variations in the behavioral context of an experiment (*i.e.*, range of behavioral options) may determine whether a given manipulation produces a measurable effect upon drug self-administration.

Brief Experiments

The conduct of experimental studies of human drug self-administration imposes certain methodological requirements which do not generally arise within animal studies. Prior recognition of and attention to such requirements makes possible the establishment of experimental controls and conditions adequate for the conduct of systematic research. However, human research may at times require the use of methodologies which would not seem optimal if considered for use in animal laboratory studies. One must devise a methodology which is compatible with the fact that a lesser degree of experimental control is attainable in human research. One indicator of this reduced experimental control is the fact of brief experimental participations by human subjects. Discussed below are several factors relating to the limited durations of human experiments and a suggested methodology for coping with this fact.

Short-term subject participation. Human volunteers usually participate in research only for durations which are quite brief in relation to the usual durations of experimentation with other species. In our laboratory the usual duration of volunteer participation is between 4 and 6 weeks. Occasional subjects will re-enlist, and provide continuous participations of 8 to 12 weeks. However, since immediate re-enlistments are not common, one must design experiments to achieve completion within 4 to 6 weeks. Consequently, experimental designs which require prolonged periods for stabilization of behavior under each of a series of experimental conditions are impractical.

Subject withdrawal. Perhaps the most obvious indicator of the diminished degree of experimental control available in human studies is the fact that human subjects are, of course, free to discontinue their research participation at any time. This fact has practical implications for research design. Any study which relies upon exposure of subjects to a sequence of experimental conditions (*e.g.*, A-B-A, or A-B-C-A designs) is vulnerable to a costly loss of data if subjects elect to withdraw before completion of the study. If subjects do withdraw before completion of the experiment, the experimenter may find himself in some conflict over how to handle that portion of the data which is available. The simplist solution is to exclude from consideration all data from subjects who do not complete the full experiment. The greatest conflict might arise

under conditions where only partial data are available but they show an effect opposite to that observed in subjects who complete the full experiment.

The problem of how to handle incomplete data is not unique to human research, although it is probably somewhat more likely to occur with people than with other species. The point of the present discussion is to emphasize that one should be aware of the possibility of abrupt withdrawal by volunteer human subjects and should attempt to design the sequence of experimental conditions to decrease this risk. Specifically, one should anticipate that early subject withdrawal will increase if a sequence of experimental conditions is used in which the early conditions are more desirable and the later conditions are less desirable by subjects' standards. Some subjects may elect to withdraw when the relatively more aversive conditions are introduced.

Temporal drifts. Occasionally one will observe drifts in subjects' data over time under apparently constant conditions. Such drifts might be reflective of gradual changes in the research-context (*e.g.*, social changes among staff or patients). Such drifts might confound any experimental designs which involve exposure of subjects to a sequence of conditions (*e.g.*, A-B, or A-B-C designs).

Rapid variation of experimental conditions. In our laboratory, we now frequently design experiments which involve rapid variation of experimental conditions among all the conditions to be studied. Experimental conditions are changed daily in a mixed order. This technique of experimental design offers protection against the above-noted problems of: a) subjects' short-term participation and the consequent impracticality of waiting for stabilization of the data each time conditions are changed; b) withdrawal of subjects before data are collected under all experimental conditions; and c) superimposition of the experiment upon a data baseline which is gradually drifting over time. At present we assume that this procedure reveals the same general functional relationships which would result from stabilization after chronic exposure. This assumption requires empirical examination.

Possible Sources of Confounding

Discussed below are several factors to which careful attention should be directed in designing studies of the determinants of human drug self-administration. These factors relate to the unique laboratory management problems involved in human research and represent common potential sources of serious accidental confounding of experimental conditions.

Token economies. Token economies are commonly used as management systems in the operation of human research environments (14). Token economies are artificial closed economies in which special tokens serve as the medium of exchange—analogous to money in society-at-large. Token economies permit one to establish specific relationships between subjects' behavioral output and access to various goods and services (12). Such economies can also introduce certain complications into an experiment which is superimposed upon an operating economy. Of most significance is the fact that economies which permit the carryover from day-to-day of token earnings can reduce the independence of experimental conditions. This is especially true if the drug being self-administered must be purchased with token economy earnings. Token economies must be designed and managed so as to prevent this possible contamination. A system in which all tokens must be cashed in on the day they are earned is therefore necessary. Otherwise, subjects' economic behavior and drug self-administration under one set of experimental conditions may be partially determined by conditions which prevail during other phases of the experiment. In addition, one must also design the economy to maintain economic independence between subjects. That is, token economies must be designed to prevent any illicit exchanging of tokens

among subjects, and to insure that subjects earn tokens contingent only upon their own behavior.

Instructions. Great care must be taken to assure that subjects are given no explicit or implicit instructions about the "expected" or "proper" way to behave during experimental conditions. There is no way to guarantee the success of this effort so long as studies are conducted within a social context and involve prior explanation to subjects. Within our laboratory all staff are instructed to refrain from discussing experiments with subjects except to provide an objective description of the parameters currently in effect about which the subject must be informed. To minimize the risk of transmitting accidental instructions to subjects, we do not routinely reveal data summaries, experimental results, or research reports to the general ward staff (though these are available to staff who indicate an interest).

Successive participation of subjects. To date human drug self-administration research has been conducted within a social context involving both multiple staff and multiple subjects. In many studies all subjects have participated simultaneously in the same experiment. Such an arrangement greatly reduces the independence of the behavioral observations obtained. A more powerful procedure requires subjects to participate successively rather than simultaneously in a given experiment. In our laboratory, several different experiments are conducted simultaneously. This procedure obviates the confounding of particular experiments with a specific social context. Further, subjects participate independently, and experiments are independently replicated under several different contexts. Such a procedure greatly enhances the generality of experimental observations.

Experimental Sedative Self-administration: Effects of Cost Variations

We report here a preliminary study involving the experimental analysis of sedative self-administration by volunteer human subjects. The goal of this study was to demonstrate that sedative self-administration can be brought under sufficient experimental control to provide both a stable and a sensitive measure with which to assess the effects of experimental manipulations. In this experiment, daily drug self-administration by volunteer former abusers was permitted, and the cost per dose was experimentally manipulated.

Method

Subjects

Two White male volunteers participated. Both subjects were referred by treatment service agencies and gave their sober informed consent in writing before research participation. A documented history of previous sedative drug abuse was a prerequisite to participation. During research participation subjects were allowed to self-administer only drugs and maximum dosages for which they had a history of prior abuse. Subject characteristics are summarized in table 1. Both subjects reported that their illicit sedative use often occurred in combination with the drinking of alcoholic beverages.

Subject SS-WN2 had previously participated in a number of behavioral pharmacology experiments in this laboratory. Sub-

TABLE 1

Subject characteristics

Subjects	Assigned Drug	Age	Weight	Drug Abuse History
			kg	
SS-WN2	Diazepam	34	90.9	Alcohol, benzodiazepines
SS-AJ3	Sodium pentobarbital	20	67.3	Barbiturates, benzodiazepines, amphetamines, narcotics

ject SS-AJ3 was participating for the first time as an experimental subject.

Procedure

General. Subjects were given the opportunity under experimental conditions to self-administer orally a sedative drug which they had previously abused. Subject SS-WN2 was given access to diazepam (10 mg/dose). Subject SS-AJ3 was given access to sodium pentobarbital (30 mg/dose). Each subject participated in an experiment in which the cost of individual doses of drug was varied in a mixed order across days. For 2 days preceding the beginning of the experiment the number of doses available for self-administration was gradually increased, reaching 20 on day 3. The experiment began on day 3 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 between 8:00 A.M. and 3:00 P.M. A maximum of 20 doses was available per session (200 mg of diazepam or 600 mg of sodium pentobarbital). A minimum interval of 15 min was required between each successive dose as a precaution against acute overdosage. Individual doses were purchased with tokens earned by exercising on an exercycle. Each subject had an exercycle which was available only to him for the $7\frac{1}{2}$ hr interval between 7:30 A.M. and 3:00 P.M. daily. Subjects earned one token for each 2 min of cycle operation (timed by research staff with mechanical timers). Multiple tokens could be earned in single episodes of exercise. 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 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, 5, 8, and 10 tokens per dose. Each subject was exposed to each cost value for a minimum of three sessions. Subjects were informed daily of the token cost when they were wakened (between 7:00 and 7:30 A.M.). 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 individual 10 mg doses and sodium pentobarbital as individual 30 mg doses. Each dose of drug was dispensed by the ward nursing staff at the subject's request and upon his presentation of the proper number of tokens. For both drugs, tablets were crushed at the time of dispensing and dispensed in suspension with water. Oral consumption was monitored by the nursing staff. Only a single dose was dispensed at each ingestion.

Results

Variation of the response cost per dose had a similar effect upon the self-administration of sedatives by both subjects: as cost increased, drug intake decreased. Drug intake as a function of cost per dose for each subject is shown in figure 1.

At the lowest cost level (1 token per dose) both subjects consumed all or nearly all of the available doses. However, at increasing cost levels drug intake progressively de-

clined in both subjects. Drug intake occasionally fell to zero in subject SS-AJ3, whereas subject SS-WN2 reduced his intake only to 50% of the maximal level.

The number of tokens paid for drug as a function of cost per dose is shown in figure 2. Both 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 subject SS-AJ3 showed a marked decrease in mean token expenditures, whereas token expenditures for subject SS-WN2 leveled off at the higher token cost values but did not show a significant decrease.

The data in figure 2 also provide a description of the absolute amount of time subjects spent working for drug (each token spent represents 2 min of exercising). Subject SS-WN2 always exercised between 3 1/3 and 4 1/3 hr per session except when the cost per dose was one token. Subject SS-AJ3 generally exercised a lesser amount, attaining 3 hr or more on only two occasions.

Discussion

The present study demonstrates the feasibility of submitting human sedative self-administration to experimental behavioral analysis within the laboratory. The

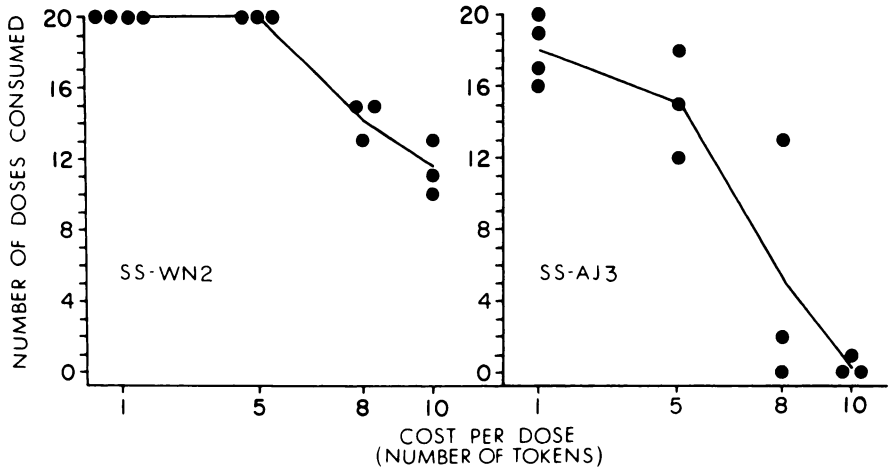

FIG. 1. The number of doses consumed is shown as a function of cost per dose for two subjects. Each point represents a single daily session total. Means are connected. Doses were 10 mg of diazepam for SS-WN2 and 30 mg of sodium pentobarbital for SS-AJ3.

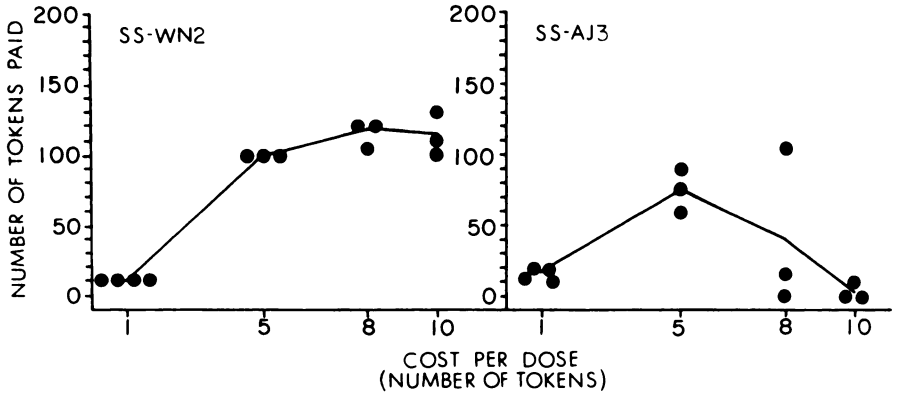

FIG. 2. The number of tokens paid for drug is shown as a function of cost per dose for two subjects. Each point represents a single daily session total. Means are connected. Unit doses were 10 mg of diazepam for SS-WN2 and 30 mg of sodium pentobarbital for SS-AJ3.

techniques described allow one to observe and validate orderly functional relationships between human drug self-administration behavior and its environmental determinants. The data obtained indicate that cost, in terms of the response requirement to obtain the drug, is a potent environmental determinant of sedative self-administration by human sedative abusers. A similar relationship between cost, drug intake and response output was observed by Bigelow and Liebson (2) in a study of ethanol self-administration by alcoholics. A substantial number of laboratory animal drug self-administration studies have also observed that response output increases and drug intake decreases as cost per dose increases (7, 15, 25, 26). Thus, one major contribution of the present studies of human drug self-administration is that they provide empirical evidence for validating the cross-species generality of functional relationships previously observed in animal drug self-administration laboratories.

These studies do more than just demonstrate simple cross-species generality. They extend the generality to a very unique population subgroup—*e.g.*, human drug abusers. Experimental studies of human drug self-administration reveal that even though these individuals may have developed idiosyncratic patterns of drug abuse through various complicated and unknown individual, social, and environmental histories, powerful control over their sedative self-administration continues to be exerted by the environmental circumstances to which the individual is exposed.

The development of stable and sensitive patterns of experimental sedative self-administration by volunteer abusers introduces the possibility of an experimental analysis of drug abuse treatment. Subjects enter the experimental situation with a pre-existing high probability or rate of abusive sedative self-administration. It is possible to begin examining manipulable environmental events and circumstances which might be arranged to reduce the use of sedative drugs.

Conclusion

The present study demonstrates that one can establish conditions, within an experimental context, under which human sedative self-administration can be observed, measured, and to a degree influenced by prevailing environmental conditions. The model developed, based upon previous research with human ethanol self-administration, provides for the establishment of stable performance under constant conditions and the sensitivity of that performance to the effects of manipulable experimental variables. Our contention is that stability and sensitivity of drug self-administration behaviors are an essential prerequisite to systematic experimental analysis of human sedative self-administration determinants.

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