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Self-Administration of Barbiturates and Benzodiazepines: A Review

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ATOR, N. A. AND R. R. GRIFFITHS. *Self-administration of barbiturates and benzodiazepines: A review.* PHARMACOL BIOCHEM BEHAV 27(2) 391–398, 1987.—Studies of barbiturate and benzodiazepine self-administration are categorized by species and route of administration. Reinforcement, defined as self-administration of drug greater than of a non-drug control, has been demonstrated most often in studies employing the IV route, and there has been greater reliability in this result for a given drug among barbiturates rather than among benzodiazepines. Most studies of PO self-administration in rodents have not demonstrated reinforcement, despite a number of behavioral manipulations to induce drug intake. Studies of PO barbiturate self-administration in monkeys have demonstrated reinforcement but recent studies of PO benzodiazepine self-administration in baboons have not, although physical dependence was demonstrated. Reinforcement via the IG route has not been reliably demonstrated. Behavioral variables, including interreinforcement interval and drug self-administration history, appear to be important determinants of whether or not reinforcement will be demonstrated, particularly among the benzodiazepines; but the range of conditions under which behavioral and pharmacological variables interact to promote or lessen the likelihood of self-administration of these drugs remains to be determined experimentally.

Self-administration Barbiturates Benzodiazepines Humans Monkeys Rodents

SHORTLY after the barbiturates came into clinical use at the beginning of the 20th century, it was found that chronic use of these drugs rapidly resulted in physical dependence with a severe and life-threatening withdrawal syndrome. Efforts to warn against barbiturate abuse in the 40's apparently helped to popularize the barbiturates as a new way to "get drunk" [39]. Introduction of the benzodiazepines into clinical use in the 1960's represented an enormous breakthrough. Their lethality, when taken alone, is far less than the barbiturates. Although it is now clear that the benzodiazepines also can produce physical dependence, the spontaneous withdrawal syndrome as studied to date with the frequently prescribed benzodiazepines is not likely to be as severe as that for the barbiturates they have replaced, probably due to differences in elimination [35]. On the other hand, the high incidence of prescription of the benzodiazepines, reports of cavalier over-prescription by some physicians, and a general lack of appreciation for the dependence potential of the benzodiazepines led to concern about abuse of these drugs, epitomized by a Congressional hearing on use and misuse of benzodiazepines [68].

Laboratory study of self-administration of barbiturates and benzodiazepines in the past 20 years has provided valuable information toward understanding the pharmacological profile of these drugs and toward understanding drug self-administration in general. A self-administration procedure, most simply defined, involves making a drug available to a subject and observing how much of it is taken. Tables 1 and 2 show the types of subjects and routes of administration for which such basic self-administration data have been collected with barbiturates and benzodiazepines, respectively. Only studies in which the subjects had opportunities to take the drug *and* could exercise some option in doing so in some phase of the experiment were included. This excluded conditions of oral self-administration with fluid-deprived animals (e.g., [70]). In order to facilitate cross-drug comparisons only studies with subjects not physically dependent at the beginning of the study were included in the tables (see [6, 9, 38, 51, 61] for studies of self-administration in dependent subjects).

By far the majority of the studies, and also the ones that incorporated dose manipulations as the primary independent variable, have been done using the IV route with rhesus monkeys and baboons. Only the oral route has been employed in experimental studies with these drugs in human subjects; but there is an interesting recent case report of a man's repeatedly feigning an acute dystonic crisis in order to obtain IV injections of diazepam at a hospital emergency room [48].

Studies with nonhuman subjects typically involved mul-

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TABLE 1

BARBITURATE SELF-ADMINISTRATION REFERENCES CATEGORIZED BY SPECIES, ROUTES OF ADMINISTRATION AND ELIMINATION HALF-LIFE

	Humans			Monkeys									Rodents			
Drug	PO			IV			IG			PO			IV		IG	PO
Slow Elimination (>24 hr)																
Barbital				71												49⁻ 53⁻
Phenobarbital				†									12⁻			67⁻ 89
Intermediate-Short Elimination (8–48 hr)																
Amobarbital				33⁺	71								13	14		66⁻
Pentobarbital	8	21⁻	28	7⁺	16	25	2⁻	73⁻	83	17⁺	55⁺	56⁺	12⁺			57⁻
	29⁺	30⁺		33⁺	40⁺	42⁺				59⁺						
				43⁺	45	54⁺										
				71⁺	82	83										
Secobarbital				23⁺	31	33⁺										
Thiopental				71									13			52⁻
Ultrashort Elimination (<8 hr)																
Hexobarbital				†									13			
Methohexital				*+	†+	50				5⁺	11⁺		12⁺	62⁺		
				71⁺												
Thiamylal				44⁺												

Numerals are reference numbers. A reference is not listed if self-administration had been recorded for all subjects in another published paper. Only nondependent subjects are included. ⁺ Indicates that at least two subjects were studied and that at least one drug dose maintained more behavior than a nondrug control for the majority of the subjects; ⁻ indicates that at least two subjects were studied and the the nondrug control maintained as much or more behavior than any drug dose. Lack of ⁺ or ⁻ indicates either that there was no nondrug control for that drug or that insufficient information on the results was provided. Elimination information is largely from Gilman *et al.* [24]; elimination half-lives generally parallel the traditional duration of action classification of barbiturates (e.g., [10]).

*J. Bergman, personal communication.

†Lamb and Griffiths, unpublished data.

tiple opportunities to take the drug across each day or within experimental sessions of 2 or 3 hours duration. In the studies with human subjects, most but not all [8, 28, 29] of these opportunities and options were in the context of procedures that first required the subjects to sample one distinctive capsule each day until all drugs and/or doses of interest had been taken. The subjects then were given the opportunity to take one of two different drug options on each of a number of choice days [18–21, 30, 34, 46]. Analogously, some studies with nonhuman subjects, particularly studies using the IV route with monkeys, also virtually assured "sampling" of the compound under study by first reinforcing lever pressing with a drug known to maintain regular self-administration (such as cocaine, codeine, or pentobarbital), and then substituting the benzodiazepine or barbiturate of interest [7, 33, 36, 43, 54]. Rather than using the substitution paradigm described above, some studies with nonhuman subjects have focussed on whether drug-taking could be induced as a function of other environmental events, such as a concurrent schedule of food reinforcement (i.e., schedule-induced drug-taking: [22, 41, 52, 64, 67], delivery of electric shock [13, 14, 47], a history of food reinforcement of the drug-taking response [37], or hypothalamic stimulation [3].

DRUG REINFORCEMENT

Although some of the studies with nonhuman subjects have focussed merely on whether the animals would take the drug and how much they would take, most studies did focus to some extent on demonstrating drug reinforcement by comparing self-administration of drug with self-administration of drug vehicle. Sorting the studies in Tables 1 and 2 into those that did or did not demonstrate reinforcement is somewhat difficult because the reports vary a great deal in level of data presentation and description of procedures and results. The studies in the tables in which (a) at least two subjects were studied and (b) drug reinforcement was demonstrated at one or more doses for a majority of the subjects are indicated by a plus (+) sign. In most of these studies drug reinforcement was demonstrated by showing that drug maintained more behavior than some nondrug control, usually, but not always, the vehicle in which the drug had been dissolved or suspended (i.e., some studies used a saline control condition although the drug was delivered in some other vehicle). Some studies also incorporated demonstrations that the subject would respond more on the drug lever than on a lever for which there were no programmed consequences [13, 62, 71]. Reference numbers in the tables which are followed by a minus sign (−) are those which studied at least two subjects and failed to find evidence for drug reinforcement compared to a vehicle condition.

Some studies may not have met the criterion described above for demonstrating reinforcement but did provide evi-

TABLE 2

BENZODIAZEPINE SELF-ADMINISTRATION REFERENCES CATEGORIZED BY SPECIES, ROUTE OF ADMINISTRATION, AND ELIMINATION HALF-LIFE

	Humans			Monkeys							Rodents			
Drug	PO			IV			IG		PO		IV		IG	PO	
Slow Elimination (usually >24 hr)															
Chlordiazepoxide				23	44+	54+	1	83		15+		15+	37+	41	47−
				83	*								64+	66−	72−
Clobazam							88−								
Clonazepam				33+			80−								
Clorazepate				33+			79+								
Diazepam	8	19−	21−	7+	33+	36−	1−	73	*−	12−	63+		3−	4	60−
	28	29+	30	40+	83+		75−						89		
	34+	46−													
Fludiazepam							77−								
Flurazepam	20−			33+	43+	44+				12−					
				45	54+	†+									
Halazepam							81−								
Medazepam				33−								26+			
Nordiazepam				†+											
Oxazolam							83								
Prazepam							84−								
Intermediate-Short Elimination (5–24 hr)															
Alprazolam				†+			87−								
Bromazepam				†+											
Estazolam				43+			86−								
Flunitrazepam							76−								
Lorazepam	18−			43+	45		85−								
Nitrazepam							75−								
Oxazepam	34+														
Quazepam							75−								
Temazepam				†+											
Ultra-Short Elimination (<5 hr)															
Midazolam				33+	54+	†+								22	
Triazolam				32+	54+	†+	78+		32− *−						

See footnote to Table 1. The elimination information ($t^1/_2$) is largely from Greenblatt *et al.* [27], and takes into account the elimination half-life of pharmacologically active metabolites.

*Ator and Griffiths, unpublished data.

†C. E. Johanson, personal communication.

dence that the subjects repeatedly self-administered behaviorally active amounts of the drug. Such evidence was provided in some cases by measures of the subjects' behavior after taking drug (e.g., observations of ataxia, verbal reports by humans [8,28]; anesthetization in monkeys [83]). Some studies reported that sufficient drug was self-administered to produce physical dependence (IV pentobarbital: [16,82]; PO diazepam and triazolam: [32], Ator and Griffiths, unpublished data; PO midazolam: [22]).

Intravenous Self-Administration

Reinforcement has been demonstrated via the IV route with all the barbiturates studied that have intermediate to ultra-short elimination half-lives except thiopental and hexo-barbital. Not a great deal of work has been done with the very slowly-eliminated barbiturates. Reinforcement was demonstrated in the one rhesus monkey studied with IV barbital [71], but there was a clear lack of reinforcement in studies with IV phenobarbital in rats [12].

Studies of benzodiazepine self-administration via the IV route have demonstrated reinforcement according to the criterion above with the exception of those with medazepam [33]. The benzodiazepine results differ from the barbiturate results, however, in that numbers of injections taken at the peak reinforcing dose have been lower [33] and/or demonstrating reinforcement has seemed more difficult [7]. Studies with baboons compared benzodiazepine and barbiturate self-administration under the same cocaine baseline substitution procedure. These results showed differences in self-administration profiles of the two classes of drugs in that the number of injections of peak reinforcing doses of benzodiazepines have not reliably attained the maximum available (eight in 24 hours) whereas number of injections of the peak reinforcing dose of barbiturates have ([33]; Lamb and Griffiths, unpublished results). This difference holds up regardless of speed of elimination of the benzodiazepines al-

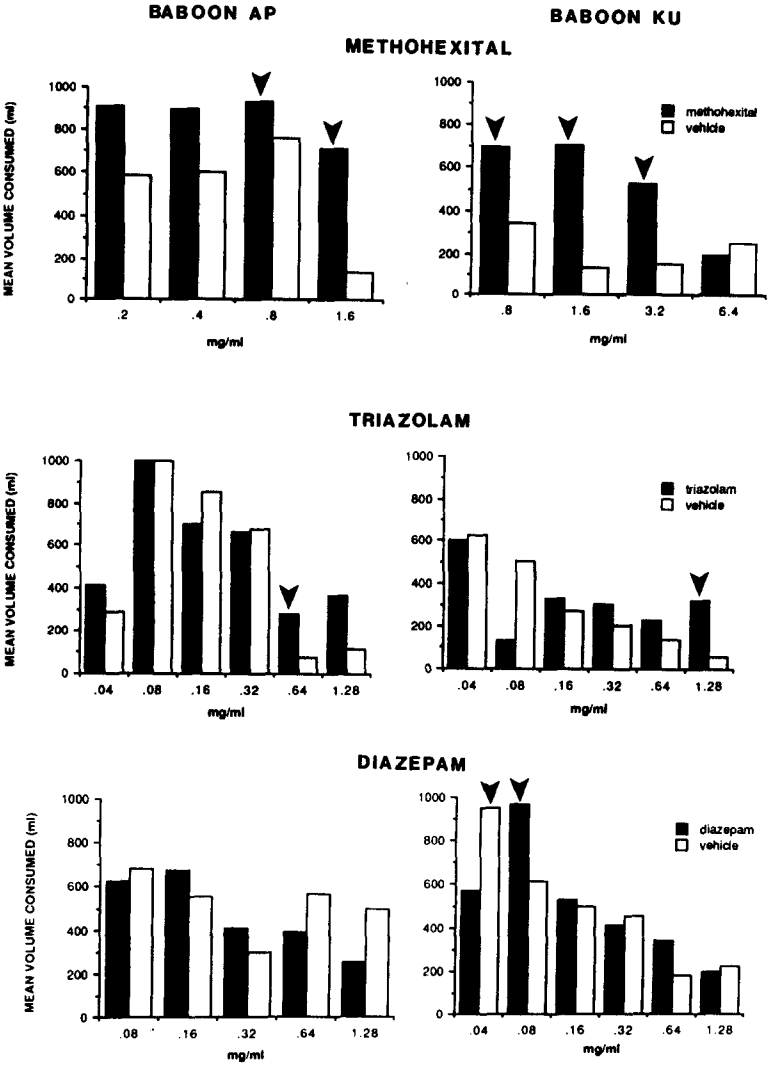

FIG. 1. Oral methohexital, triazolam, and diazepam self-administration in baboons. Mean volumes consumed in the last four sessions in choice conditions in which each drug concentration was available concurrently with the drug vehicle (water for methohexital; water with a suspending agent for triazolam and diazepam). Side position of drug and vehicle alternated daily; the two drinkometers and stimulus lights were identical, regardless of which fluid was available through each. Arrows indicate the concentrations at which the range of drug and vehicle volumes consumed in the four sessions did not overlap. Note that there is clear evidence for methohexital preference under these conditions, but not for triazolam and diazepam. (The methohexital data are replotted from [5] and the triazolam data are replotted from [32].)

though peak numbers of injections have been higher for the more rapidly eliminated benzodiazepines than for the more slowly eliminated benzodiazepines.

There also has been more inconsistency across studies with the benzodiazepines than with the barbiturates in whether reinforcement was demonstrated even when studies used the same route and species. There could be any of a number of reasons for differences in outcome ranging from procedural to subject variables to interactions between the two. One variable that has been reported to affect whether or not reinforcement will be demonstrated in an IV self-administration procedure with rhesus monkeys is whether a benzodiazepine is substituted for cocaine or for pentobarbital. Under a pentobarbital baseline procedure with low response requirements (1 or 10 responses per injection), diazepam maintained self-administration greater than vehicle in 2 or 3 hr sessions but reinforcement was not shown when diazepam was substituted under a cocaine baseline procedure [7]. In further work with this same procedure, self-administration of alprazolam, bromazepam, flurazepam, nordiazepam, temazepam, and triazolam (but not midazolam) was reported to be more reliable when the benzodiazepine was substituted under a pentobarbital rather than a cocaine baseline procedure (C. E. Johanson, personal

communication). Historical variables also have emerged as likely candidates for differences in diazepam choice results in human PO studies. Studies using subjects with documented histories of sedative abuse found clear dose-related preferences for diazepam [30,34], while studies using subjects without such histories found that only a small minority chose diazepam over placebo [19,46]. Interestingly, subjects meeting clinical criteria for anxiety disorder also generally failed to chose diazepam over placebo [19].

Intragastric Self-Administration

Studies of IG self-administration have not revealed strong evidence for self-administration of either benzodiazepines or barbiturates despite recent work involving a number of methodological manipulations [73] and the reliance on this route by Yanagita and his colleagues in their drug screening procedures [74–88]. This may be somewhat surprising given the more positive results with PO self-administration, but the difference in outcome probably indicates the importance of either taste variables in mediating the delay between drug ingestion and drug effect and/or the role played by buccal absorption of some of the orally delivered drug.

Oral Self-Administration

Oral self-administration procedures that have used animals not otherwise deprived of water, specifically the food-induced drinking procedure developed by Meisch and his colleagues [58], have been more likely to demonstrate reinforcement (e.g.,[5, 11, 17, 59]). Oral self-administration studies with benzodiazepines and barbiturates that "forced" drug sampling by making the drug solution the only fluid available for prolonged periods of time did not find evidence for drug preference when drug and water later were available concurrently [37, 49, 53, 66]. On the other hand, experiments have not specifically studied this variable for a given benzodiazepine or barbiturate, although some research with ethanol [69] suggested that forced drinking may decrease the probability of subsequent drug self-administration when drug and water are concurrently available.

Clear evidence for reinforcement via the oral route seems more problematic for benzodiazepines than for barbiturates. Pentobarbital [17, 55, 56, 59] and methohexital [5,11] reinforcement via the oral route have been clearly demonstrated in rhesus monkeys and baboons. For example, in a study with baboons, amounts of methohexital were consumed that caused anesthesia in some animals; when water and methohexital were available concurrently, three out of the four baboons reliably consumed significantly more methohexital than water [5]. In a subsequent study of triazolam and diazepam self-administration in which some of the same baboons served as subjects, reinforcement was not clearly demonstrated under conditions of concurrent access to drug and vehicle (Fig. 1). Under both triazolam and diazepam self-administration conditions, however, physical dependence developed, as shown by precipitated withdrawal syndromes when the benzodiazepine antagonist Ro 15-1788 was administered ([32]; Ator and Griffiths, unpublished results). When vehicle was substituted for drug for a number of sessions, volume consumed was below that when drug had been available. Concommitantly, however, there was a spontaneous withdrawal syndrome, characterized by tremor and decreased food intake. In this context, the suppression of vehicle intake below that of drug may have been due to the withdrawal syndrome and could not be unequivocally interpreted as demonstrating drug reinforcement.

Another variable complicating interpretation of oral benzodiazepine reinforcement is that benzodiazepines can increase fluid intake per se, and this point was demonstrated by administering IP chlordiazepoxide to rats given access to water [64]. In the self-administration condition of that same study, however, the within-session patterning of drinking shown in the cumulative records does not indicate that drinking increased across the 60-min session as a function of ingested chlordiazepoxide; rather drinking was fairly constant from the beginning of the sessions shown [64]. Similarly, in the oral triazolam and diazepam self-administration work described above, the baboons typically drank the majority of the total session intake in the first 30 to 60 min of the 3-hr session (Ator and Griffiths, unpublished data). The temporal patterning of drinking shown in these studies then is not the one of increased drinking across the session that one might expect to see if the drinking were largely a function of benzodiazepine ingested early in the session. Thus, while benzodiazepines can increase fluid intake, it is not clear that this capability completely, or even primarily, determines oral self-administration of these drugs. However, it may be a factor that complicates demonstration of preference in conditions of concurrent access to a benzodiazepine and vehicle.

SCHEDULES OF REINFORCEMENT

Virtually all the self-administration studies with benzodiazepines and barbiturates have employed fixed-ratio schedules of reinforcement. Because many studies were concerned simply with whether a given drug would be self-administered at all, response requirements were chosen that would constrain drug-taking behavior as little as possible. Only recently have oral self-administration studies required any response other than the ingestive one [11, 17, 55, 56, 59]. An early IV pentobarbital study found that number of infusions per session maintained by pentobarbital in rhesus monkeys decreased when the response requirement was increased from 1 to 10 whereas a similar number of infusions per session maintained by cocaine did not, and the authors suggested that higher response requirements might be more difficult to maintain with pentobarbital due to the rate-decreasing effects of the self-administered pentobarbital [25]. When these effects were limited, however, by imposing a 3-hour timeout after each infusion, appropriate doses of pentobarbital, amobarbital, and secobarbital maintained the same number of injections per session as cocaine at a response requirement of 160 [33].

It sometimes has been difficult to demonstrate drug reinforcement when response requirements are very low and, in some studies, increasing the response requirement made it possible to show that a difference in intake between the drug and vehicle conditions could be demonstrated [7]. This has been especially evident in studies of oral pentobarbital self-administration in rhesus monkeys, i.e., as the response requirement increased more drug than vehicle was consumed [17,59]. Recent work explored the limits of this relationship showing that apparent pentobarbital preference demonstrated in this manner broke down at very high response requirements [55], but could be reinstated by increasing reinforcement magnitude [56]. In the studies of oral triazolam and diazepam self-administration described above, however, higher response requirements were not maintained by drug

than by vehicle when the fluids were separately available (Ator and Griffiths, unpublished results).

Schedules of reinforcement which constrain rate of reinforcement but leave response rate free to vary, such as fixed-interval schedules of reinforcement, have not often been used in studies of barbiturate or benzodiazepine self-administration. The few studies that have been done (using the IV route in monkeys) found that patterns of responding typical of such schedules have been maintained (e.g., pentobarbital: [42]; methohexital: [50]; J. Bergman, personal communication).

VERBAL REPORT MEASURES

Experimental studies of self-administration have been used as a way of providing information relevant to an understanding of the reinforcing properties of a drug. Verbal report measures, such as scales of drug liking, have been proposed as providing an indirect measure of drug reinforcement in studies with human subjects. Usually, but not always, these liking ratings correspond to drug choice for individual subjects. For example, in a study of diazepam choice [19], eight subjects liked 5 mg diazepam better than placebo and indeed six of the eight chose that dose over placebo on the majority of the choices. On the other hand, nine subjects said they liked 10 mg diazepam more than placebo, but only four of these subjects chose this dose over placebo the majority of the time; furthermore five subjects reported no difference in liking between 10 mg diazepam and placebo, yet four of the five chose placebo over the 10 mg dose. It may be that the variables that control liking ratings differ somewhat from the variables that control choice [30,65]. It is sometimes assumed that verbal report measures will predict drug abuse equally well as self-administration measures, but this may be true only under some circumstances, e.g., for populations with certain types of drug histories.

CONCLUSION

Early problems with chronic clinical use and, subsequently, with abuse of the barbiturates predated laboratory study of drug self-administration generally. Self-administration studies later demonstrated barbiturate reinforcement *per se* and that, like man, nonhuman species would also self-administer these drugs to the point of physical dependence. Laboratory findings such as these with barbiturates, as well as with other historically abused drugs such as cocaine and morphine, contributed to the establishment of the self-administration paradigm as one which might usefully aid in determining the probability of abuse of newer compounds. A number of the studies with the benzodiazepines seem to have been designed with a major emphasis on that purpose. The barbiturates have emerged as positive controls against which benzodiazepines, which have largely supplanted barbiturates clinically, have been judged. While it is now clear that reinforcement by both barbiturates and benzodiazepines can be demonstrated relatively easily by different routes of administration (with the possible exception of the IG route), variability in results across studies raises questions about the types of variables (e.g., behavioral, biological, pharmacological) that determine reinforcement with these drugs. Although there has been more documented variability in results across studies with benzodiazepines than barbiturates, anecdotal reports from some laboratories suggest that there is more variability in establishing some of the barbiturates as reinforcers than the published literature might indicate. Thus further work on the variables determining barbiturate self-administration may be indicated. The increasingly sophisticated body of information on the pharmacokinetics of the benzodiazepines [27] may make it possible to determine the extent to which some of these variables (particularly those related to speed of onset and duration of effect) influence self-administration. Manipulating schedules of reinforcement may provide information about the circumstances of availability that maximize or minimize the self-administration of compounds with different pharmacokinetic profiles. Recent work also suggests that under some schedules of reinforcement, benzodiazepine self-administration may be influenced in an important way by immediate self-administration history but the limits of this variable have not been demonstrated.

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