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Relative Abuse Liability of Triazolam: Experimental Assessment in Animals and Humans

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GRIFFITHS, R. R., R. J. LAMB, N. A. ATOR, J. D. ROACHE AND J. V. BRADY. *Relative abuse liability of triazolam: Experimental assessment in animals and humans.* NEUROSCI BIOBEHAV REV 9(1) 133–151, 1985.—The abuse liability of a drug is a positive, interactive function of the reinforcing and adverse effects of the drug. The relative abuse liability of the hypnotic benzodiazepine, triazolam, has been controversial. This paper reviews animal and human studies bearing on its relative abuse liability, including data on pharmacological profile, reinforcing effects, liking, speed of onset, discriminative stimulus effects, subjective effects, physiological dependence, rebound and early morning insomnia, drug produced anxiety, lethality in overdose, psychomotor impairment, interactions with ethanol, anterograde amnesia, impaired awareness of drug effect, and other psychiatric and behavioral disturbances. It is concluded that the abuse liability of triazolam is less than that of the intermediate duration barbiturates such as pentobarbital. Although there are considerable data indicating similarities of triazolam to other benzodiazepines, there is also substantial speculation among clinical investigators and some limited data suggesting that the abuse liability of triazolam is greater than that of a variety of other benzodiazepines, and virtually no credible data or speculation that it is less. Further research will be necessary to clarify definitively the abuse liability of triazolam relative to other benzodiazepines.

Abuse liability Triazolam Benzodiazepines Barbiturates Reinforcing effects Adverse effects Drug self-administration Drug liking Drug discrimination Subjective effects Dependence Lethality Psychomotor impairment Ethanol interactions Amnesia Psychiatric disturbance Animals Baboons Humans

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BENZODIAZEPINES are among the most widely used of all prescribed drugs. Concern about the potential for drug abuse/dependence has prompted the development of clinical and preclinical methods for assessing various pharmacological effects of these drugs which are relevant to their relative abuse liability. A series of excellent review papers addressing various aspects of the relative abuse liability of benzodiazepines as a class has been written recently [49, 60, 96, 116, 117, 136, 157].

Of all the marketed benzodiazepine anxiolytics and hypnotics, the relatively new hypnotic, triazolam, has been the most controversial with respect to physiological dependency potential and other adverse effects. Part of this controversy was directly responsible for the removal of triazolam from the drug registry in the Netherlands in 1979 [31, 86, 88]. Although some of the issues related to this initial controversy appear to have been resolved, a variety of new issues has been raised (cf. [73, 76, 146]), prompting the speculation that triazolam "will have the highest abuse potential of all the benzodiazepines yet marketed" [25].

The major purpose of this paper is to review all available data on the abuse liability of triazolam relative to the intermediate duration barbiturates, such as pentobarbital, and to other marketed benzodiazepines. A secondary purpose is to use triazolam as a case study to illustrate the complexity of the concept of abuse liability by providing an analysis of the wide range of measures and methodological approaches which may be considered relevant.

CONCEPTUAL DEFINITION OF ABUSE LIABILITY

Considerable confusion surrounds the meaning of the term abuse liability. Historically, drug abuse liability has been used to refer to: (1) the liability for abuse (i.e., the likelihood that a drug will be abused) and/or (2) the liability of abuse (i.e., the untoward effects of abusing the drug). For purposes of this review, the term will be used in both senses—the liability for and of abuse. These two senses of abuse liability correspond directly to two major characteristics of drugs of abuse: (1) they have *reinforcing properties* (they have the capacity to maintain drug self-administration), and (2) they produce *adverse effects* (they have the capacity to harm the individual and/or society). The presence of both characteristics is necessary to define a drug of abuse (cf. Brady *et al.* [17]). A drug devoid of reinforcing effects but producing significant adverse effects should be considered a poison, not a drug of abuse (e.g., cyanide). Similarly, a drug having some reinforcing properties but producing no adverse effects is not meaningfully considered a drug of abuse (e.g., a nontoxic, nonnutritive sweetener). The relative abuse liability of a compound is an interactive function of the degree of reinforcing properties and adverse effects. Thus, compounds with high abuse liability could be: (1) highly efficacious reinforcers producing highly significant adverse effects (e.g., phencyclidine), (2) equivocal reinforcers producing highly significant adverse effects (e.g., lysergic acid diethylamide), or (3) highly efficacious reinforcers producing modest adverse effects (e.g., moderate cocaine doses). Compounds with low abuse liability must necessarily be those which are marginal reinforcers and produce marginal adverse effects (e.g., caffeine). It should be recognized that reinforcing properties and adverse effects are not necessarily independent dimensions. For example, a highly efficacious drug reinforcer may produce adverse effects solely by virtue of maintaining high levels of drug seeking and self-administration behaviors to the exclusion of more socially desirable behavior. A further illustration of the nonindependence of reinforcing properties and adverse effects is that some adverse effects (e.g., physiological dependence) can modulate the reinforcing properties of drugs.

CHEMICAL STRUCTURE/PHARMACOLOGICAL PROFILE

Chemical structure, molecular mechanism of action, and simple pharmacological profile sometimes provide crude information for estimating the abuse liability of a new compound based on degree of similarity with known drugs of abuse. Triazolam shares with diazepam and most marketed benzodiazepines a common chemical structure (1,4-benzodiazepine), putative molecular site of action (benzodiazepine receptor), and simple pharmacological profile (sedative/anxiolytic) [130]. Since a variety of preclinical, clinical, and epidemiological data suggests that benzodiazepines such as diazepam have less abuse liability than intermediate-duration barbiturates such as pentobarbital [49, 60, 96], the similarities between triazolam and other benzodiazepines suggest that triazolam may have a modest benzodiazepine-like abuse liability.

REINFORCING EFFECTS

Reinforcing efficacy of a drug refers to the relative effectiveness in maintaining behavior on which the delivery of the drug is dependent [56]. A valid estimate of the relative reinforcing properties of a drug is central to the assessment of abuse liability. These properties can be assessed in both animals and humans.

REINFORCING EFFECTS IN ANIMALS

Drug self-administration procedures in laboratory animals permit assessment of the relative efficacy with which different drugs maintain drug self-administration. The validity of this approach for providing information relevant to human drug abuse is supported by the good correspondence between those drugs that are self-administered by laboratory animals and those that are self-administered and abused by humans [51] or produce profiles suggesting abuse liability in human experiments [50].

Self-administration of a variety of benzodiazepines has been studied in rats and nonhuman primates [49]. Triazolam self-administration has not been studied in rodents, but five such studies have been conducted in nonhuman primates. Three have involved the intravenous route and one each has involved the intragastric and oral routes.

Intravenous Self-Administration

The first study [89] used procedures described in detail elsewhere [57] to examine self-injection of diazepam, triazolam, pentobarbital, and chlorpromazine in baboons. Intravenous injections of drug were dependent upon completion of 160 lever presses (a 160-response fixed-ratio schedule). A 3-hr timeout followed each injection, permitting a maximum of eight injections per day. Before testing each dose of drug, self-injection performance was established with cocaine. Subsequently, a test dose was substituted for cocaine for a period of either 12 or 15 days. For triazolam, the dose levels in mg/kg/injection and number of animals studied at each dose level (indicated in parentheses) were: 0.0001 (2), 0.001 (2), 0.0032 (3), 0.01 (4), 0.032 (2), 0.1 (2),

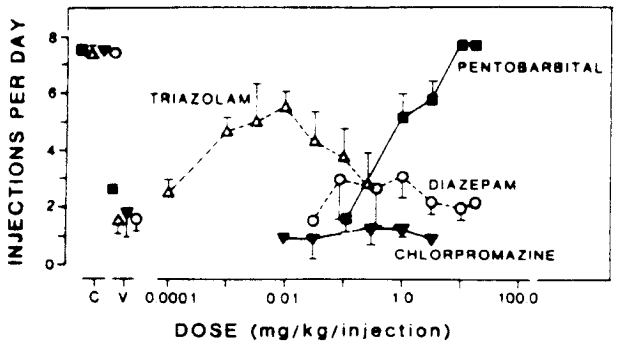

FIG. 1. Baboon intravenous drug self-injection results with triazolam, pentobarbital, diazepam, and chlorpromazine. Y-axis: injections per day; X-axis: dose (mg/kg/injection), log scale. C indicates mean of all 3-day periods with cocaine that immediately preceded every substitution of a drug dose or vehicle. V indicates mean of the last 5 days after substitution of the drug vehicle. Drug data points indicate mean of the last 5 days after substitution of a drug dose. Brackets indicate one S.E.M. unless encompassed by the data point. Data with pentobarbital, diazepam, and chlorpromazine are replotted from Griffiths *et al.* [57].

and 0.32 (2). These details for diazepam, pentobarbital, and chlorpromazine have been reported previously [57]. Figure 1 shows that chlorpromazine failed to maintain self-injection performance above vehicle control levels. Diazepam was associated with relatively low levels of self-injection (3.1 injections/day, maximum) which exceeded vehicle control levels in two of three animals tested. Triazolam maintained levels of self-injection (5.6 injections/day, maximum) which were substantially higher than vehicle levels but clearly below cocaine control levels in all animals tested. Finally, pentobarbital was associated with dose-dependent increases in self-injection performance, with maximal levels (7.7 injections/day) maintained in the range of cocaine.

The second intravenous study was conducted by Romer [125] using standard procedures [27] to evaluate the self-administration of four benzodiazepines in three or four male rhesus monkeys. Access to triazolam (0.001, 0.0032 mg/kg), temazepam (0.01, 0.032 mg/kg), flurazepam (0.18, 0.56 mg/kg), chlordiazepoxide (0.32 mg/kg), and saline was provided 23 hr/day under a lever pressing schedule (probably fixed-ratio 1) with a 10-sec timeout following each injection. The lowest dose of each drug presumably was selected as a proportion of a dose which produced CNS depressant effects in naive monkeys. Drug doses were studied for at least 4 weeks. During the first week of drug availability, there was a 15-min period each day during which each lever press produced both a drug injection and a food pellet. Subsequently, the food condition was eliminated and lever presses only produced drug injections. The results showed that triazolam maintained more consistent and greater numbers of injections than any of the other drug conditions. For instance, during the first week during which drug alone was available, triazolam maintained an average of 112 and 123 inj/23 hr at 0.001 and 0.0032 mg/kg respectively, compared to a saline control and all the other drug conditions which ranged between 12–63 inj/23 hr. The rank ordering of the mean number of inj/23 hr on the fourth week of drug alone availability was: 146 (0.001 triazolam), 118 (0.0032 triazolam), 103 (0.032 temazepam), 33 (0.18 flurazepam), 25 (0.56 flurazepam), 18 (0.01 temazepam), 13 (0.32 chlordiazepoxide).

The third intravenous study [21] compared the self-administration of pentobarbital and three benzodiazepines in female rhesus monkeys. Drug was available during daily 4-hr sessions under a fixed-ratio 1 schedule of lever pressing with a 20-sec injection duration. High rates of self-injection were initially established with cocaine (0.2 mg/kg), and subsequently the test drug was substituted for cocaine. After 7 days at an initial dose of the test drug, the dose was increased and that dose remained available for the next 7 days. This doubled dose level of each test drug was selected as a proportion of a dose which produced observable CNS depression. Each of the four test drugs was tested in four monkeys with drug order counterbalanced across animals. The rank ordering of the mean number of injections per session for the last 3 days was 105.9, 103.3 (pentobarbital 0.1 and 0.2 mg/kg, respectively), 33.3, 32.2 (triazolam 0.001 and 0.0016 mg/kg, respectively), 25.7, 28.7 (flurazepam 0.05 and 0.1 mg/kg, respectively), 15.4 and 13.4 (diazepam 0.12 and 0.25 mg/kg, respectively). Although absolute differences between compounds were sometimes small, the same rank ordering was also apparent with these data on a within subject basis (i.e., within all four monkeys mean injections for the last 3 days maintained by the four drugs were: pentobarbital > triazolam > flurazepam > diazepam). Except for one monkey with diazepam, the mean injections for the last 3 days with all four compounds exceeded that for a saline control period obtained when the animals were drug naive.

Intragastric Self-Administration

Some limited data are available concerning triazolam self-administration intragastrically. Using standard procedures [167] involving a fixed-ratio 1 schedule of continuous drug availability in rhesus monkeys, Yanagita and colleagues reported that three out of four animals showed an increased daily self-administration rate over previous vehicle control levels when 0.06 mg/kg/inj triazolam was substituted for vehicle for a 4-week period. However, these monkeys decreased their self-administration rate when the dose was subsequently changed to 0.015 or 0.24 mg/kg [165]. In summarizing these data, Yanagita [162] concluded that triazolam was intragastrically self-administered by monkeys at daily rates similar to or slightly higher than diazepam.

Oral Self-Administration

It has been difficult to obtain voluntary oral intake of behaviorally active drug doses in laboratory animals, and this applies also to the few attempts to study oral benzodiazepine self-administration [49].

The only experiment conducted to date on oral self-administration of triazolam is one with baboons trained under food-induced drinking procedures [3]. Under food-induced drinking procedures, it has been possible not only to establish high levels of oral drug intake with a number of different drugs, and to maintain substantial drinking after the original inducing procedures were suspended, but also to demonstrate clearly reinforcing efficacy of these drugs (e.g., ethanol [62,64]; pentobarbital [28]; methohexital [5]).

In the study with triazolam, two caged baboons were studied in 3-hr daily experimental sessions during which 1000 ml of fluid were available through an automated drinking device [63]. Drink duration was controlled by the baboon with a maximum of 30 sec. The baboons had free access to water except during this daily session. Ingestion of a large volume of fluid in a brief period of time was promoted by

delivering the daily ration of dry food all at once 1 hr into the session. Triazolam was suspended with BIO-SERV Agent K and triazolam concentration was raised gradually across sessions. A substantial proportion of the total volume consumed per session (35% or more) soon was taken in the hour before food delivery, and within-session food delivery was discontinued at 0.03 mg/ml triazolam. The concentration then was increased across sessions to 0.04, 0.08, 0.16, 0.32, 0.64, and 1.28 mg/ml. Drinking at each of these concentrations was studied for at least 10 sessions and until volume consumed showed no increasing or decreasing trends for 4 consecutive sessions. Volume consumed generally remained constant across concentrations and thus the amount of triazolam received (mg/kg) generally increased monotonically. Peak intake was 10.6 mg/kg for one baboon and 21.3 mg/kg for the other. This relationship between drug concentration and intake (mg/kg) was similar to that obtained in previous research with the short-acting barbiturate methohexital in these same baboons [5] but different from that seen earlier with ethanol [62]. With ethanol, volume consumed by these baboons decreased as ethanol concentration increased such that ethanol intake (g/kg) remained generally constant.

At each triazolam concentration of 0.04 mg/ml and above, a two-bottle choice procedure was instituted after drinking under the single-bottle condition was stable. Positions of triazolam and vehicle alternated daily. Figure 2 presents the results of these two-bottle conditions with triazolam and, for comparison, results of the two-bottle conditions conducted during the previous study of methohexital with these and two other baboons [5]. Higher mean volumes of methohexital than water were consumed at a number of methohexital concentrations by three of the four baboons studied; arrows indicate conditions in which the ranges of methohexital and water volumes did not overlap during the last four sessions, thus indicating clear preference for methohexital over water. In contrast, when two of these baboons that showed methohexital preference were studied in this same procedure under conditions of triazolam availability, the ranges of triazolam and vehicle volumes overlapped during these sessions at all but one concentration for each baboon.

In a procedure analogous to that used in some studies of intravenous drug self-administration, the baboons next were required to press a lever a fixed number of times for each triazolam drink. Response requirements were raised gradually until volume consumed in each session was suppressed to virtually zero. Under these fixed-ratio (FR) schedules of reinforcement, triazolam did not maintain greater responding than vehicle at any response requirement. Responding was suppressed for one baboon at FR 8 and for the other baboon at FR 128.

The results of this initial work with oral triazolam self-administration are intriguing in that baboons that were not water-deprived consumed large quantities of triazolam reliably over many months and, as will be described below, showed signs of physiological dependence. Yet, these same baboons did not show strong triazolam preference over drug vehicle as had been shown in tests with methohexital [5] and with ethanol [62].

Conclusions From Animal Self-Administration Studies

The results of these five triazolam self-administration studies with baboons and rhesus monkeys are consistent with the results of previous research in nonhuman primates

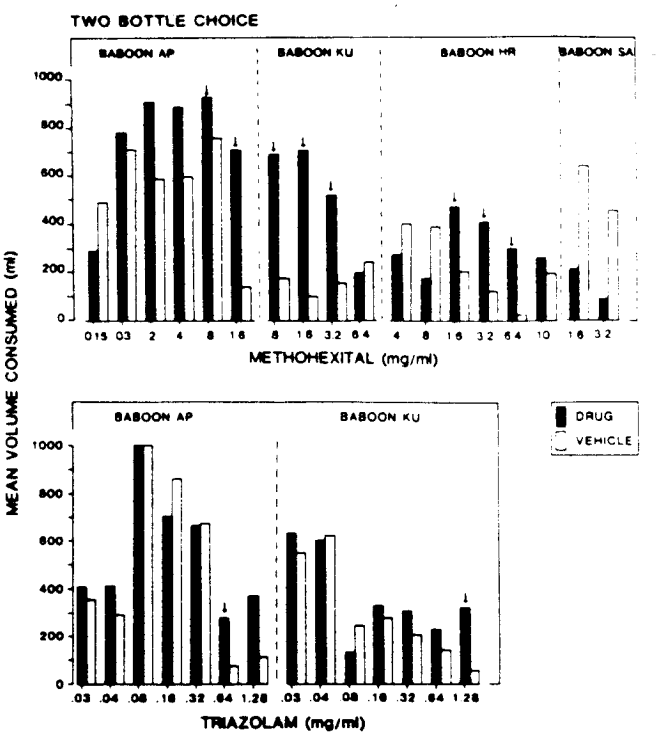

FIG. 2. Oral triazolam and methohexital self-administration in baboons. Y-axes: mean volumes consumed in the last 4 sessions in two-bottle choice conditions. Each drug concentration was available concurrently with the drug vehicle (water for methohexital; water with a suspending agent for triazolam). Each condition was studied until volumes consumed of both drug and water showed no increasing or decreasing trends across four sessions. Arrows indicate the concentrations at which drug volume consumed was higher than the vehicle in all four sessions. The methohexital data are replotted from Ator and Griffiths [5].

(cf. [49]) showing that: (1) benzodiazepines are more efficacious as reinforcers than some drugs, including chlorpromazine, imipramine, haloperidol or perphenazine; and (2) benzodiazepines are less efficacious as reinforcers than a range of other drugs, including pentobarbital, amobarbital, secobarbital, and cocaine.

It is possible that elimination rate is a determinant of rates of self-injection. The finding that triazolam (and possibly temazepam) maintain higher levels of self-injection than a variety of other benzodiazepines which are slowly eliminated or have active metabolites which are slowly eliminated in man is consistent with the results of a previous study which showed that midazolam maintained higher levels of intravenous self-injection than clonazepam, clorazepate, diazepam, flurazepam, and medazepam [57]. These latter five compounds are also slowly eliminated in humans; triazolam and midazolam, in contrast, are rapidly eliminated. However, independent of elimination rate, the possibility also remains that triazolam and midazolam are more efficacious reinforcers than the other benzodiazepines, and thus may have a higher abuse liability. While differences in elimination rate appear to provide an explanation for differences in self-injection between benzodiazepines, they do not account for the differences in self-injection observed between the barbiturates and benzodiazepines. In spite of the fact that both triazolam and midazolam are more quickly eliminated than

pentobarbital, pentobarbital maintained more reliable and higher mean levels of self-injection.

REINFORCING EFFECTS IN HUMANS

The reinforcing properties of drugs in humans can be investigated by adapting procedures developed in the animal drug self-administration laboratory. The validity and appropriateness of such an approach is demonstrated in studies with subjects with histories of drug abuse which have shown that the reinforcing efficacy of diazepam is greater than that of chlorpromazine and oxazepam, but less than that of pentobarbital [53, 55, 59].

There are two experimental studies and one case report which provide some limited information about reinforcing properties of triazolam. Fleming [40] described a patient with a history of multiple drug abuse (including psychomotor stimulants, opioids, marijuana, alcohol, and diazepam) who preferred triazolam to all other medications he had used or abused. While the limitations of such case reports are substantial, it is noteworthy that analogous case reports of preference for a benzodiazepine over all other drugs in patients with histories of multiple drug abuse are nonexistent.

In the two experimental studies, Bechelli *et al.* [11] and Boissl *et al.* [16] used similar double-blind crossover designs to investigate in humans the reinforcing properties of triazolam in comparison to zopiclone, a nonbenzodiazepine hypnotic with a putative site of activity at the benzodiazepine receptor. Chronic alcoholics who had just completed withdrawal treatment were told that the study involved testing drugs that may give the same kind of feelings they get from alcohol, and that they should take the test capsules whenever they felt like taking an alcoholic drink. Subjects were permitted to take up to eight capsules per day of either 0.25 mg triazolam or 3.75 mg zopiclone. On days 1 and 2 subjects received one color-coded treatment and on days 3 and 4 the other color-coded treatment. They were then permitted to choose which color-coded treatment they would receive on days 5 and 6. Although significantly more subjects choose triazolam than zopiclone (25 vs. 15 subjects) in the Bechelli study [11], this effect was not replicated (22 vs. 18 subjects) in the Boissl study [16].

The implications of these experimental results for triazolam are rather limited. Other studies have shown benzodiazepine and sedative reinforcement effects to be dose dependent [52, 53, 99]. Thus, the lack of dose manipulations substantially limit the possible conclusion from the Bechelli study that triazolam is a more efficacious reinforcer than zopiclone. Furthermore, in the absence of a placebo control, one cannot conclude with certainty that triazolam per se served as a positive reinforcer. Finally the failure to replicate this finding in a similarly designed experiment only further reduces confidence in the finding. At best, these limited results in humans are not incompatible with the animal drug self-administration results which suggest that triazolam is a more efficacious reinforcer than other pharmacologically related anxiolytics and sedatives.

RATINGS OF LIKING AND MONETARY VALUE BY HUMANS

One indirect approach to providing information about the reinforcing properties of drugs is to utilize placebo controlled, double-blind methodologies to characterize the pleasant subjective effects produced by drugs in subjects with histories of drug abuse. The appropriateness of using subjects with histories of drug abuse in such evaluations of subjective effects is supported by its face validity and by the results of experiments showing that there was a closer correspondence between experimental results and clinical observation when studies were conducted with "postaddict" populations rather than with "normals" or "patient populations" [12]. With this approach, the reinforcing properties are assumed to be a function of the degree to which a drug produces pleasant subjective effects (sometimes called euphoria or liking) or estimates of "street" monetary value. Such effects can be assessed by using various scale- or item-based questionnaires. Although it is sometimes explicitly or implicitly assumed that the reinforcing effect of a drug is causally dependent on the pleasant subjective effects it produces [70] such assumptions can be reasonably questioned [137]. Furthermore, although there appears to be a generally good correspondence between pleasant subjective effects and reinforcing effects, there have been reports of dissociations between these effects [55,72]. Thus, assessment of such subjective effects is useful as a measure of abuse liability only to the extent it actually predicts reinforcing properties.

The experimental literature demonstrating that benzodiazepines and barbiturates produce pleasant subjective effects in subjects with histories of drug abuse has been reviewed recently [60]. There is only one study to date assessing pleasant subjective effects of triazolam in such subjects. Using a double-blind Latin Square design, Roache and Griffiths [123] compared oral doses of placebo, triazolam (0.5, 1.0, 2.0, and 3.0 mg) and pentobarbital (100, 200, 400, and 600 mg). At 1, 2, 3, 4, 6, 8, 12, and 24 hr after drug administration various questionnaire and performance measures were taken. The two drugs produced similar dose-related effects with area under the time-action curve (AUC) data from a variety of performance measures (psychomotor performance, digit-symbol substitution task performance, staff ratings of magnitude of drug effect); statistically valid relative potency estimates were obtained indicating triazolam was approximately 200 times more potent than pentobarbital. With subject ratings of magnitude of drug liking (AUC), however, statistically valid relative potency estimates could not be obtained because, even though triazolam produced elevations in liking, pentobarbital produced substantially greater increases than did triazolam. Figure 3 shows the estimated "street" monetary value of placebo, triazolam, and pentobarbital. Subjects estimated monetary value of a given dose of drug on the morning following the day on which drug was administered. Analysis of variance and post hoc comparisons showed that only 2 mg of triazolam, and 400 and 600 mg of pentobarbital were significantly different from placebo. Pentobarbital produced significant dose-related increases in estimated street value (600 mg was significantly different from either the 100 or 200 mg doses). In contrast, the effect of triazolam was not a monotonically increasing function of dose and there were no significant differences among doses.

Overall, these data with liking and estimated monetary value suggest that triazolam has somewhat less abuse liability than pentobarbital. This conclusion is consistent with a series of human studies reviewed elsewhere [60] which showed that the pleasant subjective effects and/or reinforcing properties of pentobarbital were greater than those of the benzodiazepines diazepam and chlordiazepoxide. Ratings of pleasant subjective effects and monetary value have also

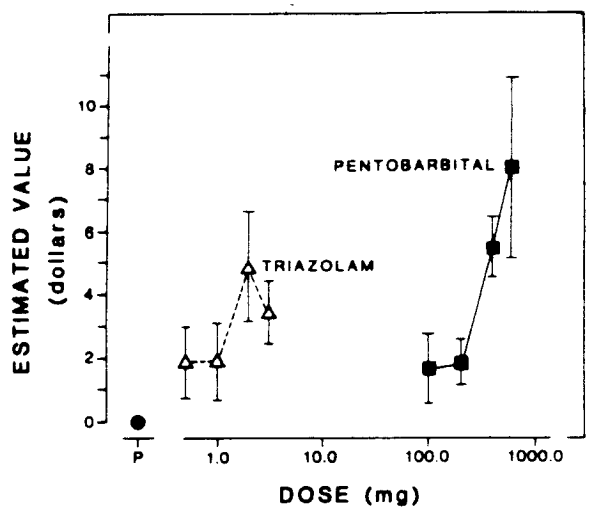

FIG. 3. Estimated "street" monetary value of triazolam and pentobarbital in nine subjects with histories of sedative drug abuse. Y-axis: estimated value in dollars; X-axis: dose (mg), log scale. P indicates placebo. Points show means; brackets show ±S.E.M. Oral doses of triazolam (0.5, 1.0, 2.0 and 3.0 mg) and pentobarbital (100, 200, 400, and 600 mg) produced similar dose-related suppression in psychomotor performance. Monetary street value of each dose was estimated in the morning following the day on which drug was administered. Data are replotted from Roache and Griffiths [123].

been used as a basis for comparing different benzodiazepines. Although conclusions from some studies have been limited because only a narrow range of doses was investigated, the results to date suggest that there are differences among benzodiazepines; lorazepam has been suggested to have reinforcing/subjective effects similar to diazepam, while oxazepam, halazepam, and chlordiazepoxide may have reinforcing/subjective effects less than diazepam [60]. Unfortunately no study to date has compared triazolam with another benzodiazepine with respect to such ratings of pleasant subjective effects and/or monetary value.

SPEED OF ONSET OF DRUG EFFECTS IN HUMANS

It is widely believed that the efficacy of drug reinforcers is partly determined by speed of onset of drug effects. Anecdotally, drug abusers appear to prefer routes of administration resulting in rapid absorption (e.g., intravenous, inhalation) over those resulting in slower absorption (e.g., oral). Consistent with this, drugs are much more readily shown to be reinforcing in animal self-administration when delivered intravenously as opposed to orally or intragastrically. Some limited experimental data also support the proposition that speed of onset is a partial determinant of reinforcing effects. When the dose and duration of intravenous cocaine infusions were manipulated in rhesus monkeys [9] and drug abuser subjects [39], the speed of infusion was directly related to measures of reinforcing efficacy in monkeys and euphoria in humans.

Many abused drugs (e.g., cocaine, amphetamine, heroin, phencyclidine) can be readily taken via routes resulting in rapid onset of effect (e.g., intravenous, inhalation, snorting). With benzodiazepines and barbiturates, in contrast, solubility limitations and injection-related toxicity discourage intravenous abuse, and reports of abuse via inhalation or snorting are virtually nonexistent. Given that speed of onset of drug effect is a determinant of reinforcing efficacy, it follows that the relative abuse liability of benzodiazepine and barbiturates may be importantly determined by speed of onset after oral administration. Support for this within the benzodiazepine class comes from a recent set of studies which involved a variety of subjective, behavioral, and epidemiological measures and concluded that the abuse liability as well as the actual incidence of abuse of diazepam was greater than that of oxazepam [58,59]. Inspection of time-action functions showed that onset of effect was more rapid and time to maximal effect was shorter with diazepam than oxazepam (time to maximal effect was 1–2 hr with diazepam vs. 4–12 hr with oxazepam). Interestingly, when subjects were asked to write comments about what they liked about the drugs which had been administered double-blind, subjects often cited the rapid onset of effects as being a desirable feature of the diazepam effect.

Triazolam absorption after oral administration is rapid with maximum serum concentrations generally occurring at 1–2 hr [8, 32, 45]. Time-course studies of the effects of 0.25 mg triazolam on performance on a psychomotor task and digit-symbol-substitution task (DSST) in normal subjects show peak effects at 1–2 hr [8,108]. In the study by Roache and Griffiths [123] comparing triazolam and pentobarbital in drug abusers, analysis of time-course of psychomotor and DSST performance showed that the drugs were associated with similar rapid onset of effects with the mean peak-effect of triazolam (1–2 hr) occurring somewhat sooner than that of pentobarbital (2–3 hr).

To the extent that speed of onset of effects is a determinant of drug reinforcing efficacy, the relatively rapid onset of effects with triazolam suggests that triazolam may have greater abuse liability than pharmacologically similar compounds (i.e., benzodiazepine hypnotics and anxiolytics) which have slower onset profiles, such as oxazepam [58], and halazepam ([69] and Roache and Griffiths, unpublished observations). Although thorough onset time-course comparisons apparently have not been done, the possibility also remains that triazolam may have less abuse liability than pharmacologically similar compounds which have exceptionally fast onset latencies, such as diazepam [36].

DISCRIMINATIVE STIMULUS EFFECTS IN ANIMALS

Drug discrimination procedures provide information about the interoceptive stimulus properties of drugs. Degree of discriminability with such procedures is not necessarily related to abuse liability [115]. However, under appropriate training and testing conditions, drug discrimination procedures permit the categorization of the interoceptive stimulus properties of a test drug as being similar or dissimilar to standard compounds. If the test drug occasions responding similar to a standard training drug, the test drug and standard are sometimes assumed to have similar abuse liability. This assumption, however, is valid only to the extent that the discriminative stimulus properties covary with the reinforcing and adverse effects of the standard and test compound. While under appropriate training conditions the correlation between discriminative stimulus and reinforcing properties is remarkably high within some drug classes [159], there are notable exceptions. For instance, although racemic *N*-allylnormetazocine (SKF 10,047) produces discriminative stimulus properties similar to phencyclidine [18], phencyc-

lidine maintains drug self-administration (i.e., is a reinforcer) in contrast to racemic *N*-allylnormetazocine which does not [141]. Thus, appropriate caution must be exercised in interpreting drug discrimination results in terms of abuse liability.

In drug discrimination procedures, animals are trained to respond differentially depending on the nature of the drug pretreatment. The most frequently used procedures have involved either a T-maze (e.g., go left if drugged; go right if not drugged) or a two-lever choice situation (e.g., left lever responses produce food if drugged; right lever responses produce food if not drugged). After training, test sessions are conducted in which novel drug conditions are presented. When different doses of the training drug are tested, responding generally is similar to that with the training drug dose except at low doses. When other drugs are compared, drugs from the same or similar pharmacological classes also tend to produce responding like that under the drug training conditions at some doses, while drugs from different classes do not.

The discriminability of benzodiazepines has been demonstrated in studies in which animals were trained to discriminate a benzodiazepine from saline (e.g., chlordiazepoxide, diazepam, flurazepam, or oxazepam [114]). When other drugs were substituted in benzodiazepine-trained animals, drug-appropriate responding has occurred consistently for all other benzodiazepines, inconsistently for other sedative-hypnotics, and not at all for antipsychotics; thus indicating some specificity of effect (e.g., [10,23]).

To date, three studies have investigated the discriminative stimulus properties of triazolam. In two studies with rats [81,140], triazolam was similar to other benzodiazepines (including diazepam, chlordiazepoxide, flurazepam, flunitrazepam, nitrazepam, bromazepam, and midazolam) in that triazolam occasioned drug-lever responding in both diazepam- and pentobarbital-trained animals.

In the third study, which used drug discrimination procedures described in detail elsewhere [4,6], baboons and rats were trained to discriminate either lorazepam (1.0 mg/kg) vs. no drug or pentobarbital (5.6 or 10.0 mg/kg in baboons; 10.0 mg/kg in rats) vs. no drug in a two-lever drug discrimination procedure. Food delivery depended on 20 (baboons) or 10 (rats) consecutive responses on one lever in sessions preceded by intraperitoneal (rats) or intramuscular or oral (baboons) administration of drug, and on the same number of consecutive responses on the other lever following no drug. Drug pretreatment time was 60-min in baboons and 15 (pentobarbital) or 60 (lorazepam) min in rats. All animals reliably completed 100% of the response runs on the appropriate lever in training sessions. Test sessions were conducted in which a drug dose different from the training dose was administered, and the appropriate number of consecutive responses on either lever produced food. In the lorazepam-trained baboons and rats, diazepam, triazolam, and lorazepam but not pentobarbital occasioned drug-lever responding. Figure 4 shows these results with diazepam, triazolam, and pentobarbital in baboons. Interestingly, although pentobarbital failed to occasion drug lever responding in lorazepam-trained animals, diazepam, triazolam, lorazepam, as well as pentobarbital produced drug-lever responding in pentobarbital-trained baboons and rats. This asymmetrical generalization with lorazepam and pentobarbital training conditions suggests a specificity of discriminative stimulus effects which has not been clearly documented in previous drug discrimination experiments with benzodiazepines and barbiturates.

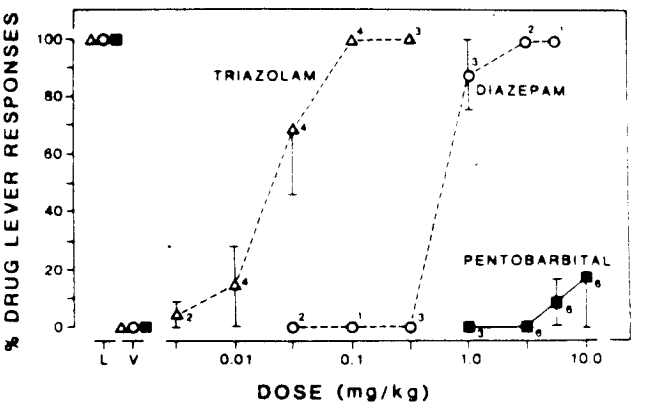

FIG. 4. Baboon drug discrimination results with triazolam, diazepam, and pentobarbital in animals trained to discriminate lorazepam (1.0 mg/kg, IM or PO) from the no-drug condition. Y-axis: drug lever responses expressed as a percentage of total session responding; X-axis: dose (mg/kg), log scale. L and V indicate test session results after administration of 1.0 mg/kg lorazepam or vehicle, respectively. Points indicate means; brackets show ±S.E.M. unless encompassed by the data point. Numerals indicate number of baboons tested at each dose. Administration of triazolam was oral, pentobarbital was intramuscular, and diazepam was both oral (two baboons) and intramuscular (one baboon). A higher dose of pentobarbital (17.8 mg/kg) markedly suppressed responding in four of the six baboons tested.

The findings in lorazepam-trained animals suggest that triazolam produces interoceptive stimuli similar to lorazepam and diazepam, but dissimilar to pentobarbital. To the extent that such interoceptive stimuli covary with reinforcing properties, these data suggest that the abuse liability of triazolam may be more like diazepam and lorazepam than pentobarbital. That the benzodiazepines occasion drug lever responding in pentobarbital-trained animals may be relevant to the drug abuse phenomenon of illicit "look-alike" or "counterfeit" drugs. In recent years, diazepam has appeared in the illicit drug abuse market in preparations designed to resemble hypnotic compounds such as methaqualone which are believed to have substantial abuse liability. The fact that triazolam produces pentobarbital-like interoceptive stimuli in pentobarbital-trained animals suggests the possibility that triazolam could be similarly misused as a "look-alike" hypnotic.

CATEGORIZATION OF SUBJECTIVE DRUG EFFECTS BY HUMANS

Despite the demonstrated utility of the drug discrimination procedure in the animal laboratory, there have been relatively few attempts to adapt this methodology for use in human studies and no attempts to evaluate anxiolytic or sedative-hypnotic drugs with such techniques. However, data which may be analogous to animal drug discrimination can be provided in the context of double-blind evaluation of drugs in subjects with histories of drug abuse. Subjects can be asked to categorize the subjective effects of a test compound as being similar or dissimilar to standard compounds with which they presumably have had experience. The abuse liability of the test compound is assumed to be similar to that of the standard compound(s) with which it is categorized. Such a procedure has been used to distinguish between mor-

phine and pentobarbital, morphine and nalorphine, and morphine and *d*-amphetamine [70]. Such a procedure has also been used to differentiate between two benzodiazepine anxiolytics. Although diazepam and oxazepam were equally often categorized as "benzodiazepine," diazepam was more frequently categorized as "barbiturate" than oxazepam [58,59].

One study has evaluated triazolam using categorization procedures in subjects with histories of drug abuse [123]. This study (described in more detail in *Ratings of Liking and Monetary Value by Humans* section) involved the double-blind evaluation of placebo, triazolam, and pentobarbital. Subjects were informed that various drugs would be administered and that these could include neuroleptics, minor tranquilizers, sedatives, stimulants, and placebo. Other than receiving this general information, subjects were blind to the type of drug administered. At 1, 2, 3, 4, 6, 8, 12, and 24 hr after drug administration subjects completed a questionnaire which involved categorizing the drug effects as being most similar to one of 13 categories of psychoactive drugs. The questionnaire provided descriptive titles for, and examples of, drugs in each of the following drug categories: placebo, opioids, phenothiazines, barbiturates and sleeping medications (examples included pentobarbital, phenobarbital, Tuinal, Nembutal, reds, yellows, methaqualone, quaaludes, Placidyl), antidepressants, hallucinogens, benzodiazepines (examples included Valium, Librium, Tranxene), stimulants, alcohol, cocaine, marihuana, phencyclidine, and other.

Except for potency differences, both drugs produced similar dose-related effects on various performance measures. Table 1 shows the results of subject categorization of drug effects. Placebo was reliably categorized as "placebo or blank." While the lowest doses of triazolam and pentobarbital were rated as placebo by some subjects, higher doses of both drugs were consistently rated as similar to a psychoactive drug category. Interestingly, as reflected by this procedure, triazolam and pentobarbital produced clearly different effects: triazolam was categorized predominately as a "benzodiazepine" while pentobarbital was categorized predominately as a "barbiturate or sleeping medication."

The present results are consistent with the animal drug discrimination results presented in *Discriminative Stimulus Effects in Animals* section. As with the results obtained with benzodiazepine-trained baboons and rats, the human data suggest that the interoceptive stimulus properties of triazolam may be more diazepam-like than pentobarbital-like. To the extent that such interoceptive stimulus properties covary with reinforcing and adverse effects, the animal and human data suggest that the abuse liability of triazolam is more diazepam-like than pentobarbital-like. As discussed previously, categorization of drug effect by humans has also been used as a basis for differentiating between benzodiazepines. Regretably such procedures have not been used to compare triazolam with other benzodiazepines.

TABLE 1

CATEGORIZATION OF DRUG EFFECT BY NINE SUBJECTS WITH HISTORIES OF SEDATIVE DRUG ABUSE

Dose/Drug Administered	(N)	Percent Subjects Selecting Category			
		Placebo	Barb	Benzo	Other
Placebo	(9)	100	0	0	0
0.5 mg TZ	(9)	22.2	0	77.8	0
1.0 mg TZ	(9)	11.1	0	77.8	11.1
2.0 mg TZ	(9)	0	22.2	77.8	0
3.0 mg TZ	(9)	0	11.1	88.9	0
Total TZ	(36)	8.3	8.3	80.6	2.8
100 mg PB	(9)	44.4	11.1	22.2	22.2
200 mg PB	(9)	22.2	55.6	0	22.2
400 mg PB	(9)	0	77.8	22.2	0
600 mg PB	(9)	0	77.8	11.1	11.1
Total PB	(36)	16.7	55.6	13.9	13.9

After receiving oral doses of triazolam (TZ), pentobarbital (PB), and placebo, subjects were required to identify the drug effect as being most similar to one of several categories of psychoactive drugs, including "Blank or placebo" (PLACEBO), "Barbiturates and sleeping medication" (BARB), and Benzodiazepines (BENZO). Data show the percentage of subjects selecting a given category; row totals do not always equal 100 percent because of rounding errors. With a given dose of drug, if a subject selected more than one drug category during the multiple daily ratings, the most frequently chosen category was used. Data are derived from Roache and Griffiths [123].

PHYSIOLOGICAL DEPENDENCE

Although at times people appear to believe that the ability of a drug to produce physiological dependence is the *sine qua non* of an abused drug, this has long been realized not to be the case, and is constantly being rediscovered not to be the case [68, 85, 106]. For instance, there are drugs that produce physiological dependence without eliciting drug seeking behavior (e.g., cyclazocine, nalorphine [97]); there are also drugs which are thought not to produce physiological dependence, but do produce substantial drug seeking behavior (e.g., cocaine, amphetamine [38,48]); and finally, there are situations in which the drug doses and/or schedules of drug availability preclude the development of physiological dependence yet are associated with drug-seeking behavior [42, 120, 158].

Physiological dependence may contribute to the abuse liability of a drug in two ways: (1) as an adverse effect of drug use that is revealed upon discontinuation of drug use; and (2) as a potential mechanism by which the reinforcing effects of a drug may be enhanced. While this latter point seems reasonable and is consistent with some clinical descriptions of benzodiazepine abuse, a clear experimental demonstration of this mechanism is not available. In fact, there are some animal drug self-administration data which suggest that, while physiological dependence increases the reinforcing properties of morphine, such is not the case with diazepam [160,163]. In any event, physiological dependence certainly represents a significant adverse effect of drug use and thus should be considered in a balanced analysis of the abuse liability of benzodiazepines.

PHYSIOLOGICAL DEPENDENCE IN ANIMALS

Three general methods have been used to assess the ability of benzodiazepine-like compounds to produce physiological dependence in laboratory animals: (1) substitution tests in which the ability of the test drug to suppress withdrawal signs of animals physiologically dependent on another drug

is assessed; (2) precipitated withdrawal tests in which the test drug is given chronically and the presence or absence of precipitated withdrawal signs is noted when a benzodiazepine antagonist is given; and, (3) spontaneous withdrawal tests in which the test drug is given chronically and animals are assessed for withdrawal signs when drug administration is abruptly terminated.

Substitution Tests

Two groups have assessed the ability of triazolam to substitute for a barbiturate in barbiturate dependent animals. Yanagita [161,165] reported that triazolam (0.25 and 1.0 mg/kg, PO) suppressed withdrawal signs in rhesus monkeys normally maintained on barbital (75 mg/kg; PO: b.i.d.). Other benzodiazepines were also effective at suppressing barbital withdrawal signs [161]. However, not all sedative drugs studied with this procedure were able to suppress barbital withdrawal signs (e.g., benzoctamine and methaqualone [164,167]). Therefore, these effects cannot be accounted for solely in terms of the sedative effects of benzodiazepines.

Investigators at the Upjohn Company conducted two studies to assess the ability of triazolam to substitute for barbiturates in barbiturate-dependent rats. In the first study [20] female Sprague-Dawley rats were maintained on a diet of powdered Purina rat chow containing phenobarbital (0.14%) for at least 3 months prior to beginning of a test phase in which they were tested repeatedly with an interval of at least three weeks between tests. Tests consisted of first depriving the rats of food (and drug) for one day. On the next day the rats were allowed access to powdered rat chow without phenobarbital and were given either drug or placebo (orally in a suspension) at approximately 8:30 a.m. and 3:30 p.m. On the morning of the third day amount eaten and change in body weight were recorded. On the first day, rats that were exposed to the phenobarbital diet lost amounts of weight (approximately 24 g) that were similar to those lost by identically treated control rats never exposed to phenobarbital. However, rats on the phenobarbital diet regained only about 7 g when given placebo on day 2, while the control rats regained essentially all the weight lost. When triazolam (3, 6, and 12 mg/kg) was administered, only the 6 mg/kg dose increased weight gain above placebo levels, but this dose did not produce weight gains as great as those produced by phenobarbital (15–40 mg/kg). Like triazolam, diazepam (15–60 mg/kg), flurazepam (30–120 mg/kg), and barbital (25–100 mg/kg) also showed weak effects. In another study [22], the ability of triazolam to suppress intravenous self-administration (continuous reinforcement) of pentobarbital-sodium (3.2 mg/kg/inj; mean intake approximately 250 mg/kg/day) by female Sprague-Dawley rats was examined. Test drugs were administered by mixing with the rats' powdered diet. Triazolam (at concentrations of 0.01 and 0.03%) and diazepam (at 0.1 and 0.3%) were tested for two days. Except for potency differences the effects of the two drugs were similar. The highest concentrations of triazolam and diazepam resulted in an average intake of 16 and 109 mg/kg/day, respectively; these levels of intake reduced pentobarbital self-administration by approximately 31% for both drugs.

The latter two studies suggest that triazolam and other benzodiazepines show weak or incomplete cross-dependence with phenobarbital and pentobarbital, a result compatible with a report of Martin and co-workers [98] which showed that diazepam did not completely suppress pentobarbital withdrawal signs in rats. However, these results contrast with those of Yanagita [161] showing triazolam and other benzodiazepines were effective in suppressing barbital withdrawal in rhesus monkeys. Clearly, this topic of cross-dependence between benzodiazepines and barbiturates needs further study. At present, however, there is little that distinguishes triazolam from other benzodiazepines in this regard, except potency.

Precipitated Withdrawal Test

Administration of Ro 15-1788, a benzodiazepine antagonist, to animals treated chronically with a benzodiazepine precipitates signs suggesting a benzodiazepine withdrawal syndrome (e.g., [26, 87, 90, 91, 100, 126]). Whether this withdrawal syndrome differs from the spontaneous withdrawal syndrome only in the kinetics of agonist-receptor dissociation or along some other dimension as well is presently undecided [90,100]. However, most investigators do agree that the Ro 15-1788 precipitated withdrawal syndrome is relevant in assessing the degree of physiological dependence produced by benzodiazepine administration.

With respect to triazolam, Cumin and co-workers [26] reported that administration of Ro 15-1788 (100 mg/kg) to cats that had received triazolam (1 mg/kg/day × 16 days) produced rigidity, vocalization, and hypersalivation. They also reported that administration of Ro 15-1788 to squirrel monkeys that had received triazolam (3 mg/kg/day × 15 days) produced rigidity, loss of reactivity and refusal of food.

In our laboratory, we conducted precipitated withdrawal studies in three baboons receiving triazolam and three receiving diazepam. Observations were conducted on four of these baboons while they were subjects in triazolam (two baboons) or diazepam (two baboons) oral self-administration experiments (cf. *Reinforcing Effects* section) in which they consumed drug during daily 3-hr sessions. The two other baboons received triazolam (one baboon) or diazepam (one baboon) via continuous intragastric infusion. Mean drug exposure at the time of testing was 3.0, 5.0, and 8.9 mg/kg/day for the three triazolam-exposed animals, and 2.6, 16.3, and 20 mg/kg/day for the three diazepam-exposed animals. Animals received intramuscular injections of Ro 15-1788 (5.0 mg/kg) or vehicle and were observed for withdrawal signs using methods similar to those previously described [90]. Figure 5 shows that baboons displayed more precipitated withdrawal signs following Ro 15-1788 administration than after vehicle administration.

These results and those of Cumin *et al.* [26] indicate that triazolam, like other benzodiazepine agonists such as diazepam, flurazepam, and lorazepam, produces physiological dependence as revealed by Ro 15-1788 precipitated withdrawal. Data presently available do not provide a basis for distinguishing triazolam from these other benzodiazepine agonists.

Spontaneous Withdrawal Test

Yanagita and co-workers [165] conducted a study in six rhesus monkeys which involved administration of: triazolam (2–4 mg/kg/day) during weeks 1–4, no drug during week 5, triazolam (4–6 mg/kg/day) during weeks 6–9, and no drug during week 10. Using standard withdrawal criteria [167], during the first withdrawal period three monkeys showed intermediate grade withdrawal signs while the other three showed mild grade signs. During the second withdrawal

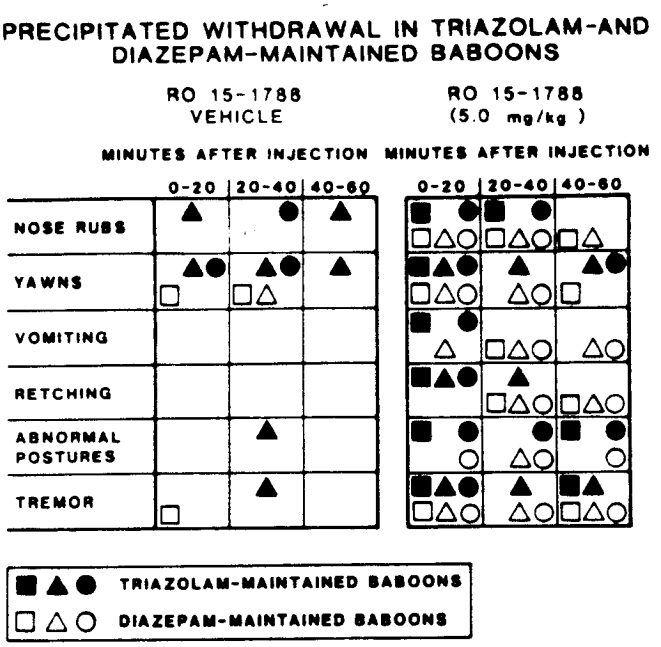

FIG. 5. Benzodiazepine antagonist precipitated withdrawal in baboons. Three triazolam-maintained animals (filled symbols) and three diazepam-maintained animals (open symbols) were observed for withdrawal signs after receiving intramuscular injections of Ro 15-1788 vehicle and Ro 15-1788 (5.0 mg/kg). Presence of symbols indicates withdrawal sign occurred one or more times during the time block.

period, severe, intermediate and mild grade withdrawal signs were observed in two monkeys each. These results with triazolam are generally similar to those reported by Yanagita with diazepam and a variety of other benzodiazepine agonists (e.g., [166, 167, 168]).

The only other study of spontaneous withdrawal from triazolam in non-human primates consists of observations made in our laboratory in two baboons which had histories of oral triazolam self-administration and Ro 15-1788 precipitated withdrawal tests, as previously described in this section and *Reinforcing Effects* section. At the time of the spontaneous withdrawal test, baboons AP and KU had been self-administering various amounts of triazolam orally in daily 3-hr sessions for 210 and 48 days, respectively, with average daily doses during the last 10 days being 21.8 and 2.7 mg/kg, respectively. Neither animal had received Ro 15-1788 during the preceding 3-months. The spontaneous withdrawal test involved replacing triazolam with vehicle alone for a period of 11 (AP) or 16 (KU) days, and then reinstating the triazolam. The baboons were observed for withdrawal signs [90] during 15-min observation periods twice daily, once in the morning and once in the afternoon. After terminating triazolam, abnormal posturing and scratching/nose-rubbing increased over previous baseline levels and returned to those baseline levels when triazolam was reinstated. These withdrawal signs were relatively mild compared to some of the observations made by Yanagita in rhesus monkeys undergoing spontaneous triazolam withdrawal [165]. Whether the withdrawal signs are any milder than would be observed after comparable treatment of baboons with other benzodiazepines is unknown. It may be that the baboon is generally less sensitive to benzodiazepine withdrawal than the rhesus monkey because spontaneous withdrawal signs as severe as those described by Yanagita after diazepam and lorazepam treatment in rhesus monkeys [167,168] have not been observed following abrupt termination of these same drugs in baboons [87,90].

Investigators at the Upjohn Company have examined triazolam spontaneous withdrawal in two studies with rodents. In the first study [133], separate groups of female Sprague-Dawley rats were fed a diet of powdered Purina rat chow containing either 0.0017% or 0.005% triazolam, 0.017% or 0.05% diazepam, 0.017% chlorpromazine, or no drug. The drug concentrations were increased at weekly intervals by units of 0.15 $\log_{10}$, and by the fourth week the average amount of drug consumed per day was 3.6 and 9.6 mg/kg of triazolam, 31.7 and 94.8 mg/kg of diazepam, and 27.8 mg/kg of chlorpromazine. When drug was eliminated from the food on weeks 5 and 6, body weights and food intake were not affected in the chlorpromazine or no drug groups but were decreased in a dose-dependent fashion in the triazolam and diazepam groups. For both triazolam and diazepam, weight loss peaked on day 2 of withdrawal and recovered to pre-withdrawal levels by days 6–7 with the low dose groups and by days 9–10 with the high dose groups. A key-rattle stimulus on day 2 of withdrawal elicited seizures in 15%, 37%, 0%, and 0% of the triazolam, diazepam, chlorpromazine, and control (no drug) animals, respectively.

In a second study at the Upjohn Company [132], separate groups of female mice were fed a Purina chow diet containing either triazolam (three concentrations), flurazepam (four concentrations), diazepam (three concentrations), phenobarbital (three concentrations), or no drug for 15 days. Thirty hours after drug was eliminated from the diet, electroshock seizure thresholds were obtained using an up-and-down titration method [82] (0.1 sec, 60 Hz starting at 7.1 mA and changed by mA units of 0.05 $\log_{10}$). Following this, mice were returned to the drug diet for a further 15 days. Drug was then eliminated and seizure thresholds determined daily for 4 days. Drug intake was an increasing function of concentration for all drugs, with average daily consumption for the three triazolam groups being 0.41, 1.1, and 3.3 mg/kg before drug withdrawal. Reliable dose-dependent decreases in seizure threshold were not obtained after 15 days but were obtained after 30 days with all four drugs. Peak withdrawal, as indicated by lowered thresholds, occurred on day 1 under all drug conditions except for high dose flurazepam which occurred on day 2.

A final study on triazolam spontaneous withdrawal was conducted by Tanabe and colleagues [144] in rats and mice. During the 2-month course of oral administration of gradually increasing doses of triazolam, spontaneous withdrawal was assessed during 1 to 2 day drug abstinence periods. Measures of pentylenetetrazole-induced convulsion, body weight, and wet weight of brain, heart, kidney and testicles provided no evidence of physiological dependence on triazolam. This finding is at variance with the four previously cited studies on triazolam spontaneous withdrawal. Unfortunately, for purposes of this review the Tanabe study was available in abstract form only. Thus, insufficient detail of the Tanabe results preclude reconciliation of the discrepant findings.

Overall, the animal studies on spontaneous withdrawal show that triazolam produces dose-dependent physiological dependence, but provide no basis for distinguishing qualitatively or quantitatively between the withdrawal signs observed after abrupt termination of triazolam and that observed after termination of other benzodiazepines.

PHYSIOLOGICAL DEPENDENCE IN HUMANS

The signs and symptoms associated with termination of treatment with benzodiazepines has been extensively described and reviewed (cf. [96, 116, 117, 136]). These signs and symptoms include headache, anxiety, hypersensitivity to sensory stimuli and other perceptual disturbances, depersonalization, tremor, insomnia, anorexia, hallucinations, delirium, diaphoresis, and convulsions. The more severe of these signs and symptoms, e.g., delirium and convulsions, have been seen only infrequently. Several studies report triazolam-related insomnia and anxiety which may represent manifestations of physiological dependence.

Rebound Insomnia

Kales and co-workers [78] coined the term rebound insomnia to describe the significant worsening of sleep which occurred following abrupt termination of several of the benzodiazepine hypnotics which had been administered in single doses nightly for relatively short periods. These investigators first noted the phenomenon with relatively rapidly eliminated benzodiazepines, and hypothesized that the intensity of these withdrawal related effects should be inversely related to the elimination rate. Rebound insomnia has been reported following termination of treatment with a wide range of benzodiazepines having short to intermediate half-lives, including triazolam, flunitrazepam, nitrazepam, lorazepam, lormetazepam, and midazolam (cf. [80]). With flurazepam or quazepam which have slowly eliminated active metabolites, evidence for rebound insomnia has either not been found [80,95], or the sleep disturbance noted has been rather modest [46, 80, 102, 103]. It is possible that a bias toward demonstrating rebound insomnia with quickly eliminated compounds but not with slowly eliminated compounds may result from a statistical artifact produced by variable rates of drug elimination across subjects in combination with withdrawal periods of insufficient duration [103]. However, Bixler and associates [14] in reanalyzing individual data from a 15-withdrawal night study [75] with flurazepam and quazepam found no such statistical bias. Although further research is needed, individuals who have been treated for longer periods of time and with higher doses would appear to be at greatest risk for rebound insomnia as well as other withdrawal signs following termination of benzodiazepine treatment.

With respect to triazolam, it is clear that transient deterioration of sleep can occur following termination of treatment [1, 74, 77, 95, 103, 128, 153, 154]. When triazolam-associated insomnia does occur, its onset is rapid (maximal effects may occur in one day [1, 95, 103, 154]), and sleep loss may be substantial (maximal sleep loss may be 1–3 hr or more per night [1, 77, 95, 103]). The rapid speed of onset of withdrawal effects distinguishes triazolam from some of the more slowly eliminated benzodiazepines such as flurazepam, chlordiazepoxide, and diazepam which are associated with slower onset of withdrawal signs (cf. [67, 102, 103, 118, 156]).

Early Morning Insomnia

Kales and co-workers [79] were first to describe the phenomenon of benzodiazepine-related early morning insomnia which is characterized by an increase in time awake during the last few hours of sleep (i.e., the early morning) during hypnotic drug treatment. These investigators reported the effect during 1 or 2 weeks administration of the rapidly eliminated benzodiazepines, triazolam and midazolam, but not during treatment with the slowly eliminated benzodiazepines, flurazepam and quazepam. As with rebound insomnia, early morning insomnia can be interpreted as a manifestation of physiological dependence.

Further research will be necessary to determine the conditions under which triazolam-induced early morning insomnia reliably occurs, as well as to clarify the interpretation of the phenomenon. In the one study demonstrating early morning insomnia [79] the mean early morning increase in wake time for the condition during triazolam was small (5.2 min); however, when three individual nights at the end of the condition were analyzed, wake time was consistently greater than baseline, reaching statistical significance on one night (18.1 minutes vs. 8.3 minutes, respectively). Two recent studies which may have used data averaged across nights failed to find evidence of early morning insomnia [1,95]. Finally, while early morning insomnia was proposed to be a drug withdrawal sign, an alternate interpretation is that patients tend to wake earlier because they have slept soundly, and that flurazepam and quazepam prevent this awakening by their prolonged hypnotic action.

Daytime Anxiety During Hypnotic Treatment

Another phenomenon hypothesized to be related to the development of benzodiazepine physiological dependence is daytime anxiety during treatment with the rapidly eliminated hypnotics, triazolam and midazolam. Morgan and Oswald [104] briefly reported that nightly use of triazolam was associated with a progressive increase in patient-rated daytime anxiety, and Kales and co-workers [79] came to similar conclusions in analyzing data from previous studies with triazolam and midazolam.

Clarification of the generality and interpretation of triazolam-associated daytime anxiety will require more data and less debate [105, 107, 109, 112, 113]. Neither study describing the phenomenon [79,104] reported the absolute magnitude of increased anxiety, and one study has failed to obtain the effect [95]. It is possible that the increased anxiety represents increased wakefulness in insomniac patients rather than the development of physiological dependence [15,19].

Case Reports of Physiological Dependence

Compared with the numerous case reports of physiological dependence with diazepam and some of the other widely used benzodiazepines (cf. [96,116]), there have been relatively few case reports of withdrawal reactions with triazolam [40,151]. This low rate has no meaningful implication for relative risk of dependence because triazolam is a relatively new compound and the rate of such reports is undoubtably a function of drug usage. One case report of acute triazolam overdose suggests the interesting possibility of an acute physiological dependence syndrome [145]. After taking more than 5 mg triazolam the patient presented as anxious, sweating profusely, confused, belligerant, suffering visual and auditory hallucinations, and tremulous. The authors state that the clinical picture 8 to 12 hr after ingestion resembled that of hypnotic withdrawal delirium.

CONCLUSIONS ON PHYSIOLOGICAL DEPENDENCE

Triazolam, like other benzodiazepine anxiolytics and hypnotics, can produce physiological dependence in animals

and humans. The frequency and severity of withdrawal reactions are probably an increasing function of dose and duration of drug administration, although there is surprisingly little evidence of this from the animal and human studies reviewed. The available animal studies provide insufficient information to distinguish triazolam from other benzodiazepines with respect to probability and severity of withdrawal signs, as well as time of onset of spontaneous withdrawal signs. Human studies, however, show that onset of peak withdrawal effects may occur more rapidly with triazolam than with some of the more slowly eliminated benzodiazepines, such as flurazepam, chlordiazepoxide, and diazepam. Studies of rebound insomnia indicate that the consistency and magnitude of this withdrawal sign are greater with triazolam than with flurazepam and quazepam. The triazolam-associated phenomena of early morning insomnia and daytime anxiety during hypnotic treatment require further study to determine the conditions under which they reliably occur as well as their status as withdrawal-related events.

As a whole, these data on physiological dependence do not provide a strong basis for making predictions about the relative abuse liability of triazolam. Although Tyrer [146] has said that the rapidly eliminated compounds triazolam and lorazepam are associated with more severe withdrawal symptoms than slowly eliminated ones, evidence for this viewpoint is not strong, especially with triazolam. One study showed that in self-referred patient groups participating in a benzodiazepine detoxification study, the severity of early withdrawal symptoms and the dropout rate with lorzaepam was higher than with diazepam after abrupt drug withdrawal [148,149]. Other investigators have implied that there is an unusually high frequency of case reports of severe withdrawal signs after abrupt termination of drugs like lorazepam [66,116]. Part of the belief that triazolam and lorazepam should be associated with severe withdrawal signs is based on the pharmacokinetic hypothesis that withdrawal severity should be a function of the rate at which drug leaves the brain. Although a relationship between plasma level and withdrawal intensity or probability of withdrawal symptoms was shown in one study [148], other studies failed to confirm this effect [2, 103, 147]. Finally, and with specific reference to triazolam, Hollister [66] expanded the pharmacokinetic hypothesis by suggesting that withdrawal severity should be an inverted U-shaped function of elimination rate. Thus, under ordinary divided dose schedules of administration, extremely rapidly eliminated compounds such as tybamate, produce less dependence than rapidly eliminated compounds such as lorazepam, presumably because it is difficult to maintain continually high levels of drug. From this perspective, the extremely rapidly eliminated triazolam (mean half-life 2–3 hr [45,71]) would be predicted to produce relatively less intense withdrawal than rapidly eliminated compounds such as lorazepam (mean half-life 14 hr [43]). Overall, although triazolam indisputably produces physiological dependence, neither scientific data nor pharmacokinetic hypotheses provide a basis for making a strong prediction about the relative physiological dependence potential of triazolam compared to that of other benzodiazepines.

ADVERSE EFFECTS

An understanding of the extent of adverse effects that might emerge with misuse/abuse of a drug is important to a meaningful assessment of relative abuse liability of a compound. The diversity of possible adverse effects is clearly enormous (cf. [33,138]) and spans the range of physiological systems in which benzodiazepines are active (e.g., central nervous system, metabolic/endocrine, immunologic, gastrointestinal, hepatic, etc.). For purposes of this review, discussion will be limited to five categories of central nervous system adverse effects which may have particular relevance to evaluation of the relative abuse liability of triazolam: A. Lethality in overdose; B. Psychomotor impairment; C. Interactions with ethanol; D. Anterograde amnesia; E. Impaired awareness of degree of drug effect; F. Other psychiatric and behavioral disturbances.

LETHALITY IN OVERDOSE

With central nervous system depressant compounds, the lethality of the drug in overdose is perhaps the single most important adverse effect relevant to drug abuse/misuse. The relatively high mortality associated with barbiturate overdose is an important determinant of the high abuse liability of this class of compounds and contrasts with the relatively low mortality associated with benzodiazepine overdose [24]. With regard to triazolam, animal laboratory studies suggest that triazolam is similar to other marketed benzodiazepines in having a remarkably favorable therapeutic ratio in contrast to barbiturates. For instance, the therapeutic ratio (LD_{50}/ED_{50}) for anticonvulsant effects in mice exceeds 11,000 for triazolam [131] in contrast to a therapeutic ratio of 9.3 for phenobarbital [121]. The absence of mortality in clinical case reports of substantial overdose with triazolam [88,145] is consistent with overdose reports with other benzodiazepines [37,44], and attests to the remarkable safety of these compounds.

PSYCHOMOTOR IMPAIRMENT

Next to lethality the most important adverse effect relevant to the abuse/misuse of central nervous system depressant compounds is probably impairment of psychomotor or gross behavioral performances, which increases the risk of automobile and other accidents. As with other benzodiazepine and nonbenzodiazepine hypnotics and anxiolytics, a variety of studies has shown that triazolam produces such impairments in a dose-related fashion in normal, insomniac, and drug abuser subjects (cf. [108, 123, 129, 142]). Although there are clear differences between compounds with respect to time-course of impairments, the limited comparative studies to date provide no basis for drawing meaningful qualitative distinctions between triazolam and other hypnotics and anxiolytics with respect to such drug-induced psychomotor impairments.

INTERACTIONS WITH ETHANOL

Given the frequency of ethanol ingestion in western society, the interaction of a drug with ethanol may represent a potentially serious adverse effect. Concurrent ingestion of benzodiazepines and ethanol generally produce greater impairment than either agent alone [30], and most deaths associated with benzodiazepine overdoses also involve concurrent ethanol ingestion [37].

Three studies of triazolam-ethanol interactions showed that, as with other benzodiazepines, triazolam and ethanol together produce greater impairments on some measures, but not all measures, than either drug alone [29, 30, 65]. This effect is not due to pharmacokinetic interactions [29, 30, 110]. There is some indication that, compared to other ben-

zodiazepines, triazolam may produce greater impairments in combination with ethanol. On the basis of a study (published as an abstract) involving triazolam (0.125 mg) and ethanol (breath concentrations of 800–950 mg/l), Dorian and coworkers [29] concluded that "the triazolam-ethanol combination results in marked impairment of psychomotor function which is greater than that produced by other benzodiazepines when combined with ethanol." In a similar study using a higher dose of triazolam (0.25 mg), these same investigators concluded that the magnitude of impairment produced by triazolam-ethanol combinations was similar to that produced by other benzodiazepines, which they estimated to be 20–30% greater than either drug alone [30]. Their graphically presented data, however, showed peak triazolam-ethanol impairment to be 50–80%. Only two studies have directly compared triazolam and another benzodiazepine with respect to ethanol interactions. Hill *et al.* [65] showed a higher frequency of ataxia, slurred speech, hiccups, nausea and vomiting, diplopia and blurred vision, and amnesia after a combination of triazolam (0.5 mg) and ethanol (0.8 g/kg) than after ethanol combined with flurazepam (30 mg) or a lower dose of triazolam (0.25 mg). A related study [101] showed that the interactions of triazolam and ethanol may be of a shorter duration than the interactions of flurazepam and ethanol.

Conclusions based on these data must be tentative given the few rigorous cross-drug comparisons and lack of substantial dose manipulations. However, from the limited ethanol interaction studies conducted to date, it would appear that triazolam could be relatively more toxic than other benzodiazepines.

ANTEROGRADE AMNESIA

A well documented effect of some benzodiazepines is that they produce short-term anterograde amnesia, i.e., memory loss for events occurring after drug administration. Although this effect is used to clinical advantage when benzodiazepines are administered as a premedication for some types of surgical procedures, anterograde amnesia represents a potentially serious adverse consequence of drug use/abuse outside of closely monitored medical settings. Studies suggest that there may be meaningful differences in the degree of anterograde amnesia effects produced by oral doses of several benzodiazepines (lorazepam, diazepam, and clorazepate) which are used primarily as anxiolytics [61, 94, 135, 155].

With respect to triazolam, there have been both anecdotal reports [77, 119, 122, 139] and experimental studies [124, 127, 142] of anterograde amnesia after oral administration as a hypnotic. Two studies comparing the amnestic effects of triazolam with those of lorazepam, flurazepam, and secobarbital concluded that these effects were neither drug specific nor drug-class specific, but were simply related to the hypnotic properties of the compounds [124,127]. Unfortunately, lack of dose effects and possible use of nonequivalent doses limits the generality of this conclusion.

Data from the previously discussed study which compared oral triazolam and pentobarbital in drug abusers have demonstrated the dissociability of sedative and anterograde amnestic effects [123]. In this study a picture memorization session was scheduled approximately 1.75 hours after drug administration which had occurred at 10:00 a.m. During a 1-min session subjects studied a piece of paper on which was printed a set of 10 black and white pictures of easily recognizable items (i.e., ball, fork, dog, etc.). At 8:30 a.m. the following day subjects were given a booklet containing 165 pictures from which they attempted to identify the 10 pictures presented previously. Figure 6 shows that triazolam produced markedly greater amnestic effects than pentobarbital; post hoc comparisons showed that all four doses of triazolam were associated with significantly fewer correctly identified pictures than placebo and 100, 200, and 400 mg pentobarbital. This effect cannot be attributed to administering non-equivalent doses because both drugs produced similar dose-related effects on other performance measures. Further, the difference cannot be explained as a failure of memory consolidation due to sleep onset (cf. [124,127]) because no subject slept for at least 2 hr after the memorization session.

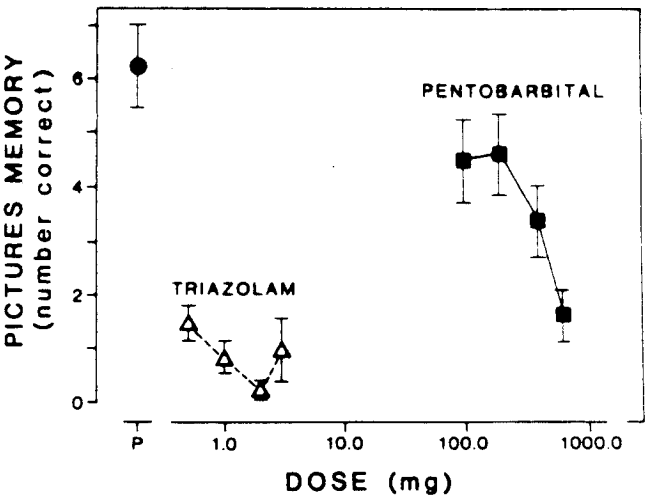

FIG. 6. Effects of triazolam and pentobarbital on recognition memory in eight subjects with histories of sedative drug abuse. Y-axis: number of pictures correctly identified; X-axis: dose (mg), log scale. P indicates placebo. Points show means; brackets show ±S.E.M. Oral doses of triazolam (0.5, 1.0, 2.0, and 3.0 mg) and pentobarbital (100, 200, 400, and 600 mg) produced similar dose-related suppression in psychomotor performance. Pictures were presented 2-hr after drug administration, and the recognition task was conducted 23-hr after drug administration. Data are replotted from Roache and Griffiths [123].

The precise implications of these data on anterograde amnesia for the relative abuse liability of triazolam are not clear. Unquestionably, such amnestic effects represent a potentially serious side effect of triazolam. While amnestic effects might represent a desirable aspect of drug action for some individuals, it is also plausible that such an effect could substantially limit the appeal of triazolam as a drug of abuse. In fact, after receiving doses of triazolam several subjects in the Roache and Griffiths study spontaneously and independently commented that they wished to avoid taking that unknown drug "on the street" because of the remarkably and unusually high degree of memory impairment. Also, no experimental study has compared triazolam with other benzodiazepines with respect to anterograde amnestic effects.

IMPAIRED AWARENESS OF DEGREE OF DRUG EFFECT

An interesting but apparently not widely recognized adverse effect of some benzodiazepines is that individuals receiving high doses may have an impaired awareness of the

magnitude of drug effect/impairment. Two studies with subjects with histories of drug abuse showed that, compared with other CNS depressant drugs such as pentobarbital and chlorpromazine, subjects were relatively less aware of the degree of impairment/effect produced by high doses of diazepam [53,54]. An analogous effect with triazolam was shown in the previously cited study by Roache and Griffiths [123] in which the effects of triazolam and pentobarbital were compared in drug abuser subjects. In this study, subjects participated in psychomotor performance and digit-symbol substitution tasks, and staff and subjects rated the magnitude of drug effect at 1, 2, 3, 4, 6, 8, 12, and 24 hr after drug administration. Statistically valid relative potencies were obtained with area under the time-action curve data from psychomotor performance, digit-symbol substitution task performance, and staff ratings of magnitude of drug effect, but not with subjects' ratings of magnitude of drug effect. Figure 7 shows these effects for staff and subject ratings. Analysis of variance and post hoc comparisons showed that although subject ratings with both triazolam and pentobarbital were higher than placebo, subject ratings with 400 and 600 mg pentobarbital were significantly greater than all doses of triazolam. During the study subjects were given no objective feedback (i.e., their scores) on the psychomotor and digit-symbol substitution tasks. After each performance session subjects were required to estimate how well they had performed relative to their "normal" performance by using a 100 mm visual analog rating scale going from "much worse" to "normal" to "much better." A comparison of those ratings with actual performance on the tasks provided a measure of the extent to which subjects underrated the degree of performance impairment. Analysis of variance and post hoc comparisons showed that triazolam produced dose-related underrating of impairment in contrast to pentobarbital which did not.

Clearly, additional studies are needed to determine the extent and pharmacological specificity of the impaired awareness of degree of drug effect. As with anterograde amnesia, because of the very nature of this potentially serious side effect, it is likely to be underreported by patients and thus may escape detection in clinical trials not specifically designed to assess the effect. Since studies to date indicate that this adverse effect is associated with the administration of diazepam and triazolam, but not pentobarbital or chlorpromazine, it may represent a general property of benzodiazepines having anxiolytic and hypnotic activity.

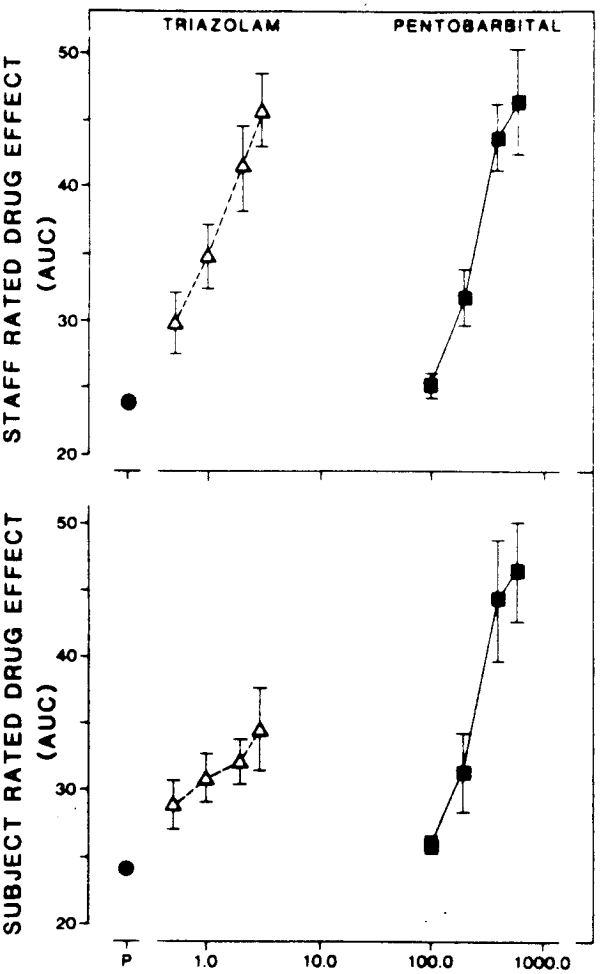

FIG. 7. Staff- and subject-rated magnitude of drug effect in nine subjects with histories of sedative drug abuse. Y-axis: staff- and subject-rated drug effect expressed as area under the time-action curve (AUC); X-axis: dose (mg), log scale. P indicates placebo. Points show means; brackets show ±S.E.M. unless encompassed by the data points. Oral doses of triazolam (0.5, 1.0, 2.0, and 3.0 mg) and pentobarbital (100, 200, 400, and 600 mg) produced similar dose-related increases in staff ratings, however, triazolam produced smaller increases than pentobarbital in subject ratings. Data are replotted from Roache and Griffiths [123].

OTHER PSYCHIATRIC AND BEHAVIORAL DISTURBANCES

There has been, at a fairly low frequency, a variety of behavioral and mood disturbances associated with use of benzodiazepine hypnotics and anxiolytics in clinical situations, including increased hostility, depression, paranoid tendencies, suicidal tendencies, confusion, sleepwalking, and hallucinations (cf. [54,88]). Because such observations have been relatively rare, it has often been assumed that such effects represent idiosyncratic reactions to benzodiazepines. A series of controlled studies using normal doses in healthy subjects [41, 83, 84, 134] and higher than normal doses in drug abusers [54,55] suggests that some of these adverse effects may represent common rather than idiosyncratic effects of benzodiazepines insofar as they occur reliably under experimental conditions. Despite these experimental findings, by "normal" standards for evaluating adverse effects of psychomotor drugs, the benzodiazepine hypnotics and anxiolytics are relatively safe and free from adverse effect.

With respect to triazolam, there have been case reports attributing a wide variety of adverse effects, including all those adverse effects cited above which were attributed to other benzodiazepines [34, 35, 119, 143, 150, 151, 152]. Noteworthy among these reports are those from a Dutch psychiatrist [150,151] which resulted in substantial media attention and ultimately suspension of triazolam from the drug registry in the Netherlands [31, 86, 88]. Subsequent position papers, in combination with a more extensive and systematic analysis of data from clinical trials have provided conflicting results and interpretations regarding the suggestion that triazolam is associated with a high frequency or unusual profile of such adverse effects [7, 13, 47, 76, 86, 88, 92, 93, 111, 152]. At present, there is no strong basis for differentiating triazolam from other benzodiazepine hypnotics and anxiolytics with respect to these adverse effects.

CONCLUSIONS ABOUT RELATIVE ABUSE LIABILITY OF TRIAZOLAM

The data reviewed indicate that the abuse liability of triazolam is clearly less than that of the intermediate duration barbiturates such as pentobarbital. Support for this conclusion comes from data on: (1) chemical structure/pharmacological profile; (2) reinforcing properties in animals; (3) human liking and ratings of monetary value; (4) discriminative stimulus effects in animals; (5) human categorization of drug effect; and (6) lethality in overdose. Although there are data indicating that triazolam has a more rapid onset of activity than pentobarbital, this difference is apparently unimportant because it is not reflected in the other measures assumed to reflect reinforcing properties. There are also data suggesting that triazolam has greater amnestic effects than pentobarbital, and that triazolam is associated with a greater impairment of awareness of degree of drug effect than pentobarbital. Although these represent potentially serious adverse effects, their importance is certainly less than that of lethality in overdose for which pentobarbital indisputably has the greater risk. Although important pieces of comparative data are not available, such as studies comparing reinforcing properties in humans, the presently available data are compelling, and it would seem unlikely that additional studies will alter the conclusion that triazolam has relatively less abuse liability than the intermediate barbiturates such as pentobarbital.

Conclusions about the abuse liability of triazolam relative to other benzodiazepine anxiolytic/hypnotics are less clear. The data on chemical structure/pharmacological profile, drug discrimination in animals, physiological dependence in animals, lethality in overdose, and psychomotor impairment are derived from reasonable studies and provide no strong basis for distinguishing triazolam from other marketed benzodiazepines. However, there are at least three types of data suggesting that triazolam may have greater abuse liability than at least some other benzodiazepines: (1) reinforcing effects in animals; (2) speed of onset in humans; and (3) interaction with ethanol. Finally, there are seven areas about which insufficient data exist to draw firm conclusions about the abuse liability of triazolam relative to other benzodiazepines: (1) reinforcing effects in humans; (2) ratings of liking and monetary value in humans; (3) categorization of subjective drug effects by humans; (4) physiological dependence in humans; (5) anterograde amnesia; (6) impaired awareness of drug effect; and (7) psychiatric/behavioral disturbances. It is noteworthy, however, that in three of these areas, concerned clinical investigators have speculated and cautioned that triazolam may have relatively greater toxicity than other benzodiazepines: physiological dependence in humans including rebound insomnia, early morning insomnia, and daytime anxiety [25, 80, 104, 143, 146]; anterograde amnesia [73, 119, 122, 139]; psychiatric/behavioral disturbances [13, 35, 76, 119, 150, 151, 152]. There has been little or no speculation on part of clinicians that triazolam may have relatively less abuse liability than other benzodiazepines.

In conclusion, triazolam has less abuse liability than the intermediate duration barbiturates. Although there are considerable data indicating similarities of triazolam to other benzodiazepines, there is substantial speculation among clinical investigators and some limited data suggesting the abuse liability of triazolam to be greater than that of a variety of other benzodiazepine anxiolytics and hypnotics, and virtually no credible data or clinical speculation that it is less. Further animal and human laboratory research along with careful epidemiological monitoring will be necessary to clarify definitively the status of the abuse liability of triazolam relative to other benzodiazepine anixolytic/hypnotics.

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