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Experimental Abuse Liability Assessment of Benzodiazepines

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The topic of this article is the experimental psychology and experimental pharmacology of benzodiazepines as applied to their abuse liability assessment.[1] The issues of physiological and psychological dependence on benzodiazepines are considered to be separate topics and will be examined as such.

Physiological dependence indicates a particular state of an organism during drug treatment such that discontinuation of treatment is followed by the development of a time-limited withdrawal reaction that can be prevented by continuing drug administration or reversed by resuming administration following interruption. Important in the definition is the time-limited nature of the withdrawal syndrome: in chronic drug treatment of certain disorders, discontinuation of medication may lead to the reappearance of those symptoms that originally indicated the need for medication. These symptoms, which may persist indefinitely following termination of drug treatment, should not be considered part of the withdrawal syndrome.

Physiological dependence is often contrasted with behavioral or psychological dependence. *Psychological dependence* is characterized by a tendency to repeatedly seek and self-administer a drug. Often, the term psychological dependence is used to denote a condition not necessarily involving physiological dependence, but characterized by a craving for a drug or drug effect that fulfills some psychological need of the individual. Much of what is connoted by the term is unnecessary in the evaluation of the behavioral effects of psychological dependence.

In terms of both historical descriptions and the current scientific view, the essential feature of psychological dependence is continued drug seeking or self-administration. Additionally, the most important aspect of drug

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self-administration is reinforcement, a process in which the probability that a person will engage in a particular behavior is increased or maintained by an environmental event that follows the behavior. For example, if changing physicians leads to drug procurement and this behavior becomes more frequent, then changing physicians may be said to be an instance of reinforced drug-seeking behavior. In addition, the act of taking the drug itself may be said to be reinforced by the drug effect, if, for example, the drug capsules are taken more frequently than placebo capsules. Obviously, in most clinical or experimental settings, drug-taking behavior is not attended to in great detail. Some of the experiments described below, however, were designed specifically to examine that behavior.

Finally, distinct from the definitions of physiological and psychological dependence is abuse liability. The *abuse liability* of a compound is defined as its capacity to produce physiological or psychological dependence in conjunction with the capacity to alter behavior in a manner that is detrimental to the individual or his/her social environment.

Two different kinds of procedures can be used to evaluate physiological dependence in animals. One procedure assesses cross-dependence between compounds: it assesses the capacity of one compound to suppress withdrawal from dependence on another compound. For instance, a barbiturate can be used to induce dependence in an animal, and once reliable measures of the withdrawal syndrome from the barbiturate have been established, another drug can be studied in terms of its capacity to suppress the syndrome in this animal. The second kind of procedure used to study physiological dependence in animals consists of the assessment of direct dependence to a compound following its chronic administration. This may be a more appropriate procedure than the assessment of cross-dependence. That is to say, the majority of cross-dependence studies in animals has found that indeed there is some cross-dependence among various kinds of propanediols, alcohol, barbiturates and benzodiazepines. However, some recent studies of direct- and cross-dependence suggest that these findings of cross-dependence may have overgeneralized the similarities among some of these compounds.

These recent studies have been reported by Martin, McNicholas and Cherian (1982) at the University of Kentucky. These investigators noted some differences in withdrawal signs seen after repeated administration of diazepam or pentobarbital. The signs that were specific to withdrawal from these drugs in rats were seizures and grand mal convulsions for pentobarbital, and what the authors called "explosive awakenings" (a rigid jump or turn that propelled the rat against the sides of the cage) for diazepam. Martin and colleagues concluded that the withdrawal syndromes produced by the two drugs were qualitatively different, though not as a result of differences in the pharmacokinetics of the drugs. They found that the most compelling argument for the qualitative nature of the difference was that

while each drug partially suppressed the withdrawal syndrome of the other, the effects reached a plateau in their dose-effect evaluation. Thus, pentobarbital completely suppressed, in a dose-related manner, its own withdrawal syndrome. In contrast, the maximal extent to which diazepam suppressed pentobarbital withdrawal occurred at a dose of 10 mg/kg, and a four-fold increase in dose failed to produce any further suppression of withdrawal. Thus, despite the apparent cross-dependence of benzodiazepines and barbiturates, these investigators demonstrated an incomplete cross-dependence between pentobarbital and diazepam. What distinguishes these observations from those of previous investigators is that Martin and colleagues described the entire withdrawal syndrome in precise and detailed terms, whereas previous investigators tended to draw inferences about a state of dependence or cross-dependence based on observations of a single sign of withdrawal.

The largest series of studies to date on benzodiazepine dependence in animals has been conducted by Tomoji Yanagita (1981) at the Central Institute for Experimental Animals in Kawasaki, Japan. In these experiments, which have been carried out in Rhesus monkeys, withdrawal severity has been assigned three different grades. The first is a mild withdrawal syndrome, indicated by apprehension, hyperirritability, mild tremor, anorexia and piloerection. These signs continue in intermediate withdrawal, which is more specifically recognized by aggravated tremor, rigidity, impaired motor performance, retching, vomiting and a considerable amount of weight loss. The most severe withdrawal that can be observed is indicated by grand mal convulsions and some indication of delirium (as inferred from behavior directed toward what appears to be imaginary objects in the environment), nystagmus, some dissociation from the environment and a substantial hyperthermia. Thus, as the severity of the syndrome increases, signs of withdrawal include more extensive pathophysiology.

Based on his studies of the vast majority of benzodiazepines that are on the market in this country, in Europe and other parts of the world, as well as a number of experimental compounds, Yanagita concludes that all of the benzodiazepines are capable of producing at least mild and intermediate withdrawal syndromes. These experiments demonstrated qualitative and quantitative differences in the dependence produced respectively by benzodiazepines and barbiturates. Furthermore, they demonstrated that all the benzodiazepines studied to date apparently share the ability to produce some degree of physiological dependence. If there were qualitative differences among the benzodiazepines in this regard, it seems reasonable to assume that they would have emerged in Yanagita's studies.

Henry Swain (personal communication, 1982) at the University of Michigan has made some interesting observations relevant to low-dose physiological dependence. These contrast with Yanagita's studies, which

tend to use very large doses of compounds, attempting to obtain very high levels of intoxication. Swain's experiments, on the other hand, used small doses: an eighth or a quarter of a milligram per kilogram of diazepam, delivered subcutaneously every 6 hours over a 5-month period, after which an examination of behavioral change was conducted over a 10-day period. Withdrawal signs were found under these conditions. The signs observed were twitching, tremor, irritability, some peculiar posture of the monkeys and considerable abdominal tenderness. These signs appeared on the first day, became slightly more severe on the second and third days, and persisted for a period of up to 10 days. These data suggest that there is a mild withdrawal syndrome from these lower doses of diazepam.

These data further present the opportunity, with the use of the recently described benzodiazepine antagonists, of designing experiments that approximate therapeutic dose conditions and might allow some of the issues described by Leo Hollister (1983) regarding the actual variables associated with dependence development at therapeutic dose levels to be unraveled.

There appears to be little doubt that chronic administration of high doses of some benzodiazepines can result in physiological dependence in humans, as demonstrated by withdrawal signs that can appear in approximately 4 to 10 days and continue up to 2 weeks (Hollister *et al.*, 1963; Hollister, Motzenbecker & Degan, 1961). Clearly documented instances of dependence development to therapeutic doses of benzodiazepines have also been provided by Winokur and colleagues (1980), although apparently only a small percentage of patients may actually develop such dependence. It is quite unclear as to what causes some people to develop dependence to therapeutic doses, although the possibility that concurrent or prior alcohol abuse may predispose to such dependence should be considered and evaluated.

Although such studies usually emphasize the capacity of benzodiazepines to produce physiological dependence, they do not indicate what the significance of this dependence might be. People who develop dependence often discover that fact for themselves only when they attempt to terminate drug administration. Thus, the state of physiological dependence is not a consequence of compulsive drug seeking with concomitant escalation of drug intake. Although the discomfort of withdrawal may prompt the individual to consider resuming drug administration, this distress could possibly be minimized with proper instruction on gradual reduction of drug dosage. Reports on benzodiazepine withdrawal rarely indicate that patients request more drugs.

The basic procedures for evaluating psychological dependence, as defined previously, consist of self-administration studies in animals and humans. This entails training an animal to make a specific response that will deliver the drug in some way: making the drug available either as a fluid for oral consumption or through an intragastric or intravenous cannula. With

respect to these routes of administration, it is very interesting to note that the accumulated evidence makes it very difficult to contend that any of the benzodiazepines act as reinforcers when delivered by either the oral or the intragastric route of administration, which obviously represent the routes of most relevance to therapeutics as well as to virtually all cases of abuse. From the point of view of the scientists who study drug self-administration, the intravenous route is the best, in that animals will on occasion self-administer benzodiazepines when delivered intravenously. But even here, the results are not particularly striking. In these experimental procedures, it is difficult to induce amounts of drug by self-administration sufficient to produce significant degrees of intoxication.

The best evidence for strong reinforcing effects in animal self-administration procedures comes from studies (e.g., Lukas & Griffiths, 1982) of 2 short-acting benzodiazepines. One is midazolam, a compound that is being evaluated for potential use in anesthesia, and the other is triazolam.

Comparisons in animal studies suggest that barbiturates of intermediate or ultrashort durations of action are more often effective reinforcers in some experimental situations than any of the benzodiazepines. In direct preference studies, or in studies in which the rate of response is used as a measure of the strength of the reinforcing effect, barbiturates of equivalent duration of action tend to show a much stronger reinforcing effect (Griffiths *et al.*, 1981).

Steven Paul (personal communication, 1982) has suggested that differences in receptor mechanisms might, in part, underlie differences in the pharmacological effects of benzodiazepines and barbiturates. Such receptor differences may be related to the differences in reinforcing properties of benzodiazepines and barbiturates. For the present, however, this is simply speculation.

There have been very few formal studies of human benzodiazepine self-administration. These have virtually been completely restricted to studies of diazepam and they have been of different types: either drug preference studies in normal volunteer subjects with significant sedative drug self-administration histories, or studies in special populations of patients, such as those in psychiatric wards or methadone patients.

First, in normal human subjects, a study done by Johanson and Uhlenhuth (1980) at the University of Chicago compared preference for diazepam in three different doses to a placebo. The same study also included amphetamine as a positive control. The subjects were given color-coded capsules on four occasions and asked to fill out questionnaires regarding mood states at various times after the drug administration. After experiencing each drug or placebo condition twice, subjects participated in five sessions at which they could choose between the capsules while other conditions remained the same. Diazepam was not selected in more than 50 percent of the trials in any of these sessions. In some preference tests, a

placebo was chosen more often than diazepam. Nevertheless, amphetamine was preferred significantly to the placebo. Diazepam produced significant subjective effects that appeared to reflect decreases in vigor and arousal, and increases in fatigue or confusion.

The same investigative team (DeWit *et al.*, 1982) did some followup experiments with diazepam in anxious subjects and the results were no more positive than they were with normal subjects. That is to say, small doses of diazepam cannot really be said to be reinforcing in the sense that they would produce a preference. At large doses, placebo is preferred to diazepam. The point here is that in anxious subjects (at least those without histories of sedative abuse) it is difficult to show a reinforcing effect, despite the fact that diazepam reduces reported anxiety.

In sedative abusers, there have been two types of experiments involving either measurement of the direct maintenance of a response by a benzodiazepine or those involving measurement of a drug preference (a measurement of the capacity of the benzodiazepine to maintain self-administration behavior relative to another substance). In one study (Griffiths, Bigelow & Liebson, 1979), subjects had to ride a bicycle to produce the opportunity to self-administer 1 of the 2 doses (10 or 20 mg) of oral diazepam. Diazepam very weakly and transiently maintained self-administration behavior, but the behavior was much better maintained by 90 mg of pentobarbital. Preference studies (Griffiths *et al.*, 1980) in sedative abusers show that when diazepam is offered at the very high doses required to produce subjective effects comparable to those of pentobarbital at intermediate doses, there is a very clear preference for pentobarbital over diazepam in virtually all comparisons. These findings support the animal data rather convincingly.

Other studies, though not formal studies of drug self-administration, suggest that when patients in psychiatric wards or chronically anxious outpatients are allowed to self-regulate their doses of benzodiazepines, they tend to be reduced over long periods of time (e.g., in the range of 6 months). Finally, while there are a variety of case reports that indicate that high doses of benzodiazepines are indeed self-administered, these are almost invariably in the context of multiple drug use. It is difficult to draw the conclusion that the benzodiazepine involved is indeed the major culprit.

In conclusion, these experiments, taken as a whole, lead to a rather conservative view of the abuse liability of the various benzodiazepines. The amount of information on dependence liabilities of the increasing number of benzodiazepines varies quite dramatically among members of the class. Far more is known about the older members than about those that are very new, which makes it particularly difficult to draw rational, reasonable comparisons across members of the class when reviewing the literature.

As mentioned previously, all of the benzodiazepines show some capacity to produce physiological dependence. Even for the oldest compounds,

about which there is considerable literature, there seems to be no compelling evidence that the dependence liability of these drugs is associated with significant individual or social detriment: abuse liability. In the absence of such evidence, it seems most appropriate to balance assessment of the risk of benzodiazepine abuse with evaluation of the public health and social benefits that accompany appropriate benzodiazepine use.

NOTE

1. This article is excerpted from a larger review that this author conducted together with two colleagues in pharmacology at the University of Michigan, Jonathan Katz and Gail Winger. One purpose of the review was for presentation to a World Health Organization committee on international drug control during their deliberations with respect to scheduling benzodiazepines under the United Nations Convention on Psychotropic Substances.

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