Individual Differences in Acute Effects of Drugs in Humans: Their Relevance to Risk for Abuse

Harriet de Wit

It is known that individuals differ in their likelihood of becoming drug abusers. Many people never take any drugs at all, even on a single occasion. Of those who take drugs at least once, only a small number go on to use the drugs on a regular basis, and even fewer go on to use them in excessive quantities or abusive patterns. The differences in numbers of individuals who have ever tried drugs and those who become regular users is roughly illustrated by data from a national household survey (National Institute on Drug Abuse 1992): 37 percent of U.S. adults reported having used an illicit drug at least once in their lives, while only 6.3 percent report having used an illicit drug in the past month. "Illicit drug" here includes marijuana, nonmedical use of psychotherapeutics, inhalants, cocaine, hallucinogens, or heroin. Similarly, in 1993, 43 percent of U.S. high school students reported having tried an illicit drug at least once in their lives, while only 18 percent used any drugs in the past month (National Institute on Drug Abuse 1994). Many individuals limit their use to an initial sampling of the drug. Other individuals become occasional users, but use the drugs in moderation without developing any problems of abuse or dependence. However, a small but significant proportion of young individuals appears to progress rather rapidly (i.e., in their late teens and early twenties) to excessive use, and continue to use drugs despite harmful consequences. Why some individuals and not others are susceptible to drug or alcohol abuse is unclear. Some researchers have investigated risk factors through epidemiological or longitudinal studies designed to detect predictors and correlates of heavy drug use (see Tarter, this volume). Other researchers have used laboratory-based procedures to investigate individual differences in acute responses to drugs. This chapter will focus on a series of studies that used the latter approach to examine individual differences in response to acute doses of benzodiazepines.

Individuals may differ on a wide range of physiological, psychological, and demographic variables, any of which may potentially contribute to the susceptibility to use or abuse drugs. They may differ in biological makeup, either because of inherited factors (such as sex or genetic predisposition to alcoholism) or because of fluctuations in

their current state (e.g., nutritional or hormonal). Individuals may also differ on a range of psychological variables, including their current psychiatric state or their underlying personality traits. Many theories of the etiology of drug abuse postulate that certain psychological states or traits predispose certain individuals to use drugs. Finally, individuals differ in their prior experiences (e.g., history of prior drug use), which, through learning or physiological processes, may affect their pharmacological responses to drugs and thus their susceptibility to use drugs repeatedly. Some of these postulated variables can be investigated under controlled laboratory conditions.

It is widely assumed that the acute subjective, or mood-altering, effects of a drug play an important role in whether it will be abused. This relationship has been well established in comparisons across drugs and across drug classes: there is a good correspondence between drugs that produce euphoria and feelings of well-being and those that are abused (Fischman and Foltin 1991). The relationship is so well established that subjective responses to drugs are often used to screen new agents for abuse liability (Jasinski 1991). The relationship between subjective response to drugs and their abuse liability may also apply to individual differences in vulnerability to abuse drugs. It is known that individuals vary in their subjective and behavioral responses to acute administration of drugs, and these differences may be related to differences in the likelihood of repeated use, or risk for excessive drug use. For example, individuals who experience feelings of euphoria and well-being from a particular drug are more likely to repeat their use of that drug than individuals who do not experience these effects, or who experience unpleasant effects (Haertzen et al. 1983). The relationship between the subjective, or mood-altering, effects of a drug and the likelihood of taking the drug can be investigated in laboratory studies using placebo-controlled, double-blind choice procedures. Individual differences in subjects' responses in these procedures can thus be used to try to identify individuals who might be at risk for excessive drug use.

The author's laboratory has conducted a series of drug preference studies measuring subjective and behavioral effects of drugs in human volunteers. Subjective drug effects are measured using standardized, self-report questionnaires, and behavioral preference is measured by the number of times subjects choose to take an active drug over a placebo. In these studies, drugs from several classes have been investigated, including stimulants, tranquilizers, alcohol, and marijuana (Chait 1993, Chait et al. 1989; de Wit et al. 1987, 1989). Marked

individual differences have been observed in both the quality and magnitude of subjective responses to drugs in humans, and these differences bear systematic and intuitively logical relations to differences in behavioral preference, or the likelihood of consuming the drug in a behavioral test. In some studies it has been found, as might be expected, that subjects who experience the greatest euphoria and who report the highest liking of a drug's effects are the most likely to take the drug during choice sessions. However, depending on the drug and the subject population tested, the relationships between the quality of subjective drug effects experienced and drug preferences may vary. Closer examination of these relationships may reveal potential predictors of risk for substance abuse.

The subjects in the author's studies have been healthy young volunteers (aged 21 to 35), who have no history of substance abuse. This is in contrast to many other studies of drug abuse in humans, which have used subjects with histories of substance abuse. Although individuals with histories of substance abuse are most appropriate for studying certain aspects of drug abuse (e.g., maintenance, withdrawal, relapse), volunteers without extensive drug use histories may be more appropriate for studying vulnerability, or factors that predispose to the *development* of drug use. The subjects in the author's studies were recruited from around a major urban university. Potential subjects were carefully screened to exclude anyone with any history of drug- or alcohol-related problems, and to exclude anyone with psychiatric or medical disorders for which administration of the drug under study would be contraindicated.

The choice procedure used in these studies consisted of a sampling phase (four sessions), followed by a choice phase (three sessions). During the sampling sessions, subjects experienced the effects of a drug and placebo, each associated with a color code. Subjects were instructed to associate any drug effects with the code for later identification. On choice sessions, the subjects were permitted to choose between the two sampled substances, and they ingested whichever substance they preferred. The number of times they chose the drug over placebo was the indicator of preference. Sessions were typically conducted one or two times per week, usually in the evenings in a laboratory-based "recreational" environment, in which subjects were tested in social groups of three or four. The drugs were administered under double-blind conditions, and subjects were told they might receive a stimulant, tranquilizer, placebo, and sometimes alcohol. Other, secondary dependent measures include psychomotor performance, memory and attention, and physiological effects such as

heart rate and temperature. The studies reported here investigated the effects of diazepam, a drug that is commonly prescribed, and is abused, by a small number of individuals (Woods et al. 1992).

The author's laboratory has employed two strategies to study individual differences in responses to diazepam: (a) studies testing a priori hypotheses, in which subjects were recruited based on a criterion or characteristic believed to be potentially associated with abuse or dependence; and (b) posthoc analyses, conducted using data from heterogeneous samples of subjects exploring correlates of drug preference.

A PRIORI STUDIES

The a priori approach has been used in three studies to examine potential risk factors. These are described in detail below. In one study, diazepam preference was compared in anxious versus nonanxious control subjects. This study was based on the self-medication hypothesis of drug use, which postulates that a drug will be more highly preferred by individuals in whom the drug relieves an aversive state (e.g., relief from anxiety). In another study, diazepam preference was compared in moderate versus light alcohol drinkers. Clinical observations indicate that heavier consumption of alcohol increases the likelihood of abuse of benzodiazepines. Therefore, it was hypothesized that diazepam preference would be directly related to alcohol consumption. In a third study, diazepam preference was compared in males with and without a family history of alcoholism. Risk for alcoholism is thought to be in part inherited, and this study investigated whether the presence of family alcoholism would influence responses to another drug, diazepam.

Study 1: Diazepam Preference in Anxious Versus Control Subjects (Chutuape and de Wit 1995)

Participants in this study were 21 volunteers who met DSM-III-R criteria (American Psychiatric Association 1987) for an anxiety disorder and 23 nonanxious control subjects. The subjects in these groups did not differ on demographic characteristics (e.g., sex, age, education) or on their prior experience with drugs. They participated in a seven-session choice procedure, in which diazepam (20 mg) was compared to placebo. In this study, diazepam was administered during sampling sessions in five divided doses of 4 mg each, taken at 30-minute intervals. During the choice sessions, subjects first selected the drug they preferred (i.e., diazepam or placebo) and then also selected the dose they preferred (i.e., from 4 mg to a maximum of 28 mg). Diazepam choice differed between the two groups: whereas the normal control group

chose diazepam on average at about chance level (45 percent), the anxious group chose the diazepam more often than placebo (65 percent drug choice; figure 1). Moreover, subjects in the anxious group on average took higher doses of the diazepam when they chose the drug (average dose 22 mg for the anxious group compared to 18 mg for the control group). These findings suggest that, under these testing conditions, individuals with higher levels of anxiety are more likely to take diazepam. Whether this is indicative of risk of abusing the drug, or whether it is evidence of appropriate self-medication of their anxiety state is not clear. One way to address this question might be to examine the anxious subjects' subjective responses to the drug. Interestingly, the anxious subjects on average did not report measurable decreases in self-reported anxiety after diazepam, but they did report increases on a measure of drug-induced euphoria (i.e., the Morphine-Benzedrine Group scale of the Addiction Research Center Inventory; Martin et al. 1971; figure 2). This pattern of results suggests that anxious individuals might indeed be at higher-than-average risk for repeated nonmedical use of diazepam.

Study 2: Light Versus Moderate Alcohol Drinkers (de Wit and Doty 1994)

In this study, diazepam preference was compared in 13 light drinkers and 14 moderate drinkers. Light drinkers were defined as individuals who drank, on average, one to five alcoholic drinks per week, and moderate drinkers were those who consumed from 7 to 20 drinks per week. Again, these subjects had no history of drug- or alcohol-related problems. It was hypothesized, and found, that heavier drinkers would show a greater preference for diazepam. The moderate drinkers chose the diazepam-containing capsule on 73 percent of available occasions, whereas the light drinkers chose the drug on only 40 percent of occasions. However, despite the relatively high level of diazepam choice among the moderate drinkers, this group did not report significant increases in subjective measures of euphoria. Although they reported feeling the drug's effects and liking these effects, the profile of subjective effects were not indicative of a drug with high potential to be abused. The light drinkers,

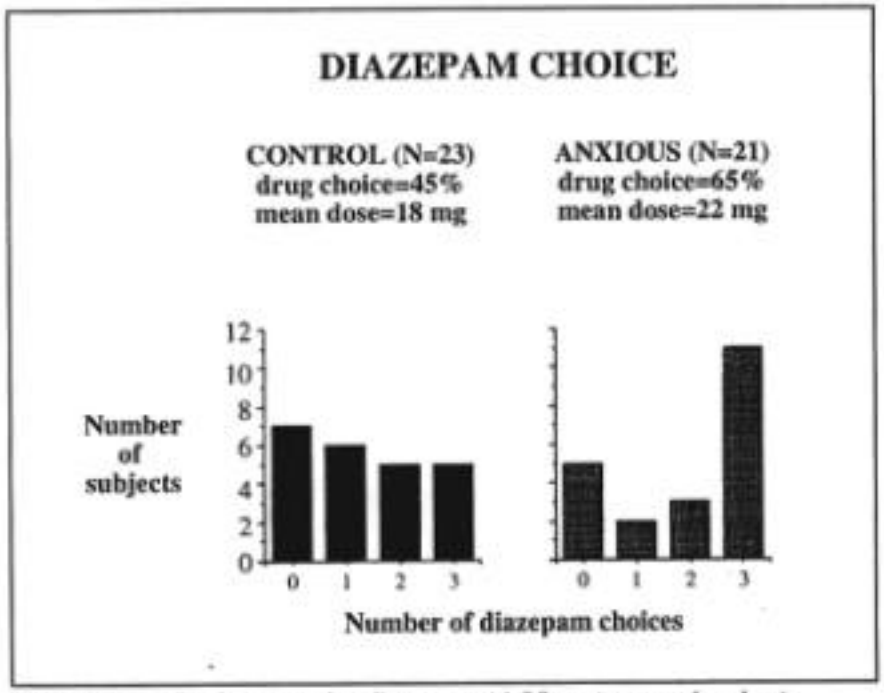

FIGURE 1. *Preferences for diazepam (4-28 mg) over placebo in control subjects (CTL; N = 23) and in volunteers with an anxiety disorder (ANX; N = 21). Bars indicate the number of subjects in each group who chose the diazepam- over the placebo-containing capsules on 0 through 3 of the choice opportunities. Also shown are the mean number of times diazepam was chosen overall, and the mean dose of diazepam taken on sessions when diazepam was chosen.*

on the other hand, reported experiencing apparently aversive subjective effects that were consistent with their relatively low choice: compared to the moderate drinkers, they reported greater confusion, dysphoria, and fatigue. Thus, this study demonstrated that drug use history (i.e., habitual alcohol consumption) did influence preference for diazepam and subjective responses to diazepam. However, the differences in subjective responses indicated that the higher drug choice in the moderate drinkers was due more to a relatively lower sensitivity to the aversive effects than to the drug's euphorigenic effects. Thus, these results suggest that habitual alcohol consumption may slightly, but not strongly, increase the risk for abuse of benzodiazepines.

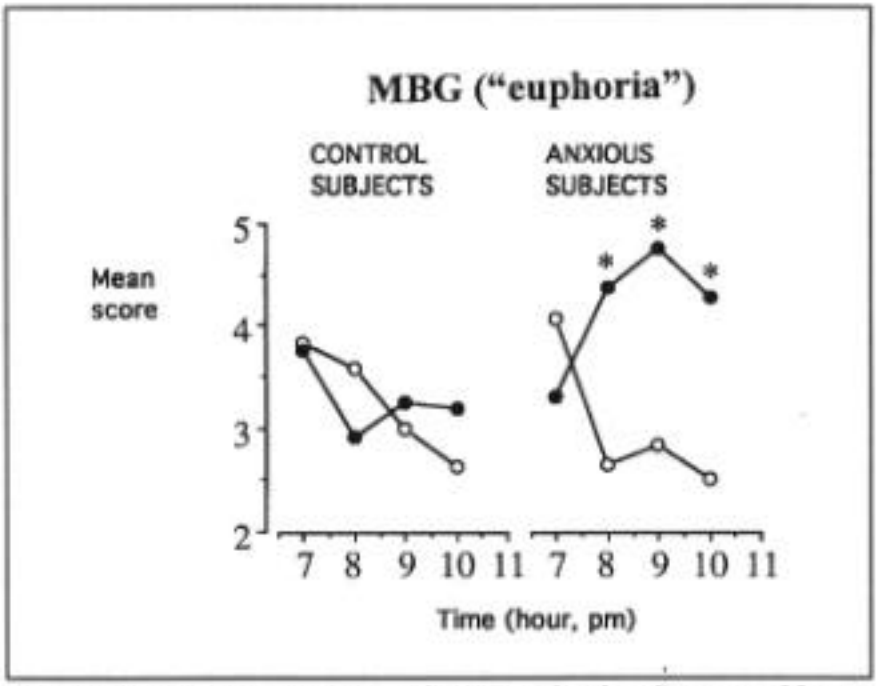

FIGURE 2. *Mean scores on "euphoria" scale after diazepam (20 mg; filled symbols) and placebo (open symbols) in normal controls (CTL; N = 23) and volunteers with an anxiety disorder (ANX; N = 21), before capsule ingestion (7 p.m.) and at regular intervals after capsule ingestion. Asterisks indicate significant differences between diazepam and placebo.*

Study 3: Family History of Alcoholism (de Wit 1991)

In this study, acute responses to diazepam were compared in males with at least one first-degree alcoholic relative (family history positive or FHP) versus males with no alcoholic relatives (family history negative or FHN). The subjects were moderate social drinkers in their early twenties who had no personal history of drug- or alcohol-related problems. The groups did not differ on demographic variables such as age, education, or current or past drug use. This study used the same divided dosing procedure as that described earlier in study 1, in which subjects could regulate their dose during the choice sessions. It was found that FHP subjects chose the diazepam about as often as FHN subjects (FHP 48 percent diazepam choice versus FHN 38 percent diazepam choice), and the FNP group chose only a slightly higher dose of the drug during the choice sessions (24 mg versus 19 mg). There were no significant differences between the two groups in

subjective responses to the drug. Thus, these results suggest that family history of alcoholism is not a strong risk factor for repeated benzodiazepine use.

POSTHOC COMPARISONS

The posthoc approach of comparing subjects who choose a drug most and least often has been used to explore the correlation between drug preference and both intraexperimental variables (i.e., differential responses to drug administration) and extraexperimental variables (e.g., demographic and personality characteristics).

Study 1: Posthoc Comparison of Diazepam Choosers Versus Nonchoosers (Chutuape and de Wit 1994)

Using data from a total of 88 subjects who participated in various diazepam preference studies, this study compared the subjects who chose diazepam on all three choice sessions ("choosers"; N = 32) to those who never chose the diazepam ("nonchoosers"; N = 21). The choosers and nonchoosers were compared on a range of variables, including extra-experimental variables such as demographic characteristics, current and past drug use and psychiatric rating scales, as well as intraexperimental variables mostly related to their responses to the drug. Table 1 shows the data for several representative extraexperimental variables. The choosers and nonchoosers did not differ in gender, age, education, occupation, or marital status. The groups did differ on several measures of self-reported recreational drug use: a significantly higher proportion of diazepam choosers currently used marijuana, and a higher proportion had ever used stimulants. The diazepam choosers also reported heavier current and lifetime use of every other class of recreational drug, although these differences did not reach statistical significance. Thus, greater diazepam preference was correlated with greater recreational drug use. The two groups were also compared on their subjective responses to diazepam: the diazepam choosers showed a very slight decrease in self-reported anxiety after receiving the drug, and an increase in ratings of friendliness, whereas neither of these effects was reported by the nonchoosers. On other measures of diazepam's effects the groups did not differ (e.g., decreased arousal, increased confusion). Thus, these findings suggest that among normal healthy individuals without histories of drug or alcohol abuse, those who report heavier recreational drug use

TABLE 1. *Demographic characteristics and recreational drug use of diazepam nonchoosers and choosers. Nonchoosers selected diazepam over placebo on zero of three choice sessions, and choosers selected diazepam on all three of the choice sessions.*

	Diazepam Non choosers (N = 21)	Diazepam Choosers (N = 32)
Gender (% female)	19	28
Age (mean years)	24.2	24.1
Education		
High school or partial college (%)	33	28
College or advanced degree (%)	67	72
Occupation		
Full-time student (%)	62	47
Marital status		
Single, never married (%)	76	84
Current recreational drug use		
Alcohol use (mean drinks/week)	6.6	9
Caffeine use (mean drinks/week)	10.8	12.4
Current marijuana user (% yes)	9	44*
Lifetime recreational drug use		
Marijuana use: % used > 10 times	57	75
Stimulants: % ever used	38	75*
Hallucinogens: % ever used	29	68
Tranquilizers: % ever used	12	28

KEY: * = Significant ($p < 0.05$) group differences (chi-square test).

are more likely to choose diazepam in a double-blind choice test. There was, however, little evidence that the drug is strongly euphorigenic, even among those subjects who chose the diazepam most consistently.

Study 2: Relationships of Drug Preference to Personality (de Wit and Bodker 1994)

For this analysis, data were also pooled from a series of diazepam choice studies (total N = 96). Subjects who chose diazepam on two or three of the three choice opportunities (N = 54) were compared to those who chose the drug on zero or one occasion (N = 42). The two groups were compared on several measures of personality, including the Tridimen-sional Personality Questionnaire (Cloninger 1987), the Eysenck Personality Inventory (Eysenck and Eysenck 1968), and the Sensation-Seeking Scale (Zuckerman 1979), and a measure of attitudes toward drug use, the Drug Attitudes Scale (Goodstadt et al. 1978). None of these measures were strongly or consistently related to diazepam preference.

In summary, the studies described here illustrate how studying the responses of normal volunteers to acute drug administration may reveal some of the factors that influence interindividual variability in risk for drug abuse. The studies are based on the assumption that individuals who experience positive (i.e., euphorigenic) subjective responses to drugs, and who exhibit preference for a drug over placebo, are more likely to repeat their use of a drug once they have experienced its effects. The actual impact of these individual differences are likely to be limited by the myriad other social and cultural factors that influence drug use outside the laboratory. For example, factors such as limited drug availability, legality and social sanctions against drug use are also likely to be powerful determinants of actual drug use and abuse. Nevertheless, the knowledge that individuals differ in their subjective and behavioral responses to drugs of abuse may be useful in the development of prevention and treatment strategies to reduce the incidence of problematic patterns of drug use.

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AUTHOR

Harriet de Wit, Ph.D.
Associate Professor
Department of Psychiatry
The University of Chicago
MC3077
5841 South Maryland Avenue
Chicago, IL 60637

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