

Benzodiazepine Use, Abuse, and Dependence

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Although benzodiazepines are invaluable in the treatment of anxiety disorders, they have some potential for abuse and may cause dependence or addiction. It is important to distinguish between addiction to and normal physical dependence on benzodiazepines. Intentional abusers of benzodiazepines usually have other substance abuse problems. Benzodiazepines are usually a secondary drug of abuse—used mainly to augment the high received from another drug or to offset the adverse effects of other drugs. Few cases of addiction arise from legitimate use of benzodiazepines. Pharmacologic dependence, a predictable and natural adaptation of a body system long accustomed to the presence of a drug, may occur in patients taking therapeutic doses of benzodiazepines. However, this dependence, which generally manifests itself in withdrawal symptoms upon the abrupt discontinuation of the medication, may be controlled and ended through dose tapering, medication switching, and/or medication augmentation. Due to the chronic nature of anxiety, long-term low-dose benzodiazepine treatment may be necessary for some patients; this continuation of treatment should not be considered abuse or addiction.

(J Clin Psychiatry 2005;66[suppl 2]:28–33)

Benzodiazepines serve an important purpose in alleviating the stress and anxiety of patients suffering from anxiety disorders. Although physicians often prefer to prescribe benzodiazepines over other drugs because of their low toxicity, concerns about the dependence-producing or addictive nature of these drugs have been expressed for decades. Benzodiazepines may, indeed, cause dependence or even be abused; however, the abuse potential of benzodiazepines is quite low and should be weighed against their beneficial anxiolytic properties.

BENZODIAZEPINE ABUSE

The abuse of benzodiazepines can be divided into 2 abuse patterns: deliberate abuse by people who use drugs for their euphoriant effects and unintentional abuse by patients who begin using benzodiazepines to treat an anxiety disorder and end up using them inappropriately. Deliberate abusers usually take benzodiazepines in an attempt to get high and often abuse other substances for the same purpose. Within this same constituency, benzodiazepines may also be used to self-medicate the withdrawal effects

of other substances such as cocaine and alcohol. Individuals who unintentionally abuse benzodiazepines use prescribed benzodiazepines inappropriately by taking them in higher doses than their prescribing doctor intended or for a longer duration than needed after remission of the anxiety disorder. Unintentional abusers may resort to other sources of benzodiazepines if their doctors stop prescribing them, but their initial benzodiazepine use most often starts legitimately to treat a diagnosed anxiety disorder.

People who abuse benzodiazepines may become dependent on them, although abuse and dependency are not always mutually inclusive. An abuser of benzodiazepines is not necessarily dependent (for example, when an individual irregularly takes benzodiazepines at parties to get high), and a patient who is physiologically dependent on benzodiazepines is not necessarily abusing them. There are 2 types of dependence that may develop: physical or pharmacologic dependence and addiction (called “dependence” in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision [DSM-IV-TR]¹). It is vital that physicians differentiate between these two types.

PHARMACOLOGIC DEPENDENCE VS. ADDICTION

Although an individual who is addicted to benzodiazepines is usually physiologically dependent on the medication, a patient may have a physical dependence without being addicted. Addiction requires evidence of compulsive drug-seeking behavior and loss of control as detailed in the DSM-IV. Among legitimate users of benzodiazepines, physical dependence can result from long-term

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This article is derived from the roundtable discussion “Utilizing Benzodiazepines in Clinical Practice: An Evidence-Based Discussion,” which was held August 16, 2004, in Boston, Mass., and supported by an unrestricted educational grant from Pfizer Inc.

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regular use according to a physician's instructions, but this does not constitute addiction.

Pharmacologic dependence is a natural physiologic adaptation in response to the continual use of many types of drugs that affect the nervous system. This adaptation is the biological basis for pharmacologic tolerance and withdrawal symptoms or rebound phenomenon upon discontinuation of drug use. Haefely² describes this drug-induced adaptive syndrome as an inevitable result of the repeated interaction between an organism and almost all classes of drugs.

On the other hand, addiction implies compulsive use and drug-seeking behavior in the pursuit of getting high. Called substance dependence by the DSM-IV,¹ addiction generally includes the following: tolerance to the drug and the need for increasing amounts to achieve intoxication or the desired effect; withdrawal symptoms upon discontinuation and, often, self-administration of the substance to relieve the withdrawal symptoms; drug-seeking and/or drug-using behaviors that require a considerable amount of time or effort (e.g., going to multiple doctors for prescriptions, buying substances on the street, buying illegal prescriptions, forging prescriptions); negligence of important familial or occupational obligations or discontinuation of previously important recreational, social, or occupational activities; and continued use despite negative consequences. Although physiologic dependence (manifested by tolerance and withdrawal) is typical of addiction, physiologic dependence is not a required criterion for addiction.

DELIBERATE ABUSE OF BENZODIAZEPINES

Deliberate abuse of benzodiazepines often begins as deliberate prescription misuse and is usually a recreational and thrill-seeking behavior. In addition to benzodiazepines obtained from legitimate prescriptions, abusers acquire these drugs from various other sources. They may buy illegal prescriptions or forge prescriptions themselves. Benzodiazepines are also bought on the street from dealers who obtain them through illicit channels. Although benzodiazepines bought on the street are possibly used appropriately by patients who are unable or unwilling to see a doctor for anxiety disorders, this method of drug procurement is suspicious and usually linked to a pattern of abuse.³

Abusers most often use benzodiazepines to get high.³ Sometimes these drugs are used in conjunction with other substances to improve the euphoriant effects, especially to augment methadone. Heroin addicts taking methadone may take diazepam or another benzodiazepine approximately 2 hours after the methadone to augment the high they experience. Benzodiazepines are also used by abusers to self-medicate the symptoms of opiate withdrawal or to treat the adverse effects of other drugs like cocaine or alcohol.

Table 1. Half-Life and Speed of Onset for Common Benzodiazepines^a

Benzodiazepine	Half-Life (range, h)	Speed of Onset
Alprazolam	12–15	Intermediate
Chlordiazepoxide	10–30	Intermediate
Clonazepam	18–50	Slow
Diazepam	20–80	Fast
Lorazepam	10–20	Intermediate
Oxazepam	5–10	Slow
Przepam	50–200	Slow

^aData on all drugs except clonazepam from Bailey et al.⁴; data on clonazepam from Estivill et al.⁵

Variables Affecting the Abuser's Choice of Benzodiazepine

Drug effect. Obviously, most drugs used recreationally are chosen because of their euphoriant effects and their lack of dysphoriant effects. Among benzodiazepines, each drug's effects and, therefore, its appeal to abusers depend largely on the drug's half-life, speed of onset, and speed of offset and on the age of the individual taking the medication.

Benzodiazepines vary widely in their elimination half-life, which is the amount of time required for half of the drug taken into the body to be removed from the blood. Speed of onset of the effect is a major factor in the degree of euphoria, with faster onset indicating more immediate and desirable euphoriant effects. Clinical experience indicates that benzodiazepines with a slower onset tend to be abused less often, but this has not been proven with experimental data. In some cases, the ingested drug is really a pro-drug requiring metabolism to an active metabolite for effects to occur. Thus, drug effects are delayed, and the benzodiazepine is not likely to be abused. A rapid offset, occurring in drugs with a short half-life, may increase abuse potential because the user tends to repeat the dosing frequently to maintain the effect. Withdrawal seizures are more likely to be caused by a short half-life drug such as alprazolam, which is also very potent. Although diazepam has a long half-life because of active metabolites, it has a rapid onset; consequently, it may be abused because of its immediate effects, but withdrawal may be delayed and milder due to the long duration of the active metabolites. The half-lives and speed of onset of some of the most common benzodiazepines are listed in Table 1.^{4,5} The age of the individual greatly affects the half-life of the medication⁶; in older patients, benzodiazepines tend to have much longer half-lives and, therefore, a tendency to accumulate with daily dosing. This can produce dementia and may be mistaken for Alzheimer's disease.

Tolerance. While there is controversy about whether or not patients develop tolerance to the anxiolytic effects of benzodiazepines, tolerance to some of the other effects, including the sedation generally brought on by benzodiazepines, does develop.⁷ This may affect the abuser's

choice of benzodiazepine and cause him or her to require higher and higher doses to get the desired euphoria.

Relative high. Several studies⁸⁻¹¹ have asked individuals who have a history of substance abuse to subjectively rate various benzodiazepines according to the highs experienced when taking them. Of the benzodiazepines, abusers rate diazepam as having the greatest high. Lorazepam and alprazolam scored slightly (but not significantly) lower in relative high than diazepam.⁸ Funderburk and colleagues⁹ found diazepam and lorazepam similar in subjective ratings of drug effect and drug liking by abusers. Clorazepate received significantly lower subjective ratings of liking from drug abusers than diazepam or lorazepam.¹⁰ Ratings of relative high were significantly less for oxazepam and chlordiazepoxide compared with diazepam, lorazepam, and alprazolam.^{11,12}

Street value. Although the relative high received from the drug affects the popularity and desirability of the drug, the street value is also affected by the reputation that the drug has on the street and by how much money abusers are willing to pay for it. According to Cole's 1988 presentation of data from Boston substance abusers,¹³ methaqualone 300 mg had the highest street value. (Methaqualone is a sedative-euphoriant that was widely available and widely abused until it was placed on Schedule I in 1984.¹⁴) Methaqualone was followed by diazepam 20 mg, which had about half the street value (Table 2).¹³ Because street value is affected by drug reputation and supply and demand, these values do not necessarily make rational sense. For instance, a 20-mg tablet of diazepam was valued higher (\$1.60) than 2 10-mg tablets of diazepam (\$1.40). This same street value discrepancy occurred in ratings for 2-mg and 4-mg tablets of lorazepam.

"Use again" value. Drug abusers were also asked to rate various benzodiazepines according to whether or not they would use them again.^{13,15} Again, methaqualone 300 mg and diazepam 20 mg scored highest, and lorazepam 2 mg and placebo scored lowest (see Table 2).¹³

DEPENDENCE ON BENZODIAZEPINES WITHOUT INTENTIONAL ABUSE

Long-term use of benzodiazepines may cause physical dependence; if unaccompanied by drug-seeking behavior, this is neither an abuse nor an addiction. Few cases of addiction or abuse arise from legitimate benzodiazepine use. Physical dependence is more relevant to clinicians than deliberate abuse because it occurs in patients who begin taking prescribed benzodiazepines for an anxiety disorder under the direction of their doctors. Most unintentional abusers are unaware of their benzodiazepine dependence until they try to abruptly discontinue using the drugs. Symptoms experienced after benzodiazepine discontinuation may be pharmacologic withdrawal symptoms, or they may constitute a return of the anxiety disorder for

Table 2. Street Value and "Use Again" Value of Benzodiazepines^a

Benzodiazepine	Street Value	"Use Again" Value ^b
Methaqualone 300 mg	\$3.00	12.2
Diazepam 20 mg	\$1.60	8.7
Diazepam 10 mg	\$0.70	6.3
Lorazepam 4 mg	\$0.80	6.8
Lorazepam 2 mg	\$0.30	6.0
Alprazolam 2 mg	\$0.70	8.0
Prazepam 40 mg	\$0.60	7.1
Placebo	\$0.20	3.3

^aData from Cole.¹³

^b"Use again" values are rated on a 16-point scale, where 0 indicates "would never use the drug again," 8 indicates "maybe," and 16 indicates "would definitely enjoy using drug again."¹⁵

which the medication was originally taken. Some patients who were prescribed benzodiazepines for a certain stressful time in their lives may experience hypnotic-induced insomnia when they stop taking them. Other patients who began using benzodiazepines to treat anxiety may experience a withdrawal syndrome that includes a return of anxious symptoms after discontinuation of use. These withdrawal syndromes are usually short in duration and should be differentiated from a relapse of anxiety, which will be discussed later in Withdrawal vs. Relapse of Anxiety.

LONG-TERM USE OF BENZODIAZEPINES

One of the biggest controversies surrounding benzodiazepine use has been the efficacy and safety of long-term use. In the 1980s, some psychiatrists, including many in the United Kingdom, stated that benzodiazepines did more harm than good because the dependence developed by some long-term users outweighed their potential anxiolytic benefits.^{16,17} This disapproval of long-term use was supported with the hypothesis that patients develop a tolerance to the antianxiety effects of benzodiazepines, which, if true, would mean that benzodiazepines would be medically useful only for short-term treatment, and patients would not need to use benzodiazepines long enough to develop a dependence. However, clinical evidence does not support the development of this tolerance^{7,18}; in fact, anecdotal evidence from prescribing psychiatrists often indicates long-term anxiolytic effectiveness of benzodiazepines.^{18,19}

Tolerance seems to develop selectively to different drug effects. Although chronic users of benzodiazepines do develop a tolerance to the sedation and psychomotor impairment caused initially by benzodiazepines, tolerance to the acute short-term memory effects does not develop.⁷ Thus, it is theoretically possible that antianxiety effects do not show tolerance, but this has been difficult to address experimentally.

The reticence of British psychiatrists to use benzodiazepines for long-term treatment may also stem from the

inappropriate long-term prescribing that took place in the United Kingdom in the 1970s at the height of benzodiazepine popularity. During this time, studies^{20–23} showed that U.K. patients had higher long-term and repeat use rates than patients in other developed countries and that many British patients were receiving repeat prescriptions without a physician consultation. At the same time, long-term benzodiazepine use in the United States was lower than in the United Kingdom.²⁴

WITHDRAWAL FROM BENZODIAZEPINES

Withdrawal symptoms occur when there is a decline in the blood or tissue concentration of any dependence-forming substance that an individual has been continuously taking. Symptoms of withdrawal are time-limited, usually occurring for only 1 or 2 weeks after the discontinuation of the drug, but the duration varies according to the drug and the individual person.²⁵ These symptoms are generally the opposite of the acute effects of the drug, or they may mimic the symptoms for which the drug was originally taken. For example, withdrawal from habit-forming painkillers may include symptoms of pain, and withdrawal from sleep aids may include symptoms of insomnia. Withdrawal symptoms are usually relieved by administration of the substance from which the patient is withdrawing.²⁵

For patients who experience withdrawal from benzodiazepines, 3 factors seem to influence the intensity and/or duration of the withdrawal. The most significant determinant of withdrawal is the amount of time spent in treatment. The longer the treatment is, the more likely it is that the patient will experience withdrawal symptoms upon abrupt discontinuation of treatment. The dose of medication also affects withdrawal, but it does so in combination with duration of treatment. In a study of patients (N = 180) taking diazepam, 15 to 40 mg/day,²⁶ only 5% of the patients who had been taking the drug for less than 8 months experienced withdrawal symptoms, while 43% of the patients taking diazepam for 8 months or more experienced withdrawal. Even at low doses, long-term use results in physical dependence and withdrawal more often than short-term use.²⁵ Conversely, higher doses may cause withdrawal after short-term use. In a study of patients (N = 109) taking alprazolam, 2 to 10 mg/day, for only 8 weeks,²⁷ distinct transient withdrawal symptoms occurred in 35% of the patients, and rebound panic attacks occurred in 27%. The third factor affecting withdrawal is the half-life of the benzodiazepine. Withdrawal symptoms tend to be more severe and have a quicker onset in patients taking benzodiazepines with shorter half-lives.^{28,29}

WITHDRAWAL VS. RELAPSE OF ANXIETY

Because withdrawal symptoms often mimic the disorder for which the medication was originally taken, it may

sometimes be difficult to determine whether a patient is experiencing benzodiazepine withdrawal or a relapse of anxiety. It is important, however, to differentiate between these situations so that patients who are experiencing a brief withdrawal do not unnecessarily begin antianxiety treatment again.

There are 2 specific differences between withdrawal from anxiolytic psychotropics and a relapse of anxiety. The first difference is the length of time between discontinuation of treatment and appearance of symptoms, as well as tendency of the symptoms to improve or worsen. True withdrawal symptoms usually develop within a few days of stopping the medication; they are most severe directly after discontinuation of benzodiazepine use but continue to lessen until, as time progresses, these symptoms eventually disappear.³⁰ However, both the length of time between benzodiazepine discontinuation and appearance of withdrawal symptoms and the subsequent duration of the withdrawal syndrome vary according to the half-life of the benzodiazepine. Drugs with longer half-lives take longer to leave the system or reach a level low enough to produce withdrawal symptoms, so withdrawal may not become evident for a week after discontinuation of longer half-life benzodiazepines like diazepam. In contrast to withdrawal syndromes, relapses of anxiety generally manifest as anxious symptoms that return more than a week after benzodiazepine discontinuation and get progressively worse until treated.

The second difference between withdrawal and relapse is in the symptoms themselves. Symptoms of benzodiazepine withdrawal include anxiety, agitation, irritability, increased sensitivity to light and sound, paresthesias (strange sensations), muscle cramps, myoclonic jerks, fatigue, insomnia, headache, dizziness, concentration difficulties, seizures, nausea, loss of appetite, weight loss, and depression.^{25,31} Although anxiety relapses encompass some of the same symptoms, such as nervousness, difficulty sleeping, and difficulty concentrating, several other symptoms of withdrawal are not characteristic of anxiety—sensitivity to light and sound, tinnitus, feelings of “electric shocks,” tremors, myoclonic jerks, perceptual changes, and even seizures in cases of high-dose dependency.^{29,31}

Pseudowithdrawal is another phenomenon that must be considered when deciding if a patient is experiencing benzodiazepine withdrawal. Pseudowithdrawal is a psychological or subjective withdrawal that occurs as a result of a patient’s apprehension about discontinuing medication. A review of research²⁵ found that patients who are not aware that they have discontinued medications because placebo was substituted for their benzodiazepine may have fewer withdrawal symptoms; conversely, patients who continue to take medication but believe that they are receiving placebo may experience withdrawal symptoms without actual discontinuation of medication. Psychological withdrawal or pseudowithdrawal generally consists

of anxious symptoms unaccompanied by the other true withdrawal symptoms described above.^{25,32}

CLINICAL OPTIONS FOR DISCONTINUING BENZODIAZEPINE TREATMENT

There are several clinical options that help patients avoid withdrawal symptoms when it is time to discontinue benzodiazepine treatment for anxiety. Some of the clinical approaches that show success include, either individually or in combination, gradual tapering of the current benzodiazepine, switching to a long-acting benzodiazepine, phenobarbital substitution, and treatment of withdrawal symptoms with other medications.

Gradual Taper

As with all discontinuation programs, the patient should be willing to stop using the drug, and the clinician should explain why a gradual taper is better than abrupt discontinuation. Although the rate of reduction that will allow the patient to avoid withdrawal symptoms varies from patient to patient and depends on the original dose and duration of treatment, a quarter of the daily dose is generally the maximum amount the medication should be reduced each week.¹⁷ The minimum time for tapering from full dosage to total discontinuation, therefore, should be 4 weeks. If this reduction is too drastic for the patient and he or she experiences withdrawal symptoms, the dose may be returned for a short period to the level just above the amount that brought on symptoms; tapering should then continue from this level. Nonetheless, the physician and patient must remember that the patient may still experience some withdrawal symptoms for as long as the tapering continues.²⁵

Substitution With a Long-Acting Benzodiazepine or Phenobarbital

Because short-acting benzodiazepines are more likely to cause dependence and withdrawal upon discontinuation than long-acting benzodiazepines, switching to a long-acting benzodiazepine such as clonazepam may help to prevent or lessen withdrawal symptoms.³³ In a study of patients switching from alprazolam to clonazepam,³⁴ patients rated clonazepam better than alprazolam because it lessened their mid-dose anxiety. This positive ranking was attributable to the slow onset and long half-life of clonazepam. Slowly absorbed and slowly eliminated benzodiazepines yield a more sustained and gradual antianxiety effect,³⁵ so these drugs may facilitate a smoother discontinuation than benzodiazepines with a faster onset and shorter half-life without negative withdrawal sequelae.

The barbiturate phenobarbital is another long-acting, cross-tolerant medication that may be effectively substituted for short-acting benzodiazepines upon which a patient has developed dependence. When compared with

clonazepam,³⁶ phenobarbital was found less effective in successfully tapering sedative hypnotics but equally or more effective when used to counter recurrent or rebound anxiety.

Treating the Symptoms of Withdrawal

Other medications, including carbamazepine, clonidine, and propranolol, may be used to treat withdrawal symptoms such as tremor, anxiety, and seizure experienced upon either abrupt or gradual discontinuation of benzodiazepines.³⁷ When compared with supplemental doses of buspirone, imipramine, and placebo,³⁸ supplemental doses of the anticonvulsant carbamazepine aided the largest percentage of patients in successfully discontinuing their benzodiazepines. In a study of benzodiazepine-withdrawn rats,³⁹ carbamazepine was able to normalize the stress-response system that was impaired by diazepam withdrawal. The beta-blocker propranolol has been used effectively to treat tremor and cardiovascular withdrawal symptoms,⁴⁰ and patients receiving medication augmentation with propranolol were more likely to discontinue or decrease their benzodiazepine use.⁴¹

Continued Treatment With Benzodiazepines

If discontinuation of benzodiazepine treatment is especially distressing to the patient, if pharmacologic dependence is extremely high, or if rebound anxiety occurs after several attempts to discontinue the benzodiazepine, another option may be the most viable: continuation of benzodiazepine treatment. Generalized anxiety disorder is now recognized as a chronic illness that impairs daily functioning and causes patients to suffer for many years.⁴² Continual treatment with a low-dose benzodiazepine may provide some patients the most functionality with the fewest negative effects.

CONCLUSION

The individuals who deliberately abuse benzodiazepines and those who inadvertently become dependent on them differ greatly in intention, purpose, and treatment. Deliberate abuse of benzodiazepines is most often found within a polydrug use pattern as an attempt to get high or treat the effects of other drugs used for this purpose; benzodiazepines are rarely used as the primary drug of abuse. This type of abuse is most appropriately treated in a substance abuse setting and may be partially avoided by not prescribing short-acting, euphoriant benzodiazepines for individuals with known substance abuse issues. The number of people who start taking benzodiazepines to treat anxiety and end up abusing them or becoming truly addicted is very small.

For those patients who inadvertently become dependent on therapeutic doses of benzodiazepines, several clinical approaches can assist those who are willing and able to dis-

continue their medication to do so in the most symptom-free way possible. Nonetheless, because anxiety is a chronic disorder that may need long-term continual treatment, a need for sustained benzodiazepine treatment should not necessarily be considered dependency or addiction. A patient taking regular benzodiazepine treatment for chronic anxiety may be similar to an asthmatic who must always have medicine on hand or a patient suffering from allergies who must take allergy medicine daily for years. A benzodiazepine that successfully performs its intended duty as an anxiolytic—aiding in the daily functioning of the patient without adding impairment—serves a legitimate medical purpose and improves the quality of life for chronic anxiety patients.

Drug names: alprazolam (Xanax and others), buspirone (BuSpar and others), carbamazepine (Tegretol, Carbatrol, and others), chlordiazepoxide (Librium and others), clonazepam (Klonopin and others), clonidine (Duraclon, Catapres, and others), clorazepate (Gen-Xene, Tranxene, and others), diazepam (Valium and others), imipramine (Tofranil, Surmontil, and others), lorazepam (Ativan and others), methadone (Methadose, Dolophine, and others), oxazepam (Serax and others), propranolol (Innopran XL, Inderal, and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, carbamazepine, phenobarbital, propranolol, and clonidine have not been approved by the U.S. Food and Drug Administration for the treatment of benzodiazepine withdrawal.

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