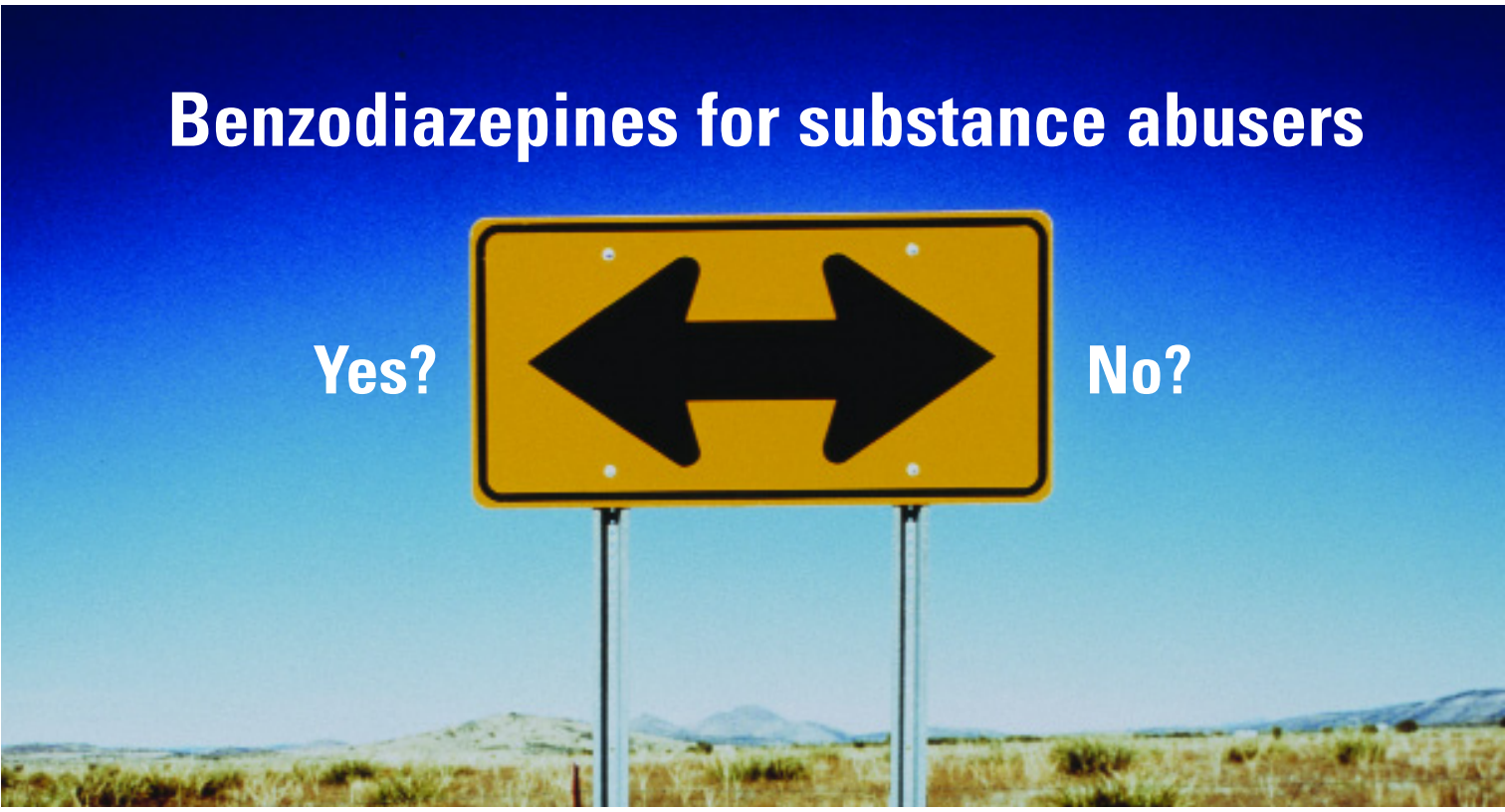
Current PSYCHIATRY

Benzodiazepines for substance abusers



Do addiction worries outweigh the need for effective anxiety treatment? A sobriety-based algorithm addresses both concerns.

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How should you treat anxiety in substance-abusing patients: deny them benzodiazepines and risk under-treatment, or prescribe benzodiazepines for the anxiolytic effect and risk contributing to addiction?

There is no definitive answer, but one thing is clear: Among psychiatric patients, substance abusers are most likely to abuse benzodiazepines and become addicted to them.

Some argue that the abuse potential is overstated, but only limited data suggest that benzodiazepines can be safely prescribed to patients who are abusing alcohol or drugs. In this article, we discuss benzodiazepine use in these patients and offer a sobriety-based treatment approach.

continued

Table 1

Benzodiazepines' potency and half-lives, including half-lives of active metabolites

Potency	Shorter half-life (hr)	Longer half-life (hr)
High	Alprazolam (6 to 12) Lorazepam (10 to 20) Triazolam (2)	Clonazepam (18 to 50)
Low	Oxazepam (4 to 15) Temazepam (8 to 22)	Chlordiazepoxide (5 to 30) [36 to 200]* Clorazepate [36 to 200]* Diazepam (20 to 100) [36 to 200]* Flurazepam [40 to 250]*

* [active metabolite]

Source: Ashton CH. *Benzodiazepine equivalence table.* Available at www.benzo.org.uk

BENEFITS AND RISKS

Considered a safe substitute for barbiturates, benzodiazepines were heralded as wonder drugs when they were introduced in the 1950s. Reports of their addictive potential surfaced in the 1970s, and since then researchers have disagreed on whether benzodiazepines should be prescribed to substance-abusing or -dependent patients.

Clinical utility. Benzodiazepines are used in many clinical situations because of their:

- anxiolytic, hypnotic, anticonvulsant, antipanic, antidepressant, amnestic, anesthetic, and antispastic effects
- relatively mild side effects, when compared with alternatives such as barbiturates.

In psychiatry, benzodiazepines are used to treat anxiety disorders, agitation, and insomnia. Because of cross-tolerance with alcohol and barbiturates, benzodiazepines also are used to manage alcohol or barbiturate withdrawal.

Interactions. Benzodiazepines can interact with other psychotropics, including lithium, antipsychotics, and selective serotonin reuptake inhibitors (SSRIs). Respiratory arrest has been reported in patients taking both a high-potency benzodiazepine and clozapine.[1]

Overdose and withdrawal symptoms. Benzodiazepine overdose is characterized by slurred speech, sedation, memory impairment, incoordination, respiratory depression, hypotension, stupor, and coma. Abrupt withdrawal may produce life-threatening delirium, hallucinations, grand mal seizures, and symptoms similar to those of alcohol withdrawal (insomnia, anxiety, tremor, hyperactivity, nausea, vomiting, and psychomotor agitation).[1]

ABUSE PATTERNS

The few empiric studies examining benzodiazepines' abuse potential in substance abusers have shown inconsistent results. However, it is generally accepted that:

- long-term benzodiazepine use may lead to tolerance and physiologic dependence
- withdrawal symptoms can occur if benzodiazepines are stopped suddenly, especially after long-term (months to years) use.

Even though most benzodiazepine prescriptions are not abused,[2] a history of alcohol and drug abuse suggests high potential for benzodiazepine abuse. Also, long-term users of prescribed benzodiazepines often develop tolerance and may escalate their doses to get the same desired effects. If their supply is threatened, these patients may seek benzodiazepines illicitly.

Benzodiazepines may enhance or prolong the elation ("high") associated with other drugs or mitigate the depression ("crash") that follows a stimulant "high." Sometimes benzodiazepines are the drug of choice, as high doses of potent,

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short-acting agents may provide a stimulant "high."

WHO ABUSES BENZODIAZEPINES?

Alcohol and substance abusers tend to ingest benzodiazepines for recreational purposes. Thirty to 50% of alcoholics undergoing detoxification and 44% of IV drug abusers also may be abusing benzodiazepines.[3]

Benzodiazepines are cross-tolerant with alcohol, and alcoholics may use them with alcohol or as a substitute when alcohol is unavailable. They also may self-medicate with benzodiazepines to ease alcohol's withdrawal symptoms. Opiate, amphetamine, and cocaine abusers may use benzodiazepines with their drugs of choice, as may younger abusers of MDMA ("Ecstasy") and LSD.

Even patients who begin taking benzodiazepines for legitimate reasons may end up abusing them. In one study of 2,600 patients prescribed diazepam, up to 60% had abused and/or become dependent on it.[4]

Benzodiazepine abuse may start with other sedative/hypnotic abuse or as experimentation with drugs or alcohol, typically around age 13 or 14.[5] The average benzodiazepine abuser is age 19 to 31, and the male-to-female ratio is about 2:1.[6]

Multi-drug abuse. Benzodiazepines are usually not the preferred or sole drug of abuse. Roughly 80% of benzodiazepine abuse may be a component of poly-drug abuse, most commonly with opioid addiction.[7] A 2-year National Institute on Drug Abuse study of heroin abusers suggested that 15% also abused benzodiazepines daily for more than 1 year, and 73% had abused benzodiazepines several times during the previous week.[8] Other studies suggest that up to 90% of methadone users regularly abuse benzodiazepines, often at high doses.[9]

Table 2

Should benzodiazepines be prescribed to substance abusers?

YES: Arguments for

- Studies showing risks of benzodiazepine abuse in substance users were based on faulty data (Maletzky & Klotter).[17]
- Long-term benzodiazepine treatment of anxiety—even in substance abusers—is similar to treatment of other chronic conditions (Lader).[18]
- Studies suggesting that alcoholics and drug abusers are at high risk of benzodiazepine abuse are inconclusive (Ciraulo et al).[19]
- Abuse potential is minimal, and undue restrictions cause patients to suffer needlessly (Berner).[20]
- Prolonged benzodiazepine use decreases morbidity in chronic conditions (Schatzberg).[21]
- Other treatments are often ineffective (Lader).[22]

NO: Arguments against

- Prescribing benzodiazepines promotes drug abuse (Sellers et al).[23]
- Physiologic tolerance and dependence occurs with every long-term benzodiazepine use, and these risks are compounded in substance abusers (Hamlin).[24]
- Long-term benzodiazepine use may cause structural brain damage (Piesiur-Strehlow et al).[25]
- Guilt and failure to spend enough time with patients are the main reasons physicians prescribe benzodiazepines (Bendtsen et al).[26]
- Benzodiazepines should be reserved for detoxification and withdrawal in individuals with type 2 alcoholism (Linnoila).[27]

ILLICIT USE POTENTIAL

Prescriptions are the primary source of supply for benzodiazepine abusers. These patients are doctor shoppers and often change pharmacies. They

visit emergency rooms frequently and may feign symptoms to obtain benzodiazepine prescriptions. They fill prescriptions for personal use or sell the drugs to illicit sources to support their addictions.

Without convincing data, psychiatrists must decide the merits of using benzodiazepines, usually case by case.

On the street, brand-name benzodiazepines are worth much more than generics because they can be identified by photographs of brand-name benzodiazepines on the Internet or in reference books. In many cities, the street value of the Xanax or Klonopin brands may be $5 to $10 per pill. A 5-mg tablet of Valium-brand diazepam may sell for $5, and 10-mg tablets are worth up to $10.

Higher abuse potential. All benzodiazepines have abuse potential, and most have been reported in the literature as being abused. Those most likely to be abused have a short half-life[10] (*Table 1*) or rapidly cross the blood brain barrier, such as alprazolam.[11]

Alprazolam and lorazepam are popular among benzodiazepine abusers. In experienced but nondependent users, 1 mg of alprazolam produces a sense of elation and carries an abuse potential similar to that of 10 mg of dextroamphetamine.[12] Lipophilic agents such as diazepam also have a high abuse and addiction potential.

In the United States, diazepam and alprazolam appear to be the most abused benzodiazepines.[13] Flunitrazepam has become popular among high school students and drug addicts, particularly in the south and southwest. This potent benzodiazepine is not approved for use in the United States but is diverted from Latin America or Europe in the illegal drug trade.

Lower abuse potential. Benzodiazepines with longer half-lives generally are less likely to be abused, although diazepam—with a half-life of up to 100 hours—is the exception. Chlordiazepoxide has been reported to produce a lower "high" than other benzodiazepines.[14] Among the short half-life benzodiazepines, oxazepam may have a relatively low abuse potential.[14] Clonazepam—a high-potency benzodiazepine with a long half-life—is generally safe and may have a lower abuse or addiction potential, although its abuse has been reported.[15] Similarly, oxazepam, clorazepate, and chlordiazepoxide may be less reinforcing than other benzodiazepines, although reports have linked these agents to abuse as well.[16]

TO PRESCRIBE OR NOT TO PRESCRIBE

Opponents blame benzodiazepines for promoting the drug culture and argue that prescribing benzodiazepines promotes drug abuse. Advocates of benzodiazepine therapy contend that restricting an effective and safe medication is unethical, even in substance abusers. Arguments from each perspective are summarized in *Table 2*.[17-27]

In 1990, an American Psychiatric Association task force concluded that alcohol and substance abusers could be prescribed benzodiazepines with very close monitoring but did not recommend specific standards.[28]

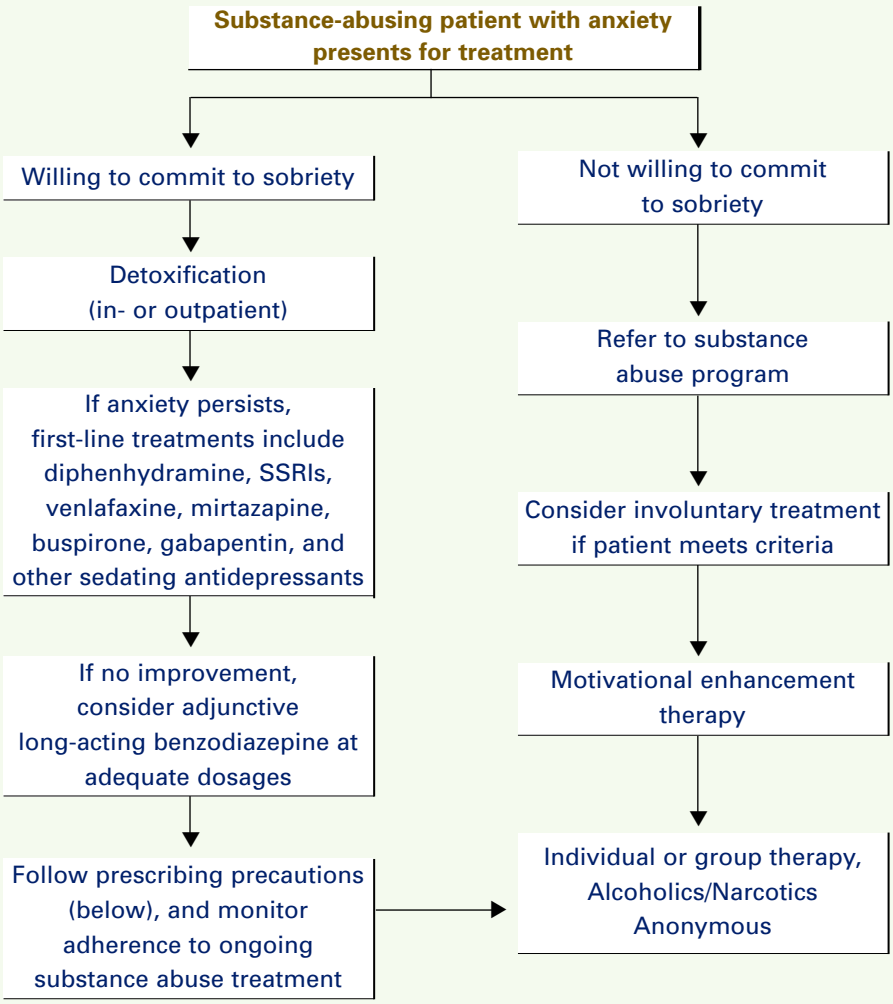
RECOMMENDATIONS

Prescribing benzodiazepines to substance abusers is not absolutely contraindicated, despite an elevated relative risk of abuse or dependence. In the absence of convincing data, physicians must decide on their own—usually case by case—the merits of using benzodiazepines to treat anxiety in substance abusers.

A sobriety-based approach. Our group at the Substance Abuse Treatment Center, VA Medical Center, Omaha, Nebraska, has developed a treatment algorithm for substance abusers presenting with anxiety (*see Algorithm*). It is based on clinical experience, more than 200 relevant articles,

Algorithm

Sobriety-based protocol for treating anxiety in substance abusers



Precautions for prescribing benzodiazepines

- **Inform patient** of planned duration of therapy
- **Prescribe for brief periods** (weeks to months), with follow-up at least monthly
- **No refills without follow-up,** and no refills over the phone
- **Use random urine toxicology** screening every 1 to 3 months to monitor for relapse
- **Attempt to taper dosage** after 3 to 6 months—even if patient resists—and monitor for objective withdrawal
- **If no objective withdrawal,** terminate benzodiazepine; continue other medications
- **If objective withdrawal,** continue benzodiazepine and reattempt taper in 3 to 6 months; continue Alcoholics/Narcotics Anonymous

and the consensus of psychiatrists trained and certified by the American Board of Psychiatry and Neurology and the American Society of Addiction Medicine.

We suggest that you begin by encouraging sobriety and referring willing patients to detoxification. Because most addicts deny or greatly minimize their substance abuse, investigate all potential drug or alcohol abuse thoroughly and address it appropriately.

Keep patient records current, with attention to dates of visits and quantity of benzodiazepines prescribed

If anxiety persists after detoxification, begin drug therapy with nonbenzodiazepines:

- Diphenhydramine, 50 to 100 mg/d, may reduce anxiety and often improves sleep, but consider its anticholinergic side effects before prescribing.
- Some SSRIs and venlafaxine are used to treat anxiety, but they generally take weeks to produce a therapeutic effect and some patients cannot wait that long.
- Mirtazapine, 15 to 30 mg/d, provides relatively rapid sedation and helps with sleep and anxiety.
- Buspirone may reduce anxiety, especially when given at 30 to 60 mg/d.
- Gabapentin, 100 to 300 mg tid or higher, may reduce anxiety and help with sleep.
- Tricyclic antidepressants may be considered, but watch for cardiac and anticholinergic side effects and overdose risks.

If anxiety does not improve with an adequate trial of first-line agents, consider adding long-acting benzodiazepines at sufficient dosages, such as clonazepam, 0.5 to 1 mg bid to tid. Prescribe scheduled doses, rather than "as needed." Continue the first-line antianxiety agent, and reiterate to the patient that benzodiazepine therapy will be short-term.

Observe prescribing precautions (*see Algorithm*), and screen patients' urine randomly every 1 to 3 months to monitor their adherence to substance abuse treatment.

Keep patient records current, with attention to dates of visits and prescriptions and quantity of benzodiazepines prescribed. To ensure proper continued use of benzodiazepines, consider consulting with physicians who have expertise in treating similar patients. Watch for possible signs of benzodiazepine dependence and abuse, such as requests for dose increases or early refills.

Related resources

- Parran TV. Prescription drug abuse. A question of balance. *Med Clin North Am* 1997;81:967-78.
- Lader M, Russell J. Guidelines for the prevention and treatment of benzodiazepine dependence: summary of a report from the Mental Health Foundation. *Addiction* 1993;88(12):1707-8.
- National Institute on Drug Abuse. www.nida.nih.gov
- National Institute on Alcohol Abuse and Addiction. www.niaaa.nih.gov

DRUG BRAND NAMES

Alprazolam • Xanax
Buspirone • BuSpar
Chlordiazepoxide • Librium
Clonazepam • Klonopin
Clorazepate • Tranxene
Diazepam • Valium
Flurazepam • Dalmane
Gabapentin • Neurontin
Lorazepam • Ativan
Mirtazapine • Remeron
Oxazepam • Serax
Temazepam • Restoril
Triazolam • Halcion
Venlafaxine • Effexor

DISCLOSURE

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NONDRUG TREATMENTS

Nondrug treatments have been shown to reduce substance use and control anxiety in some studies. These include cognitive-behavioral therapy, motivational enhancement therapy, interpersonal therapy, and brief dynamic therapy, among others. Their use requires specific training or referral to more experienced colleagues. For information on these treatments, consult the Web sites of the National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism (*see Related resources*).

Group and self-help therapies such as Alcoholics Anonymous or Narcotics Anonymous also have been shown to reduce substance use.

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Bottom Line

When substance abusers present with anxiety, attempt detoxification and prescribe non-benzodiazepines. If these steps do not work, consider adding short-term, long-acting benzodiazepines only for patients committed to sobriety, and follow precautions carefully.