# Benzodiazepines and Addiction: Myths and Realities (Part 1)

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The advent of benzodiazepines in the 1960s and their use in a variety of neuropsychiatric conditions allowed the discontinuation of potentially lethal and addicting barbiturates. The myorelaxing and anticonvulsive effects of benzodiazepines benefit patients with epilepsy or spasmodic disorders. Their anxiolytic and hypnotic properties make benzodiazepines the treatment of choice for insomnia and anxiety problems. These agents are also used in alcohol withdrawal and in anesthesia.

Benzodiazepines have low toxicity if they are not combined with other respiratory depressors, and they have a favorable adverse-effect profile. However, soon after the first benzodiazepine, chlordiazepoxide (Librium), came into use in 1960, reports appeared about withdrawal symptoms and a potential risk of dependence.[1,2] Diazepam (Valium), introduced in 1963, was much more potent than its predecessor and became the most prescribed drug in the United States in the 1970s. Yet, its potential for abuse and increased tolerance (necessitating dosage escalations) were also frequently discussed in the scientific literature[3] and in popular media (eg, the 1966 Rolling Stones' song *Mother's Little Helper*). In the early 1980s, the dangers of benzodiazepines were described in Barbara Gordon's autobiography, *I'm Dancing as Fast as I Can,* which became a bestseller and was made into a movie. The positive attitude toward benzodiazepines started to decline, which gave rise to the prescription controversy.[4]

This article will appear in 2 parts. Here the focus is on the use of benzodiazepines for anxiety disorders and sleep problems. I will also discuss their use in substance abusers and in elderly patients. In part 2, considerations related to long-term use of and withdrawal from benzodiazepine therapy will be emphasized.

## A review of basic definitions

Considerable confusion remains about some basic concepts in most of the studies that examined benzodiazepine use.[5]

- *Abuse* is a maladaptive pattern of substance use outside of the standard norms that leads to social consequences, interpersonal conflicts,

or legal problems (DSM-IV 305.40).

- *Misuse* refers to the inappropriate use of a substance, such as taking it in larger amounts or for a longer period than recommended.
- *Harmful use* is a pattern of psychoactive substance use that causes damage to physical or mental health (ICD-10).
- *Intoxication* is the state of being inebriated as a result of an excessive consumption of a substance and is associated with substance-specific symptoms (DSM-IV 292.89).
- There are discrepancies in the definitions of *addiction* in the medical literature: it is described as a loss of control over substance use or as the compulsive seeking and taking of a drug despite its negative or dangerous consequences. Addiction is sometimes used as a synonym for *psychological dependence;* it implies nonmedical use and use for pleasure purposes.[6,7]
- *Craving* is an intense or abnormal desire or longing for the substance.
- *Tolerance* refers to decreased drug effect at a constantly administered dose, such that increasingly higher doses are needed to achieve the same effect.
- *Withdrawal* is a state of painful physical and psychological symptoms, some substance-specific, following drug discontinuation (DSM-IV 292.0).
- *Physical dependence* is a physiological adaptation required to maintain use of the substance, with evidence of tolerance, withdrawal, or both. Although physical dependence and DSM-IV substance dependence often coexist, physical dependence should not be equated with the DSM-IV definition of substance dependence (DSM-IV 304.10).

## Symptoms of benzodiazepine withdrawal

Rebound anxiety and rebound insomnia consist of a worsening of the initial symptoms to below pretreatment levels, which are frequently observed after benzodiazepine disruption.[8] Although these rebound effects may give rise to physical dependence, they are independent, time-limited phenomena that often occur in the absence of other symptoms of benzodiazepine withdrawal or tolerance.

The symptoms appear to occur more frequently with short-life benzodiazepines, which often leads to a rapid retaking of the drug. This, in turn, plays an important role in long-term use of a benzodiazepine. Because a marked withdrawal syndrome may develop in patients who are taking therapeutic doses when treatment is disrupted, some researchers have suggested the existence of low-dose dependence on benzodiazepines.[9] There is, however, no clear consensus on the exact criteria of benzodiazepine dependence (and its eventual subtypes), although a set of criteria has been suggested[10]:

- Acquisition strategies: frequent requests for repeated prescriptions; simulating symptoms to acquire prescriptions; prescriptions by several physicians at the same time; acquisition of benzodiazepines through relatives, friends, and the black market
- Abuse: higher dosages than usual; extra doses; wishes or attempts to stop; the need to increase

the dosage (tolerance); benzodiazepine use to induce euphoria
- Rebound and withdrawal

The confusion may persist because DSM-IV diagnoses of abuse and of dependence are likely to merge into a single diagnosis of a "sedative, hypnotic, or anxiolytic-use disorder" in DSM5. There will be the sole addition of craving and its distinction between moderate (2 or 3 positive criteria) and severe (4 or more positive criteria), with or without physiological dependence.

## Characteristics of the benzodiazepines

γ-Aminobutyric acid (GABA) is the most common inhibitory neurotransmitter in the human CNS. Benzodiazepines facilitate GABAergic neurotransmission via a specific binding site on the $GABA_A$ receptor, which they (unlike barbiturates) cannot directly activate; this explains their safety in overdosage.[11] Relatively large doses and prolonged treatment may correlate with a higher risk of benzodiazepine abuse and dependence.

The *potency* of the molecule—measured by its affinity to the $GABA_A$ receptor—is another factor that may increase the potential for abuse and dependence. A strong affinity is presumably correlated with a higher risk of dependence.[12] *Clinical onset of action,* roughly measured by (although not equivalent to) the *time to maximum (peak) plasma drug concentration,* is another factor that may increase the risk of abuse. The quicker a substance is absorbed, the more risk there is of abuse.

Furthermore, the *duration of action* (as measured by the half-life of the molecule) can influence the risk of abuse, because rapid elimination can produce more rebound and withdrawal symptoms. There are 2 types of half-life:
- The alpha half-life: the initial decline following peak concentration due to redistribution of the drug
- The beta half-life: the terminal decline in plasma concentration due to its metabolism

The classification of benzodiazepines as long-, intermediate-, and short-"acting" is frequently based on the terminal beta half-life, but their duration of action appears to be much more dependent on the alpha half-life.[13] Slowly absorbed and slowly eliminated molecules have been found to be more appropriate for treating anxiety, while agents that are rapidly absorbed and slowly eliminated are more suitable for sleep problems.[14] Finally, some benzodiazepines are partially active prodrugs that need to be converted into their active metabolites; these may have a very long half-life, with attendant risk of accumulation.

Useful charts on benzodiazepines, anxiety, and sleep disorders may be found on the RxFiles Web site (http://www.rxfiles.ca).

## Benzodiazepines and anxiety disorders

Treatment guidelines for anxiety disorder have undergone major changes in the past 20 years. In 1992, benzodiazepines were considered to be first-line treatment for panic disorder, generalized anxiety disorder (GAD), simple phobia, and adjustment disorder. A β-blocker was frequently used to treat social phobia. A tricyclic antidepressant was used for agoraphobia and obsessive-compulsive disorder (OCD).[15] In 1997, recom-

mendations shifted in favor of SSRIs; guidelines now generally recommend these agents as first-line treatment—often in combination with cognitive-behavioral therapy (CBT)—for anxiety disorders.

Although the evidence for benzodiazepine efficacy is good, these agents are currently considered to be second-line treatment because of their abuse potential. The World Council of Anxiety has recommended high-potency benzodiazepines for panic disorder, clonazepam for social phobia, and short-term benzodiazepine for treatment of GAD.[16]

According to the British National Institute for Health and Clinical Excellence, benzodiazepines are associated with fewer favorable outcomes than other treatment options such as SSRIs and should not be used beyond 2 to 4 weeks for the treatment of GAD or for long-term treatment of panic disorder.[17] The British Association for Psychopharmacology's evidence-based guidelines for the treatment of anxiety disorders[18] acknowledge benzodiazepines, among other drugs, to be a short-term treatment of GAD and panic disorder. However, benzodiazepines should be considered for long-term use only in patients who have responded to other pharmacotherapies.

In the first revision of the World Federation of Societies of Biological Psychiatry treatment guidelines for anxiety, OCD, and posttraumatic stress disorder (PTSD), benzodiazepine use is recommended only in treatment-resistant cases, when the patient does not have a history of substance abuse.[19] According to the second edition of the American Psychiatric Association's practice guideline for the treatment of patients with panic disorder, benzodiazepines can be used as short-term monotherapy in the absence of a comorbid mood disorder.[20]

Data regarding the optimum duration of benzodiazepine maintenance therapy are scarce. However, clinical experience suggests that many patients can continue to take stable dosages of benzodiazepines without significant dosage escalation. To avoid physiological dependence and enhance control over symptoms, as-needed use is commonly prescribed—especially for long-term benzodiazepine users. This practice is not supported by available data and is justified only in the treatment of acute distress (eg, air travel, dental phobia). Indeed, as-needed use of benzodiazepines leads to fluctuating blood levels that may aggravate anxiety and reduce anxiolytic efficacy over time; it may also lead to greater cognitive impairment and worse CBT outcomes. Moreover, as-needed use leads to daily benzodiazepine consumption.[21] A regular time-fixed dosing scheme that prevents anxiety symptoms is preferable to trying to reduce symptoms once they occur.

Benzodiazepines should be avoided in PTSD; they appear to be ineffective and may promote or worsen the disorder.[22] Also, little evidence has been found for the effectiveness of benzodiazepines in OCD; these agents should be reserved for treatment-resistant cases only.[23]

In comorbid depressive disorders, antidepressants remain the treatment of choice. A combination of benzodiazepines and antidepressants in the first weeks of treatment—before the onset

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of symptom reduction with the antidepressant—may decrease the additional anxiety associated with the initial adverse effects of the antidepressant and increase compliance.[24] However, this combination should not be systematic because the risk of discontinuation of the antidepressant in favor of the benzodiazepine is increased, even though benzodiazepines do not have an antidepressive effect.

Benzodiazepines are effective in many anxiety disorders, but guidelines currently recommend these agents mainly for the acute phase of anxiety treatment. Clinical reality differs from these guidelines, however, and benzodiazepines are still largely prescribed as first-line treatments in the acute and chronic phases of anxiety disorders.[25] Although long-term benzodiazepine use is necessary in some patients with chronic anxiety symptoms, prescribing one of these agents for a treatment-refractory patient who has undergone at least 2 alternative (psychopharmacological and/or psychological) trials is not yet general clinical practice.[26]

Benzodiazepines are frequently used for long-term treatment because of prescribing traditions, patient preference, and the difficulties associated with benzodiazepine withdrawal (even in patients taking low doses). These agents have a rapid clinical onset of action and good efficacy with few initial adverse effects. Moreover, alternative drugs are associated with an incomplete therapeutic response and adverse effects.

In weighing the beneficial therapeutic response of a benzodiazepine against the drug's potential risks, keep in mind the safety concerns associated with alternative medications. SSRIs produce no craving or physiological dependence, but discontinuation symptoms can occur on their withdrawal.[27] No clear guidelines exist for SSRI treatment during pregnancy, and studies indicate that they produce sexual dysfunctions, hyponatremia, and sleep disturbances.[28,29] SSRIs have also been associated with an increased risk of extrapyramidal syndrome and cardiovascular problems, prolonged bleeding time, suicidality, and a higher frequency of bone fractures.[30] Some authors therefore point out that the rationale for the shift from benzodiazepines to SSRIs is insufficient.[31]

### Benzodiazepines and sleep problems

Many treatment options are available for patients who have insomnia, including benzodiazepines, nonbenzodiazepine $GABA_A$ receptor modulators (the "Z-drugs," including zaleplon, zolpidem, zopiclone, eszopiclone), melatonin-receptor agonists, antihistamines, and antidepressants (eg, trazodone, mirtazapine, amitriptyline, doxepin).[32] These options produce similar short-term outcomes in primary insomnia.[33] CBT and relaxation techniques are usually recommended as first-line treatments in combination with sleep hygiene education. If an additional pharmacological therapy is selected, patient-specific factors should be considered, including age, proposed duration of treatment, primary sleep complaint, comorbidity, history of substance abuse, and cost.[34]

There is consensus for the initial use of non-benzodiazepine hypnotics, and the Z-drugs have become the most widely prescribed hypnotics.[35] The effectiveness of benzodiazepines is only documented for the first month of treatment and their regular nightly use appears not to be useful for most patients. Although benzodiazepines significantly increase total sleep time, they only slightly decrease sleep latency, alter sleep architecture, and make it difficult to recall memories and dreams.[36] They can cause a hangover effect, daytime drowsiness, and lack of motor coordination.

Benzodiazepines should not be prescribed for patients with respiratory dysfunction, and they may be particularly hazardous in the elderly. They are ineffective for late-night insomnia, which is common in the senior population. Other options, such as melatonin, may be a better choice for the elderly.[37] However, evidence regarding the most appropriate long-term strategy for elderly persons with insomnia is scarce, and more research is needed.[38]

One of the main reasons for long-term use may be the frequency of rebound insomnia associated with benzodiazepines. This phenomenon may also occur with the use of zopiclone or zolpidem.

### Benzodiazepines and substance abuse

Benzodiazepine abuse is uncommon, except among those who abuse alcohol and/or other drugs. Fatal overdose with benzodiazepines is rare but can occur in combination with the use of alcohol or opioids. This has led to recommendations of generally excluding patients with a history of substance abuse or dependence from benzodiazepine treatment—a recommendation that some see as discriminatory. Some researchers argue that restricting the use of an effective and safe medication is unethical, even in substance abusers, and that there is little evidence to indicate that a history of substance abuse is a major risk factor for future benzodiazepine abuse or dependence.[39,40] An alternative solution to prescribing benzodiazepines for persons with a history of substance abuse could be close monitoring in specialized care settings. This was proposed by the 1990 American Psychiatric Association task force report on benzodiazepine dependency, toxicity, and abuse, which did not, however, recommend any specific standards.[41]

The distinction between abuse, addiction, high-dose, and therapeutic-dose dependence is of particular importance.[42] Patients who take benzodiazepines for their euphorogenic effects or to modulate the effects of illegal drugs or alcohol are clearly misusing the medication. Refer such patients for appropriate care and do not provide further prescriptions.[43] High-dose use should also lead to a strict treatment plan aimed at progressive tapering and alternative therapies. Long-term treatment with therapeutic doses of benzodiazepines is not considered abuse or addiction; however, patients may have a pharmacological dependence and manifest withdrawal symptoms with abrupt discontinuation of therapy.

### Benzodiazepines and the elderly

Benzodiazepines remain one of the main risk factors for falls, fractures, and other accidents in the elderly. The increased risk of hip fracture ranges from 50% to 110%.[44] The risk of motor vehicle accidents is also markedly increased.[45] A recent critical review, however, recalls that all psychotropics—benzodiazepines, antidepressants, and antipsychotics—are associated with a risk of falling, and that SSRIs also pose a high risk in the elderly.[46] One study found that policies leading to reductions in the use of benzodiazepines do not necessarily lead to a decreased incidence of hip fracture in this population.[47] In the anxious older patient, the switch from a benzodiazepine to an antidepressant therefore might not necessarily be safer. Studies are needed of the relative risk of falls associated with benzodiazepines versus SSRIs in the elderly.

Benzodiazepines can also affect cognition and can cause paradoxical disinhibition in older persons. Long-term benzodiazepine treatment may lead to cognitive dysfunctions and worsen preexisting cognitive deficits; patients may not recover their previous level of functioning after treatment is discontinued.[48] Because of their anticholinergic and antihistaminergic activity, tricyclic antidepressants should also be avoided in the senior population. With their positive effects on cognition, SSRIs are first-line therapy for the treatment of depression in the elderly.[49]

The costs and benefits of psychiatric medications should be carefully weighed when treating older adults. Advise patients of potential negative cognitive effects associated with long-term benzodiazepine therapy.

### Conclusion

Even though benzodiazepines have been in use for half a century, long-term outcome studies are relatively scarce. Addiction and high-dose dependence are rare, but many patients develop physiological low-dose dependence and coping strategies vary. The conflict between proponents and opponents can assume religious proportions.[50] A good knowledge base of the particular profile of a specific benzodiazepine, the identification of risk populations, clear indications, and the courage to discontinue the treatment if it is no longer useful may limit the problems associated with benzodiazepines.

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## Category 1 Posttest

1. Symptoms of rebound anxiety and rebound insomnia appear to be more frequent with the discontinuation of which of the following type(s) of benzodiazepine?
   A. Short-life
   B. Long-life
   C. Both short- and long-life

2. The suggested criteria for identifying benzodiazepine dependence includes which of the following?
   A. Frequent requests for repeat prescriptions
   B. Higher dosages than the norm
   C. Increased tolerance
   D. All of the above
   E. None of the above

3. A strong affinity to the GABA$_A$ receptor is correlated with a higher risk of dependence.
   A. True
   B. False

4. The duration of action of benzodiazepines is much more dependent on their initial alpha half-life than their terminal beta half-life.
   A. True
   B. False

5. The shift from first-line to second-line treatment for anxiety disorders with benzodiazepines has come about because of their
   A. Tolerance issues
   B. Lack of effectiveness
   C. Abuse potential
   D. All of the above
   E. None of the above

6. There is strong evidence that suggests that benzodiazepines are very effective for treating posttraumatic stress disorder and obsessive-compulsive disorder.
   A. True
   B. False

7. Which of the following are reasons for long-term use of benzodiazepines?
   A. Patient preference
   B. Rapid clinical onset
   C. Ineffectiveness of alternative treatments
   D. All of the above
   E. None of the above

8. What is the main concern when treating elderly persons with benzodiazepines?
   A. The risk of tardive dyskinesia
   B. An increase in sleep disorders
   C. Worsening of cognitive function
   D. All of the above
   E. None of the above

9. Regarding use of benzodiazepines to treat sleep problems, which of the following statements is *incorrect*?
   A. For patients with primary insomnia, a variety of effective treatment options is available.
   B. CBT and relaxation techniques are generally recommended as first-line treatments in combination with sleep hygiene education.
   C. There is consensus for the initial use of benzodiazepine hypnotics in patients with primary insomnia.
   D. Benzodiazepines are ineffective for late-night insomnia, which is common among elderly persons.

10. Which of the following statements is *false*?
    A. Benzodiazepine abuse is uncommon, except in persons who abuse alcohol and/or other drugs.
    B. Fatal overdoses with benzodiazepines are rare but can occur in combination with alcohol or opioid use.
    C. Significant evidence indicates that a history of substance abuse is a major risk factor for benzodiazepine abuse.
    D. Close monitoring in specialized care settings has been recommended for patients taking benzodiazepines who have a history of substance abuse.

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