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Dr. Casher: Addressing abuse of benzodiazepines

Benzodiazepines: A versatile clinical tool

Evidence supports their use for alcohol withdrawal, insomnia, anxiety disorders, and other conditions

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Since the discovery of chlordiazepoxide in the 1950s, benzodiazepines have revolutionized the treatment of anxiety and insomnia, largely because of their improved safety profile compared with barbiturates, formerly the preferred sedative-hypnotic.[1] In addition to their anxiolytic and sedative-hypnotic effects, benzodiazepines exhibit anterograde amnesia, anticonvulsant, and muscle relaxant properties.[1] Psychiatrists use benzodiazepines to treat anxiety and sleep disorders, acute agitation, alcohol withdrawal, catatonia, and psychotropic side effects such as akathisia. This article highlights the evidence for using benzodiazepines in anxiety and other disorders and why they generally should not be used for obsessive-compulsive disorder and posttraumatic stress disorder (***Box 1, page 59***).

Pharmacokinetic properties

Most benzodiazepines are considered to have similar efficacy; therefore, selection is based on pharmacokinetic considerations. ***Table 1*** (***page 60***) compares the indication, onset, and half-life of 12 commonly used benzodiazepines.[2-6] Although ***Table 1*** lists approximate equivalent doses, studies report inconsistent data. These are approximations only and should not be used independently to make therapy decisions.

A diverse range of indications

Alcohol withdrawal. Benzodiazepines are the treatment of choice for alcohol withdrawal syndrome, particularly to prevent seizures.[7] Research supports symptom-triggered therapy using the revised

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Benzodiazepines

Clinical Point

For treating social anxiety, benzodiazepines have better efficacy than SSRIs, MAOIs, and anticonvulsants

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Clinical Institute Withdrawal Assessment for Alcohol. Benzodiazepines reduce CNS sympathetic hyperactivity to mitigate withdrawal from alcohol by decreasing tachycardia, tremor, insomnia, agitation, and anxiety. Furthermore, these agents provide prophylaxis against serious sequelae such as seizures and delirium.

Insomnia. The American Academy of Sleep Medicine considers benzodiazepine receptor agonists (BzRAs, which include benzodiazepines and non-benzodiazepines) and ramelteon first-line pharmacotherapy for primary insomnia.[8] However, pharmacologic treatment should be short-term. Agents with short to intermediate half-lives and rapid onset, such as triazolam, can aid sleep initiation. Those with longer half-lives, such as temazepam, could address sleep maintenance. If a patient does not respond to the initial agent, try another medication within the same class, because patients may respond differently. Use lower starting doses in geriatric patients.[9] Closely monitor for adverse effects, rebound insomnia, and potential abuse or tolerance. Identify comorbid conditions and medications that may impair sleep, and address them accordingly.

Psychological and behavioral treatments given over 4 to 8 weeks can yield stable sleep improvements for up to 2 years. If available, these interventions may be considered first-line for treating insomnia because of their lasting effects compared with BzRAs.[10]

Generalized anxiety disorder (GAD). Benzodiazepines effectively treat GAD because they work quickly and are well tolerated. However, there are better first-line treatment options when considering efficacy studies and dependence and tolerance concerns. One effect-size comparison of 21 double-blind, placebo-controlled trials showed that the efficacy of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and pregabalin are comparable to benzodiazepines.[11] Benzodiazepines can be used in the first 2 to 3 weeks after initiating antidepressants to alleviate and prevent worsening of anxiety that may occur at the start of antidepressant therapy. Recent treatment guidelines recommend benzodiazepines as a second-line treatment or for treatment-resistant GAD in patients who do not have a substance abuse history.[12,13]

Panic disorder. Efficacy of benzodiazepines for panic disorder is comparable to SSRIs, SNRIs, and tricyclic antidepressants (TCAs). SSRIs and SNRIs are considered first-line treatments for panic disorder because of their favorable side effect profile.[14] In practice, benzodiazepines often are combined with SSRIs, SNRIs, or TCAs. A randomized controlled trial demonstrated that paroxetine and clonazepam (mean dose 1.6 mg/d at 5 weeks) resulted in a more rapid response compared with paroxetine alone, although this difference lasted only a few weeks.[15] Furthermore, this study suggested that brief treatment with clonazepam followed by a taper is as effective as sustained treatment with paroxetine and clonazepam.[15]

There is a lack of high-quality data on combining cognitive-behavioral therapy (CBT) and benzodiazepines for panic disorder, although a Cochrane Review found that adding a benzodiazepine to CBT did not lead to a significant difference in response compared with psychotherapy alone.[16] A recent randomized controlled trial demonstrated that tapering benzodiazepines combined with CBT was associated with successful discontinuation of the drug and prevented return of panic symptoms.[17]

Social anxiety. A meta-analysis found that for treating social anxiety, benzodiazepines have better efficacy than SSRIs, monoamine oxidase inhibitors, and anticonvulsants.[18] Longer-acting benzodiazepines may be more effective than shorter-acting agents. One study of patients with social anxiety showed a 38% response rate for alprazolam vs 20% for placebo over 12 weeks, and a similar 10-week study demonstrated a 73% recovery rate with clonazepam vs 22% for placebo.[19] In addition, studies have observed that patients can be maintained on clonazepam for up to 2 years without symptom relapse and will tolerate slow-

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Box 1

When not to use benzodiazepines: OCD and PTSD

Current evidence indicates little support for using benzodiazepines for obsessive-compulsive disorder (OCD). The American Psychiatric Association (APA) and the World Federation of Biological Psychiatry do not recommend benzodiazepines for treating OCD because of a lack of evidence for efficacy.[a,b] An earlier study suggested clonazepam monotherapy was effective for OCD[c]; however, a more recent study did not show a benefit on rate of response or degree of symptom improvement.[d] Augmentation strategies with benzodiazepines also do not appear to be beneficial for OCD management. A recent double-blind, placebo-controlled study failed to demonstrate faster symptom improvement by augmenting sertraline with clonazepam, although the study had a small sample size and high drop-out rate.[e]

Because benzodiazepines have negligible action on core posttraumatic stress disorder (PTSD) symptoms (re-experiencing, avoidance, and hyperarousal), selective serotonin reuptake inhibitors and other agents largely have supplanted them for PTSD treatment.[f] Use of benzodiazepines for PTSD is associated with withdrawal symptoms, more severe symptoms after discontinuation, and possible disinhibition, and may interfere with patients' efforts to integrate trauma experiences. Although benzodiazepines may reduce distress associated with acute trauma, there is evidence—in clinical studies and animal models—that early benzodiazepine administration fails to prevent PTSD and may increase its incidence.[g] The International Consensus Group on Depression and Anxiety, the APA, and the British Association for Psychopharmacology all highlight the limited role, if any, for benzodiazepines in PTSD.[h-j]

Source: For reference citations, see this article at CurrentPsychiatry.com

taper discontinuation.[18,20] Sedation and drowsiness can be lessened by limiting clonazepam doses to 2 to 3 mg/d.

Akathisia and tremor. Akathisia, a syndrome of motor restlessness and inner turmoil, is associated with antipsychotics but can occur with SSRIs. Reducing the dosage or switching to another, usually less potent agent often can relieve akathisia. When these remedies are not tenable, consider benzodiazepines along with other medications—including beta blockers and anticholinergic agents—with demonstrated efficacy in reducing akathisia symptoms. Lorazepam, diazepam, and clonazepam have demonstrated efficacy for relieving akathisia in comparison studies with placebo, propranolol, and diphenhydramine.[21,22]

Drug-induced postural tremor can occur with several psychotropics, including lithium, valproic acid, antidepressants, and antipsychotics. A tremor is considered mild if a patient can drink a glass of water with 1 hand without spilling and severe if holding a glass with 2 hands is difficult. Propranolol is most commonly prescribed for these tremors, but alprazolam and clonazepam have demonstrated efficacy, either as monotherapy or coadministered with a beta blocker.[23]

Acute agitation. Agitated patients often have acute psychosis and/or mania or dyscontrol secondary to axis II disorders.[24] Patients may be paranoid, hostile, disruptive, and combative. Rapidly initiating medication can prevent the need for more restrictive measures, such as seclusion or restraint. Antipsychotics—especially high-potency agents such as haloperidol—and benzodiazepines, as monotherapy or in combination, are a mainstay treatment. Although treatment protocols favor atypical antipsychotics over typical antipsychotics, benzodiazepines are a viable option because of their anxiolytic and sedative effects. Advantages of benzodiazepine monotherapy include decreased extrapyramidal symptoms, greater patient acceptance/preference, and increased sedation compared with antipsychotics. Lorazepam, 1 to 2 mg intramuscularly (IM) or orally, is well tolerated because of its favorable drug-drug interaction profile and lack of significant cardiac side effects. Benzodiazepines can cause respiratory depression in patients with chronic lung disease and additive sedation secondary to opiates, other sedatives/hypnotics, or alcohol. Behavioral disinhibition is rare and is associated with preexisting CNS pathology or mental retardation.[25] The IM

Clinical Point

Benzodiazepines have negligible action on core PTSD symptoms: re-experiencing, avoidance, and hyperarousal

Benzodiazepines

Clinical Point

Benzodiazepines have anticonvulsant properties that may interfere with the therapeutic efficacy of ECT

Table 1

Oral benzodiazepines: Indications, onset, half-life, and equivalent doses

Drug	FDA-approved indication(s)	Onset of action	Approximate half-life (hours) in healthy adults	Approximate equivalent dose (mg)[a]
Alprazolam	Anxiety disorders, panic disorder	Intermediate	6.3 to 26.9 (IR), 10.7 to 15.8 (XR)	0.5
Chlordiazepoxide	Anxiety disorders, acute alcohol withdrawal, preoperative apprehension and anxiety	Intermediate	24 to 48	10
Clonazepam	Seizure disorders, panic disorder	Intermediate	18 to 50	0.25 to 0.5
Clorazepate	Anxiety, seizures, acute alcohol withdrawal	Fast	40 to 50	7.5
Diazepam	Anxiety disorders, acute alcohol withdrawal, muscle spasms, convulsive disorders	Very fast	20 to 100	5
Estazolam	Insomnia	Intermediate	10 to 24	0.3 to 2
Flurazepam	Insomnia	Intermediate	47 to 100	30
Lorazepam	Anxiety	Intermediate	10 to 20	1
Oxazepam	Anxiety, acute alcohol withdrawal	Slow to intermediate	5 to 20	30
Quazepam	Insomnia	Intermediate	39 to 73	5 to 15
Temazepam	Insomnia	Intermediate	3.5 to 18.4	30
Triazolam	Insomnia	Fast	1.5 to 5.5	0.25

IR: immediate release; XR: extended release

[a]Interpret with caution, conflicting data exist

Source: References 2-6

olanzapine package insert warns against coadministering IM lorazepam because of additive cardiorespiratory depressive effects and excessive somnolence.[26]

Catatonia. The characteristic symptoms of catatonia are immobility, negativism, muteness, and failure to eat or drink. Benzodiazepines improve these symptoms in approximately 70% to 80% of catatonic patients with affective disorders. Response rates are lower in catatonia in patients with schizophrenia.[27] If catatonia in a patient with psychosis is missed, giving antipsychotics before benzodiazepines may worsen catatonic symptoms or precipitate neuroleptic malignant syndrome in some cases. When you suspect a patient has catatonia, start with lorazepam, 1 to 2 mg IV or IM, and examine the patient for diminishing catatonic signs within 1 to 2 hours. If catatonia signs lessen, begin regularly scheduled lorazepam, with dosing varying by age—be more cautious in geriatric patients—and symptom severity. Titrate benzodiazepines for stuporous patients more slowly (eg, 1 mg 3 times a day as a starting dose) than for excited catatonic patients. Lorazepam can be increased gradually as tolerated; it is not unusual for patients to require up to 8 to 12 mg/d. Electroconvulsive therapy (ECT) is the treatment of choice when catatonic patients respond poorly or partially to high-dose benzodiazepines.[28,29]

	Comments
	Increased risk for abuse because of greater lipid solubility
	Risk for accumulation because of long-acting metabolites (desmethyldiazepam, oxazepam)
	Use caution in patients with liver disease
	Risk for accumulation because of long-acting metabolites (desmethyldiazepam, oxazepam)
	Risk for accumulation because of long-acting metabolites (temazepam, desmethyldiazepam, oxazepam). Increased risk for abuse because of quick onset
	None
	Avoid in geriatric patients or patients with liver impairment
	Preferred for patients with liver impairment and geriatric patients
	Preferred for patients with liver impairment and geriatric patients
	Risk for accumulation because of long-acting metabolites (desmethyldiazepam, oxazepam)
	Preferred for patients with liver impairment and geriatric patients
	Lacks active metabolites

Benzodiazepine reversal for ECT

Benzodiazepines have anticonvulsant properties that may interfere with the therapeutic efficacy of ECT.[30] A multi-center study demonstrated that lorazepam (up to 4 mg/d as needed) in the 48 hours before the first ECT session was not associated with effects on seizure threshold or duration; however, larger lorazepam dosages were associated with briefer EEG seizure duration.[31] Some patients may not tolerate withholding or tapering benzodiazepines in preparation for ECT. Studies investigating flumazenil for pre-ECT benzodiazepine reversal are lacking. One retrospective analysis showed that flumazenil administration immediately before and after ECT resulted in adequate seizures with no difference in clinical outcome compared with patients who were not receiving benzodiazepines or flumazenil.[32]

Tapering benzodiazepines

Slow discontinuation of benzodiazepines is recommended to avoid withdrawal symptoms, such as rebound anxiety, agitation, insomnia, or seizures, particularly when use exceeds 8 weeks. The onset of withdrawal symptoms varies, depending on the medication used. Withdrawal symptoms may appear in 1 to 2 days for agents with shorter half-lives, but may not appear until 3 to 7 days for agents with longer half-lives.[33] ***Table 2*** (***page 62***) lists recommended durations for tapering benzodiazepines.[33,34] In general, decrease the total daily dose by 25% the first week, another 25% the second week, then 10% a week until discontinuation. When benzodiazepine use exceeds 1 year, a slower taper is recommended; for example, decrease 10% every 1 to 2 weeks. When 20% of the dosage remains, begin a 5% dose reduction every 2 to 4 weeks. Monitor patients for withdrawal symptoms or symptom exacerbation. If either occur, consider maintaining the current benzodiazepine dose or increasing the dose for 1 to 2 weeks or longer, if necessary, then continue to taper at a slower rate.[34]

Risks of benzodiazepine use

For most indications, benzodiazepine therapy should be short-term.[35] Use exceeding 2 to 4 weeks increases the risk for dependence and withdrawal. Tell patients to avoid alcohol while taking a benzodiazepine because this combination is potentially lethal. Benzodiazepines are commonly abused and abuse can lead to unintentional drug overdose. Benzodiazepines accounted for 37% of unintentional drug overdose deaths in West Virginia in 2006; in 46% of these cases, benzodiazepines were used for nonmedical purposes. Clinicians can help reduce the risk of diversion by limiting prescriptions to 30 days with no refills.[36]

Older patients taking benzodiazepines are at increased risk of falls and hip frac-

Clinical Point

Benzodiazepine use should be short-term; use exceeding 2 to 4 weeks increases the risk for dependence and withdrawal

Benzodiazepines

Table 2

Recommendations for tapering benzodiazepines

Duration of use	Recommended taper length	Comments
<6 to 8 weeks	Taper may not be required	Depending on clinical judgment and patient stability/preference, consider implementing a taper, particularly if using a high-dose benzodiazepine or an agent with a short or intermediate half-life, such as alprazolam or triazolam
8 weeks to 6 months	Slowly over 2 to 3 weeks	Go slower during latter half of taper. Tapering will reduce, not eliminate, withdrawal symptoms. Patients should avoid alcohol and stimulants during benzodiazepine withdrawal
6 months to 1 year	Slowly over 4 to 8 weeks	
>1 year	Slowly over 2 to 4 months	

Source: References 33,34

Clinical Point

Agents with shorter half-lives such as lorazepam and oxazepam are preferred for older patients

Box 2

Using benzodiazepines during pregnancy

Benzodiazepine use during pregnancy has been associated with cleft palate and urogenital and neurologic malformations in the fetus.[38] Although data are conflicting—particularly among recent meta-analyses that fail to demonstrate an association—some experts advise against benzodiazepine use in the first trimester. Participate in shared decision making with your patients and educate them about the potential risks and benefits of benzodiazepine use during the first trimester and throughout pregnancy. After delivery, newborns may develop "floppy baby syndrome"—which is associated with lethargy, difficulty eating, and respiratory depression—or withdrawal.[38] To minimize this risk, consider tapering the benzodiazepine as the patient approaches delivery.

tures.[37] Lorazepam, oxazepam, and temazepam—agents with shorter half-lives that are not greatly affected by pharmacokinetic changes associated with aging—are preferred for these patients.[34] Patients with dementia or other CNS-compromising conditions may become confused or delirious with regular benzodiazepine dosing. Educate patients to whom you prescribe benzodiazepines about the importance of gauging their level of sedation before driving or engaging in other tasks for which sedation could compromise their safety. Benzodiazepine use during pregnancy requires a careful discussion of risks and benefits (***Box 2***).[38]

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Related Resources

- Substance Abuse and Mental Health Services Administration. www.samhsa.gov.
- National Institute on Drug Abuse resources for medical and health professionals. www.drugabuse.gov/medical-health-professionals.
- American Academy of Sleep Medicine. www.aasmnet.org.

Drug Brand Names

Alprazolam • Xanax
Chlordiazepoxide • Librium, Limbitrol
Clonazepam • Klonopin
Clorazepate • Tranxene
Diazepam • Valium
Diphenhydramine • Benadryl, others
Estazolam • ProSom
Flumazenil • Romazicon
Flurazepam • Dalmane
Haloperidol • Haldol
Lithium • Lithobid
Lorazepam • Ativan
Olanzapine • Zyprexa
Oxazepam • Serax
Paroxetine • Paxil
Pregabalin • Lyrica
Propranolol • Inderal, InnoPran XL, others
Quazepam • Doral
Ramelteon • Rozerem
Sertraline • Zoloft
Temazepam • Restoril
Triazolam • Halcion
Valproic acid • Depakene, Stavzor, others

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Clinical Point

Benzodiazepine use during pregnancy has been associated with cleft palate and urogenital and neurologic malformations

Bottom Line

Benzodiazepines often are used first-line for insomnia; however, nonpharmacologic treatment and other factors that may interfere with sleep must be examined. Evidence supports benzodiazepine use for acute generalized anxiety disorder, panic disorder, and social anxiety, but not obsessive-compulsive disorder or posttraumatic stress disorder. Because of the potential for misuse, clinicians must take precautions to ensure these medications are used safely and appropriately.

Box 1

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