

Benzodiazepine and Z-Drug Safety Guideline

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Guidelines are systematically developed statements to assist patients and providers in choosing appropriate health care for specific clinical conditions. While guidelines are useful aids to assist providers in determining appropriate practices for many patients with specific clinical problems or prevention issues, guidelines are not meant to replace the clinical judgment of the individual provider or establish a standard of care. The recommendations contained in the guidelines may not be appropriate for use in all circumstances. The inclusion of a recommendation in a guideline does not imply coverage. A decision to adopt any particular recommendation must be made by the provider in light of the circumstances presented by the individual patient.

Background

Benzodiazepines and Z-drugs (i.e., newer GABA receptor agonists, like zolpidem [Ambien]) are overprescribed, and the reasons behind many prescriptions are not based on evidence or on published guidelines. Despite warnings about the long-term use of benzodiazepines, millions of prescriptions are still issued for benzodiazepines and Z-drugs each year. As a result, clinicians may encounter patients who have been prescribed benzodiazepines or Z-drugs on a long-term basis and are resistant to discontinuation.

The purpose of this guideline is fivefold:

- To reduce inappropriate prescribing of benzodiazepines and Z-drugs,
- To clarify when short-term prescribing of benzodiazepines and Z-drugs may be indicated,
- To confirm that long-term use of benzodiazepines and Z-drugs is rarely, if ever, indicated,
- To aid primary care and behavioral health providers in identifying and managing patients on long-term benzodiazepines and Z-drugs, and
- To provide appropriate advice to providers for discontinuing benzodiazepine and Z-drug use.

Target population

The recommendations in this guideline apply to patients who are:

- Already on **prescribed** long-term benzodiazepine or Z-drug therapy, or
- Being considered for initiation of short-term therapy with either drug class.

Exclusions

This guideline does not apply to patients who are using benzodiazepines illicitly. These patients may require treatment in Chemical Dependency and should be referred to Behavioral Health Services.

About benzodiazepines and Z-drugs

Benzodiazepines are gamma-aminobutyric acid (GABA) receptor agonists that have hypnotic, anxiolytic, muscle relaxant, and anticonvulsant properties.

Benzodiazepines are commonly divided into three groups according to how quickly they are eliminated from the body:

- Short-acting (half-life less than 12 hours), such as midazolam and triazolam.
- Intermediate-acting (half-life between 12 and 24 hours), such as alprazolam, lorazepam, and temazepam.
- Long-acting (half-life greater than 24 hours), such as diazepam, clonazepam, clorazepate, chlordiazepoxide, and flurazepam.

Z-drugs (e.g., zaleplon, zolpidem, and eszopiclone) were developed as alternatives to benzodiazepines.

- Like benzodiazepines, they are GABA receptor agonists, but since they have a different structure, they produce fewer anxiolytic and anticonvulsant effects.
- Z-drugs are not “safer” than benzodiazepines, and patients on benzodiazepines should not be switched to Z-drugs to try to improve safety. (See drug alerts on next-day sedation with [zolpidem](#) and [eszopiclone](#), available on the staff intranet.)

Both benzodiazepines and Z-drugs are considered a “high-risk medication in the elderly” and are listed on the [American Geriatrics Society Beers Criteria list](#).

Prescribing

Except where noted, statements about benzodiazepines in this guideline also apply to Z-drugs.

Prescribing considerations

Before initiating a course of benzodiazepine treatment,

- Explicitly advise the patient regarding the duration of treatment. Use of benzodiazepines beyond 6 weeks is **not recommended**.
- Review with the patient the risks and side effects, including the risk of dependence. Keep in mind that some patients will have difficulty discontinuing the medication at the end of acute treatment.
- Discuss exit strategies, such as short tapering or switching to alternative treatments.
- Discuss alternative treatments.
 - Antidepressant medications (e.g., SSRIs, SNRIs, tricyclic antidepressants)
 - Psychotherapy (e.g., cognitive behavioral therapy)
 - Serotonergic agents for anxiety (buspirone)
 - Anticonvulsant medications for restless legs (e.g., pramipexole, ropinirole, gabapentin)
 - Adjunctive symptomatic medications (see Table 4)
- The patient and health care provider should agree on one provider to be the benzodiazepine prescriber for that patient. This designated prescriber will be also responsible for prescribing other medications with abuse potential, specifically central nervous system (CNS) stimulants and narcotics.

Note for patients aged 65 years and over

- If prescribing for patients who are frail or aged 65 and older, consider initiating the medication at half the adult dose.
- Individuals aged 65 and older are especially vulnerable to the adverse effects of hypnotic drugs, as their metabolic rates decline with age. Patients in this age group are:
 - More susceptible to CNS depression and cognitive impairment, and may develop confusional states and ataxia leading to falls and hip fractures.
 - At risk of drug interaction with other medications.
 - At risk of permanent cognitive impairment when using high doses of benzodiazepines (e.g., diazepam 30 mg or equivalent) on a regular basis.

Table 1. Major indications (short-term) for benzodiazepines (BZDs) and Z-drugs

Indication	BZDs	Z-drugs	Considerations
Insomnia	Yes	Yes	<ul style="list-style-type: none"> • Both are effective in the relief of short-term (1–2 weeks) but not long-term insomnia. • The treatment period should not exceed 2 weeks, as sleep studies have shown that sleep patterns return to pre-treatment levels after only a few weeks of regular use.
Anxiety	Yes	No	<ul style="list-style-type: none"> • Not first-line therapy, but may be used as an adjunct while waiting for definitive therapy to work. • Continuing beyond 4–6 weeks will result in loss of effectiveness, development of tolerance or dependence, potential for withdrawal symptoms, persistent adverse side effects, and interference with the effectiveness of definitive medications and counseling. • Counseling referral strongly recommended.
Muscle relaxant	Yes	No	<ul style="list-style-type: none"> • Indicated for short-term relief (1–2 weeks) of muscle discomfort associated with acute injuries or flare-ups of chronic musculoskeletal pain. • Benzodiazepines should not be combined with other sedatives, hypnotics, or muscle relaxants.

Other short-term indications for benzodiazepines only

- As part of a protocol for treating alcohol withdrawal
- Urgent treatment of acute psychosis with agitation or acute mania
- Single-dose treatment of phobias, such as flying phobia
- Seizures and a limited number of neurologic disorders
- Sedation for office procedures

Long-term use

Benzodiazepines and Z-drugs are **not recommended** for long-term use (longer than 6 weeks), apart from in exceptional circumstances (e.g., for terminally ill patients). There is no evidence to support the long-term use of these drugs for insomnia or any mental health indication. There are concerns regarding their safety.

Contraindications

- Active or history of substance abuse
- Pregnancy or risk of pregnancy
- Treatment with opioids for chronic pain or replacement therapy for narcotic addiction
- Medical and mental health problems that may be aggravated with benzodiazepines, such as fibromyalgia, chronic fatigue syndrome, somatization disorders, depression, bipolar disorders (except for urgent sedation in acute mania), attention deficit hyperactivity disorder, kleptomania, and other impulse disorders
- Cardiopulmonary disorders such as asthma, sleep apnea, chronic obstructive pulmonary disease, congestive heart failure, and other cardiopulmonary disorders, since benzodiazepines may worsen hypoxia and hypoventilation

Adverse effects of *both* benzodiazepines and Z-drugs

- Dependence: Potent benzodiazepines with short or intermediate half-lives (e.g., alprazolam, lorazepam) appear to carry the highest risk of causing problems with dependence. Psychological or physical dependence can develop over a few weeks or months and is more likely to develop with long-term use or high doses, and in patients with a history of anxiety problems.
- Tolerance to the hypnotic effects, which may develop after only a few days of regular use
- Daytime somnolence
- Dizziness
- Impaired driving performance leading to an increased risk of road traffic accidents
- Depression and increased anxiety
- Slowness of mental processes and body movements
- Particularly high risk of overdose when combined with sedative drugs, such as opioids or alcohol
- Increased risk of mortality (Weich 2014)

Adverse effects of benzodiazepines (in addition to the above list):

- Tolerance to the anxiolytic effects, which may develop after a few months of use. (This doesn't apply to Z-drugs because they are not anxiolytic.)

Management of Patients on Chronic Benzodiazepines and Z-Drugs

All patients should be encouraged to discontinue chronic use of benzodiazepines and Z-drugs. Providers should create a treatment care plan to help patients with tapering and discontinuation.

- For most people in primary care settings, even a minimal intervention, such as a letter with self-help information from the treating physician or a single brief consultation, can be effective in reducing or stopping benzodiazepine use.
- For patients who do not want to stop the drugs, discuss the benefits of stopping. Set the expectation of revisiting the topic at least annually, and more frequently when there are changes in the patient's care plan.

Components of a chronic benzodiazepine or Z-drug visit

1. Encounter

Epic Tip: Use the SmartPhrase **.benzovisit** to include all of the recommended elements of the initial or follow-up visit.

When initiating or monitoring chronic benzodiazepine or Z-drug therapy, perform and document the following:

- **Medical screening** for issues that affect sedative risk (e.g., COPD, CHF, renal or hepatic compromise, obstructive sleep apnea, pregnancy risk)
- **Patient history and physical exam**
- **Depression screening** with PHQ-9 (See Depression Guideline.)
- **Alcohol use screening** as needed with AUDIT-C (See Adult Unhealthy Drinking Guideline.)
- **Drug use screening** as needed with DAST

2. Problem List

Epic Tip: Use the SmartPhrase **.benzoproblast** to establish and update the problem list.

3. Care Plan

Epic Tip: Use the SmartPhrase **.benzocareplan** to include all of the elements of the treatment plan.

All patients should receive an After Visit Summary that outlines their care plan.

Frequency of monitoring

Patients should be followed up annually, at a minimum. More frequent follow-up may be needed for patients who have problems following the treatment care plan, such as making early refill requests, escalating the dose without consulting the physician, or requesting benzodiazepines from multiple prescribers.

Tapering and Discontinuation

Tapering considerations

- Assess the patient's underlying condition for which the drugs were originally prescribed; discuss alternative treatments as needed.
- Assess the patient for readiness/suitability to taper off of benzodiazepines. Patients are considered suitable if they:
 - Are willing and committed, with adequate social support.
 - Have no previous history of complicated drug withdrawal.
- Cognitive behavioral therapy should be available to assist with the withdrawal process and help the patient deal with rebound anxiety.
- Consider referral to a specialist for patients who: have a history of alcohol use disorder or other drug use disorders; have a concurrent severe medical or psychiatric disorder; are on a high dose of benzodiazepines; are taking amphetamines or opiates concurrently; or have a history of drug withdrawal seizures.
- Consult Mind Phone if you have specific questions about tapering.

Tapering recommendations for patients aged 65 years and over

- If the patient is established on a **long- or intermediate-acting benzodiazepine**, gradually taper the medication per Table 2a or Table 2b.
- If the patient is established on a **short-acting benzodiazepine or one that doesn't easily allow for small dose reductions**, switch to lorazepam and gradually taper per Table 2a or Table 2b.
- If the patient is established on a **Z-drug**, choose one of these options:
 - Stop the Z-drug and start an alternative medication (such as melatonin, trazodone, or mirtazapine).
 - Gradually taper the Z-drug by decreasing the number of days per week the patient takes the medication (for example: take 6 nights per week x 2 weeks, then 5 nights per week x 2 weeks, and so on).
 - Switch the Z-drug to lorazepam and gradually taper per Table 2a or Table 2b.

Gradual tapering

The most effective strategy to manage benzodiazepine discontinuation and prevent adverse outcomes associated with the development of severe withdrawal is a gradual taper of benzodiazepines.

Indication	Taper method
<ul style="list-style-type: none">• Medication adverse effects indicate risks are greater than benefit, or• Comorbidities increase risk of complication.	10% per week
<ul style="list-style-type: none">• Function is not improved, or• Tolerance has developed with long-term prescription, or• Comorbidities increase risk of complication.	10% every 2–4 weeks

- Consider converting patients to a longer-acting benzodiazepine; see section below.
- Tapering should be guided by individual choice and severity of withdrawal symptoms. Drug discontinuation may take 3 months to a year or longer. Some people may be able to discontinue the drug in less time.
- Review the patient’s progress frequently to detect and manage problems early and to provide advice and encouragement during and after tapering.
- If they do not succeed on the first attempt, encourage the person to try again. Emphasize that any reduction in use is beneficial. Treat any underlying problems before trying again.
- Discontinuation of Z-drugs is less well studied than discontinuation of benzodiazepines, but given that they work similarly, the same approach for tapering benzodiazepines is recommended for tapering Z-drugs.

Rapid discontinuation

Table 2b. Clinical indications for rapid discontinuation of benzodiazepine or Z-drug therapy

Indication	Rapid discontinuation method
<ul style="list-style-type: none"> • Urine drug screen is consistent with substance abuse concerns, or • Patient’s behavior suggests possible misuse or diversion of medication. Such behaviors might include: <ul style="list-style-type: none"> ○ Selling prescription drugs ○ Forging prescriptions ○ Stealing or borrowing drugs ○ Frequently losing prescriptions ○ Aggressive demand for benzodiazepines ○ Injecting oral/topical benzodiazepines ○ Unsanctioned use of benzodiazepines ○ Unsanctioned dose escalation ○ Concurrent use of illicit drugs ○ Getting benzodiazepines from multiple prescribers ○ Recurring emergency department visits 	<p>25% per week</p> <p>and/or</p> <p>Refer patient for chemical dependency or addiction counseling. (See Referral Criteria.)</p>

Switching to a longer-acting benzodiazepine

Diazepam (patients aged 64 and under)

There is a lack of good-quality evidence on switching to diazepam, but it is recommended for some people because diazepam has a long half-life (20–80 hours) and thus has fewer fluctuations in the plasma levels. It is also available in a variety of strengths and formulations, which facilitates stepwise dose substitutions from other benzodiazepines or Z-drugs and allows for small incremental reductions in dosage. Switching is best carried out gradually and usually in a stepwise fashion.

Switching to diazepam is recommended for individuals who are:

- Using the short- to intermediate-acting potent benzodiazepines (e.g., alprazolam and lorazepam)
- Using preparations that do not easily allow for small reductions in dose (e.g., alprazolam or flurazepam)
- Experiencing difficulty or who are likely to experience difficulty withdrawing directly from temazepam or Z-drugs due to a high degree of dependency (associated with long duration of treatment, high doses, or history of anxiety problems)

Alprazolam (Xanax) note: Care should be taken not to taper alprazolam too rapidly or to switch to another benzodiazepine too abruptly, as withdrawal seizures are more prone to occur with alprazolam than with other benzodiazepines. If difficulty tapering the last 1–2 mg of alprazolam: taper more gradually (0.25 mg/week) or substitute diazepam gradually over 1 week and taper as usual.

Lorazepam (patients aged 65 and over)

Switching to diazepam in patients aged 65 and over is **not** recommended, as case reports suggest that it may be associated with delirium. For older adults, lorazepam, oxazepam, and temazepam are

the safest options because they don't have metabolites that can accumulate. Of these, lorazepam is the best in terms of dosing options—available as 0.5, 1, and 2 mg tabs, and as 2 mg/mL oral solution.

How to make the switch

1. Substitute diazepam or lorazepam for one dose of the current benzodiazepine at a time, usually starting with the evening or nighttime dose to avoid daytime sedation. Replace the other doses, one by one, at intervals of a few days or a week until the total approximate equivalent dose (Table 3) is reached before starting the reduction.
2. For patients on diazepam, the long half-life should enable them to take a single dose at night or a twice-daily dose at most.
3. For patients on lorazepam, twice-daily dosing is recommended.

Table 3. Approximate dose equivalent to 5 mg diazepam			
	Trade name	Half-life (hours)	Dose equivalent to 5 mg diazepam ¹
Benzodiazepines			
Alprazolam	Xanax	12–15	0.25–0.5 mg
Chlordiazepoxide	Librium	5–30	15 mg
Clonazepam	Klonopin	18–50	0.25–0.5 mg
Diazepam	Valium	20–80	5 mg
Lorazepam	Ativan	10–20	0.5–1 mg
Temazepam	Restoril	3.5–18.5	10 mg
Triazolam	Halcion	1.5–5.5	0.25 mg
Z-drugs			
Eszopiclone	Lunesta	6–9	2 mg
Zaleplon	Sonata	1	10 mg
Zolpidem	Ambien	1.4–4.5	10 mg
¹ Approximate equivalencies vary depending upon the resource referenced.			

Diazepam prescribing notes

- Prescribe 5 mg or 2 mg diazepam tablets only.
- Starting dose should not exceed 40 mg. Consult with Behavioral Health Services if considering a higher dose.

Treatment of Withdrawal Symptoms

Signs and symptoms of withdrawal

Withdrawal symptoms may occur after as little as 1 month of daily use.

Acute

The majority of acute withdrawal symptoms are anxiety-related, and include restlessness, agitation, tremors, dizziness, panic attacks, palpitations, shortness of breath, sweating, flushing, shakiness, difficulty swallowing, poor sleep, sensation of choking, and chest pain. Additional symptoms of acute withdrawal include seizures, bowel/bladder problems, changes in appetite, tiredness, faintness, poor concentration, and many others.

Long-term

Long-term withdrawal symptoms may take months or years to resolve and include anxiety, confusion, depression, depersonalization, psychosis, paranoid delusions, rebound insomnia, poor memory and cognition, motor symptoms (pain, weakness, muscle twitches, jerks, seizures), and abnormal perception of movement.

Prevention and treatment of withdrawal symptoms

Symptom	Medication	Dosing
Seizure prevention	Carbamazepine ¹	Start 200 mg twice daily, adjust dose weekly up to 400 mg twice daily. Continue for 2–4 weeks after stopping benzodiazepines and then taper anticonvulsant.
	Valproic acid ^{1,2} or Divalproex sodium EC ^{1,2}	Start 500 mg twice daily, adjust dose weekly up to 2,000 mg daily. Continue for 2–4 weeks after stopping benzodiazepines and then taper anticonvulsant.
Tachycardia, hypertension, tremors, sweats, anxiety, restlessness	Propranolol	10 mg three times daily as needed for 3 days
Hypertension, tremors, sweats, anxiety, restlessness	Clonidine	0.1 mg three times daily as needed for 3 days
Anxiety, restlessness	Hydroxyzine ³ or Diphenhydramine ³	25 mg every 6 hours as needed
Insomnia ⁴	Hydroxyzine ³ or Diphenhydramine ³	25–50 mg daily before bed as needed
Nausea	Promethazine ³	25 mg every 6 hours as needed
	Metoclopramide	10 mg every 6 hours as needed
Dyspepsia	Calcium carbonate	500 mg 1–2 tabs every 8 hours as needed
	Mylanta, Milk of Magnesia	Follow package instructions.
Pain, fever	Acetaminophen	500 mg every 4 hours as needed, not to exceed 3,000 mg in 24 hours
	Ibuprofen	600 mg every 6 hours as needed

¹ In patients with liver impairment, consider topiramate, gabapentin or levetiracetam. Check CBC and liver function tests at baseline.

² Check CBC and liver function tests at baseline and every 3 months during treatment.

³ These are high-risk medications for the elderly. Please consider alternatives for patients aged 64 and older.

⁴ Patients with chronic insomnia or worsening anxiety during the taper often do better with cognitive behavioral therapy to address these symptoms during the taper. Refer these patients to Behavioral Health Access for this specific therapy.

Referral Criteria

Consider consultation with Behavioral Health Services (BHS) for patients who have any of the following:

- A history of alcohol use disorder or other drug use disorders
- A concurrent severe psychiatric disorder
- Concurrent use of amphetamines or opiates
- A history of drug withdrawal seizures
- Suicidal thoughts

Evidence Summary and References

Methods and sources

To develop the Benzodiazepine and Z-drug Safety guideline, the guideline team considered recommendations from externally developed evidence-based guidelines and/or recommendations of organizations that establish community standards:

- National Institute for Health and Care Excellence (NICE). Benzodiazepine and z-drug withdrawal. July 2013.
- NICE. Social anxiety disorder: recognition, assessment and treatment. May 2013.
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<http://www.benzos.une.edu/documents/prescribingguidelines3-26-08.pdf>
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- NHS Fife. Guidelines for benzodiazepine prescribing in benzodiazepine dependence. April 2013.
- Southeast Permanente Medical Group: Detoxification, Benzodiazepines (outpatient). November 2010.

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Guideline Development Process and Team

Development process

To develop the Benzodiazepine and Z-Drug Safety Guideline, the guideline team adapted recommendations from externally developed evidence-based guidelines and/or recommendations of organizations that establish community standards. See the Evidence Summary and References section.

This edition of the guideline was approved for publication by the Guideline Oversight Group in August 2014.

Team

The Benzodiazepine and Z-Drug Safety Guideline development process included representatives from the following specialties: behavioral health, family medicine, pharmacy, residency, and urgent care.

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Disclosure of conflict of interest

Kaiser Permanente requires that team members participating on a guideline team disclose and resolve all potential conflicts of interest that arise from financial relationships between a guideline team member or guideline team member's spouse or partner and any commercial interests or proprietary entity that provides or produces health care–related products and/or services relevant to the content of the guideline.

Team members listed above have disclosed that their participation on the Benzodiazepine and Z-Drug Safety Guideline team includes no promotion of any commercial products or services, and that they have no relationships with commercial entities to report.