

Benzodiazepine and Z-Drug Safety Guideline

Expectations for KFHPWA Providers.....	2
Background	2
Prescribing	3
Management of Patients on Chronic Benzodiazepines or Z-Drugs.....	6
Tapering and Discontinuation	9
Treatment of Withdrawal Symptoms.....	12
Referral Criteria	13
Evidence Summary	14
References	17
Guideline Development Process and Team	18
Appendix 1	
Table A. Long-acting benzodiazepine comparison	19
Table B. Intermediate-acting benzodiazepine comparison	20
Table C. Short-acting benzodiazepine comparison.....	21

Last guideline approval: January 2019

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.

Expectations for Kaiser Foundation Health Plan of Washington Providers

Using protocols and standard documentation, Kaiser Foundation Health Plan of Washington aims to minimize practice variation in the management of patients on chronic benzodiazepine therapy to improve patient safety and increase both patient and provider satisfaction.

- ✓ **Patients should *not* be prescribed benzodiazepines if currently taking any opioid.** See “Tapering and Discontinuation,” p. 9.
- ✓ **Benzodiazepines should *not* be combined** with another benzodiazepine, Z-drug, or muscle relaxant.
- ✓ Patients treated with chronic benzodiazepines are **risk-stratified** to the highest appropriate category by the prescribing clinician and the risk level is documented on the Epic dashboard.
- ✓ Patients prescribed chronic benzodiazepines shall have **regular monitoring visits** that:
 - Occur at a **frequency** based on the patient’s risk stratification, and
 - Include **standard components**. See “Required components,” p. 7.
- ✓ Patients on chronic benzodiazepines shall **receive all benzodiazepine prescriptions from one physician and one pharmacy** whenever possible. Clinicians treating a patient on chronic benzodiazepines are expected to clarify and document—both among themselves and with the patient—which clinician holds primary prescribing responsibility.

Background

Benzodiazepines and Z-drugs (i.e., newer GABA receptor agonists, like zolpidem [Ambien]) are overprescribed, and many prescription treatment plans are not supported by scientific evidence or published guidelines. Despite warnings about the risks of 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 averse to discontinuing these treatments.

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 by an addiction specialist or chemical dependency treatment provider and should be referred to Behavioral Health Services.
- Patients who are using benzodiazepines for **treatment of alcohol withdrawal**. See the [KPWA Unhealthy Drinking in Adults Guideline](#).
- Patients who are using benzodiazepines for **treatment of seizure disorder**.
- Patients **receiving palliative, hospice, or other end-of-life care**.

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 because 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](#).

Chronic benzodiazepine use is daily or near-daily use of benzodiazepines for at least 90 days and often indefinitely, and is defined as a minimum 70-day supply of benzodiazepines dispensed in the previous 3 calendar months.

Chronic Z-drug use is daily or near-daily use of Z-drugs for at least 90 days and often indefinitely, and is defined as a minimum 70-day supply of Z-drugs dispensed in the previous 3 calendar months.

Prescribing

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

Prescribing considerations

Before initiating a course of benzodiazepine treatment, the following should be considered:

- **Do not prescribe benzodiazepines to patients already taking opioids**, as this is associated with increased risk of fatal overdose.
- Concurrent use of marijuana and benzodiazepines is **not recommended**.
- Explicitly advise the patient regarding the duration of treatment. Use of benzodiazepines beyond 2 weeks is **not recommended**.
- Use the lowest dose for the shortest time.
- 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 tapering and/or transition to alternative treatments.
- Discuss alternative treatments, which may include:
 - Antidepressant medications (e.g., SSRIs, SNRIs, tricyclic antidepressants)
 - Psychotherapy (e.g., cognitive behavioral therapy)
 - Serotonergic agents for anxiety (e.g., buspirone)
 - Anticonvulsant medications for restless legs syndrome (e.g., pramipexole, ropinirole, gabapentin)
- The patient and health care provider should agree on one provider to be the benzodiazepine prescriber for that patient. This designated prescriber should also be responsible for prescribing other medications with abuse potential, specifically central nervous system (CNS) stimulants and

narcotics; otherwise the prescriber of benzodiazepines should closely coordinate care with those who are prescribing other controlled substance medications.

- For patients who are prescribed chronic benzodiazepines for anxiety at a dose exceeding the maximum dose listed in Appendix 1, consultation with a psychiatrist is recommended.

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 metabolic capacities and rates decline with age. Patients in this age group are:
 - More susceptible to CNS depression and cognitive impairment, and may develop confusion 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. Common indications for benzodiazepines (BZDs) and Z-drugs

See Appendix 1 for full prescribing information.

Indication	BZDs	Z-drugs	Considerations
Insomnia	Temazepam ¹	Zolpidem Eszopiclone Zaleplon	<ul style="list-style-type: none"> • Both are effective in the relief of short-term (1–2 weeks continuous) 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. • Cognitive behavioral therapy for insomnia (CBT-I) is recommended for patients with insomnia. • See the KPWA Insomnia Guideline.
Anxiety	Lorazepam Alprazolam Clonazepam Diazepam	None	<ul style="list-style-type: none"> • Not first-line therapy but may be used as an adjunct to a first-line therapy (such as SSRI or cognitive behavioral therapy) while waiting for definitive therapy to work. • Continuing beyond 2 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 is strongly recommended.

¹ Temazepam is one of the few benzodiazepines with FDA approval for insomnia. Other benzodiazepines should not be prescribed for insomnia.

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
- Spasticity treatment

Long-term use

Benzodiazepines and Z-drugs are **not recommended** for long-term use (longer than 2 weeks), except 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

- Concurrent use of another benzodiazepine, Z-drug, muscle relaxant, or opioid
- Active or history of substance use disorder
- Pregnancy or risk of pregnancy
- Treatment with opioids for chronic pain or agonist therapy for opioid use disorder
- 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, and congestive heart failure, as benzodiazepines may worsen hypoxia and hypoventilation

Adverse effects of benzodiazepines

- There is an association between benzodiazepine use and dementia, increased rate of falls, and increased risk of hip fracture.
- Tolerance to anxiolytic effects, which may develop after a few weeks of use. (This does not apply to Z-drugs because they are not anxiolytic.)

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 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
- Increased risk of cognitive impairment and delirium
- Increased risk of falls and fractures, especially among older adults

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.

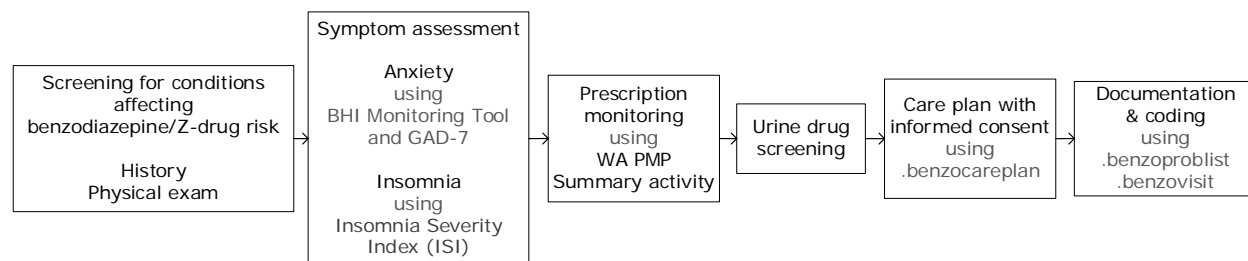
- For most people in primary care settings even a minimal intervention, such as a letter with self-help information from the treating physician or a single brief consultation, can be effective in reducing or stopping benzodiazepine use.
- For patients who do not want to stop the drugs, discuss the benefits 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.

Risk stratification and intensity of monitoring

Risk level	Criteria	Content of follow-up	Minimum follow-up interval ²
HIGH	<ul style="list-style-type: none"> • Age ≥ 65 (HRME) • Age < 25 (increased risk of substance use disorder) • More than 1 benzo (overdose risk) • Benzo + Z-drug (overdose risk) • Benzo + opioid (overdose risk) • History of substance use disorder • Use of alcohol or cannabis • COPD, severe or uncontrolled respiratory disease, or at risk of respiratory depression • History of overdose • PTSD • Fall risk • Problems following benzo care plan 	<ul style="list-style-type: none"> • PMP Summary check at every follow-up • Use .benzovisit and .benzocareplan SmartPhrases • Update Problem List or Dashboard • Insomnia Severity Index if for insomnia • BHI Monitoring Tool and GAD7 if for anxiety 	<ul style="list-style-type: none"> • Provider visit every 6 months, including at least one face-to-face office visit per year; others can be virtual • UDS required annually
STANDARD	None of the above	Same follow-up as above	<ul style="list-style-type: none"> • Provider visit annually; must be face-to-face office visit • UDS optional
¹ Monitoring visits are required for chronic benzodiazepine or Z-drug use only. The above recommendations do not apply to short-term use of these medications. ² Patients taking opioids with benzodiazepines must have a follow-up visit every 3 months at a minimum. See the KPWA COT Safety Guideline .			

For detailed pharmacological information including maximum dosing, monitoring recommendations, and metabolites that may be present in urine drug screen results, see Appendix 1.

Required components of a chronic benzodiazepine or Z-drug visit



1. Screening, history, and physical exam

Epic Tips

- Use the SmartPhrase **.benzovisit** to include all the recommended elements of the initial visit.
- Use the SmartPhrase **.benzomini** to include all the recommended elements of the 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**
- **Insomnia assessment** using ISI if drugs are being used for insomnia.
- **Depression, anxiety, alcohol and drug use screening** with BHI monitoring tool.

Note: Annual screening for behavioral health issues is part of adult standard care.

2. Prescription monitoring

Check the patient's record in the Washington State Prescription Monitoring Program (PMP) Summary to determine whether the patient is receiving benzodiazepine dosages or dangerous combinations that put them at high risk. The PMP is a central database that keeps track of schedule II–V medications that patients receive at any pharmacy in the state of Washington. Clinicians should check this database before continuing the use of benzodiazepines for a patient. Data for all controlled substances can be found in the **WA PMP Summary activity** in Epic.

3. Urine drug screening

Urine drug screening (UDS) provides objective data regarding patients on chronic benzodiazepines and can be used to directly improve patient safety. For their safety, it is important that patients take benzodiazepines as prescribed, and this test helps assess whether they are doing so. UDS should also be ordered when seeing patients already on benzodiazepines who are new to the health plan and have no record of recent UDS.

UDS is for medical purposes only. KPWA does not collect samples for use in a court of law or for workplace testing.

Clinicians should have a discussion with the patient before the UDS that includes:

- The purpose of testing
- What will be screened for
- What results the patient expects to see
- Prescriptions or any other drugs the patient has taken

- Actions that may be taken based on the results of the screen
- Possibility of cost to the patient

Patients should be notified that the results will become part of their permanent medical record. For more detailed information on urine drug screening, see Drug Screening Ordering & Interpretation (staff intranet).

For patients taking benzodiazepines, use **UDS for pain management**, and choose either the benzos only, opioids only, or opioids *and* benzos option, for screening and confirmation. This UDS does not include alcohol, fentanyl, methylphenidate, tramadol, or Z-drugs (eszopiclone, zaleplon and zolpidem). If a patient is prescribed any of these excluded drugs, a separate lab test will need to be ordered for each specific drug that the patient is taking.

Order serum drug screen for patients who are taking diuretics or cannot produce urine.

4. Problem list

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

5. Care plan

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

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

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 benzodiazepines. Patients are considered suitable if they:
 - Are willing and committed, with adequate social support,
 - Have no previous history of complicated drug withdrawal, **and**
 - *Do not* have an indication for rapid discontinuation (see Table 4).

If a taper is needed but the patient does not meet the criteria above, or if you have specific questions about tapering, consult Mind Phone or Pharmacy.

- Cognitive behavioral therapy is recommended to help the patient cope with rebound anxiety and to assist with the withdrawal process.
- Consider referral to a specialist for patients who:
 - Have a history of alcohol use disorder or other substance 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.

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 3 or Table 4.
- 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 3 or Table 4.
- 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 3 or Table 4.

Gradual tapering

The most effective strategy to manage benzodiazepine discontinuation and prevent adverse outcomes associated with severe withdrawal—such as severe seizures—is a gradual taper of benzodiazepines.

Table 3. Clinical indications for tapering benzodiazepine or Z-drug therapy

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

- A subset of patients will experience clinically significant withdrawal symptoms even with 10% dose reductions and/or gradual tapering. Consider switching 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. Development of withdrawal symptoms can be quite variable and insidious during a taper. A high index of suspicion for withdrawal-related etiology should be held if new symptoms arise during a taper. (See Treatment of Withdrawal p. 12 for more information about withdrawal symptoms.)
- If the first attempt is unsuccessful, 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 approach for tapering benzodiazepines is also recommended for Z-drugs.

Rapid discontinuation

Table 4. 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. 13.)</p>

Switching to a longer-acting benzodiazepine for tapering

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 plasma levels. It is also available in a variety of strengths and formulations, which facilitates step-wise dose substitutions from other benzodiazepines or Z-drugs and allows for small incremental reductions in dosage. Switching is best carried out gradually, usually in a step-wise fashion.

Switching to diazepam should be considered for individuals who are:

- Using short- to intermediate-acting 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 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

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 5) is reached before starting the reduction.

- For patients on **diazepam**, the long half-life can enable them to take a single dose at night or a twice-daily dose.
- For patients on **lorazepam**, twice-daily dosing is recommended.

Table 5. 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 ²	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. ² 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

Acute signs and symptoms of withdrawal

Anxiety-related withdrawal symptoms are common, 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. There is a wide range of other, less common acute withdrawal symptoms, such as seizures, bowel/bladder problems, changes in appetite, tiredness, faintness, poor concentration, tinnitus and delirium.

Long-term signs and symptoms of withdrawal

Some withdrawal symptoms can persist and may take months or years to resolve, including anxiety, fatigue, depression, poor memory and cognition, motor symptoms (pain, weakness, muscle twitches, jerks, seizures), depersonalization, psychosis, paranoid delusions, rebound insomnia, and abnormal perception of movement.

Prevention and treatment of withdrawal symptoms

Table 6. Medications used to prevent or treat withdrawal symptoms during gradual taper from benzodiazepines or Z-drugs		
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	Gabapentin	100–300 mg every 6 hours as needed
	Hydroxyzine ³ or Diphenhydramine ³	25 mg every 6 hours as needed
Insomnia ⁴	Gabapentin	100–300 mg daily before bed as needed
	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 65 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 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

The Benzodiazepine and Z-drug Safety Guideline was developed using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis.

As part of our improvement process, the Kaiser Permanente Washington guideline team is working towards developing new clinical guidelines and updating the current guidelines every 2–3 years. To achieve this goal, we are adapting evidence-based recommendations from high-quality national and international external guidelines, if available and appropriate. The external guidelines should meet several quality standards to be considered for adaptation. They must: be developed by a multidisciplinary team with no or minimal conflicts of interest; be evidence-based; address a population that is reasonably similar to our population; and be transparent about the frequency of updates and the date the current version was completed.

In addition to identifying the recently published guidelines that meet the above standards, a literature search was conducted to identify studies relevant to the key questions that are not addressed by the external guidelines.

External guidelines meeting KPWA criteria for adaptation/adoption

- 2017 Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline
- 2017 European guideline for the diagnosis and treatment of insomnia
- 2017 VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain
- 2016 Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline from the American College of Physicians
- 2015 AHRQ: Management of Insomnia Disorder; Comparative Effectiveness Review (number 159)
- 2014 National Institute for Health and Care Excellence (NICE) Guideline on Anxiety Disorders
- 2014 Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders

Key questions addressed in the KPWA guideline

1. **What is the comparative effectiveness and safety of benzodiazepines and Z- drugs, cognitive behavioral therapy, and other alternative drugs or therapies used for the treatment of insomnia and/or anxiety?**
 - There is moderate-quality evidence from an AHRQ Comparative Effectiveness Review Management of Insomnia Disorder (2015) as well as three other systematic reviews and meta-analyses of randomized controlled trials (Trauer 2015, Wu 2015, Geiger-Brown, 2015) demonstrating that cognitive behavioral therapy for insomnia (CBT-I) is effective for the treatment of chronic insomnia with or without other comorbid psychiatric or medical conditions, and that its efficacy seems to be well maintained over time.
 - There is insufficient evidence to determine:
 - The comparative effectiveness of CBT-I versus hypnotic medication.
 - The comparative effectiveness of combined hypnotic medication and CBT-I versus CBT-I alone.
 - The efficacy or comparative effectiveness of CBT-I versus tai chi or acupuncture.
 - The adjunctive efficacy of a traditional Chinese medicine approach combined with sleep medication.
 - The adverse effects of psychological and behavioral interventions.
 - The long-term (more than 3 months) safety of pharmacological therapies for insomnia disorder.

2. Is there an association between benzodiazepine or Z-drug use and prescribing pattern (dose, type and duration of use) for the treatment of insomnia and/or anxiety and an increased risk of cognitive decline and dementia in older adults?

- The results of the published studies on the association between the use of benzodiazepines (BZDs) and related drugs and cognitive decline are mixed. All published studies were observational prospective or case-control, with variations in: population sizes and characteristics; data source; setting; degree of cognitive decline, its definition, and diagnostic criteria; definition and duration of BZD use; duration of follow-up; adjustment for potential confounders; and outcome measures, among other differences.
- Although the association between the use of hypnotics and the subsequent risk of dementia is inconclusive, several studies have demonstrated an association or plausible association between the use of benzodiazepines and subsequent dementia.
- Stronger associations were demonstrated in studies that examined longer-acting BZDs used for a longer duration.
- There is a common debate on whether the association between BZD use and dementia is due to causality or reverse causation. Because insomnia, anxiety, and depression are prodromal symptoms of dementia and can occur around 10 years prior to a clinical diagnosis of the disease, it is difficult to determine whether BZD use is responsible for causing dementia or whether a BZD was used to treat the early symptoms of dementia (Zhong 2015, Picton 2018).
 - Gray and colleagues (2016) concluded that their study does not support a causal association between cumulative use of BZDs and the risk of dementia.
 - A UK case-control study also found that the high use of BZD as determined by the number of prescriptions was not associated with an increased risk of Alzheimer's disease (Imfeld 2015).
 - On the other hand, a prospective cohort study in France (Shash 2016) indicated that use of BZDs at baseline was associated with a 10% increased risk of dementia, NNH=27 for any use, and 17 for use of long-half-life (> 20 hours) BZD for a median of 8 years. The risk with short-half-life BZDs did not reach a statistically significant level. The use of psychotropic drugs was also associated with a significant increase in dementia risk, with an NNH of 16 in a median of 8 years. This rose to NNH = 10 when combined with BZD use.
 - A case-control study (Billioti de Gage 2014) also showed a significant association between the use of BZDs and the risk of Alzheimer's disease. The association was stronger with longer duration of use and longer drug half-life.
 - A systematic review investigating whether there is a plausible association between benzodiazepine use and the risk of dementia (Billioti de Gage 2015) argued that although causation of dementia with the use of BZDs is not proven, five of the nine Bradford Hill causality criteria were fulfilled by the studies, including consistency, temporality, biological gradient, plausibility, and coherence. They indicated that long-term users of BZDs have a 1.5- to 2.0-fold increased risk of dementia compared to never users. They concluded that further research is needed, but the current evidence may be sufficient to support avoiding the long-term use of benzodiazepines.
 - Zhong and colleagues (2015), also indicated that the findings in their review support a causal relationship between BZD use and dementia. This was based on the observation of a dose-response pattern, persistence of findings after adjusting for anxiety and depression, and the similar risk estimates for recent and past users.
- For ethical reasons, RCTs are unlikely to be performed.

3. Is there an association between use of benzodiazepines or Z-drugs and an increased risk of hip fracture in older adults?

- The published studies on the risks of benzodiazepines and Z-drugs were all observational. The studies indicate that the use of BZDs and Z-drugs is associated with an increased risk of falls and hip fractures. Observational studies may show an association but cannot prove a cause-and-effect relationship.
- The published evidence suggests that the risk of hip fracture associated with BZD and Z-drug use may be higher with recent starts and short-acting BZDs.

- The published results suggest that Z-drugs are not safer than BZDs, and that short-acting BZDs are not safer than the long-acting drugs.
 - Large prospective studies with minimal bias and controlling for confounding factors are needed to provide more accurate evidence on the risks of different BZDs and Z-drugs—including fracture risk related to medication type, dose, and duration of use.
- 4. Is there an association between benzodiazepine prescribing patterns (dose, type, and dosing schedule) and the risk of death among adults who are using the drugs for the treatment of insomnia and/or anxiety?**
- The published literature suggests an association between the use of benzodiazepines and the risk of death. There is insufficient evidence, however, to determine whether the observed association is a causal relationship.
- 5. Is there an association between benzodiazepine or Z-drug use in adults with insomnia—with or without anxiety and other comorbid conditions—and the risk of suicide?**
- There is insufficient evidence to determine whether the use of BZDs or Z-drugs increases the risk of suicide among patients using the drugs to treat insomnia and/or anxiety.
- 6. What are the risks associated with the concurrent use of opioids and benzodiazepines in adults?**
- The published literature demonstrates a large increase in the prescription of opioids and benzodiazepines, both separately and concurrently, over the last 15 years.
 - For ethical reasons, given potential harms, there are no published randomized controlled trials that examine the risk of prescribing opioids and benzodiazepines concurrently.
 - All published studies are observational in design, with data obtained retrospectively from patient records, pharmacy records, and administrative databases; each source of data may have its advantages and limitations.
 - The published literature shows an association between the concurrent use of opioids and benzodiazepines and the risk of fatal overdose.
 - There is insufficient evidence to determine whether the observed association between the concurrent use of opioids/benzodiazepines and risk of fatal overdose is a causal relationship.
 - The observed higher risk of death in patients receiving both opioids and benzodiazepines may be due to the synergetic sedative effect of the two drugs, or to underlying mental or physical health conditions, illness severity, addiction, illicit drug use, or other residual confounding health or environmental factors. However, the consistency of findings from different studies, the risk of current as well as previous and the linear dose-response relationship between the BZD dose and risk of fatal overdose with the concurrent use with opioids as observed in Park and colleagues study (2015) suggest a biological plausibility.
- 7. What is the comparative effectiveness of internet-based CBT-I and traditional and face-to-face CBT-I for reducing insomnia severity and improving sleep efficiency in the short and long term in adults with insomnia?**
- The published trials incorporated both behavioral and cognitive strategies for the internet-based CBT-I delivery programs, but there were variations between the trials in the components of applied therapies, duration and number of sessions, and follow-up duration, all of which may influence the results pooled in the published meta-analyses.
 - Overall, the published literature indicates that internet-based CBT-I leads to improvements in several sleep-related variables, including sleep efficiency, sleep onset latency, total sleep time, and wake time after sleep.
 - The literature also suggests that internet-based CBT-I may lead to improvements in anxiety and depression symptoms in patients with insomnia.
 - The short-term improvements observed for different sleep parameters remained significant at 6 months follow-up. One trial (Kaldo 2015) showed that the significant difference between the intervention and control groups was stable for 1 year.

References

- Billioti de Gage S, Pariente A, Bégaud B. Is there really a link between benzodiazepine use and the risk of dementia? *Expert Opin Drug Saf.* 2015 May;14(5):733-747.
- Billioti de Gage S, Moride Y, Ducruet T, et al. Benzodiazepine use and risk of Alzheimer's disease: case-control study. *BMJ.* 2014 Sep 9;349:g5205.
- Geiger-Brown JM, Rogers VE, Liu W, Ludeman EM, Downton KD, Diaz-Abad M. Cognitive behavioral therapy in persons with comorbid insomnia: A meta-analysis. *Sleep Med Rev.* 2015 Oct; 23:54-67.
- Gray SL, Dublin S, Yu O, et al. Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study. *BMJ.* 2016 Feb 2;352: i90.
- Imfeld P, Bodmer M, Jick SS, Meier CR. Benzodiazepine Use and Risk of Developing Alzheimer's Disease or Vascular Dementia: A Case-Control Analysis. *Drug Saf.* 2015 Oct;38(10):909-919.
- Kaldo V, Jernelöv S, Blom K, et al. Guided internet cognitive behavioral therapy for insomnia compared to a control treatment - A randomized trial. *Behav Res Ther.* 2015 Aug;71:90-100.
- Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert AS. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *BMJ.* 2015 Jun 10;350:h2698.
- Picton JD, Marino AB, Nealy KL. Benzodiazepine use and cognitive decline in the elderly. *Am J Health Syst Pharm.* 2018 Jan 1;75(1):e6-e12.
- Shash D, Kurth T, Bertrand M, et al. Benzodiazepine, psychotropic medication, and dementia: A population-based cohort study. *Alzheimers Dement.* 2016 May;12(5):604-613.
- Trauer JM, Qian MY, Doyle JS, Rajaratnam SM, Cunnington D. Cognitive Behavioral Therapy for Chronic Insomnia: A Systematic Review and Meta-analysis. *Ann Intern Med.* 2015 Aug 4;163(3):191-204.
- Wu JQ, Appleman ER, Salazar RD, Ong JC. Cognitive Behavioral Therapy for Insomnia Comorbid With Psychiatric and Medical Conditions: A Meta-analysis. *JAMA Intern Med.* 2015 Sep;175(9):1461-1472.
- Zhong G, Wang Y, Zhang Y, Zhao Y. Association between Benzodiazepine Use and Dementia: A Meta-Analysis. *PLoS One.* 2015 May 27;10(5):e0127836.

Guideline Development Process and Team

Development process

The Benzodiazepine and Z-drug Safety Guideline was developed using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis. See the Evidence Summary and References section.

This edition of the guideline was approved for publication by the Guideline Oversight Group in January 2019.

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.

Clinician lead: [Angie Sparks, MD](#), Medical Director, Clinical Knowledge Development & Support
Guideline coordinator: [Avra Cohen, MN, RN](#), Clinical Improvement & Prevention

Bridget Albright, PA, Urgent Care
Ben Balderson, PhD, Behavioral Health Services
Ryan Caldeiro, MD, Chemical Dependency Services, Behavioral Health
Doug Christie, MD, Behavioral Health Services
Amado Daylo, MD, Behavioral Health Services
Galen Goertzen, PharmD, Pharmacy
Dina Greene, MD, Technical Director of Laboratory
Veronica Jessick, MD, Family Medicine
Robyn Mayfield, Patient Engagement Team, Clinical Improvement & Prevention
Kushboo Mehta, MD, Family Medicine
Rebecca Parrish, MSW, LCISW, Integrated BH Clinical Consultant & Social Work Manager
Katie Paul, MD, Family Medicine
Nadia Salama, MD, PhD, Clinical Epidemiologist, Clinical Improvement & Prevention
Grant Scull, MD, Family Medicine
Ann Stedronsky, Clinical Publications, Clinical Improvement & Prevention
Melissa Sturgis, PharmD, Pharmacy
Raj Sundar, MD, Resident

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.

Appendix 1.

See Drug Screening Ordering & Interpretation (staff intranet) for more information on drug screening.

Table A. LONG-acting benzodiazepine comparison Avoid these medications in adults aged > 64 years. If no alternative treatment is available, use a half-strength dose.				
	Chlordiazepoxide	Clorazepate	Diazepam	Flurazepam
FDA-approved indications	Acute alcohol withdrawal Anxiety Preoperative anxiety	Alcohol withdrawal: symptomatic relief of acute withdrawal Anxiety disorders (short-term) Partial seizures (as adjunct therapy)	Acute ethanol withdrawal Anxiety Muscle spasm Preoperative anxiety Seizures Status epilepticus	Insomnia
Off-label indications	Seizure disorders Rapid eye movement disorders		Sedation in ICU Spasticity with cerebral palsy (short-term) (children)	
Anxiety	Adults < 65 years Mild to moderate anxiety Usual dose: 5–10 mg, 3–4 times daily Severe anxiety Usual dose: 20–25 mg, 3–4 times daily Debilitated patients Usual dose: 5 mg, 2–4 times daily Preoperative anxiety Oral: 5–10 mg, 3–4 times daily on the days preceding surgery	Adults < 65 years 30 mg/day in divided doses (range: 15–60 mg/day) or 15 mg at bedtime; adjust dose based on patient response Debilitated patients Initiate at 7.5–15.0 mg/day	Adults < 65 years 2–10 mg, 2–4 times daily if needed Debilitated patients 2.0–2.5 mg, 1–2 times daily initially; increase gradually as needed and tolerated	
Insomnia				Women < 65 years: 15 mg bedtime Men < 65 years: 15–30 mg bedtime
Maximum dose	Anxiety Adults < 65 years: 40–100 mg/day. Debilitated patients: 20 mg/day.	Anxiety Generally in 30 mg range, max 60 mg.	Depends on patient.	30 mg/day.
Monitoring		Long-term therapy CBC, liver enzymes, renal function; signs and symptoms of suicidality (e.g., anxiety, depression, behavior changes)		Daytime alertness Respiratory rate Behavior profile
Routinely detected in UDS	Yes	Yes	Yes	Yes
Expected confirmation result in UDS	Nordiazepam and/or oxazepam	Nordiazepam and/or oxazepam	Nordiazepam, oxazepam, and/or temazepam	Hydroxyethylflurazepam
Half-life (hrs)	Parent: 24–48 Active metabolite: 14–95	20–160	Parent: 44–48 Active metabolite: 100	Parent: 2–3 Active metabolite: 74–113

Appendix 1.

See Drug Screening Ordering & Interpretation (staff intranet) for more information on drug screening.

Table B. INTERMEDIATE-acting benzodiazepine comparison

Avoid these medications in adults aged > 64 years. If no alternative treatment is available, use a half-strength dose.

	Alprazolam	Clonazepam	Lorazepam	Oxazepam	Temazepam
FDA-approved indications	Anxiety disorders Panic disorder	Panic disorder Seizure disorders	Anxiety Anesthesia premedication (parenteral or sublingual) Status epilepticus (parenteral)	Alcohol withdrawal Anxiety disorders	Short-term treatment of insomnia
Off-label indications	Perioperative anxiety	Bipolar disorder (manic or mixed episodes) Burning mouth syndrome Essential tremor REM sleep behavior disorder Restless legs syndrome Tardive dyskinesia Tic disorders	Agitation in ICU patient Alcohol withdrawal delirium Alcohol withdrawal syndrome Chemotx nausea/vomiting Psychogenic catatonia Rapid tranquilization of agitated patient Status epilepticus (infants, children, adolescents)		
Anxiety	Adult IR 0.25–0.5 mg, 3 times daily	Panic disorder 0.25 mg, 2 times daily, titrated every 3 days as needed to target of 1 mg/day, max of 4 mg/day	Adults < 65 years 2–3 mg/day in 2–3 divided doses. Usual dose is 2–6 mg/day in divided doses (May vary from 1 mg/day to 10 mg/day.)	Mild to moderate 10–15 mg, 3–4 times daily Severe 15–30 mg, 3–4 times daily	
Insomnia		REM sleep behavior disorder 0.25–2.0 mg, 30 min prior to bedtime. Max 4 mg	Adults < 65 years 0.5–2.0 mg at bedtime (Winkelman 2015)		Adults < 65 years 15–30 mg at bedtime (Some patients may respond to 7.5 mg in transient insomnia.)
Maximum dose	4 mg/day	4 mg/day	Depends on diagnosis Anxiety: 6 mg Sleep: 2 mg	Depends on patient. Dosing allows for 60–120 mg high-dose range	30 mg
Comments	Manufacturer notes on dosing for panic disorder IR: 0.5 mg, 3 times daily. Mean effective dose 5–6 mg/day in 3 or 4 divided doses. Some patients may require as much as 10 mg/day ER: 0.5–1.0 mg once daily, may be titrated to range of 3–6 mg/day	Restless legs syndrome (off-label use) 1 mg 30 min prior to bedtime; increase dose by 0.5–1.0 mg at weekly intervals. Doses up to 2 mg used in clinical trials			
Monitoring		Relationship between serum concentration and seizure control is not well established. Therapeutic doses have been associated with serum concentrations of ~15–70 ng/mL (Pataslos 2008)	Long-term therapy CBC, liver function tests, LDH (If high dose, continuous IV use, or IV use in renal impairment, review of SCr, BUN, Serum lactact, osmolal gap, clinical signs of propylene glycol toxicity also recommended.)	Respiratory and cardiovascular status (as clinically indicated); CBC (periodic); liver function tests (periodic).	
Routinely detected in UDS	Yes	Not consistently	Not consistently	Yes	Yes
Expected confirmation result in UDS	Alphahydroxyalprazolam	Aminoclonazepam	Lorazepam	Oxazepam	Oxazepam and/or temazepam
Half-life (hrs)	6–27	17–60	~ 12	~ 8	3.5–18.4

References

Patsalos PN, Berry DJ, Bourgeois BF, et al. Antiepileptic drugs--best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2008;49(7):1239-1276. [PubMed [18397299](#)]

Winkelman JW. Clinical Practice. Insomnia Disorder. *N Engl J Med*. 2015 Oct 8;373(15):1437-1444. [PubMed [26444730](#)]

Appendix 1.

See [Drug Screening Ordering & Interpretation](#) (staff intranet) for more information on drug screening.

Table C. SHORT-acting Benzodiazepine and Z-drug comparison Avoid these medications in adults aged > 64 years. If no alternative treatment is available, use a half-strength dose.				
	Triazolam	Eszopiclone	Zaleplon	Zolpidem
FDA-approved indications	Short-term treatment of insomnia (generally 7–10 days)	Insomnia	Short-term treatment of insomnia	IR, SL, and oral spray forms Short-term treatment of insomnia with difficulty of sleep onset ER Treatment of insomnia with difficulty of sleep onset and/or sleep maintenance SL (Intermezzo only) As-needed treatment of insomnia with middle-of-the-night awakening followed by difficulty returning to sleep with 4 or more hours of sleep time remaining SL (Sublinox only) Short-term treatment of insomnia with difficulty of sleep onset, frequent awakenings, and/or early awakenings
Off-label indications	Oral sedation prior to outpatient dental procedures			
Insomnia	Adults 0.25 mg at bedtime 0.125 mg may be sufficient in some patients	Use lowest effective dose. Adults 1 mg before bedtime, may increase to 2–3 mg if clinically necessary (max 3 mg) Debilitated patients 1 mg immediately before bedtime (max 2 mg)	Adult 10 mg immediately before bedtime (range: 5–20 mg). 5 mg may be sufficient (max 20 mg) Debilitated 5 mg immediately before bedtime (max 10 mg)	Women IR: 5 mg immediately before bedtime ER: 6.25 mg immediately before bedtime Men IR: 10 mg immediately before bedtime ER: 12.5 mg immediately before bedtime Debilitated IR: 5 mg immediately before bedtime ER: 6.25 mg immediately before bedtime
Maximum dose	Adults: 0.5 mg/day	Adults: 3 mg Debilitated or geriatric: 2 mg	Adults: 20 mg Debilitated or geriatric: 10 mg	IR: 10 mg. ER: 12.5 mg.
Monitoring	Daytime alertness Respiratory rate Behavior profile		Daytime alertness Respiratory rate (in patients with compromised respiration) Behavior profile Tolerance, abuse, dependence	
Routinely detected in UDS	Yes	No	No	No
Expected confirmation result in UDS	Not detected in common benzodiazepine confirmation; must order as miscellaneous test	Not detected in common benzodiazepine confirmation; must order specific test in EPIC	Not detected in common benzodiazepine confirmation; must order specific test in EPIC	Not detected in common benzodiazepine confirmation; must order specific test in EPIC
Half-life (hrs)	1.5–5.5	~ 6	~ 1	1.4–4.5