Re-evaluating the Use of Benzodiazepines

A Quick Reference Guide

VA

U.S. Department of Veterans Affairs
Veterans Health Administration
PBM Academic Detailing Services

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Discussing benzodiazepine withdrawal[1-5]

1 Assess patient's willingness to discontinue or reduce the dose of benzodiazepine.

- Explore and acknowledge perceived benefits and harms and allow Veteran to express his/her concerns.
- Explain the risks of continued use (disinhibition, ineffectiveness, loss of mental acuity) and the benefits of stopping.
- If previous attempts have been made without success, explain that it is worth trying again.

ADVISE	ASSESS	ASSIST
• Provide medical advice about the risks of long-term benzodiazepine use.	• Understand patient's readiness to discontinue benzodiazepines.	• Provide written taper schedule. • Discuss alternative therapies and/or referral for behavioral services.

*See the ***Possible Risks of Benzodiazepines–Patient discussion guide*** or ***Slowly Stopping Benzodiazepines Patient guide*** to help facilitate this discussion.

2 Agree on timing and discuss the symptoms likely to occur from withdrawal.[3]

- Patients may experience withdrawal after just 4 weeks of benzodiazepine use.
- Timeline of withdrawal occurs within 1-7 days and can last 4-14 days (short vs. long half-life, respectively) after the discontinuation of benzodiazepines.
- Withdrawal symptoms are generally more severe with short half-life benzodiazepines (e.g., alprazolam) and shorter in duration than longer half-life benzodiazepines (e.g., diazepam).

Benzodiazepine withdrawal symptoms[6]

MILD	MODERATE		SEVERE
• Anxiety • Insomnia	• Diaphoresis • Headache • Irritability • Muscle pain/stiffness • Nausea/vomiting • Palpitations	• Panic attacks • Poor concentration • Sleep disturbance • Tremor • Weight loss	• Seizure • Psychosis

Common protracted benzodiazepine withdrawal symptoms[7,8]

Symptoms	Usual course
Anxiety	Gradually diminishing over a year
Insomnia	Gradually diminishing over 6-12 months
Depression	A few months: responds to antidepressants, if needed
Cognitive impairment	Gradually improving but may last a year or more and occasionally incomplete resolution
Perceptual symptoms (e.g., tinnitus, paresthesia—tingling, numbness, pain usually in limbs, extremities)	Gradually receding, but may last at least a year and occasionally persist indefinitely
Motor symptoms (e.g., muscle pain, weakness, tension, painful tremor, shaking attacks, jerks, blepharospasm)	Gradually receding, but may last at least a year and occasionally persist indefinitely
Gastrointestinal symptoms	Gradually receding, but may last at least a year and occasionally persist indefinitely

3 Provide written instructions for a structured medication taper and clearly document in the medical record. Be prepared to slow the taper if the patient reports significant withdrawal symptoms.

TIPS FOR TAPERING

- Begin the taper with the benzodiazepine prescribed.
- If a patient is unable to tolerate tapering a shorter-acting medication, switch to a long-acting option (e.g., diazepam for younger adults, lorazepam for adults age 65 and over).[9,10]
  - Patients on short- or intermediate-acting benzodiazepines have been associated with higher drop-out rates due to withdrawal symptoms compared to long-acting benzodiazepines.[11]
- The benzodiazepine used for the taper should have many strengths available (e.g., lorazepam, diazepam).[12]
- The rate of benzodiazepine taper should ultimately be determined by the patient's symptoms.

Clinical indications for tapering a benzodiazepine[1-4,12,13]

	INDICATIONS	TAPER METHOD
SHORTER TAPER	• Patients who have been on low doses of benzodiazepines for a relatively short time (less than a year)[7] • Medication adverse effects indicate risks are greater than benefit • Comorbidities increase risk of complication	• Gradually reduce total dose by 50% over the first 4 weeks (e.g., 10-15% decrease weekly) • Maintain on that dose (50% original dose) 1-2 months, *then* • Reduce dose by 25% every 2 weeks
LONGER TAPER	• Patients on high doses of benzodiazepines or those who have been taking the medication consistently for many years[7,11] • Function is not improved with benzodiazepine use • Tolerance has developed with long-term prescription • Comorbidities increase risk of complication	No faster than 10% every 2- 4 weeks

A slower or longer taper schedule is recommended in most cases. A gradual taper of benzodiazepines can prevent adverse events from severe withdrawal (e.g., seizures) and effectively aid in benzodiazepine discontinuation. *See pages 8 and 9 for example tapers.*

Benzodiazepine onset, half-life, and equivalent doses[4,7,8]

Generic name	Duration of action	Approx. equiv-alents (mg)	Time to peak plasma (hrs)	Half-life (hrs)*	Available strengths and forms
Alprazolam+	Short-acting	0.5-1	1-2	12-15	0.25, 0.5, 1, 2 mg (tablet)
Chlordiazepoxide	Long-acting	25	1-4	> 100	5, 10, 25 mg (tablet)
Clonazepam	Intermediate-acting	1	1-4	20-50	0.5, 1, 2 mg (tablet) 0.125, 0.25, 0.5, 1, 2 mg (disintegrating tab)
Diazepam	Long-acting	10	1-2	> 100	2, 5, 10 mg (tablet)
Lorazepam	Intermediate-acting	2	2-4	10-20	0.5, 1, 2 mg (tablet)
Temazepam	Intermediate-acting	15	2.5	10-20	7.5, 15, 22.5, 30 mg (capsule)

Approximate equivalencies vary depending upon the resource referenced. Short-acting benzodiazepines include midazolam and triazolam. Other treatment modalities (e.g., antidepressants for anxiety) should be considered if clinically appropriate. In geriatric patients, consider tapering the short-acting agent until withdrawal symptoms are seen then switch to a longer-acting agent.
*Includes active metabolites; +High dose alprazolam may not have complete cross tolerance, a gradual switch to clonazepam or diazepam before taper may be appropriate.

Switching to a longer-acting benzodiazepine—diazepam (< 65-years-old) or lorazepam (≥ 65-years-old)

- Diazepam has a long half-life, thus fewer fluctuations in plasma levels.
- For older adults, lorazepam is the safest option.

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 *(see examples on pages 9-10)*. This can be done prior to starting or restarting the reduction or during the reduction process.
- 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.

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.

Shorter example taper for a Veteran taking lorazepam 2 mg twice daily[1-4,13]

Milestone suggestions	Month	Week(s)	Dose of lorazepam	
			Morning	Night
Week 2: 25% of initial dose	1	1	1.5 mg	2 mg
		2	1.5 mg	1.5 mg
Week 4: 50% of initial dose		3	1 mg	1.5 mg
		4	1 mg	1 mg
Weeks 5-8: Hold dose for one to two months	2	5-8	1 mg	1 mg
Week 9 – Discontinuation: Decrease dose by 25% every two weeks	3	9-10	0.5 mg	1 mg
		11-12	0.5 mg	0.5 mg
	4	13-14	0.25 mg	0.5 mg
		15-16	0.25 mg	0.25 mg
	5	17-18	0 mg	0.25 mg

For a taper calculator and other resources, go to https://dvagov.sharepoint.com/sites/vhaacademicdetailing

Longer taper with conversion from alprazolam to diazepam*,7

	Morning	Midday	Night	Daily diazepam equiv.
Starting dose	alprazolam 2 mg	alprazolam 2 mg	alprazolam 2 mg	120 mg
Stage 1 (one week)	alprazolam 2 mg	alprazolam 2 mg	alprazolam 1.5 mg diazepam 10 mg	120 mg
Stage 2 (one week)	alprazolam 2 mg	alprazolam 2 mg	alprazolam 1 mg diazepam 20 mg	120 mg
Stage 3 (one week)	alprazolam 1.5 mg diazepam 10 mg	alprazolam 2 mg	alprazolam 1 mg diazepam 20 mg	120 mg
Stage 4 (one week)	alprazolam 1 mg diazepam 20 mg	alprazolam 2 mg	alprazolam 1 mg diazepam 20 mg	120 mg
Stage 5 (1-2 weeks)	alprazolam 1 mg diazepam 20 mg	alprazolam 1 mg diazepam 10 mg	alprazolam 1 mg diazepam 20 mg	110 mg
Stage 6 (1-2 weeks)	alprazolam 1 mg diazepam 20 mg	alprazolam 1 mg diazepam 10 mg	alprazolam 0.5 mg diazepam 20 mg	100 mg

Longer taper with conversion from alprazolam to diazepam[*,7] *(continued)*

	Morning	Midday	Night	Daily diazepam equiv.
Stage 7 (1-2 weeks)	alprazolam 1 mg diazepam 20 mg	alprazolam 1 mg diazepam 10 mg	Stop alprazolam diazepam 20 mg	90 mg
Stage 8 (1-2 weeks)	alprazolam 0.5 mg diazepam 20 mg	alprazolam 1 mg diazepam 10 mg	diazepam 20 mg	80 mg
Stage 9 (1-2 weeks)	alprazolam 0.5 mg diazepam 20 mg	alprazolam 0.5 mg diazepam 10 mg	diazepam 20 mg	70 mg
Stage 10 (1-2 weeks)	alprazolam 0.5 mg diazepam 20 mg	Stop alprazolam diazepam 10 mg	diazepam 20 mg	60 mg
Stage 11 (1-2 weeks)	Stop alprazolam diazepam 20 mg	diazepam 10 mg	diazepam 20 mg	50 mg
Stage 12 (1-2 weeks)	diazepam 25 mg	Stop midday; move 5 mg to morning and night	diazepam 25 mg	50 mg

Continue reducing dose by 10% every 2-4 weeks, adjusting taper speed based on patient response.

*Rapid taper with alprazolam or abrupt switching is not recommended due to risk of seizures. Clearly document cross taper in medical record.

Benzodiazepine withdrawal symptoms and non-drug ways to address[7,14-18]

Insomnia, nightmares, sleep disturbances

- Reviewing sleep hygiene (e.g., avoiding tea, coffee, stimulants or alcohol around bedtime)
- Relaxation tapes, anxiety management techniques
- Exercise
- Schedule most of the benzodiazepine dose at night during the taper period

Anxiety symptoms and panic attacks

- Psychological techniques
  - Individual or group behavior therapy
  - Cognitive behavioral therapy
- Physical activity (e.g., aerobics, walking, swimming)
- Yoga
- Meditation
- Acupuncture

Expected results of urine drug tests (UDT)[19-22]

Patients on chronic benzodiazepines should have urine drug tests obtained at least once annually.

Urine drug testing can generally only indicate whether an individual has used a substance one or more times within the window of detection. It cannot reveal whether there have been changes in amount, frequency, route of use, etc., nor whether these changes have had an impact on other areas of life. Therefore, it is important to incorporate patient report and clinical observations in addition to UDT results when assessing response to treatment.

Normal characteristics of a urine sample[20,23]

- Temperature within 4 minutes of voiding: 90°-100°F (cup will feel warm to the touch)
- pH: 4.5-8.0
- Creatinine*: ≥ 20 mg/dL
- Specific gravity*: > 1.002
- Volume*: ≥ 30 mL

Urine drug testing specimen validity[23,24,*]

- Urine samples that are adulterated, substituted, or diluted may avoid detection of drug use.
- Urine collected in the early morning is most concentrated and most reliable.
- Excessive water intake and diuretic use can lead to diluted urine samples (creatinine < 20 mg/dL).

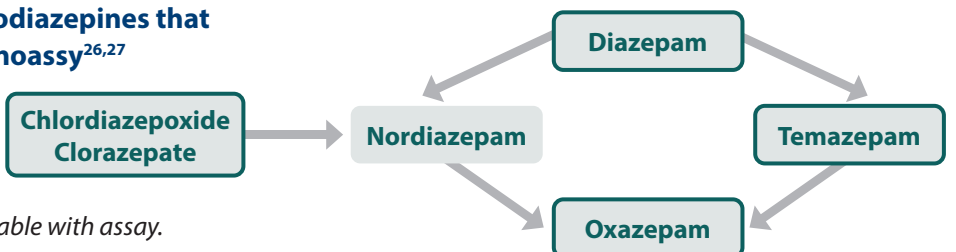
*Abnormal creatinine, specific gravity, nitrates, or volume are not necessarily indicative of invalidity. Unexpected findings should be discussed with the patient.

Benzodiazepine urine drug test[8,19,20,25]

Text and expected result	Detection period after last dose	Considerations
Benzodiazepine immunoassay – Unconjugated oxazepam	• 1-3 days for short-acting • 30 days for long-acting* *Long-term use of lipid-soluble drugs (e.g., diazepam) can be detected for a longer period of time.	• Immunoassays not sensitive to therapeutic doses, confirmatory testing recommended • Alprazolam, clonazepam, and lorazepam not often detected by immunoassay • False positives may be caused by sertraline, efavirenz, or oxaprozin

Additional monitoring could include gamma-glutamyl transferase (GGT) for alcohol use.

Metabolic pathway of benzodiazepines that can be detected with immunoassy[26,27]



Boxes with bold outline are detectable with assay.

Benzodiazepines and metabolites detected on urine drug confirmatory testing[26,27]

Prescribed Medication	Expected Results
Alprazolam	Alprazolam, Alphahydroxyalprazolam*
Chlordiazepoxide	Nordiazepam, oxazepam
Clonazepam	Aminoclonazepam*
Diazepam	Nordiazepam, oxazepam, temazepam
Lorazepam	Lorazepam
Temazepam	Oxazepam, temazepam

* Not consistently detected in UDT

Evidence-based treatment options for anxiety and insomnia

Anxiety[8]

Medications:

- Selective serotonin reuptake inhibitors (SSRIs) or serotonin/norepinephrine reuptake inhibitors (SNRIs)
- Buspirone
- Hydroxyzine
- Pregabalin

Behavioral therapies:

- Cognitive behavioral therapy
- Exposure therapy

Insomnia[28]

Behavioral therapies:

- Cognitive behavioral therapy for insomnia (CBT-I)
- Brief behavioral therapy (BBT-I)

Medications:

- Low-dose doxepin
- Non-benzodiazepine receptor agonist (e.g., zolpidem)

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