ECHO IDAHO

Opioids, Pain and Substance Use Disorders

Benzodiazepine Tapering in Primary Care

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Disclosures

- I have no disclosures.

Learning Objectives

- Discuss indications for benzodiazepine usage
- Discuss risks/harms of long-term benzodiazepine usage with patients
- Learn how to identify patients for a benzodiazepine taper
- How to do a benzodiazepine taper and identify and manage complications
- Update from ASAM on benzodiazepine tapering guidelines

What are benzodiazepines (“benzos”)?

- Sedative-hypnotic medications
- GABA-A receptor agonists that increase the affinity of the receptor to GABA (they make GABA bind more tightly to the receptor, which enhances CNS inhibitory tone)
  - Anxiolytic and sedating effects
- Controlled substances C III-V
- Benzos with active metabolites: chlordiazepoxide, diazepam, flurazepam, flunitrazepam, clorazepate
- Benzos that don’t make active metabolites: lorazepam and oxazepam
- Benzos that make active metabolites with little clinical activity: alprazolam and triazolam

Table 8. Pharmacokinetic Properties of Benzodiazepines

Benzodiazepine	Time to peak plasma level (h; via oral)	Relative lipid solubility[a]	Onset of action (min)[b]	Elimination half-life (h)[c]	Metabolism[d]
Alprazolam	1–2 h (tablet or orally disintegrating tablet [ODT]) 5–11 h extended release (XR)	Moderate	15–30	6–12	CYP3A4
Chlordiazepoxide	0.5–4 h	Moderate	15–30	5–10 36–200 (AM)	CYP3A4
Clonazepam	1–2 h	Low	15–30	18–50	CYP3A4
Clorazepate[e]	0.5–2 h	High	15		CYP2C19 CYP3A4
Diazepam	0.5–2 h	High	≤15	20–100 36–200 (AM)	CYP1A2 CYP2C9 CYP2C19 CYP3A4
Estazolam	2 h	Low	30–60	10–24	CYP3A4
Flurazepam	0.5–2 h	High	≤15	40–250 (AM)	CYP2C19 CYP3A4
Lorazepam	2–4 h	Moderate	15–30	10–20	Glucuronide conjugation
Oxazepam	2–4 h	Low	30–60	4–15	Glucuronide conjugation
Quazepam	2 h	High	15	39 73 (AM)	CYP2C9 CYP2C19 CYP3A4
Temazepam	2–3 h	Moderate	30–60	10–20	Glucuronide conjugation
Triazolam	1–2 h	Moderate	15–30	1.5–5	CYP3A4

[a] Increased lipid solubility results in more rapid onset of CNS activity but can also result in rapid redistribution into adipose tissue resulting in a shorter duration of action even in agents with long elimination half-life (e.g., diazepam)

[b] Rapid onset of action is associated with high lipid solubility and increased potential for misuse.

[c] Agents with moderate to high lipid solubility will have shorter duration of action with single or intermittent doses than suggested by the elimination half-life as these medications distribute rapidly into adipose tissue. With initial dosing, multiple daily doses may be needed to maintain effect. With chronic use and repeated dosing, accumulation is more likely to occur with these agents, especially those with long elimination half-lives (e.g., diazepam).

[d] Agents metabolized via glucuronide conjugation do not have pharmacokinetic interactions and are considered to be safer in older adults and patients with hepatic impairment.

[e] Hydrolized to nordiazepam in the stomach.

Indications for Benzodiazepines

- This is not comprehensive! There are always exceptions to every rule.
- Outpatient: panic disorder, short-term use for social anxiety or insomnia, aerophobia, seizure disorders, hospice/end of life, muscle spasticity, ambulatory alcohol withdrawal, opioid withdrawal?
- Inpatient: alcohol withdrawal, agitation, anxiety, status epilepticus, catatonia
- **General guidelines recommend limiting usage for 2-4 weeks except for severe treatment-resistant GAD, complex seizure disorders, spasticity, and sleep disorders involving abnormal movements**

What are benzodiazepines being used for?

- Long-term treatment of anxiety
- Long-term treatment of insomnia
- Stress reactions that turns into a long-term prescription
- Agitation/unpleasantness
- “Bipolar disorder”
- Patient request

When to avoid benzodiazepines

- Again, exceptions apply
- History of alcohol use disorder
- History of PTSD
- Concurrent use of opioids (respiratory depression and death risk)
- Age >65 (Beer's List)

Risks/Harms of Long-Term Benzodiazepine Use

- Cognitive impairment
- Motor vehicle crashes
- Hip fractures in the elderly (risk goes up by 50% if over age 65)
- Development of Benzodiazepine Use Disorder
- Physical dependence and withdrawal – almost all patients who take benzodiazepines for a month or longer will develop physical dependence
  - Only 1.5% will develop BUD

What is the benzodiazepine withdrawal syndrome? (symptoms to look for)

- It is an unpleasant withdrawal.
- How long can it last?
- Tremors
- Anxiety
- Perceptual disturbances – bugs on skin, delirium
- Dysphoria
- Psychosis
- Autonomic instability
- Insomnia
- Nausea
- Seizures – most severe, and why we taper rather than abruptly stop

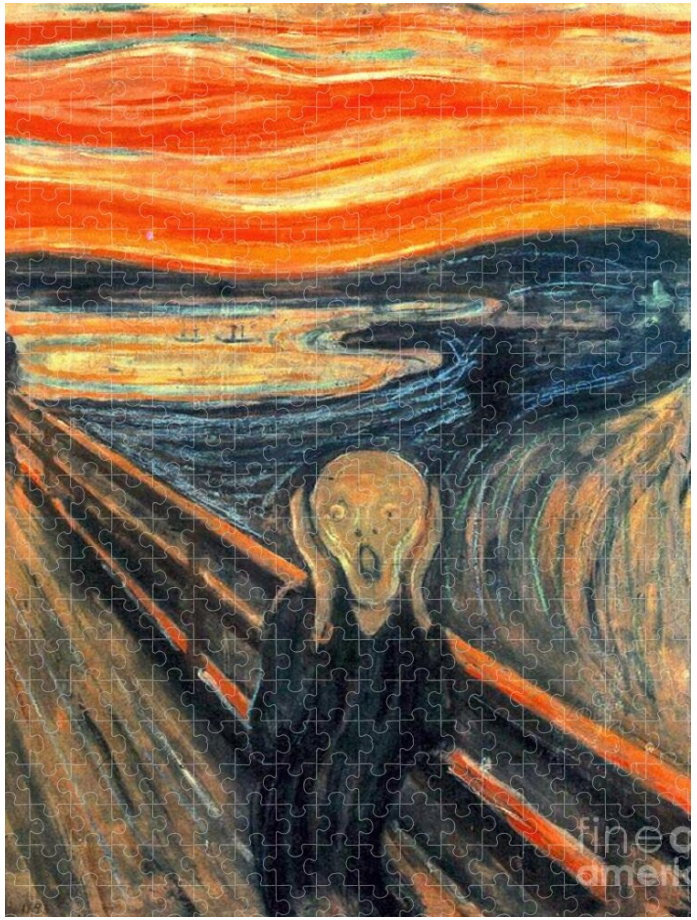

Table 2. Risk for Clinically Significant BZD Withdrawal[4]

Duration of BZD Use	Frequency of BZD Use	Total Daily BZD Dose	Risk for Clinically Significant Withdrawal[5]
Any	≤3 days per week	Any	Rare[6]
<1 month	≥4 days per week	Any	Lower risk, but possible
1–3 months	≥4 days per week	Low[7]	Lower risk, but possible
1–3 months	≥4 days per week	Moderate[8] to high[9]	Yes, with greater risk with increasing dose and duration
≥3 months	≥4 days per week	Any	Yes, with greater risk with increasing dose and duration

This table summarizes estimates of risk for experiencing clinically significant withdrawal depending on the dose, duration, and frequency of BZD use.

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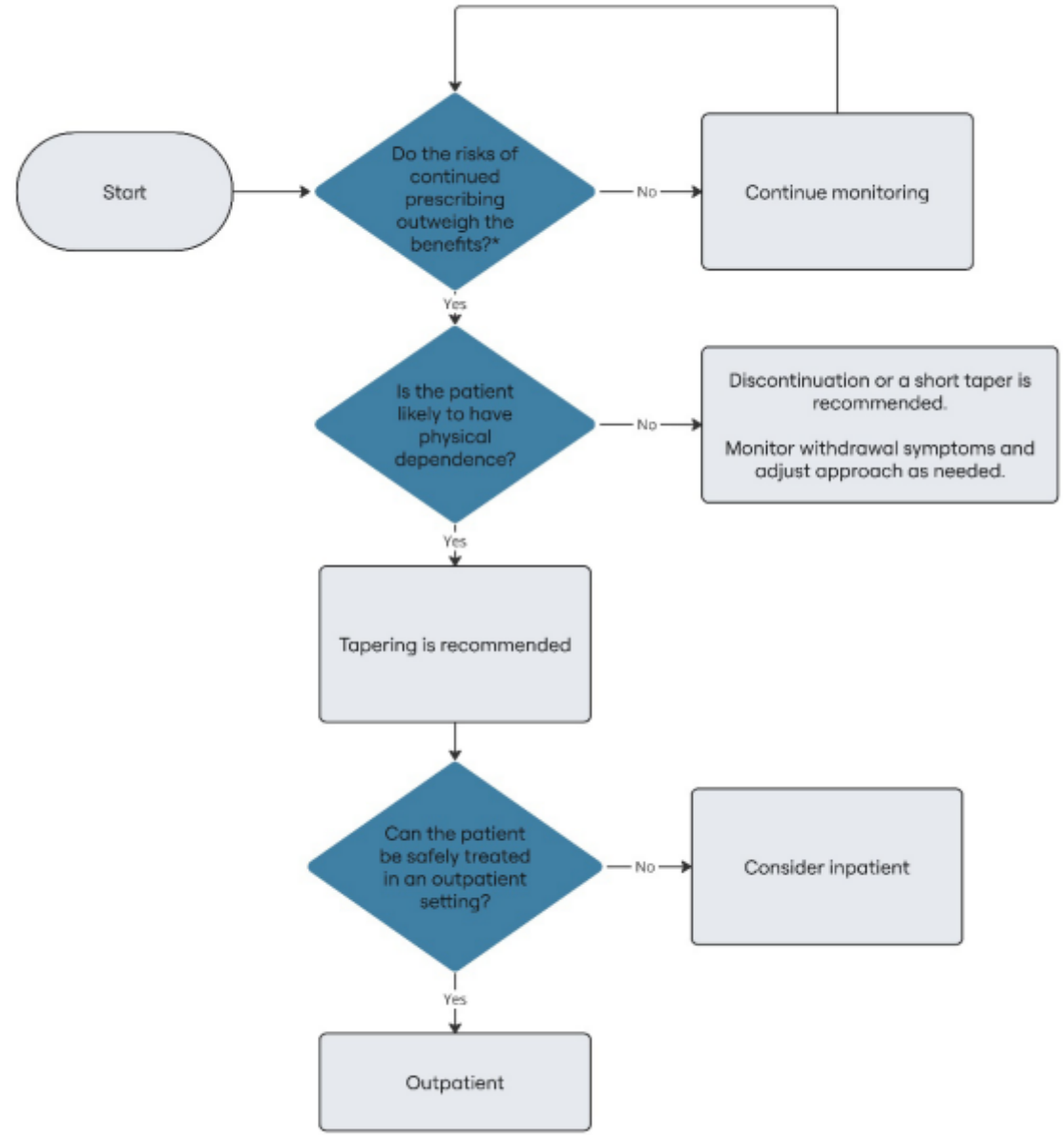
[2] Clinicians should consider the likelihood of each benefit and risk for the individual patient. The narrative notes risk/hazard ratios available in the published literature.
[3] Including compassionate use for end of life or palliative care.
[4] This table is based on clinical consensus. It is intended to provide general guidance and should *not* replace clinical judgment.
[5] Many factors influence the risk of physical dependence and BZD withdrawal syndrome, including but not limited to age, co-occurring physical and mental health conditions, other substance use, and prior history of withdrawal.
[6] Half-lives are unknown for some novel synthetic benzodiazepines available in the illicit market.
[7] A low daily dose is estimated as 10 mg diazepam equivalents or less (eg, ≤0.5mg clonazepam, ≤2 mg lorazepam, ≤1 mg alprazolam). See Table 4 for BZD dose equivalents.
[8] A moderate daily dose is estimated as 10–15 mg diazepam equivalents (eg, 0.5–1.5 mg clonazepam, 2–3 mg lorazepam, 1–2 mg alprazolam). See Table 4 for BZD dose equivalents.
[9] A high daily dose is estimated as more than 15 mg diazepam equivalents (eg, >1.5 mg clonazepam, >3 mg lorazepam, >2 mg alprazolam). See Table 4 for BZD dose equivalents.

New ASAM Guidelines!

- “Joint Clinical Practice Guideline on Benzodiazepine Tapering: Considerations when Benzodiazepine Risks Outweigh Benefits”
- Guideline was developed by many fields – psychiatry, neurology, family medicine, addiction medicine, OB/GYN, geriatrics, toxicologists, psychiatric pharmacists, APPs
- Focuses on patient-centeredness and the potentially unpredictable difficulties with tapering
- They have free webinars and modules you can sign up for!
- Digital tool – Provider Pocket Guide
- Patient pocket guides and other resources coming soon to the ASAM website
- Website: https://www.asam.org/quality-care/clinical-guidelines/benzodiazepine-tapering

Determine Whether and Where to Taper

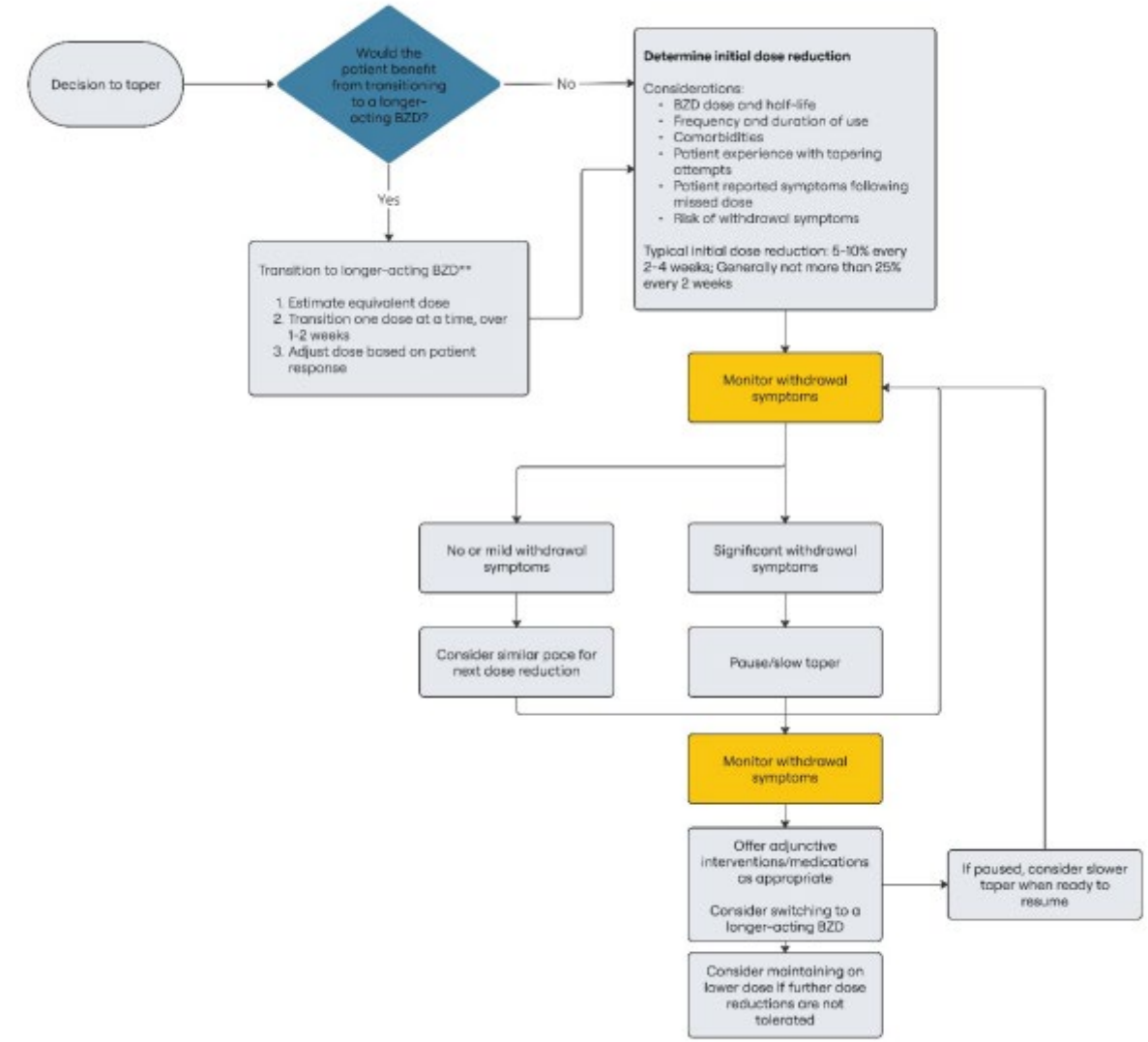


*Risks associated with BZD tapering should also be considered

How to identify patients for tapering

- The patient comes to you!
- Lack of indication for benzodiazepines
- The patient has suffered an adverse effect – fall, confusion, withdrawal syndrome
- Suspicion for benzodiazepine use disorder

Taper Management - Outpatient



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How to taper

- Informed consent
  - Why
  - Risks/benefits/alternatives
- Consider switching from short-acting to long-acting
  - Klonopin (clonazepam)
  - Valium (diazepam)
  - Librium (chlordiazepoxide)
- Slow and steady with pauses for plateaus if needed (patient-centered)
  - 5-10% every 2-4 weeks
  - Try to avoid going more than 25% every 2 weeks

Table 4. Benzodiazepine Approximate Dose Equivalents to 10 mg Oral Diazepam[11]

Benzodiazepine	ATC Therapeutic Class	VA/DoD SUD CPG (2021)[12]	Ashton Manual (2002)[13]
Alprazolam	Anxiolytic	1	0.5
Chlordiazepoxide	Anxiolytic	25	25
Clonazepam	Antiepileptic	1	0.5
Clorazepate	Anxiolytic	15	15
Diazepam	Anxiolytic	10	10
Estazolam	Sedative–Hypnotic	1	1-2
Flurazepam	Sedative–Hypnotic	15	15-30
Lorazepam	Anxiolytic	2	1
Oxazepam	Anxiolytic	30	20
Quazepam	Sedative–Hypnotic	10	20
Temazepam	Sedative–Hypnotic	15	20
Triazolam	Sedative–Hypnotic	0.25	0.5

Approximate dose equivalents of various BZD medications to a 10 mg dose of oral diazepam as determined by the VA/DoD SUD guideline and *The Ashton Manual*.

ATC: Anatomical Therapeutic Chemical classification system; **CPG:** clinical practice guideline; **DoD:** US Department of Defense; **SUD:** substance use disorder; **VA:** US Department of Veterans Affairs

Here’s another equivalency table/resource

- MD Calc (available on smart phones!) - https://www.mdcalc.com/calc/10091/benzodiazepine-conversion-calculator
- Benzo.Org.UK - https://www.benzo.org.uk/bzequiv.htm
- ClinCalc.com - https://clincalc.com/benzodiazepine/
- Risk of under- or over-dosing when using equivalents

CALDO

- Clonazepam 0.25mg
- Alprazolam 0.5mg
- Lorazepam 1mg
- Diazepam 5mg
- Oxazepam 15mg

Managing expectations during the taper

- Rebound anxiety, insomnia can occur
- Months (or years!) long process
- Psychosocial supports
  - CBT, CBT-I, other counseling
  - Behavior Modification
  - Sleep hygiene
  - Exercise/physical activity
  - Diet
  - Mindfulness
  - Progressive Muscle Relaxation
  - Anxiety Management Training (AMT)
  - Peer support

Adjunctive Medications

- Acute anxiety-related symptoms:
  - Clonidine
  - Gabapentin (risk for misuse)
  - Hydroxyzine
  - Propranolol (be careful)
- Chronic anxiety-related symptoms:
  - Buspirone
  - SSRIs, SNRIs
  - Mirtazapine
  - Prazosin
- Insomnia-related symptoms:
  - Doxepin
  - Diphenhydramine, doxylamine, hydroxyzine
  - Melatonin, ramelteon
  - Trazodone

What if it doesn’t go well?

- Reach out for help – ECHO office hours
- Re-visit the taper schedule
- Recovery supports
- Hospitalization for expedited, medically-supervised taper
  - Also indicated if the patient exhibits suicidality during the taper

Supports and further reading

- *Blood Orange Night* by Melissa Bond
- Benzobuddies.org
- Benzosupport.org
- Benzodiazepine Awareness with Geraldine Burns podcast
- The Ashton Manual (benzo.org.uk)

Key Points

- Benzodiazepines are not a harmless medication class. There are a limited number of true indications for usage.
- The taper and withdrawal process is prolonged and can be very different from person to person.
- Reach out for help when there are difficulties.

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