Center for Prescription Drug Abuse Prevention
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COLORADO CONSORTIUM for Prescription Drug Abuse Prevention

BENZODIAZEPINE DEPRESCRIBING GUIDANCE

While recommended for short-term use (<2-4 weeks),[1-3] long-term benzodiazepine receptor agonist (BZRA) therapy is a common scenario in clinical practice.[4,5] Among chronic BZRA patients, 58-100% develop physiologic dependence as reflected by withdrawal symptoms on discontinuation.[6] This is the dominant problem in this patient group-not addiction to BZRAs *per se*[7,8]-and may occur even at prescribed, therapeutic doses.[9,10] In a subset of individuals, withdrawal is a difficult (and sometimes disabling) process, with 10-15% experiencing a protracted course[11] of psychologic, neurophysiologic, and somatic symptoms that may fluctuate unpredictably in a pattern of "waves" and "windows."[8,12] Many patients experiencing BZRA withdrawal seek support from online patient forums,[13] suggesting that further support and guidance from prescribers is warranted regarding withdrawal disorders.[14]

Since BZRA benefits fade,[15,16] while adverse outcomes increase over time,[8] deprescribing should be offered to all patients (especially when use exceeds 4 weeks).[1,8,12] Current available deprescribing guidance in the literature is heterogeneous,[17] but overall consensus is that a gradual, symptom-based taper is the best approach.[12,18-20] In September 2020, the FDA updated its boxed warning for benzodiazepines to include the risks of physiologic dependence and withdrawal reactions, noting that a gradual taper can potentially mitigate withdrawal symptoms. However, the new warnings give little guidance on deprescribing protocols.[10] The following clinical practice recommendations for BZRA deprescribing are based on the existing literature, enriched by clinical and lived experience. They are not comprehensive and should not replace clinical judgement informed by individual circumstances. Please also see the companion documents, Benzodiazepine Prescribing Guidance and Peer Support.

1. Decision-Making for Deprescribing

- Indications: Adverse effects limiting function, loss of efficacy, tolerance, use >1 month,[8] patient requests taper.
- Deprescribing decisions should be collaborative between patient and prescriber. Forced tapers are not recommended (except in the case of significant respiratory compromise)**.**
- Provide **informed consent** regarding discontinuation (risks, benefits, alternatives).[21]
    - **Risks:** between 15-44% of chronic BZRA users experience moderate to severe withdrawal symptoms upon discontinuation.[22] An estimated **10-15% experience a protracted syndrome lasting months to years**,[11] possibly indefinite.[23] This may occur even with a gradual taper. Severe outcomes include suicidality,[24] akathisia, and disability.
    - **Benefits:** reduced anxiety;[12] improved psychomotor and cognitive function;[25] reduced mortality (all-cause[26,27] and overdose[28]); fewer motor vehicle accidents,[29-31] falls,[32] and drug interactions. Some individuals on chronic BZRA develop symptoms that lack an alternative neurophysiologic explanation;[33] these symptoms may also improve.

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- Assess for factors that may increase difficulty of withdrawal: central sensitization (kindling) caused by repeated BZRA use and cessation,[34-36] advanced age, and multiple comorbidities.
- If deprescribing is declined or attempted and too difficult, monitor for adverse effects. If appropriate, readdress discontinuation at future appointments.
- Note that some patients may be unable to withdraw completely, and a more suitable goal may be reduction or maintenance of the current dose.

2. Before Tapering

- Utilize shared decision-making[37-40] to establish a flexible, gradual taper plan.
- Discuss lifestyle modifications: diet, exercise, sleep hygiene, meditation and stress reduction.
- Establish a support system using a multidisciplinary approach (see Benzodiazepine Peer Support document).
- Address interdose withdrawal (if present):
    - Substitute an equivalent dose (see chart) of a longer half-life BZRA (diazepam, clonazepam, chlordiazepoxide) with a stepwise "crossover."[12] Switching abruptly is not recommended.
    - Or, dose a short half-life BZRA more frequently, spaced evenly to avoid peaks/troughs in blood levels.

3. Tapering Principles

- A symptom-based, patient-directed taper is the best approach.[12,18-20]
- Initiate with a small test reduction (≤5% of current dose). Allow the patient to lead subsequent reduction amounts/intervals based on tolerability of withdrawal symptoms.
- Lived experience suggests ≤5%-10% reduction of the total dose monthly is best tolerated.
- Skipping doses, supplemental ("rescue") doses, or up-dosing increase risk of kindling.[41] Up-dosing may be necessary in case of over-rapid reduction and severe symptomatology (e.g.,akathisia, suicidality).
- Hyperbolic (exponential) dose reductions are better tolerated than fixed reductions;[42] i.e., dose reductions should become smaller as the taper progresses.
- Complete discontinuation may take 12-18 months or longer.
- Nervous system hypersensitivity is common during withdrawal, and any foreign substance can have adverse effects. Caution is advised with any new supplement or medication.[23]

4. Taper Techniques[43,44]

- **Cut-and-Hold:** A % of the current dose (in *mgs*/fraction of *mg*) is reduced, then held until symptoms subside.
    - Pro: may be accomplished with existing forms of drug (e.g.¼ or ½ of scored 2 mg diazepam tablet).
    - Con: symptoms from larger dose reductions at once may be more intense.
    - Example: 20mg diazepam dose reduced 5% (1 mg) and held until withdrawal symptoms subside.
- **Microtaper:** Daily micro-reductions (*µg* in size), with % dose reduction (from current dose) calculated monthly.
    - Pro: may allow for finer adjustment and symptom control, since commercially available BZRA doses can be too large to taper comfortably. Many report better symptom tolerability with this method.
    - Con: off-label method that can be subject to accuracy issues.
    - Example: 20mg diazepam dose, 0.07 mg cut daily (~10% reduction over 1 month).

5. Taper Methods (* indicates off-label method)

Method a) can be used for cut-and-hold only; methods b)-f) can be used for either cut-and-hold or microtaper.

a) Commercial tablet/capsule: use lowest available mg strengths, whole or split along scored line
b) Manufacturer's Oral Liquid (alone or further diluted concentrate):[45] reductions via syringe
c) Compounded prescription:* solid drug made into smaller doses or liquid, requires custom Rx.
d) Liquid titration:[46]* tablet or capsule contents mixed w/ liquid, reductions measured via syringe.
e) Precision scale:[47]* weigh drug powder or capsule contents; dry cuts made via pill cutter, razor, or file
f) Tapering strips:[48]* tapered doses in strip packaging (custom Rx, ships from Netherlands).

6. Withdrawal Symptom Management

- Withdrawal symptoms are best managed by adjustment of taper rate and nonpharmacologic measures,[8,49] such as lifestyle modifications (see above), CBT,[2] and peer support.
- Adjunctive medication (e.g., carbamazepine, hydroxyzine) should be considered in case of severe symptoms. However, use for this indication is off-label, and there is limited evidence of benefit.[8] Use caution, as many of these medications also carry their own risks of physiologic dependence and other adverse effects.

7. Potential Pitfalls

- Physiologic dependence can develop in a matter of days, and occur at prescribed, therapeutic doses.[10]
- Stopping BZRAs abruptly (if use >2 weeks) increases risk of seizure, psychosis, death, and protracted withdrawal.
- **Physiologic dependence is not synonymous with addiction.**[50] Due to risks of abrupt cessation, addiction treatment centers are not recommended (in absence of addiction).
- Do not discount symptoms that seem bizarre[8,51] (e.g., depersonalization/derealization, agoraphobia, intrusive thoughts, burning nerve pain, irritable bowel).
- Symptoms of BZRA tolerance and withdrawal can mimic other conditions, leading to misdiagnosis and unnecessary testing and medical treatment.
- Published taper protocols are meant to be a guide only. Flexibility is key.
- Post-withdrawal recovery may take 12-18 months or longer.
- Avoid fluoroquinolone antibiotics (can precipitate acute withdrawal),[52] alcohol, and other GABAergic agents.

8. Resources for Patients and Prescribers

Further reading is encouraged for both patients and prescribers. We recommend:

- The Ashton Manual[12] https://www.benzoinfo.com/ashtonmanual/
- Benzodiazepine Information Coalition (patient- and prescriber-focused) https://www.benzoinfo.com/
- The Alliance for Benzodiazepine Best Practices (prescriber-focused) https://benzoreform.org
- The Withdrawal Project (patient-focused) https://www.withdrawal.theinnercompass.org
- Benzodiazepine Withdrawal: Clinical Aspects (Ch. 8), The Benzodiazepines Crisis: The Ramifications of an Over-Used Drug Class.[8]
- Informed Consent for Benzodiazepine Prescription[21] (written consent for use in clinical practice)

Table: BZRA Dose Conversion Chart based on Ashton, Clinical calculator*,**		
BZRA	**Ashton**[12]	**ClinCalc.com (range)**[53]
Alprazolam	0.5 mg	0.75 mg (0.5 - 2 mg)
Chlordiazepoxide	25 mg	33 mg (12-50 mg)
Clonazepam	0.5 mg	0.75 (0.5-4 mg)
Diazepam (reference)	10 mg	10 mg
Clorazepate	15 mg	13 mg (8-30 mg)
Flurazepam	15-30 mg	20 mg (8-30 mg)
Lorazepam	1 mg	1.3 mg (1-4 mg)
Oxazepam	20 mg	20 (5-40 mg)
Phenobarbital	20 mg	20 mg (15-60 mg)
Quazepam	20 mg	27 mg (15-40 mg)
Temazepam	20 mg	20 mg (5-40 mg)
Triazolam	0.5 mg	0.25 mg (0.25-1 mg)

*Adapted from Benzodiazepine Withdrawal: Clinical Aspects (Ch. 8), The Benzodiazepines Crisis: The Ramifications of an Over-Used Drug Class.[8]

****Equivalent doses vary. Aim for an equivalent dosage where withdrawal symptoms are resolved (or minimized).**

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