Benzodiazepines - Safety Considerations and Tapering Guidance

Individual agent characteristics:

Medication	Dosage Form(s) (mg)	Half-life Range (hr)	Onset after Oral Administration	Relative Equivalent Potency	THHS suggested maximum oral doses	
					< 65 years (mg/day)	≥ 65 years (mg/day)
Short to Intermediate Duration						
Alprazolam (Xanax®)	ER tab: 0.5, 1, 2, 3 ODT: 0.25, 0.5, 1, 2 Soln: 1/mL Tab: 0.25, 0.5, 1, 2	6.3 to 26.9	Intermediate	0.5	4 10 for panic disorder	2 0.75 for panic disorder**
Clonazepam (Klonopin®)	ODT: 0.125, 0.25, 0.5, 1, 2 Tab: 0.5, 1, 2	9 to 19	Slow	0.25	4***	4***
Lorazepam (Ativan®)	Inj: 2/mL, 4/mL Soln: 2/mL Tab: 0.5, 1, 2	10 to 20	Intermediate	1	10*	2**
Oxazepam (Serax®)	Cap: 10, 15, 30	5 to 15	Slow	15	120	60
Temazepam**** (Halcion®)	Cap: 7.5, 15, 22.5, 30	8 to 15	Intermediate	30	30	15
Long Duration						
Chlordiazepoxide (Librium®)	Cap: 5, 10, 25	5 to 30	Intermediate	10	100*	40*
Clorazepate (Tranxene®)	Tab: 3.75, 7.5, 15	30 to 100	Fast	7.5	60*	60*
Diazepam (Valium®)	Inj: 5/mL Rectal gel: 2.5, 10, 20 Soln: 1/mL, 5/mL Tab: 2, 5, 10	20 to 80	Fast	5	60	5**

* = larger doses may be necessary in some cases of alcohol or other substance withdrawal; ** = except when documentation shows higher doses are necessary to maintain or improve patient's function; *** = doses up to 20mg have been used to treat seizure disorders; **** = not recommended for child/adolescents ER = extended release; ODT = orally disintegrating tablet, Tab = tablet, Cap = capsule, Inj = injection; Soln = solution; THHS = Texas Health and Human Services

Important safety considerations for benzodiazepines:

- Associated with withdrawal reactions and rebound anxiety
  - Risk greater with short-acting and intermediate-acting compared to long-acting agents
- Use with caution in patients with substance use disorders due to risk of dependence
- Increased risk of accidental overdose when combined with other central nervous system depressants, including opioids
- In pregnant patients - increased risk of fetal abnormalities in the first trimester
- Older patients (> 65 years of age) may be at greater risk of falls, fractures, memory/cognitive impairment, and motor vehicle crashes when prescribed benzodiazepines
  - 2019 American Geriatrics Society Beers Criteria strongly recommend avoiding benzodiazepines in adults aged 65 years and older
- **Most common side effects:** sedation, fatigue, ataxia, slurred speech, and memory impairment
  - Cognitive impairment may persist after cessation of therapy
  - Memory impairment has been associated with high-dose or high-potency benzodiazepines, especially in older people
- Oxazepam, lorazepam and temazepam are the preferred agents in hepatic impairment

Created by: Heather Rozea Cooper, PharmD, BCPP
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Benzodiazepine US boxed warnings:

- Risks from concomitant use with opioids
- Abuse, misuse, and addiction
- Dependence and withdrawal reactions, including seizures

Concomitant use of benzodiazepines with opioids:

- May result in profound sedation, respiratory depression, coma, overdose, and death
- Relative contraindications to co-prescribing of benzodiazepines and opioids include active misuse and current or past substance use disorders involving benzodiazepines, opioids, alcohol and/or other central nervous system depressants
- Reserve concomitant prescribing for those whom alternative treatment options are inadequate
- Limit dosages to minimum required
- Follow patients closely for signs and symptoms of respiratory depression and sedation
- Utilize Texas Prescription Monitoring Program (PMP) to guide prescribing practices
- Consider prescribing naloxone rescue kit

Potential benzodiazepine tapering strategies

- **Key points**
  - No agreed upon distinct tapering strategy
  - Education and support are important in the tapering process
  - Consider providing written instructions
  - Allow for flexibility of tapering schedule
  - If unable to discontinue, reduction in dose is still valuable
- **Option 1**: Gradually taper original benzodiazepine
  - Faster taper (~3 months)
    - Reduce dose by 50% first 2-4 weeks (e.g., 25% decrease every 2 weeks)
    - Maintain dose for 1-2 months
    - Reduce by 25% every 2 weeks
  - Slower taper (~6 months)
    - Reduce dose by 10-25% every 4 weeks
- **Option 2**: Substitute with longer-acting benzodiazepine then gradually taper (approx. 4 months)

Low dose benzodiazepine taper:	**High dose benzodiazepine taper:**
Patient converted to clonazepam equivalent doses. Consider when patient is taking approximately: Diazepam 5 to 9mg/day Alprazolam 1mg/day Lorazepam 1 to 2mg/day Lorazepam < 1mg/day may start at week 5 below	Patient converted to clonazepam equivalent doses. Consider when patient is taking approximately: Diazepam 10 to 20mg/day Alprazolam 2mg/day Lorazepam 3 to 4 mg/day
Weeks 1 to 4: Clonazepam 1mg/day to 0.5mg/day **Weeks 5 to 8:** Clonazepam 0.5mg/day **Weeks 9 to 12:** Clonazepam 0.5mg/day to 0.25mg/day **Weeks 13 to 15:** Clonazepam 0.25mg every other day	**Weeks 1 to 4:** Clonazepam 2mg/day to 1mg/day **Weeks 5 to 8:** Clonazepam 1mg/day **Weeks 9 to 12:** Clonazepam 0.75mg/day to 0.5mg/day **Weeks 13 to 15:** Clonazepam 0.25mg/day

- **Option 3:** Canadian deprescribing network tapering guidance and visual tapering graphic
    - Taper slowly in collaboration with patient
    - ~25% reduction every 2 weeks and if possible, 12.5% reductions near end and/or planned drug-free days
        - If dosage forms do not allow 25% reduction, consider 50% reduction initially using drug-free days during latter part of tapering
    - Monitor every 1-2 weeks for duration of tapering

Tapering-off program

Be sure to talk to your doctor, nurse or pharmacist before you try reducing your dose or stopping your medication.

WEEKS	TAPERING SCHEDULE							✓
	MO	TU	WE	TH	FR	SA	SU	
1 and 2	Half dose	Full dose	Full dose	Full dose	Half dose	Full dose	Full dose	
3 and 4	Half dose	Full dose	Half dose	Half dose	Full dose	Half dose	Half dose	
5 and 6	Half dose	Half dose	Half dose	Half dose	Half dose	Half dose	Half dose	
7 and 8	Half dose	Quarter of a dose	Half dose	Half dose	Quarter of a dose	Half dose	Half dose	
9 and 10	Half dose	Quarter of a dose	Half dose	Quarter of a dose	Half dose	Quarter of a dose	Half dose	
11 and 12	Quarter of a dose	Quarter of a dose	Half dose	Quarter of a dose	Quarter of a dose	Half dose	Quarter of a dose	
13 and 14	Quarter of a dose	Quarter of a dose	Quarter of a dose	Quarter of a dose	Quarter of a dose	Quarter of a dose	Quarter of a dose	
15 and 16	No dose	Quarter of a dose	No dose	No dose	Quarter of a dose	No dose	Quarter of a dose	
17 and 18	No dose	No dose	No dose	No dose	No dose	No dose	No dose	

EXPLANATIONS

Full dose · Half dose · Quarter of a dose · No dose

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Potential benzodiazepine withdrawal effects and other considerations:

- Abrupt discontinuation or rapid dose reduction after continued use (>8 weeks) may precipitate acute withdrawal reactions, which can be life threatening
- Withdrawal symptoms more likely to occur with long term use (>8 weeks), higher daily dose, and short-acting agents (e.g., alprazolam, oxazepam)
- To reduce risk of withdrawal reactions, use gradual taper to discontinue or reduce dosage
- **Withdrawal symptoms** include rebound anxiety, irritability, insomnia, nightmares, agitation, aggression, seizures, depression, hallucinations, muscle stiffness, flu-like symptoms, paresthesia, GI disturbances, decreased memory and concentration, weakness, and visual disturbances
  - Short half-life agents → seizures may occur within 3 days of drug discontinuation
  - Longer half-life agents → seizures can occur up to 1 week after stopping
  - Risk factors for withdrawal seizures - high dose, long durations of therapy, concurrent ingestion of drugs that lower seizure threshold
- Withdrawal symptoms may occur in the first week of abrupt withdrawal and may persist for months to years

Benzodiazepine Discontinuation Discussion (example conversation)

Action	Provider Response
Express concern	“I would like to discuss my concerns about [benzodiazepine name].”
Provide education on potential risks	“Because of your [risk factors], I am concerned that the use of [benzodiazepine name] may put you at increased risk for [relevant consequences].”
Assess patient readiness to begin taper process	“What do you think are benefits of stopping or reducing your dose? What concerns do you have about stopping? How can I collaborate with you to address your concerns? What would be a reason you might consider changing from [benzodiazepine name] to [alternative treatment]?”
Negotiate plan	“What tapering plan and duration of time would you be most comfortable in trying? Would you like to talk with one of my colleagues to learn about supportive options during this change?”
Inform	“You may experience withdrawal symptoms, but they are temporary. Working together to slowly taper [benzodiazepine name] will decrease these symptoms. As we proceed, we can adjust the rate of taper, as necessary.”

References:

1. Bostwick JR. Medication Table 6: Benzodiazepines. in Chavez B editor. In: CPNP Psychiatric Pharmacotherapy Review Course. 2018-2019 ed. Lincoln (NE): College of Psychiatric and Neurologic Pharmacists; 2018.
2. Guina J, Merrill B. Benzodiazepines I: Upping the Care on Downers: The Evidence of Risks, Benefits and Alternatives. *J Clin Med*. 2018;7(2):17. doi:10.3390/jcm7020017
3. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2019;67(4):674-694. doi:10.1111/jgs.15767

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4. Tannenbaum, C., et al., *Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: the EMPOWER cluster randomized trial.* JAMA Intern Med, 2014. 174(6): p. 890–8.
5. Pollmann, A.S., et al., *Deprescribing benzodiazepines and Z-drugs in community-dwelling adults: a scoping review.* BMC Pharmacol Toxicol, 2015. 16: p. 19.
6. Bostwick JR, Casher MI, Yasugi S. Benzodiazepines: a versatile clinical tool. Current Psychiatry 2012;11(4):55-64.
7. Management of substance use disorders. Washington, DC: Office of quality and performance and the Veterans Affairs and Department of Defense development work group, Veterans Health Administration, Department of Veterans Affairs, 2015.
8. Vicens C, et al. Comparative efficacy of two interventions to discontinue long-term benzodiazepine use: cluster randomized controlled trial in primary care. Br J Psychiatry. 2014; 204:471-479.