Clinical Pharmacology & Toxicology Pearl of the Week

~ Benzodiazepine Tapering: Concepts & Strategies ~

Case:

- ✓ A 50 yo female is admitted to hospital for pneumonia; on review of her medication list, she is prescribed Lorazepam 1-2mg PO qhs PRN.

- ✓ In review with the patient, she endorses near nightly use of Lorazepam 2mg PO qhs, and in addition uses up to an additional 2 mg daily for anxiety throughout the day.

- ✓ She is interested in tapering off her Lorazepam, as she has tried to "quit it all together" and became quite "sick" after trying to do same.

Background:

- ✓ Benzodiazepines exert their clinical effects through inhibitory neurotransmission via GABA-A receptors; they are commonly prescribed for their sedative-hypnotic, anxiolytic, anticonvulsant, and muscle-relaxant properties (*Please refer to the prior CPT Benzodiazepine Pearl for full details)*.

- ✓ At times, patients may be inappropriately prescribed benzodiazepines chronically – this is rarely indicated and may lead to harm, especially in the elderly.
    - Careful review of indications and reasons for use is important in all patients prescribed benzodiazepines.

- ✓ Chronic use (usually weeks) can lead to physical dependence – likely a result of changes to GABA-A receptor response and expression, with a relative increase in excitatory neurotransmission.
    - Withdrawal may present as, but is not limited to:
        - Tremors
        - Anxiety
        - Perceptual disturbances
        - Dysphoria
        - Delirium
        - Insomnia
        - Seizures
    - The timeline of withdrawal symptom onset depends on the half-life and duration since last dose.

- ✓ A safe deprescribing strategy is paramount to avoid benzodiazepine withdrawal and its complications.
    - This is commonly done in the form of an inpatient or outpatient slow taper.
    - No extensive evidence exists which identifies the perfect strategy, and regimens require individualized assessment and monitoring.

Considerations:

- ✓ *Inpatient vs. Outpatient Setting*
    - Reliability, patient function, and comorbidities all play a role in determining safety when considering an outpatient tapering regimen.

- Patients in the outpatient setting should have access to frequent reassessments by the tapering physician and should be tapered at a slow rate (See below).
- Inpatient therapy may be advisable if:
  - Unsuccessful prior attempts.
  - Complicated medical comorbidities (especially a history of seizures).
  - Poor reliability or follow-up.

✓ *What benzodiazepine(s) is the patient on? Consider a dose equivalent change to a longer acting agent.*

DRUG (PO; immediate release)	Typical Adult Dose (mg/day)	Comparative Potency (mg)	Onset PO (hours)	Elimination Half-life (hrs.)
Lorazepam (Ativan)	0.5 – 6	1	0.5 – 1	10 – 14
Oxazepam (Serax)	15 – 120	15 – 30	1 – 2	5 – 15
Alprazolam (Xanax)	0.5 – 6	0.5	1	11 – 20
Clonazepam (Klonopin)	0.5 – 4	0.25 – 0.5	0.5 – 1	18 – 50
Diazepam (Valium)	4 – 40	5	0.25 – 0.5	50 – 100
Chlordiazepoxide (Librium)	5 – 100	10	1	30 – 100

*NOT COMPREHENSIVE – Data obtained from Lexicomp and UpToDate database; please refer to a trusted resource for most accurate information, as well as additional benzodiazepines not listed above.

- Although no benzodiazepine has been proven to be superior in tapering, shorter acting benzodiazepines are associated with:
  - Higher dropout rates from discontinuation studies.
  - Worse rebound symptoms.
  - More severe withdrawal.
- Agents such as Diazepam (Valium) and Chlordiazepoxide (Librium) are favored agents for tapering given their long elimination half-lives, allowing for a gentler taper and less withdrawal potential.
- It is safe to switch agents for a taper. In order to do so, it is recommended to:
  - Ensure the patient is agreeable and understands the purpose of this change.
  - Calculate the total daily dose of each benzodiazepine the patient is on, including PRNs.
  - Using the total daily dose of each and calculate the dose equivalent of a longer acting agent (e.g., Chlordiazepoxide, Diazepam).
    - Chlordiazepoxide daily dose may be divided every 6-12 hours.
    - Diazepam daily dose may be divided every 6-12 hours.
  - Ensure the patient demonstrates good symptom control and no toxicity after the change is made – may consider starting with 75% of the calculated equivalent dose and adding as needed.

✓ *Determine a safe rate of taper*

- General recommendations currently advise a 5-25% dose reduction every 1-2 weeks; however, it is important to note that monitoring for withdrawal symptoms will be paramount in determining if rates need to be slowed.
- When a dose reduction of 50% is reached, some regimens advocate for a "pause" in tapering for up to 2-4 weeks – however, there is no evidence that this is required or beneficial.
- Some regimens also recommend slowing the taper once the daily dose is <20% - however, what is more important is frequent monitoring for withdrawal and titrating based off symptoms.
- Recommendations are similar between both inpatient and outpatient settings.

Augmentative Therapies:

- ✓ Numerous theoretical adjunctive therapies have been proposed; the following are interventions which can be considered.

- ✓ Management of co-existent anxiety and depression (Baandrup 2018 & Darker 2015)
    - May be crucial in managing symptoms previously targeted by the patient's benzodiazepine use.
    - Consider first-line antidepressant/anxiety therapy in liaison with psychiatry.

- ✓ Management of insomnia
    - Based off results of a small study, Melatonin use may provide a safe way to improve perceived poor sleep quality during benzodiazepine tapers (Garfinkel 1999).
    - Additionally, may consider optimizing the timing of benzodiazepine dose qhs to assist with sleep while tapering.

- ✓ Psychosocial Augmentation: Cognitive Behavioral Therapy (CBT)
    - A meta-analysis looking at success of benzodiazepine discontinuation strategies in 9 different trials found that when CBT was added to a tapering regimen, a higher rate of successful discontinuation was seen at 3 months (Darker 2015)

Case Resolution:

- ✓ You calculate the patient's daily dose to be an estimated 4mg of Lorazepam / day and decide to convert this to the more long acting Chlordiazepoxide 2mg / day, divided q12h.

- ✓ You safely convert her to Chlordiazepoxide while she is admitted for pneumonia, and determine close follow-up in liaison with her GP, suggesting a dose taper of no more than 25% q1-2 weeks – the patient is also in agreement with this.

- ✓ Her GP helps to facilitate psychiatry involvement and CBT therapy for underlying anxiety disorder.

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA. Clinical Pharmacology consultations are also available through Netcare e-referral process and through Calgary Zone Specialist Link. Click HERE for more details.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-1212 (SK).

References / Resources

- Baandrup L et al. Pharmacological interventions for benzodiazepine discontinuation in chronic benzodiazepine users (Review). *Cochrane Database Syst Rev.* 2018;3:CD011481. doi: 10.1002/14651858.CD011481.pub2.

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- Sud P & Lee, DC. Chapter 72: Sedative-hypnotics. *Goldfrank's Toxicologic Emergencies [11th Edition]*. 2019.

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