CSAM
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# Managing Benzodiazepine Withdrawal

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## Disclosures

- None relevant

## Objectives

- Describe several methods of tapering from benzodiazepines (BZs)
- Describe evidence for effectiveness of each method
- Describe risks and benefits of each method

## History

- Benzodiazepines Rx'ed since early 1950s
- Awareness of tolerance, dependence, WD gradually emerged

## Epidemiology of BZ Use

- In 2008, 5.2% of US adults 18-80 used BZs (had at least 1 Rx during year) (Olfson, JAMA 2015)
- In 2008, 272,000 ER visits in US involving nonmedical use of BZs, of which 40% also involved alcohol (Olfson, JAMA 2015)
- In 2011, 426,000 visits

## Risks

- Older individuals at particular risk for adverse effects: cognitive impairment, limitation of mobility, falls, driving impairment
- Individuals with SUDs are at greater risk of developing a use disorder w BZs
- Other risks

## Indications for Tapering BZs

- Oversedation
- Cognitive impairment
- Motor impairment
- Concurrent Rxs or use of high-risk CNS depressants medications, e.g. other BZs, non-BZ hypnotics, and especially opioids
- Alcohol use disorder
- Overuse, misuse, abuse of BZ
- Patient request
- Other indications

## DSM-5 Diagnosis of BZ WD (sedative, hypnotic, or anxiolytic WD)

- Autonomic hyperactivity
- Hand tremor
- Insomnia
- Nausea or vomiting
- Transient visual, tactile, or auditory hallucinosis or illusions
- Psychomotor agitation
- Anxiety
- seizures

## Associated Features of WD (DSM-5)

- Timing & severity can vary
  - Short-acting BZs & those with no active metabolites, when stopped, can led to WD sx within hours
  - Long-acting BZs, with active metabolites can take 1-2 days for WD sx to emerge
  - Severe WD can be accompanied by delirium
  - Time course can vary:
    - BZs with actions lasting $\leq$ 10 hrs, e.g. lorazepam, oxazepam, temazepam produce WD sx within 6-8 hrs of decreasing blood levels; peak by the 2nd day, and improve markedly by 4-5 days.
    - BZs with longer ½ lives (eg diazepam) may have delayed onset of WD sx, sometimes as long as 1 wk, peak in intensity in the 2nd week, and decrease by 3rd or 4th wk. Additional long-term, low-level sx may persist for several months.

## Tapering Strategies: Overview

- Gradual taper of same BZ as taken by patient
- Substitution of long-acting BZ
- Substitution or augmentation with non-BZs
- Support medications
- Others

## Tapering Strategies: Taper of Same BZ

- Gradual taper of same BZ as taken by patient
- No clear evidence-based guidelines on rate
- Expert and consensus guidelines exist, e.g.:
  - Heather Ashton, MD
  - VA National Center for PTSD, 2013

## Tapering Strategies: Substitution of Long-Acting BZ for Short-Acting

- Substitution of long-acting BZ
  - Chlordiazepoxide
  - Clonazepam
  - Diazepam

## Tapering Strategies: Substitution or Augmentation with non-BZs

- Substitution or augmentation with non-BZs
  - Phenobarbital (Smith & Wesson)
  - Other anticonvulsants
    - CBZ
    - Valproate
    - Oxcarbazepine
    - Pregabalin
    - Gabapentin
    - Topiramate

## Tapering Strategies: Support Medications

- Support medications
  - Antihistamines, hydroxyzine
  - Adrenergic agents
    - Clonidine
    - Propranolol
  - Muscle relaxants
    - Baclofen
    - Tizanidine
  - Sedating antidepressants
    - Trazodone
    - Mirtazapine
    - Tricyclics
  - Others

## Experimental Approaches to WD Management

- Flumazenil
  - BZ receptor antagonist
  - Attempt to upregulate receptors
  - No large controlled trials available
  - Serious risks

## Cochrane Review

- No convincing evidence for any of these options
- Gradual taper of same agent probably best, given current limited state of knowledge

## BZ Taper Recommendations VA National Center for PTSD, 2013: Supratherapeutic Doses

- Consider admission due to greater medical risks
- Consider switch to long ½ life drug (CLON/ DIAZ)
- Reduce dose initially by 25-30%
- Then reduce by ~ 5-10% daily to weekly
- Consider anticonvulsants for high dose WD

## BZ Taper Recommendations VA National Center for PTSD, 2013: Therapeutic Doses – Bedtime (qHS) Dosing

- Reduce by ~ 25% weekly
- Anticipate/educate about rebound insomnia; can occur as early as 1 day
- Provide sleep hygiene info
- Start alternate tx options: CBT-I, non-BZs (non 'Z-drugs')

## BZ Taper Recommendations
## VA National Center for PTSD, 2013:
### Therapeutic Doses – Daytime (QD-QID) Dosing

- Anticipate/educate about rebound anxiety & recurrence of initial anxiety
- Additional psychosocial support
- Last phase of WD likely to be most difficult
- Points of dosing frequency changes (eg TID to BID) may be psychologically challenging
- Actively involve pt in tapering schedule
- Initial dose taper typically between 10-25%
  - Observe for WD signs/sx
  - Anticipate early WD sx in short ½ life BZs
  - Individualize subsequent reductions based on initial response
- Generally, further reductions of 10-25% q 1-2 wks well tolerated
  - May need to slow taper/offer psychological support to help cope w anxiety

## BZ Taper Recommendations
## VA National Center for PTSD, 2013:
### Additional Strategies for Complex Cases

- Can be helpful to be flexible with schedule
- Prolonged taper >6 mos may worsen long-term outcome
- Consider stabilizing on 50% dose for several mos before proceeding w taper
- Consider switch to long-acting BZ
- Establish team to support pt (case mgr, therapist, pharmacist, etc)

# BZ Taper Recommendations
# VA National Center for PTSD, 2013:
# BZ Equivalent Doses/Suggested Taper

| | Approximate Dosage Equivalents | Elimination Half-life |
|---|---|---|
| **Chlordiazepoxide** | 25 mg | >100hr |
| **Diazepam** | 10 mg | >100hr |
| **Clonazepam** | 1 mg | 20-50 hr |
| **Lorazpam** | 2 mg | 10-20 hr |
| **Alprazolam** | 1 mg | 12-15 hr |
| **Temazepam** | 30 mg | 10-20 hr |

**Benzodiazepine Taper:**
- Switch to a longer acting benzodiazepine
- Reduce dose by 50% the first 2-4 weeks then maintain on that dose for 1-2 months then reduce dose by 25% every two weeks

# BZ Taper Recommendations
# VA National Center for PTSD, 2013:
# Milestone Suggestions/Example

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# Conclusions

- Individualized approach is best