Pharmacological management of benzodiazepine dependence

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Benzodiazepines

Learning objectives

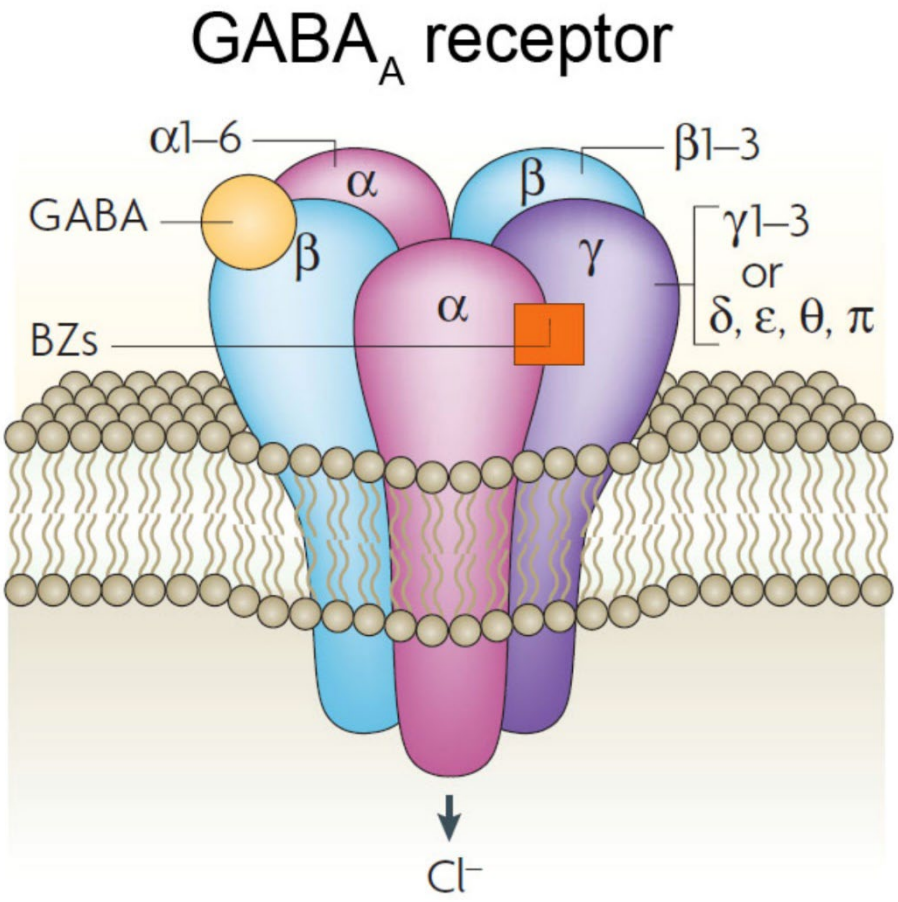
1. Review symptoms of benzodiazepine withdrawal.
2. Identify the three main indications for tapering.
3. Develop a systematic, safe and well tolerated approach to tapering benzodiazepines.

Case example

- 50M with sedative use disorder (diazepam and lorazepam)
- 30 years of daily use 50-100 mg diazepam equivalent
- Last BZD use five days prior to presentation
- Comorbid stimulant use disorder (cocaine) in early remission
- Opioid use disorder in sustained remission
- Utox: + COC + BZD
- CIWA 15
- Past psychiatric hx: significant trauma and substance-induced psychosis

Benzodiazepine pharmacology refresher

- Effects:
  - Sedative
  - Anxiolytic
  - Muscle relaxant
  - Anticonvulsant
  - Amnestic



Jacob et al., Nature Reviews Neuroscience, 2008

Benzodiazepine pharmacology refresher

- Pharmacokinetics:
  - Absorption: readily bioavailable, highly lipophilic
  - Metabolism:
    - Both oxidation (phase 1) and conjugation (phase 2)
    - **L**orazepam, **O**xazepam and **T**emazepam less reliant on oxidative metabolism
- Tolerance
  - Secondary to pharmacodynamic changes
  - Develops to sedative effects, but less so to anxiolytic effects

(Kranzler et al, 2014)

Benzodiazepine Abstinence Syndrome

- Ranges from anxiety/insomnia to seizures/psychosis
- Potentially fatal
- Influenced by 3 factors:
    - The duration of treatment*
    - The dose
    - The half-life
- Can occur after 4 weeks of daily use
- Rebound insomnia can occur after 10 days
- A small % of patients will experience protracted withdrawal

(O'Brien, 2005)

DSMV – Sedative, Hypnotic or Anxiolytic Withdrawal

- Two (or more) of:
  - Autonomic hyperactivity (eg. sweating or pulse rate greater than 100bmp)
  - Hand tremor
  - Insomnia
  - Nausea or vomiting
  - Transient visual, tactile, or auditory hallucinations or illusions
  - Psychomotor agitation
  - Anxiety
  - Grand mal seizures

  - Specify: with perceptual disturbance

Benzodiazepine Withdrawal Timeline

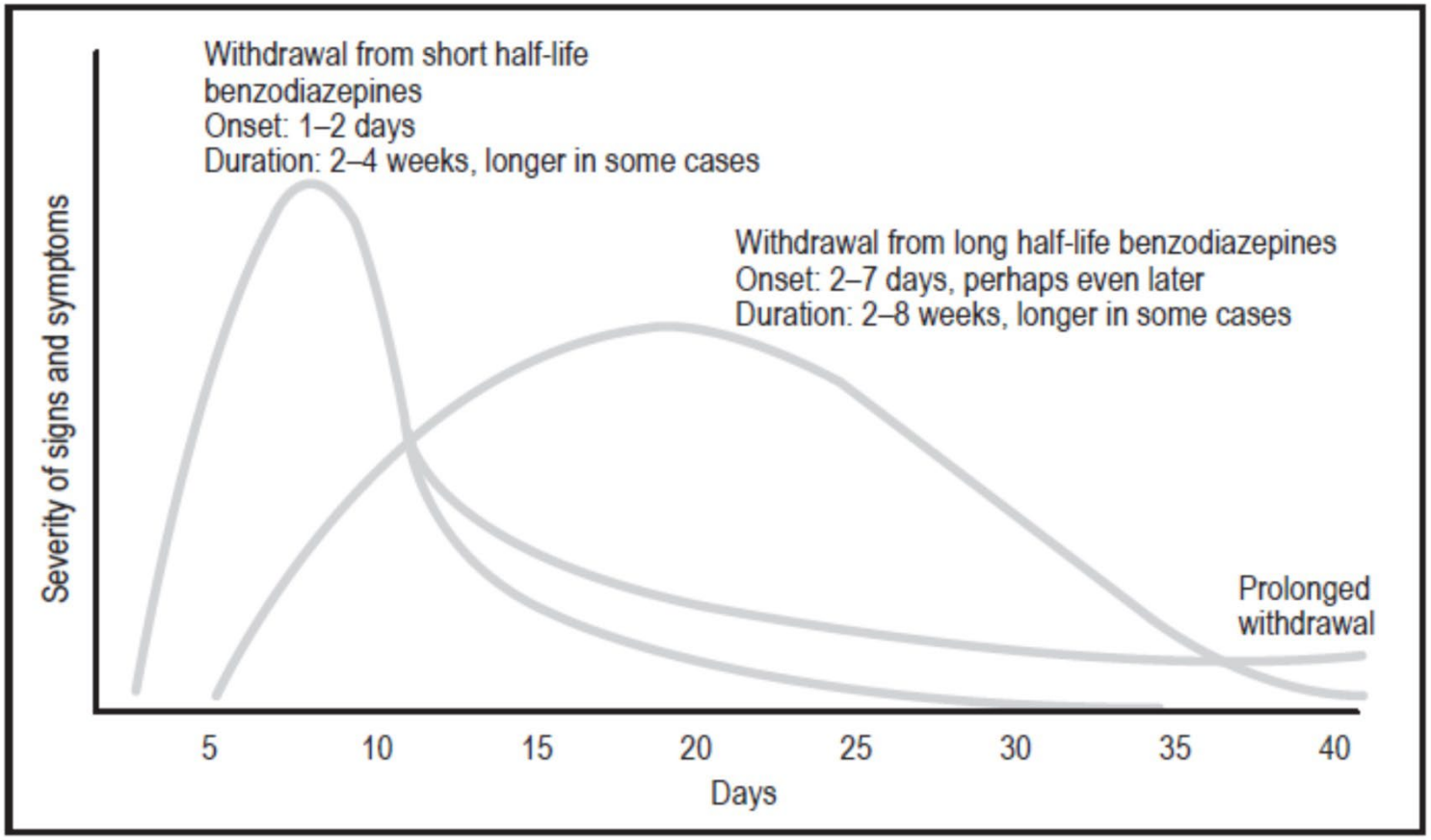


Figure 5: Symptoms and duration of benzodiazepine withdrawal

Source: NSW Health (2008, p.30)

Withdrawal vs. Relapse of Anxiety

Sx common to all anxiety states	Sx specific to benzodiazepine withdrawal
Panic attacks	Perceptual disturbances (hallucinations)
Insomnia, nightmares	Depersonalization
Depression, dysphoria	Myoclonic jerks
Excitability	Tinnitus
Poor memory/concentration	Seizures
Dizziness	Numbness
Fatigue	Sensory hypersensitivity
Tremor	

(Lader and Higgitt, 1986)

Benzodiazepines

Learning objectives

1. Review symptoms of benzodiazepine withdrawal.
2. Identify the three main indications for tapering.
3. Develop a systematic, safe and well tolerated approach to tapering benzodiazepines.

Three main indications for tapering

1. Patients on therapeutic doses who demonstrate lack of clinical efficacy or emergence of unacceptable side-effects
2. Patients on supratherapeutic doses
3. Patients with benzodiazepine use disorder and/or comorbid SUDs

(Kranzler et al, 2014)

1. Patients on therapeutic doses for whom a trial off benzodiazepines is warranted

Preparation:

- Involve patient in planning a tapering schedule
- Educate the patient about rebound anxiety/insomnia vs recurrence of initial symptoms
- Plan for additional psychosocial support
  - Introduce alternative coping skills +/- pharmacotherapy

(Pottie et al, 2018)

1. Patients on therapeutic doses for whom a trial off benzodiazepines is warranted

General tapering tips:

- Initial 10-25% dose reduction and observe for w/d
- Reductions of 10-25% every 1-2 weeks, slowing down the taper once reaching diazepam 5 mg equivalent
- For patients on long-term benzo tx (>1yr), the rate of decrease should not exceed 10% or 5 mg diazepam equivalents per week (the smallest of the two)
- Use **scheduled** dosing and not prn
- Reduce the **dose**, not the frequency
- **Pause** the taper if needed
- Using same benzodiazepine is usually adequate
- Only dispense enough to last until next appointment*

2. Patients on supratherapeutic doses

- Greater risk of severe withdrawal symptoms (seizures, psychosis, delirium)
- Can be done on an outpatient basis if:
  - good therapeutic alliance
  - frequent contact
  - slow taper 5% reduction per week
- Use diazepam or another longer-acting agent to promote smoother taper
- Consider an anticonvulsant

What is a supratherapeutic dose?

Benzodiazepine	Max. recommended daily dose
Alprazolam	6-10 mg
Clonazepam	4 mg
Diazepam	40 mg
Lorazepam	6-10 mg
Oxazepam	120 mg
Temazepam	30 mg

Lexicomp

Benzodiazepine substitution

- Always switch to a longer acting agent
- Start with half the equivalent dose of the original benzodiazepine to account for incomplete cross-tolerance
- Increase until the patient denies withdrawal symptoms, but do not prescribe above the full equivalent dose*

Benzodiazepine Equivalency Table

	Onset (hr)	Duration	T ½	Potency	Equivalent doses (mg)
lorazepam	2	Intermediate	10-20	high	1
alprazolam	1	Short	2.5	high	0.25-0.5
clonazepam	1	Long	18-50	high	0.25-0.5
diazepam	1	Long	36-200	low	5-10

(Adapted from: Guina and Merrill, 2018)

Adjunctive medications used in the treatment of benzodiazepine withdrawal

Medication class	Medications
Alpha 2 receptor agonists	Clonidine
Anticonvulsants	Carmabazepine, pregabalin, baclofen, valproic acid, **gabapentin**, topiramate
Antidepressants	**Trazodone, mirtazapine**
Beta-receptor antagonists	Propanolol

(Kranzler et al, 2014; Baandrup et al, 2018; Leung et al, 2022)

3. Patients with benzodiazepine use disorder and/or comorbid SUDs

- At greater risk of severe withdrawal symptoms
- Greater risk of diversion
- Usually requires a medically supervised setting
- Inpatient setting
  - No validated benzodiazepine-specific protocols, but CIWA is typically used
  - Determine daily benzodiazepine requirements from patient report and CIWA, and plan a tapering protocol from established daily dose

3. Patients with benzodiazepine use disorder and/or comorbid SUDs

Outpatient tips to enhance safety:

- Structured prescribing:
  - Short prescriptions without repeats
  - Involve pharmacy:
    - Daily dosing
    - Observed dosing
  - Frequent appointments
  - No early refills
  - Single prescriber
- Monitoring options:
  - Urine drug screens
  - Pill counts
  - Connecting Ontario

Case example

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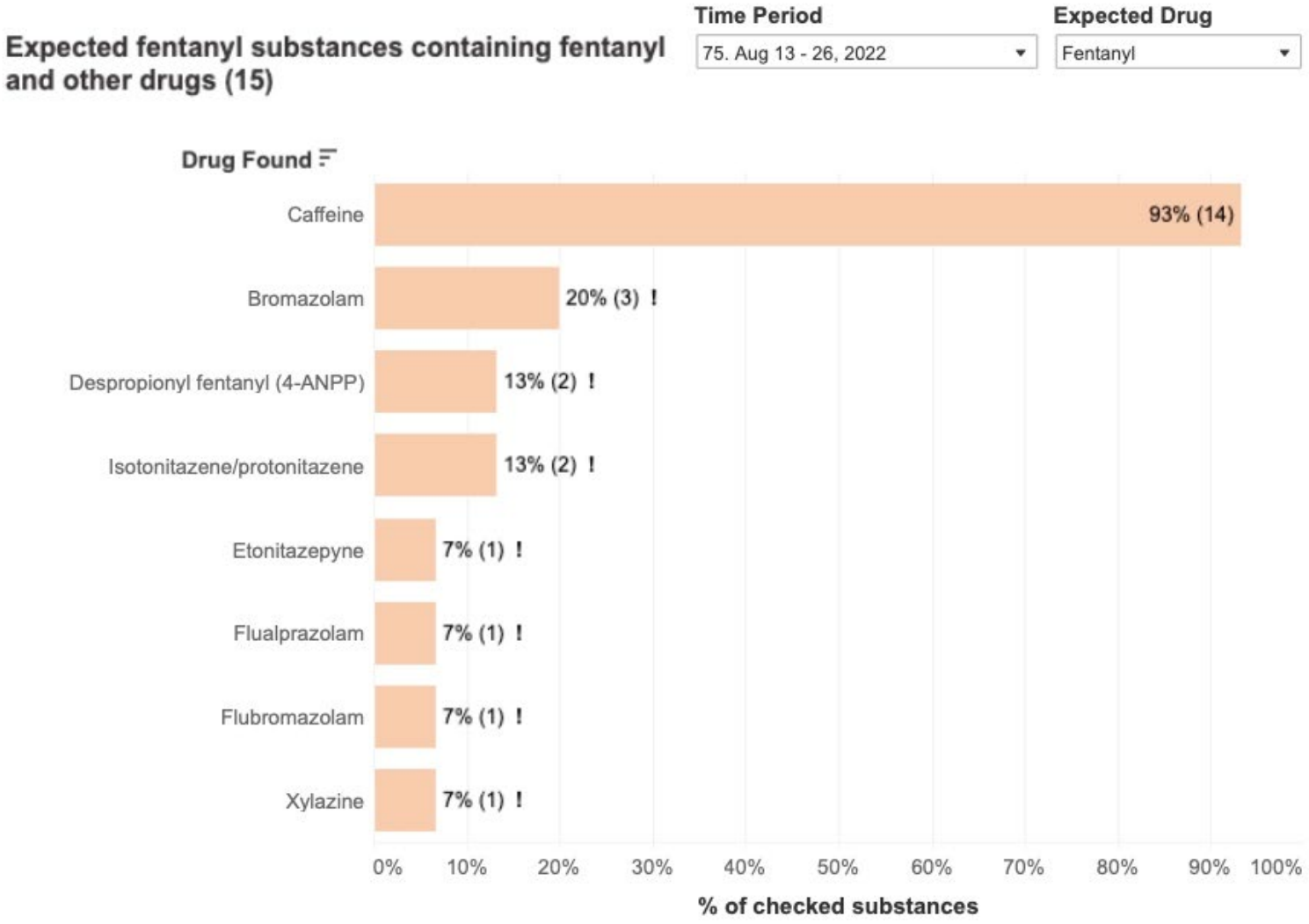
Benzo taper summary

- Benzo used for taper: Diazepam
- Dose: Taper initiated at 10 mg BID + 30 mg QHS
- Rate of decrease:
  - 2 mg decrease qweek from 50mg to 30mg (4%-7%↓ per week)
  - 2 mg decrease q2w from 30mg to 18mg (7-11% ↓ per 2 week)
  - 1 mg decrease q2w from 18mg to 0 (5% to 100% ↓ per 2 week)
- Dispensing:
  - Daily dispensing at pharmacy for first 2 months
  - Weekend carries for 3rd month
  - Q2day dispensing for 4th month
  - Weekly dispensing thereafter (covid + stable UDS)
- Treatment setting: RAAM clinic appointments
- Duration: 58 weeks
- Frequency of appointments: q 1-2 weeks depending on anxiety symptoms
- Adjunctive tx: Gabapentin, anxiety & trauma therapy, gambling therapy
- Monitoring: Urine toxicology, Connecting Ontario, letter to family doctor

Benzodiazepines as Contaminants



Novel Psychoactive Substances (NPS)

- Bromazolam
  - Brominated version of alprazolam
- Flualprazolam
  - Structurally similar to alprazolam
  - Often pressed into “Xanax bars”
- Flubromazolam
  - Effects lasting 12-18 hours
  - High tolerance to lower doses
  - Black outs and memory loss

(Orsolini et al, 2020)

Benzodiazepine withdrawal during initiation of OUD treatment

- Some patients may experience BZD withdrawal as they reduce or stop their fentanyl use
- Contaminant benzodiazepines may not show up on UDS
- Individualized approach
  - Consider BZD taper
  - Frequent follow up
  - Consider Gabapentin
  - Diazepam and methadone/buprenorphine daily observed and not increased concurrently
  - Document ++

Withdrawal vs. Relapse of Anxiety

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(Lader and Higgitt, 1986)

Additional Resources

- Ashton Manual
  - Benzoinfo.com
  - Several sample tapers
    - Alprazolam 6 mg with diazepam substitution
    - Diazepam 40 mg
    - Lorazepam 6 mg
    - Clonazepam 1.5 mg with diazepam substitution
- Mindshift App
- Bounce Back
- MindBeacon

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Thank you!