Benzodiazepines: Withdrawal and Tapering

Charlie Reznikoff, MD

Hennepin healthcare

Overview benzodiazepines

- Reminder of Benzo Pharmacology
- Benzo use/abuse patterns
- Benzo withdrawal
- Benzo tapers

Told through a bunch of cases!

Sedative/Hypnotics are Cross Tolerant

- Benzodiazepines
- Alcohol
- Z-drugs (Benzo-like sleeping aids)
- Barbiturates
- GHB
- Propofol
- Some inhalants
- Gabapentin? Pregabalin?

Examples of benzodiazepines

- Midazolam (Versed)
- Triazolam (Halcion)
- Alprazolam (Xanax)
- Lorazepam (Ativan)
- Temazepam (Restoril)
- Oxazepam (Serax)
- Clonazepam (Klonopin)
- Diazepam (Valium)
- Chlordiazepoxide (Librium)

How pharmacology affects withdrawal

- ***Potency***
  - Greater exposure to drug increases risk of withdrawal
- ***Duration*** of action
  - Continuous exposure to drug increases risk
  - Longer acting have delayed withdrawal onset
- ***Onset*** of action
  - Uncertain effect on withdrawal risk
- Active ***metabolites***
  - Self tapering properties

BENZODIAZEPINE (BZ) COMPARISON CHART

www.RxFiles.ca — Brent Jensen BSP — Jul (

Name: Generic -TRADE	Equivalent Dose/Class	Peak Level/ *ABSORPTION RATE*	Average Half-life (hr)	Active Metabolites	Comments (√ = therapeutic use)	INITIAL & MAX DOSE	USUAL DOSE RANGE	$ /Mont
SHORT ACTING: more **rebound** anxiety effect & **withdrawal reactions**, better **sedative/hypnotic**; preferred over long acting in **elderly** (**less accumulation**) & in patients with **liver disorders** (easier metabolized)								
Alprazolam -XANAX (0.25,0.5); (1[x]mg tab, TS 2[x]mg)	D 0.5mg Triazolo	1-2 hr *Medium*	12 (9-20)	Minor Oxidation [#]	√Anxiety, **Panic attacks** Severe **withdrawal** & some ? antidepressant effect **DIs: Level ↑ by:** diltiazem,Luvox, ketoconazole, grapefruit juice, nefazodone, Prozac, ritonavir; **↓ by:** theophylline.	0.25mg 4-10mg	0.25mg po tid 0.5mg po tid	1 1
Bromazepam -LECTOPAM (1.5, 3, 6mg tab)	D 3mg 2-Keto	1-4 hr *Medium*	20 (8-30)	Minor Oxidation	√Anxiety ? May exacerbate depression	3mg 30-60mg	3mg po hs 6mg po hs	1 1
Lorazepam -ATIVAN (0.5,1,2mg **po** tab; 0.5[x],1[x],2[x]mg **sl** tab; 4mg/ml **amp**[x])	D 1mg 3-Hydroxy	**PO** 1-4 hr **SL/IM** 1 hr **IV** 5-10 min *Medium*	15 (8-24)	None Conjugation [#]	√ **Anxiety**, Preanesthetic; Other: **sedative**, muscle relaxant,alcohol withdrawal;acute **mania**; **Fewer DI's**, √Status epilepticus -slower onset but longer duration vs diazepam;IM well absorbed	0.5mg 10mg	0.5mg po tid 1mg po tid 2mg po tid	1 1 1
Oxazepam -SERAX (10,15,30mg tab)	D 15mg 3-Hydroxy	1-4 hr *Medium*	8 (3-25)	None Conjugation	√ Anxiety, **alcohol withdrawal** Other: **sedative** Less affected by liver dysfunction;**Fewer DI's**	10mg 120mg	15mg po hs 30mg po hs 30mg po tid	1 1 1
Temazepam -RESTORIL (15,30mg cap)	X 10mg 3-Hydroxy	2-3 hr *Medium*	11 (3-25)	None Conjugation	√ **Sedative/hypnotic**; Other: anxiolytic May delay but not suppress REM sleep **Fewer DI's**	15mg 60mg	15mg po hs 30mg po hs	1 1
Triazolam -HALCION (0.125,0.25mg tab)	X 0.25mg Triazolo	1-2 hr *Rapid*	2 (1.5-5)	None Oxidation	√ Sedative/**hypnotic**; DI's as per alprazolam **Behavioral disturbances in elderly** **Prone to withdrawal / rebound effects**	0.125mg 0.5mg	0.125mg po hs 0.25mg po hs	1
LONG ACTING: less **rebound** symptoms;better choice **when tapering off of BZs** (e.g. clonazepam/diazepam);**withdrawal** may be **delayed** 1-2 wk **for 2-Keto group**; **bedtime** dose option for hypnotic & **anxiolytic** effect								
Chlordiazepoxide (5,10,25mg cap) -LIBRIUM	D 25mg 2-Keto	1-4 hr *Medium*	100	Yes Oxidation	√ Anxiety, preanesthetic, **alcohol withdrawal** Other: sedation; Slower onset vs diazepam	5mg 200-400mg	25mg po tid 50mg po tid	2 3
Clonazepam -RIVOTRIL (0.5,1,2mg tab)	D 0.25mg Nitro	1-4 hr *Rapid*	34 (19-60)	None Oxidation & Nitro reduction	√ Anticonvulsant, **Panic** attack Other: **sedative**, social phobia, akathisia, **acute mania**, restless leg syndrome & neuralgic pain	0.25mg 10-20mg Used for BZ withdrawal	0.5mg po tid 1mg po bid 2mg po tid	1 2 2
Clorazepate -TRANXENE (3.75,7.5,15mg cap)	D 10mg 2-Keto	0.5-2 hr *Rapid*	100 Inactive until Metabolized	Yes Oxidation	Hydrolyzed in GI → ↓ clorazepate level by **antacids** √ Anxiety, panic, alcohol withdrawal, seizures	3.75mg 60-90mg	3.75mg po bid 7.5mg po bid 15mg po bid	1 1 2
Diazepam -VALIUM (2,5,10mg **tab**; 10mg/2ml **amp**; 5mg/ml **rectal gel**; 10mg/2ml **emulsion inj**[x] DIAZEMULS)	D 5mg 2-Keto	**PO** 1-2 hr **IM** 1hr **IV** 8 min *Rapid*	100	Yes Oxidation	√Anxiety, **muscle relaxant**, seizures, **alcohol withdrawal** & preanesthetic; Other: sedative Quicker onset & **↓ duration** of action vs lorazepam, **IM** causes pain; **Diazemuls®** **IV** better tolerated	2mg 40mg Used for BZ withdrawal	2mg po tid 5mg po tid 10mg po tid	1 1 1
Flurazepam -DALMANE (15,30mg cap)	X 15mg 2-Keto	0.5-1 hr *Rapid*	100 (40-250)	Yes Oxidation	√ Sedative/**hypnotic**; Quick onset but **accumulates** →**hangover** →confusion, etc.	15mg 60mg	15mg po hs 30mg po hs	1 1
Nitrazepam -MOGADON (5,10mg tab)	U 2.5mg Nitro	0.5-2 hr *Medium*	30 (15-48)	None Nitro reduction	√ Sedative/**hypnotic**, myoclonic seizures	5mg 10mg	5mg po hs 10mg po hs	1 1

Side effects: **drowsiness**, dizziness, ataxia, **dependence**, CNS depression, disorientation, **psychomotor impairment**, confusion, aggression, excitement, **↑ falls & vehicle accidents in elderly** & anterograde **amnesia**.
Tolerance to sedative/hypnotic, muscle relaxant & anticonvulsant, but less **tolerance** for the anxiolytic & antipanic effects. No **cross-tolerance** with buspirone & SSRI'S; as well often lacks cross-tolerance with alprazolam

Duration predicts withdrawal onset

Midazolam… <1 hour duration, withdrawal begins same day

Lorazepam… 8 hours duration, withdrawal begins 36 hours

Clonazepam… 20 hours duration, withdrawal begins at one week

Active metabolites lessen withdrawal

- Diazepam, clorazepate and chlordiazepoxide (Valium, Tranxene, Librium) are metabolized to active compounds.
- These “active metabolites” then need to be broken down by the liver
- Active metabolites make the drug long acting and “self tapering,” a good thing for detox
- These meds are less likely to cause withdrawal (I am not endorsing use of these meds- many other risk!)
- People with liver disease and elderly do not effectively clear the active metabolites and can be sedated for days/weeks

Alprazolam is a wild card

- Alprazolam (Xanax) can have withdrawal at 2 days or at one week
- Unpredictable withdrawal severity and course
- Alprazolam withdrawal can be more severe, including psychosis
- Alprazolam withdrawal harder to treat due to incomplete cross tolerance with other benzos
  - Best option may be clonazepam

Benzo variables affecting withdrawal risk

- More potent benzo more risk withdrawal
- Short acting benzos withdrawal happens sooner
- Long acting more apt to increase tolerance but withdrawal happens later
- Active metabolites reduces risk of withdrawal due to self tapering
- Alprazolam is a wild card
- ***High dose continuous short acting very high risk for bad withdrawal***

58-year-old woman with anxiety and insomnia has been taking temazepam 30 MG nightly for 10 years. She does not drink alcohol or use any drugs of abuse. She has never had a seizure. She takes temazepam as prescribed. She wishes to discontinue temazepam and use other sleep aids. Which is the best choice for her benzo taper:

- 1. She does not need a benzo taper
- 2. Lower dose to 15 mg nightly for 2 weeks then discontinue
- 3. Switch to clonazepam 1 mg nightly for two weeks then discontinue
- 4. Switch to clonazepam 2 mg nightly for two weeks, then 1 mg nightly for two weeks, then discontinue

Continuous exposure to benzos

- Short/medium acting benzos, taken daily, with a daily “wash out” period, do not develop tolerance, and do not need withdrawal
- Continuous daily exposure of benzos throughout the day is required for development of tolerance
- Be mindful of cross tolerances with multiple sedatives (including alcohol)
- Bottom line:
  - Nightly temazepam or Zdrug, once daily lorazepam, do not require tapers

32-year-old woman with PTSD presents to the Emergency Department sedated and ataxic. The next day she reported to blacking out on Xanax. Repeated similar episodes are noted in the chart. The PMP demonstrates that she has a monthly prescription of alprazolam 1 MG #30. She recently picked up, and past episodes occurred after other rx pick ups. She has no history of seizures. She does not use alcohol. What is the best taper?

- 1. She does not need a benzo taper
- 2. Lower prescription to Alprazolam 1 MG #60 for one month, then #30 the next month, then 0.5 MG #30 then discontinue
- 3. Switch to clonazepam 1 mg TID for two weeks, then 0.5 mg TID two weeks, then 0.25 TID two weeks, then discontinue
- 4. Phenobarb load and taper over 10 weeks, 10% per week

Binge benzo use

- Intermittent binges of benzos, with long periods of abstinence from sedatives between do not require tapers.
- Benzo binge pattern is common among people with other addictive disorders
- Tapers provide ongoing prescriptions which will also be used not-as-directed in the binge fashion
- Instead, control their source of benzos and treat underlying mental health conditions
- Account for cross tolerance with alcohol and other sedatives.
- Bottom line:
  - Do not taper brief binge benzo users. It is not necessary and won't be taken as prescribed anyway

44-year-old woman with severe generalized anxiety disorder with panic who has taken 1 mg BID clonazepam daily for 10 years. She takes meds as prescribed. Recently she ran out while on vacation and had severe anxiety for one week before she got her next prescription. She now wants to stop. She does not drink alcohol and has never had a seizure disorder. What is the best taper?

- 1. She does not need a benzo taper
- 2. Taper is not medically necessary, but a brief taper may help the patient transition to nonbezo treatment
- 3. Design a 10-12 week taper using ten percent dose reductions every week
- 4. Reassure her that there is no reason to discontinue the clonazepam prescription

Chronic low dose benzo users

- Patients with steady chronic low dose benzos, no alcohol and no prescriptions misuse typically have such minimal tolerance that the benzos do not pose a medical risk if stopped abruptly.
- Such patients often do not tolerate abrupt disconsolation due to rebound anxiety. A brief taper may be appropriate as they adjust to nonbenzo options
- Do not let the “comfort taper” drag out! Anxious patients can become fixated on the taper and feel frozen at their dose. Reassure them and move ahead!
- Bottom line:
  - Low dose benzo users with no other risk need a taper only for comfort

44-year-old woman with severe generalized anxiety disorder with panic who has taken 4 mg BID clonazepam daily for 10 years. She takes meds as prescribed. Recently she ran out while on vacation and had severe anxiety for one week before she got her next prescription. She now wants to stop. She does not drink alcohol and has never had a seizure disorder. What is the best taper?

- 1. She does not need a benzo taper
- 2. Taper is not medically necessary, but a brief taper may help the patient transition to nonbezo treatment
- 3. Design a 10-12 week taper using ten percent dose reductions every week
- 4. Reassure her that there is no reason to discontinue the clonazepam prescription

Outpatient benzo tapers

- Patients with low risk of abuse but high risk of withdrawal can taper as an outpatient
- There is no perfect recipes for tapering benzos
- Take 3-4 months with small steps each week
- Pause if necessary
- Help the patient count and plan her doses (pill box) to avoid overuse
- Bottom line:
  - The outpatient benzo taper is for the patient with low risk of abuse but high risk of withdrawal

50-year-old man with obesity, HTN, tobacco use and severe alcohol use disorder stopped drinking alcohol 10 days ago when he was prescribed lorazepam 1 MG TID #30 by another provider. He used all of it and is out of medications. He does not want to drink again. He has not had seizures. Other than the last 10 days he has not had alcohol abstinence in 25 years. What is the best taper?

- 1. He does not need a benzo taper
- 2. Switch to Librium 60 MG daily , prescribed 14 days and reevaluate
- 3. Phenobarb load and taper over 10 weeks, 10% per week
- 4. Send to detox, an addiction treatment program capable of detox, or an emergency department for medical detox

Alcohol use disorder and benzos

- Patients who might have been at risk of alcohol withdrawal are similarly at risk of benzo withdrawal if they switch from one to the other
- This is most problematic for short or medium acting benzos (less problematic for diazepam and chlordiazepoxide)
- If The alcohol use warrants detox, that remains the best options after a switch to medium acting benzos.
- People with untreated alcohol use disorder are unlikely to manage outpatient benzo tapers
- Bottom line
  - Patients with SUD who switch from alcohol to benzos on their own probably need a structured detox

29 year old man with sever opioid use disorder on buprenorphine maintenance runs out of bup and attains an unknown quantity of illicit benzos. He reports three weeks of very heavy benzo use resulting in black outs and accidents. He ran out of benzos and presents to you sober within one day of last benzo. He does not drink alcohol and has not had seizures. He is not using opioids. He wants to restart buprenorphine. What is the best taper?

- 1. He does not need a benzo taper
- 2. Switch to Librium 60 MG daily , prescribed 14 days and reevaluate
- 3. Phenobarb load and taper over 10 weeks, 10% per week
- 4. Send to detox, an addiction treatment program capable of detox, or an emergency department for medical detox

Intense benzo use in an OUD patient

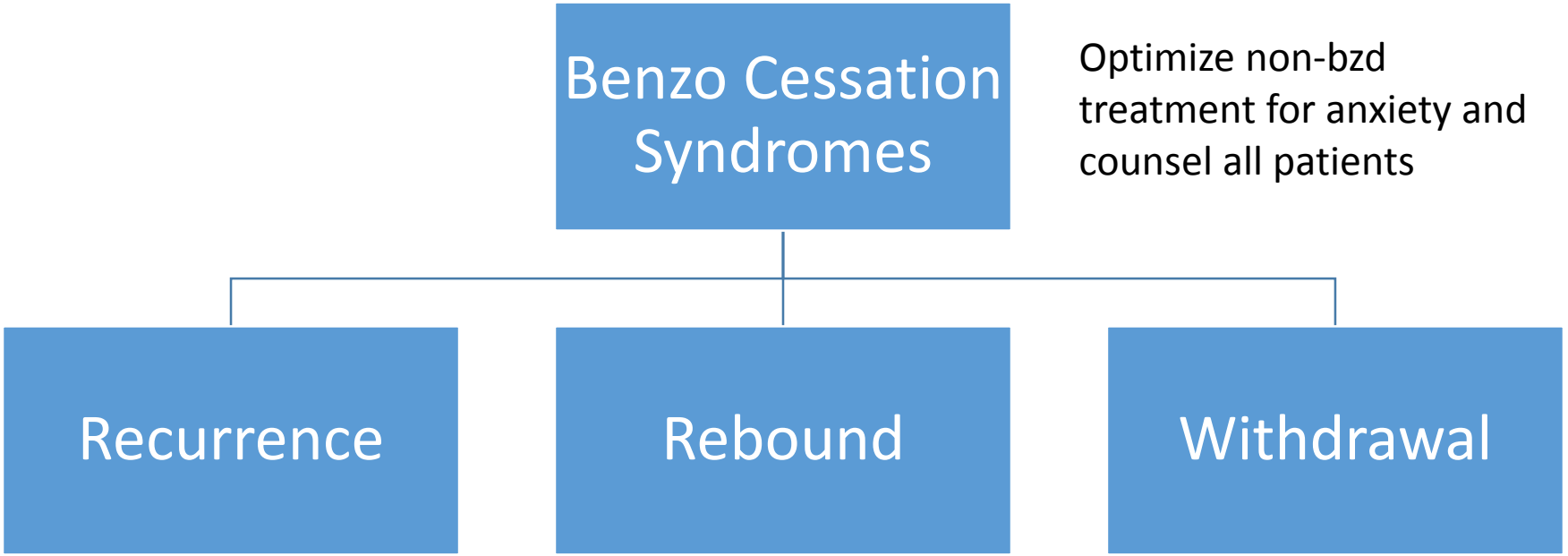
- Patients with OUD will at times binge heavily on benzos
- Such binges, less than one month (really less than three months!) do not cause enough tolerance to trigger withdrawal
- Be mindful of the patients accuracy and also preexisting alcohol use
- Bottom line
  - Sustained heavy benzo use required for withdrawal risk

35-year-old woman with seven emergency department visits for trauma, exposure, sexual assault, sedation and intoxication over the past 6 months is brought to your office by her mother. Mom tells in you that the patient obtains illicit benzos on the internet. The patient seems impaired almost every day. The mom cannot convince the daughter to stop and is worried for her safety. The daughter appears sedated and disinhibited, trying to leave the clinic room. She once had a seizure of unknown cause. What is the best taper?

- 1. She does not need a benzo taper
- 2. Use motivational interviewing to convince the patient to voluntarily go to a facility that can perform medical detox, and pursue addiction treatment.
- 3. Place a 72-hour hold, transport to a facility that can perform medical detox, and pursue commitment.
- 4. Give phenobarb load and prescribe to mom a phenobarbital taper to administer over 10 weeks, 10% per week

Benzo Use Disorder

- True benzo use disorder is rare but catastrophic
- BUD patients are high risk from using but also high risk of withdrawal
- They cannot execute a home taper on their own
- They need structured setting and may need commitment
- Bottom line
  - Identify and intervene on benzo use disorder patients


Benzo Cessation Syndromes
Optimize non-bzd treatment for anxiety and counsel all patients
Recurrence
Rebound
Withdrawal
After cessation of benzos, the underlying anxiety disorder recurs
Rebound- 2 weeks heightened underlying anxiety, troubling but not life threatening. No physiologic signs
True withdrawal is life threatening and accompanied by physiologic signs

True benzo withdrawal is life threatening and requires close monitoring and detoxification

- Hypertension, tachycardia, arrhythmias
- Diaphoresis, tremors
- Seizures
- Delirium
- Psychosis

Likelihood of true benzo withdrawal

- Past withdrawal (including seizure)
- Short acting meds
- Round the clock use of bzds
- Concomitant heavy alcohol use
- Concomitant medical illness
- High dose

Risk assessment for withdrawal

- Benzo exposure sufficient for physiologic dependence is highly variable!
    - 6 months daily use moderate dose
    - 3 months daily use 3X normal dose
    - Use throughout the day
    - Any duration in an alcohol/barbiturate dependent patient

Timing of benzo withdrawal

- Onset of withdrawal from time from last dose:
    - Short acting: 2-3 days
    - Long acting >7 days
    - Alprazolam: wild card

Patients with BUD are notoriously poor historians, and unreliable pill takers

They are not lying!
They just don’t remember

Benzo detox

For those at risk for true benzo withdrawal

No hx addiction

Leave bzd the same and slowly decrease by 10% increments over months, or over 4-6 weeks. 8 weeks, max 12 weeks!

Failed first attempt

Change bzd to long activing, shorten prescription duration, increase visit frequency, and try again

BUD, or high risk

Inpatient therapy at a facility with medical detox; often require commitment; may want to restrict providers

Taper Tips: Rxs

- Do not use multiple benzos at once
- Leave the buprenorphine alone (unless unsafe)
- Consider gabapentin low dose, carbamazepine
- Anti anxiety meds that helps sleep: mirtazapine, doxepin, ?trazodone?
- I avoid diphenhydramine and hydroxyzine (delirium)
- SSRI are acceptable
- Referral to therapist!

NEJM March 23, 2017 “treatment of benzodiazepine dependence” Soyka

You are consulted to the ICU on a 44 year old woman on hospital day 5 who is delirious and intubated, in four point restraints. She continues to "buck" despite maximum dose propofol plus moderate dose midazolam drip. She has HTN and tachycardia and rising CK, but no known medical cause for delirium after extensive work up. He boyfriend admits she abuses pills, and lately she has escalated, but he is not sure which pill or how much. She does not drink alcohol. Urine toxicology on admission shows alprazolam. What do you recommend?

- 1. This is not benzo withdrawal. She does not need a benzo taper
- 2. Already on high dose propofol and midazolam drip she is covered for withdrawal, continue care as is and follow.
- 3. Begin slow midazolam taper, followed by propofol taper
- 4. Increase the midazolam drip, or switch to lorazepam drip and titrate up until the patient is calm, then begin tapering

Dealing with serious benzo withdrawal

- You cannot start weaning until you have withdrawal under control
- Common error to underestimate the benzo needs to settle the patient down
- Once controlled, tapering too fast will lead to the return of withdrawal symptoms
- For the most serious cases of benzo withdrawal (requiring high doses to control) avoid long acting and meds with metabolites, which will build up
- Bottom line:
  - True benzo withdrawal sometimes requires eye popping doses of meds to treat!

I am not going to talk about which benzo to use (or phenobarb) because if it is that complicated we should be seeking help!

Summary

- Benzo withdrawal is not that common
  - Binge users, new users, intermittent users, routine regular dose use, none of these are likely to get true benzo withdrawal
  - Benzo rebound is problematic and may benefit from a brief taper
  - Benzo withdrawal without benzo use disorder can be weaned outpatient
- True benzo withdrawal, and true benzo use disorder are very serious when they happen
  - It requires structured environment sometimes commitment for BUD
  - Active benzo withdrawal delirium requires high dose benzos and a careful inpatient taper