Sedative Hypnotic Withdrawal

Keerthi Vejerla, MD
Addiction Psychiatry Fellow
University of Utah

Overview

- Education on benzodiazepines – for patients and prescribers
- For prescribers
- Withdrawal symptoms and management
- Tapering strategies
- Medications to avoid in recovery

THERAPEUTIC ACTIONS (IN SHORT TERM USE)

Action	Clinical Use
Anxiolytic - relief of anxiety	- Anxiety and panic disorders, phobias
Hypnotic - promotion of sleep	- Insomnia
Myorelaxant - muscle relaxation	- Muscle spasms, spastic disorders
Anticonvulsant - stop fits, convulsions	- Fits due to drug poisoning, some forms of epilepsy
Amnesia - impair short-term memory	- Premedication for operations, sedation for minor surgical procedures

Other clinical uses, utilising combined effects:

- Alcohol detoxification
- Acute psychosis with hyperexcitability and aggressiveness

Adverse effects

- Over sedation
- Memory impairment (anterograde amnesia)
- Paradoxical stimulant effects
- Drug interactions
- Depression/emotional blunting
- Elderly
- Pregnancy
- Tolerance and dependence

Tolerance to Side Effects

- Tolerance develops to
  - Sedation
  - Anxiolytic effects
  - psychomotor effects

- Whether tolerance develops to cognitive side effects remains controversial.

Dependence

1. Therapeutic dose dependence

- Taken as prescribed for several years
- "Need" BZD's to carry out daily activities
- Continued despite original indication disappeared
- Difficulty stopping/decreasing due to withdrawal symptoms
- Develop anxiety between doses

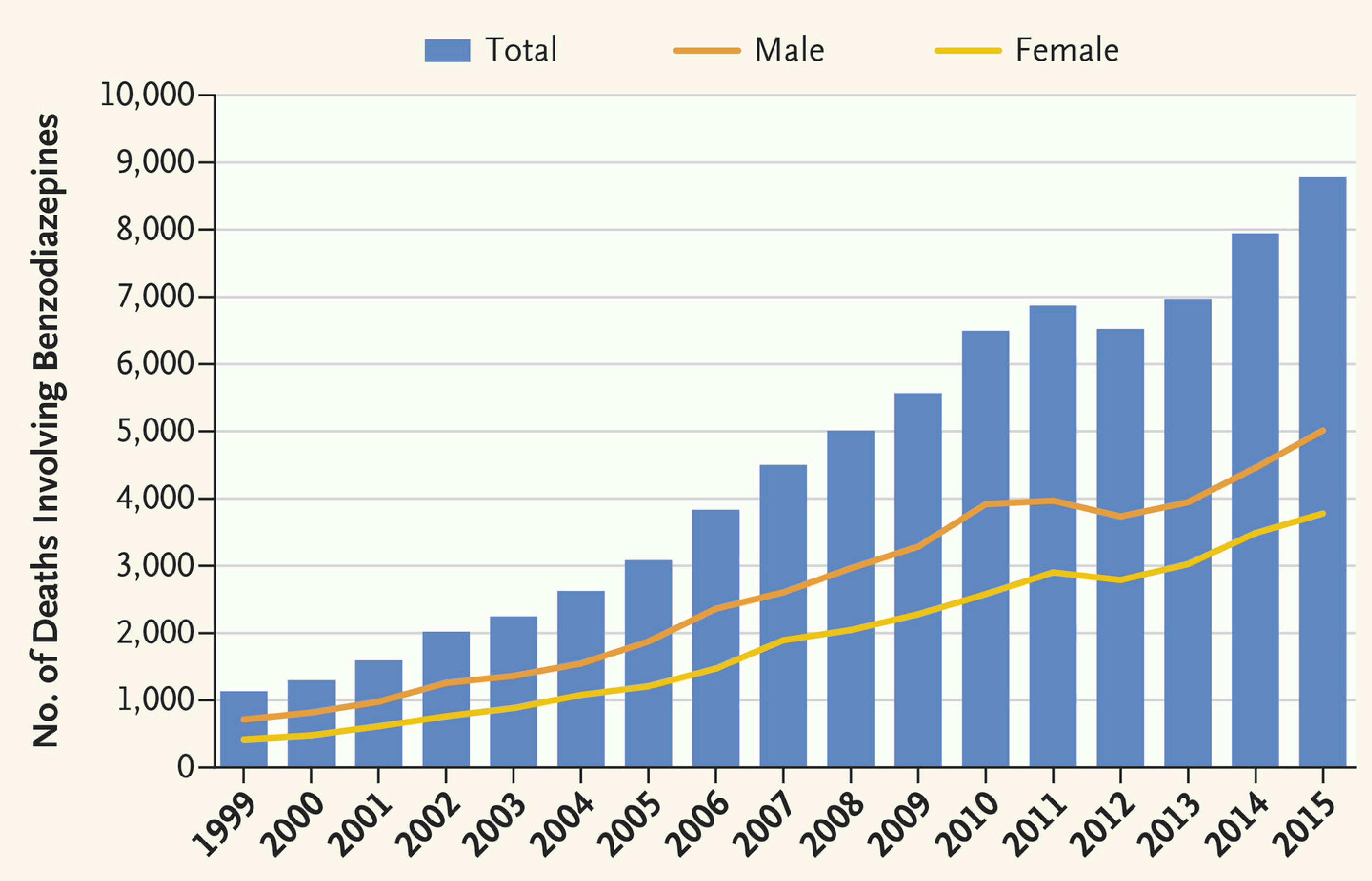
2. Prescribed high dose dependence

3. Recreational use/abuse

Risk factors for dependence

- High doses (2 – 3 weeks) vs low doses (6 – 8 months)
- Longer duration (approx. 10 – 30% of long-term users develop dependence)
- High potency (Xanax, Ativan, Klonopin, Triazolam)
- Short half-life
- Long-term use (6 – 12 months) is not synonymous with dependence.
- A special characteristic of benzodiazepines is that physical and mental dependence can develop in the absence of tolerance (low-dose dependence).

FOR PRESCRIBERS



Total
Male
Female
No. of Deaths Involving Benzodiazepines
10,000
9,000
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
0
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015

Total 24-hour dose levels for the most commonly used benzodiazepines

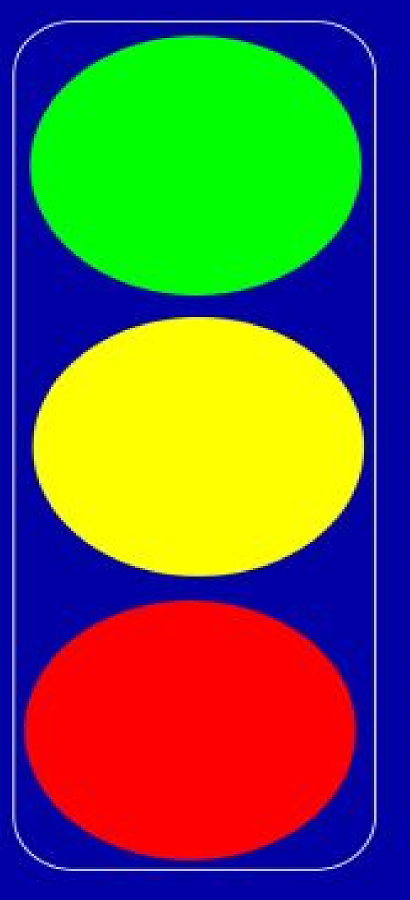
Total 24-hour Dose Levels for the Most Commonly Used Benzodiazepines

	Green Light Zone	Yellow Light Zone	Red Light Zone
Lorazepam	Up to 5 mg/d	> 5 mg up to 10 mg/d	> 10 mg/d
Clonazepam	Up to 2 mg/d	> 2 mg and up to 4 mg/d	> 4 mg/d
Diazepam	Up to 20 mg/d	> 20 mg up to 40 mg/d	> 40 mg/d
Alprazolam	Up to 2 mg/d	> 2 mg up to 4 mg/d	> 4 mg/d
Alprazolam XR	Up to 3 mg/d	> 3 mg up to 6 mg/d	> 6 mg/d

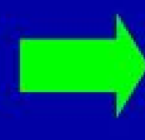
RL Dupont Curr Med Res Opin. 2005

CSAM 2016

Determining if Benzodiazepine Use is Safe or Risky (Dupont)

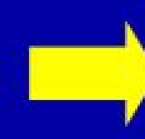


Green light zone: 1/2 or less of maximum dose listed in PDR



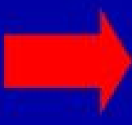
Nonaddictive patients with anxiety take benzodiazepines at low and stable doses

Yellow light zone: 1/2 up to maximum dose listed in PDR



Not many anxious patients in this zone

Red light zone: above maximum dose listed in PDR



Addictive patients reach this zone of dosing very quickly

PDR=*Physicians' Desk Reference.*

Should be avoided…

- PTSD, OCD
- Chronic respiratory disease (COPD, sleep apnea)
- Receiving other CNS depressants (opioids)
- Substance use disorder
- History of TBI
- Dementia
- Elderly

Prescription use behavior questionnaire

- Use more than prescribed
- Use more often than prescribed
- Called for early refills
- Rx obtained from > 1physician
- Used when feeling upset
- Used to get high/euphoria

ALWAYS CHECK DOPL BEFORE OR WHILE PRESCRIBING BENZODIAZEPINES.

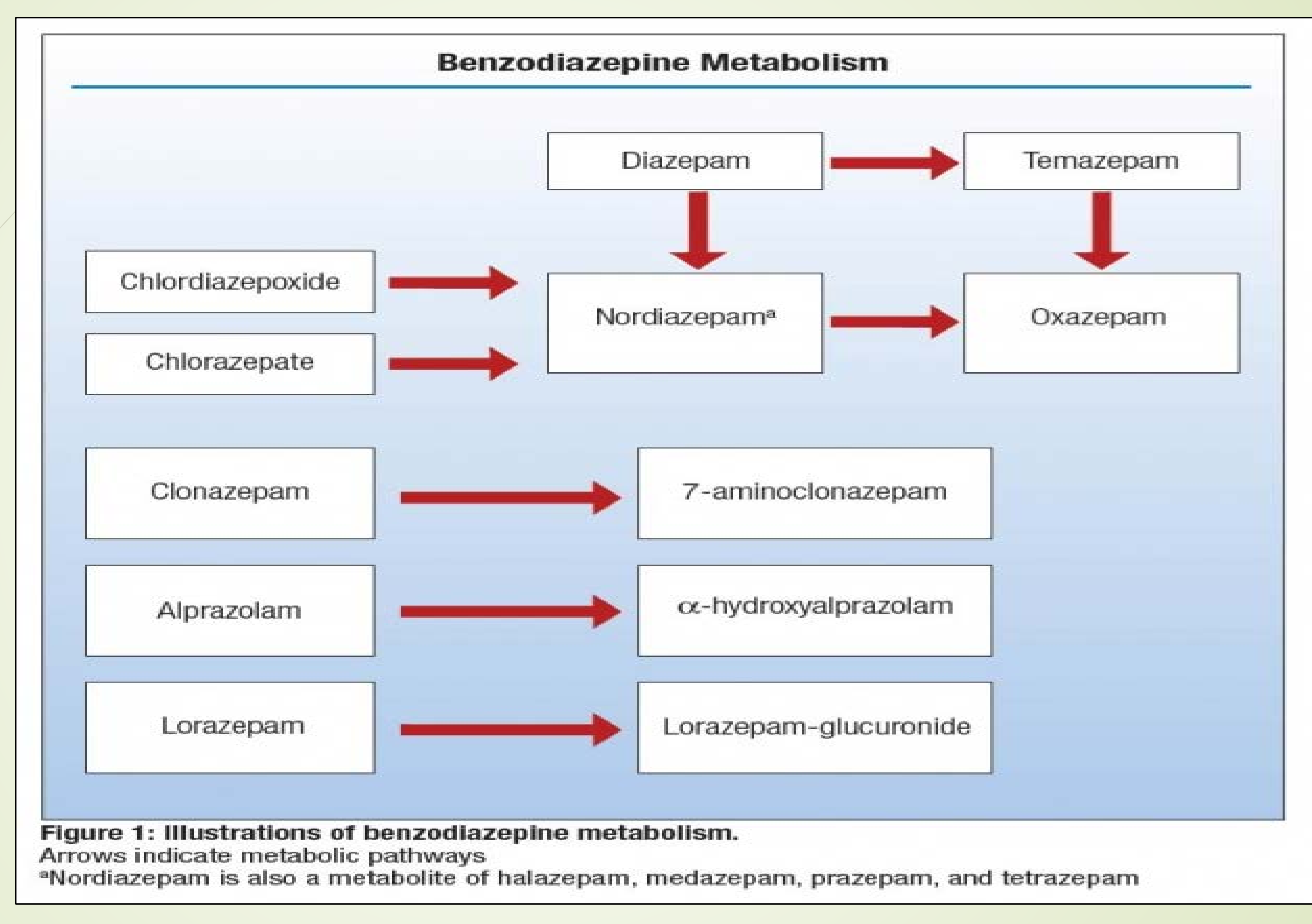


Figure 1: Illustrations of benzodiazepine metabolism.
Arrows indicate metabolic pathways
[a]Nordiazepam is also a metabolite of halazepam, medazepam, prazepam, and tetrazepam

FALSE POSITIVES

- Sertraline
- Oxaprozin – NSAID used for RA and OA (tested positive for diazepam)

Drug interactions

- Antidepressants (e.g. amitriptyline, doxepin)
- Major tranquillizers
- Neuroleptics (e.g. prochlorperazine [Compazine], trifluoperazine
- Anticonvulsants (e.g. phenobarbital, phenytoin [Dilantin], carbamazepine
- Sedative antihistamines (e.g. diphenhydramine [Benadryl], promethazine [Phenergan]),
- Opiates (heroin, morphine, meperidine), and,

***MOST IMPORTANTLY: ALCOHOL**

Equivalency chart

Drug	Dose
Alprazolam	0.5 mg
Chlordiazepoxide	25 mg
Clonazepam	0.5 mg
Diazepam	10 mg
Lorazepam	1 mg
Temezepam	20 mg
Zaleplon (Sonata)	20 mg
Zolpidem (Ambien)	20 mg
Eszopiclone	3 mg

WITHDRAWAL SYMPTOMS

Acute withdrawal

- Increased anxiety, panic attacks (temporary)
- Vivid dreams, insomnia, nightmares
- Sensory hypersensitivity, hallucinations, illusions and perceptual distortions
- Depression, aggression and obsessions
- Muscle stiffness, tension headache, tremor, jerks, spasms
- Problems with balance
- Seizures
- Psychosis and delirium
- **COURSE OF WITHDRAWAL: wax and wane**

Supportive medications

- Antidepressants (TCA's – amitriptyline, doxepin and SSRI's)
- Beta blockers – propranolol 10 mg TID
- NO barbiturates, chloral hydrate, Ambien/sonata/lunesta
- Insomnia – TCA's, antihistamines, gabapentin, pregabalin

Protracted withdrawal symptoms

Symptoms	Usual Course
Anxiety	- Gradually diminishing over a year
Depression	- May last a few months; responds to antidepressant drugs
Insomnia	- Gradually diminishing over 6-12 months
Sensory symptoms: tinnitus, tingling, numbness, deep or burning pain in limbs, feeling of inner trembling or vibration, strange skin sensations	- Gradually receding but may last at least a year and occasionally several years
Motor symptoms: muscle pain, weakness, painful cramps, tremor, jerks, spasms, shaking attacks	- Gradually receding but may last at least a year and occasionally several years
Poor memory and cognition	- Gradually receding but may last at least a year and occasionally several years
Gastrointestinal symptoms	- Gradually improving but may last a year and occasionally several years

TAPERING STRATEGIES

Benzodiazepine discontinuation factors

- Duration of use (6 months vs 1 month)
- Dose
- Rate of taper
- Half-life

Tapering strategies

- Gradually taper the original benzodiazepine

OR

- Substitute with a longer-acting benzodiazepine then gradually taper

OR

- Taper to lower dose of original benzodiazepine then switch to a long acting benzodiazepine.

ASHTON MANUAL (benzo.uk.org)

1. Taper over Months:
   1. Convert to longer acting agent like Clonazepam or Diazepam
   2. Taper gradually while starting alternative therapies if needed (months)
   3. Rebound Psych meds for Anxiety/Sleep

2. Use of Anticonvulsants:

Use of anticonvulsants in benzodiazepine withdrawal.

- Pages KP, Ries RK: Use of anticonvulsants in benzodiazepine withdrawal. American Journal on Addictions 7(3):198-204, 1998 .
- Ries RK et al;Journal of Psychoactive Drugs 23(1):73-76, 1991.

   1. Start high dose Depa or Carba, or Gaba
   2. Taper Benzo by 1/3 each day til DC
   3. Continue Anticonvulsant for at least one month, longer better.
   4. Check level of Depa and Carba after a week or two
   5. Start SSRI's or other for Dep/Anxiety

CSAM 2017

Use of Anticonvulsants in Benzodiazepine Withdrawal.

- Pages KP, Ries RK: Use of anticonvulsants in benzodiazepine withdrawal. American Journal on Addictions 7(3):198-204, 1998.
- Ries RK et al;Journal of Psychoactive Drugs 23(1):73-76, 1991.

1. Start high dose Depakote 500 tid
   or Carbamazepine 200 tid,
   or Gabapentin 800 tid
2. Taper Benzo by 1/3 each day til DC
3. Continue Anticonvulsant for at least one month, longer better.
4. Check level of Depa and Carba after a week or two
5. Start SSRI's or other for Dep/Anxiety
6. If dependent on only short acting agents- alprazolam etc, might use a one day conversion to clonazepam or diazepam then taper 1/3rd dose each day

These are case series NOT RCT's

Minimal educational interventions

- Discontinuation education letter/pamphlet.
- Single consultation with clinician to discuss risks of long term benzodiazepine use and benefits of discontinuation
- Self help instructions (e.g. sleep hygiene)
- Prescribers could be encouraged or required to check their state's prescription drug monitoring program (PDMP) before prescribing benzodiazepines

Voluntary support groups (self help groups)

Management of Benzodiazepine (BZD) Withdrawal.

Table 5. **Management of Benzodiazepine (BZD) Withdrawal.**

Situation	Treatment Approach	Level of Evidence
Approach to BZD dependence in general	Gradual withdrawal over a period of several weeks or months	High
Use of several BZDs or sedatives	Switch to use of only one BZD for detoxification (diazepam)	Good
Choice of BZD for detoxification	Switch to a long-acting BZD (diazepam)	Low
BZD withdrawal in a patient receiving opioid maintenance therapy	Adjustment of opioid dose to prevent opioid withdrawal; switch to a partial agonist (buprenorphine)	Good for adjustment of opioid dose; moderate for switch to partial agonist
Concomitant pharmacotherapy for BZD withdrawal	Carbamazepine, 200 mg twice a day	Moderate
Sleep disorders	Antidepressants, antihistaminergic drugs, melatonin; improved sleep hygiene, sleep restriction, relaxation techniques	Moderate
Other drugs for treatment of withdrawal symptoms	Pregabalin, gabapentin, beta-blockers; flumazenil	Low for pregabalin, gabapentin, and beta-blockers; experimental for flumazenil
Psychotherapy	Cognitive behavioral therapy and other approaches	Good

Soyka M. N Engl J Med 2017;376:1147-1157.

In September 2017, the FDA advised clinicians treating opioid use disorder not to withhold medication-assisted treatment with buprenorphine or methadone in patients concurrently prescribed benzodiazepines, arguing that the benefits of opioid-agonist therapy outweigh the risks of combining these opioids with benzodiazepines.

MEDICATIONS TO AVOID IN RECOVERY

1. Any alcohol containing liquid medications/OTC (Nyquil)
2. Sedative hypnotic medications – BZD's, Z drugs, Soma, Barbiturates
3. Opioid medications – Codeine, methadone, tramadol, buprenorphine
4. Stimulant medications – Ritalin, Adderall
5. Cannabinoids – Marinol, Cesamet