RUTGERS Project ECHO®

Management of Chronic Benzodiazepine Use/Disorder in Patients with Opioid Use Disorder

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RUTGERS New Jersey Medical School

State of New Jersey DHS Department of Human Services

MEDICATION-ASSISTED TREATMENT CENTERS OF EXCELLENCE

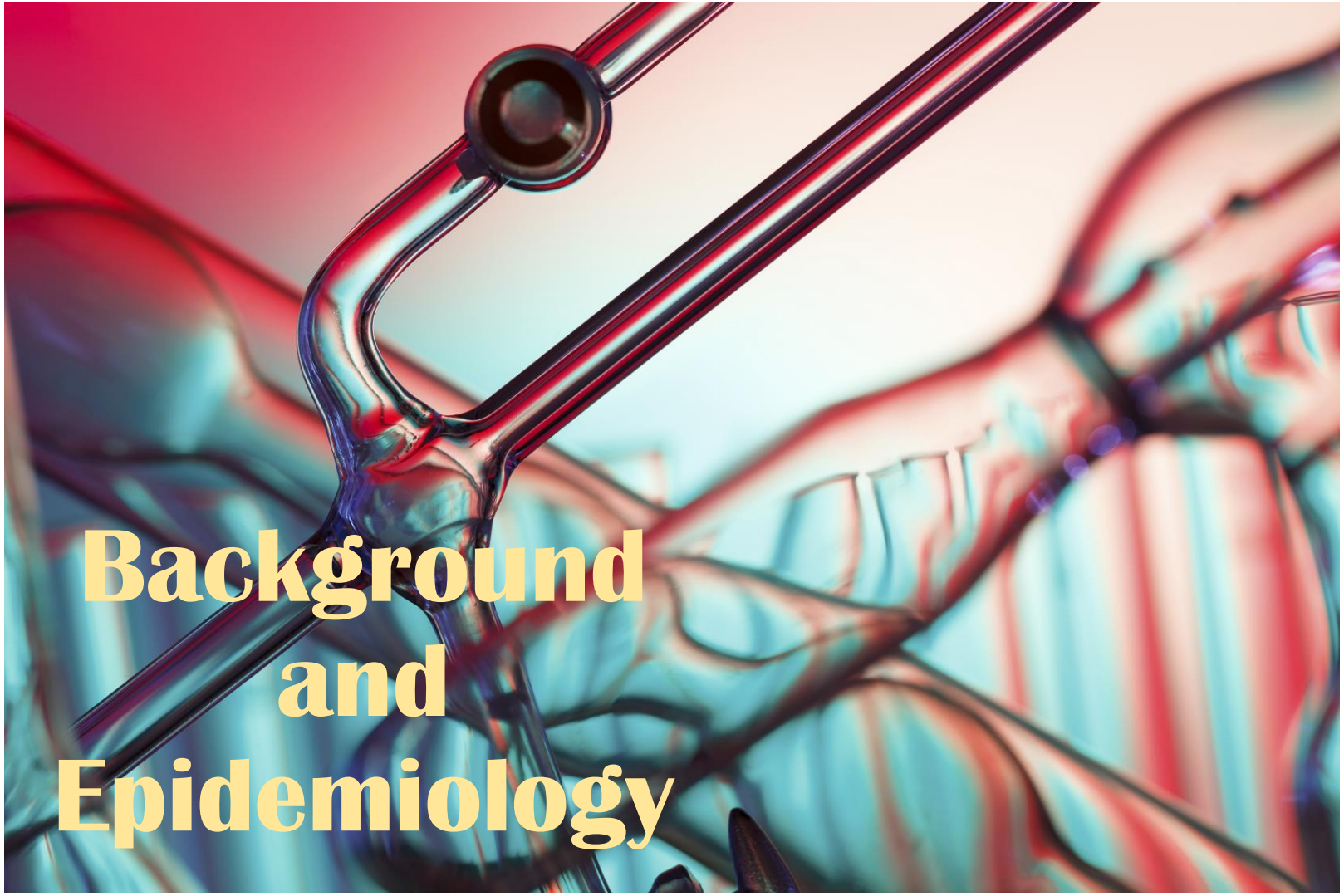
RUTGERS Robert Wood Johnson Medical School

Disclosures

- No disclosures

Learning Objectives

- Understand the epidemiology and prevalence of benzodiazepine (BZD) use/disorder, with a focus in those with opioid use disorder (OUD)
- Explain the mechanism of action of chronic benzodiazepine use and its association with dependence
- Review the literature evaluating outcomes of those patients using benzodiazepines who are on medications for opioid use disorder (MOUD)
- Understand the strategies helpful to assess and treat patients with OUD with co-morbid benzodiazepine use disorder


Background
and
Epidemiology

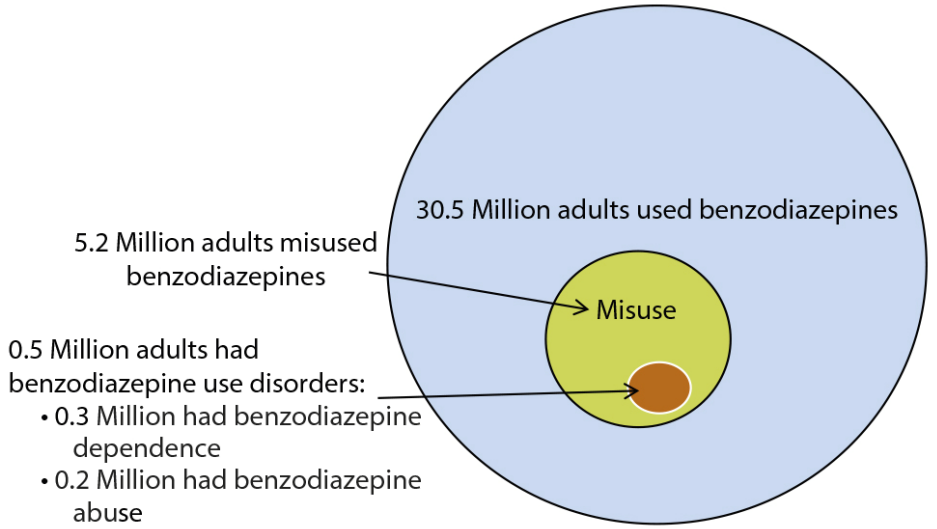
Substance Use Disorders – DSM-5

Image from: https://www.verywellmind.com/dsm-5-criteria-for-substance-use-disorders-21926

Benzodiazepine Use, Misuse → Disorder

National Surveys on Drug Use and Health

Figure 1. Benzodiazepine Use, Misuse, and Use Disorders Among Adults in the United States: Annual Averages, 2015–2016[a]

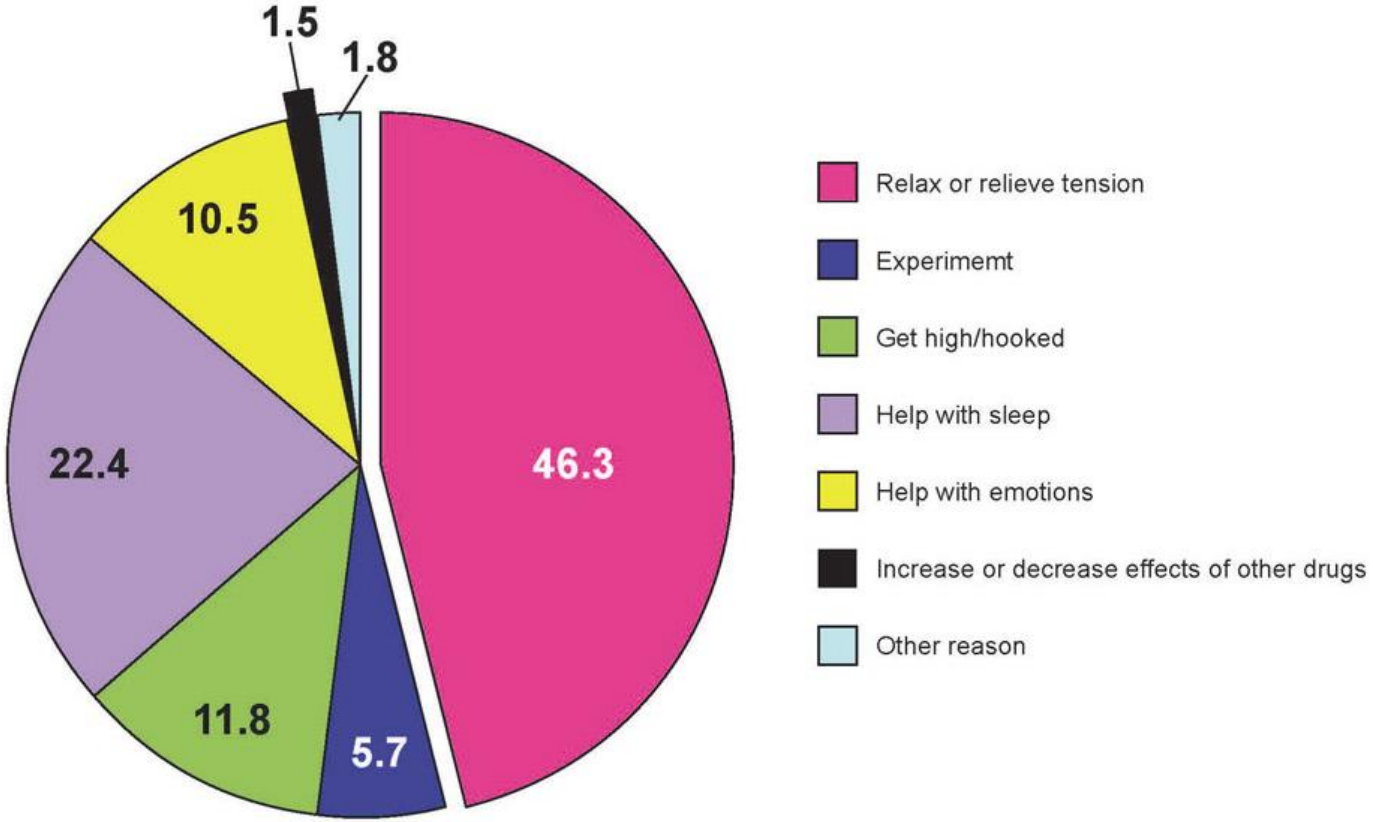


[a]Circles are approximately proportionally sized by area.

Blanco C, et al. *J Clin Psychiatry.* 2018 Oct 16;79(7):18m12174;

- Younger users
- Male sex
- Non-Hispanic Black/other
- Less than high school education
- Uninsured
- Part-time employed/unemployed
- Single
- Family income <$50,000
- Residing in a metro area
- Insurance status
- ER visits
- Concurrent mental health/substance use disorder

Rationale for BZD Misuse



https://www.drugabuse.gov/news-events/science-highlight/research-suggests-benzodiazepine-use-high-while-use-disorder-rates-are-low
Blanco C, et al. *J Clin Psychiatry*. 2018 Oct 16;79(7):18m12174.

Rationale for Combined Use and Prevalence in Patients with OUD

Social determinants of health (SDOH)?

- High levels of psychological distress
  - Depression and Anxiety
- Insomnia / sleep disturbances
- Treat withdrawal of other substances
- Treatment of protracted withdrawal
- Synergistic euphoric effects

- Lifetime prevalence of BZD use of 67% in buprenorphine-treated patients
  - Current prevalence:
    - Non-problematic: 15.3%
    - BZD abuse: 6.5%
    - Dependence: 24.1%

Lintzeris, N, et al. *Am J Addict*. Jan-Feb 2010;19(1):59-72.
Lavie, et al. *Drug Alcohol Depnd*. 2009;99:338-44.

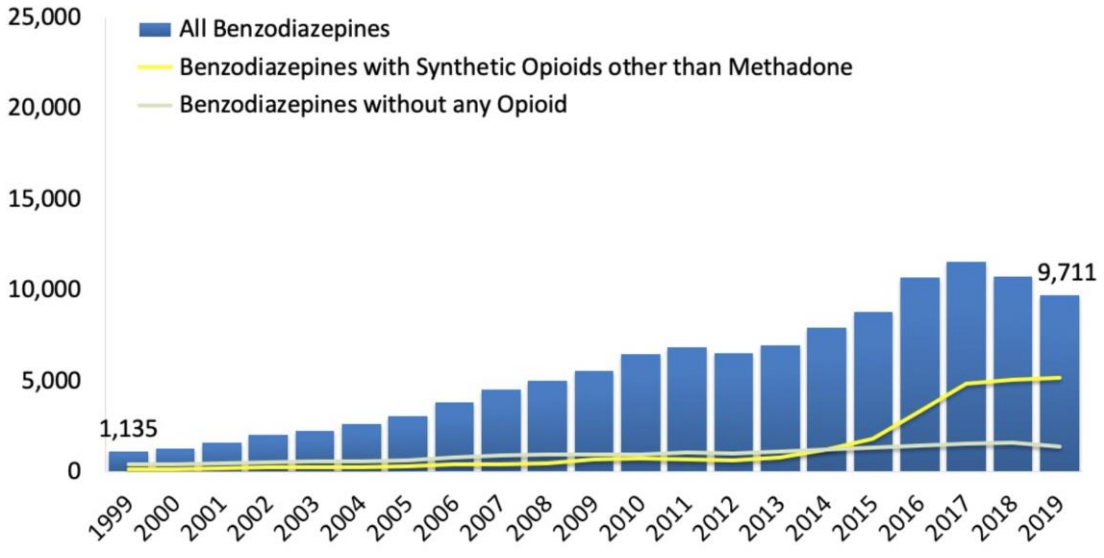
Co-Occurring OUD with BZD Misuse (+/- Use Disorder) vs. BZD Use Without Misuse

Characteristic	BZD Use vs. No Use	BZD Misuse (No Disorder) vs. BZD Use Without Misuse	BZD Misuse (With Disorder) vs. BZD Use Without Misuse
Heroin Use and Disorders	11.2	5.8	23.6
Rx Opioid Misuse and Use Disorders	27.7	3.6	31.9

Blanco C, et al. *J Clin Psychiatry*. 2018 Oct 16;79(7):18m12174.

Overdoses Involving Benzodiazepines

Figure 8. National Drug Overdose Deaths Involving Benzodiazepines*, by Opioid Involvement, Number Among All Ages, 1999-2019

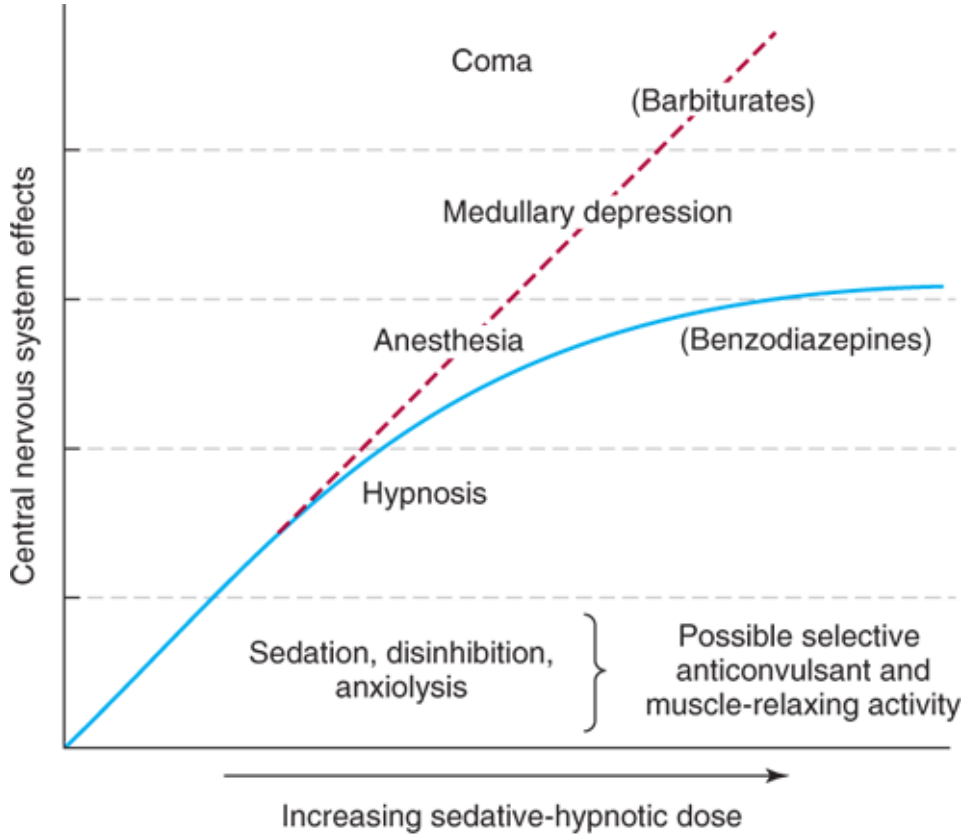


*Among deaths with drug overdose as the underlying cause, the benzodiazepine category was determined by the T402.2 ICD-10 multiple cause-of-death code. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2019 on CDC WONDER Online Database, released 12/2020.

- BZDs are present in >30% of overdoses involving opioids
- Opioids are present in 75% of deaths involving BZDs

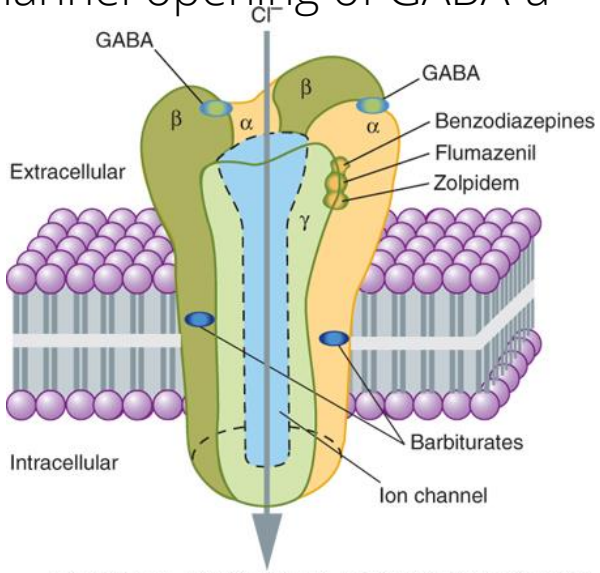
National Institutes of Health: Benzodiazepines and Opioids. February 3, 2021. Available from: https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates epines-opioids
Lintzeris, N, et al. *Am J Addict.* Jan-Feb 2010;19(1):59-72.
Bachuber MA, et al. *Am J Public Health.* 2016;106(4):686-88.

Pharmacological Basis for Addiction



B. G. Katzung, M. Kruidering-Hall, R. L. Tuan, T. W. Vanderah, A. J. Trevor
Katzung & Trevor's Pharmacology: Examination & Board Review, 13e

Benzodiazepines enhance GABA responses by increasing the frequency of chloride channel opening of GABA-a receptors



B. G. Katzung, M. Kruidering-Hall, R. L. Tuan, T. W. Vanderah, A. J. Trevor
Katzung & Trevor's Pharmacology: Examination & Board Review, 13e

Growth in BZD use and prescribing due to relative safety profile

Proposed Mechanisms of Action

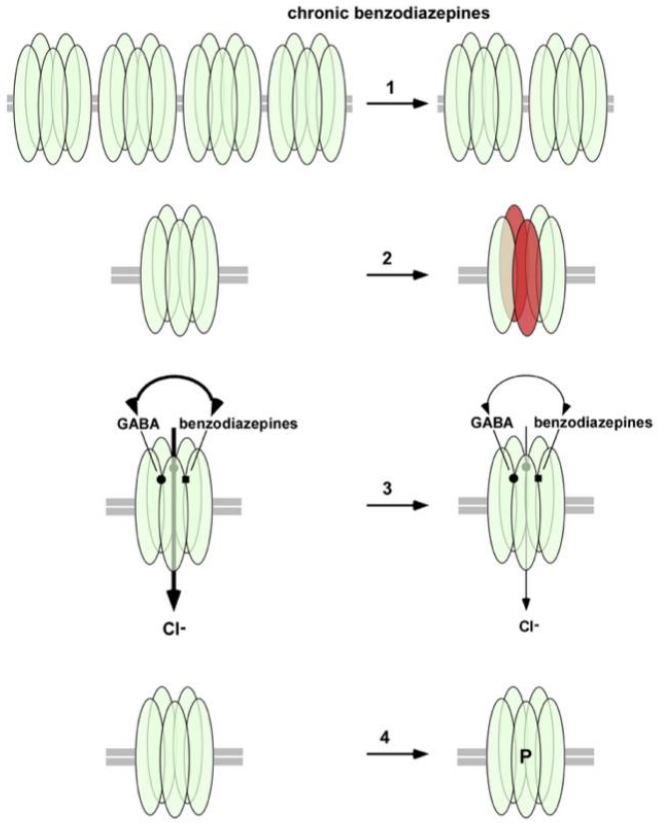


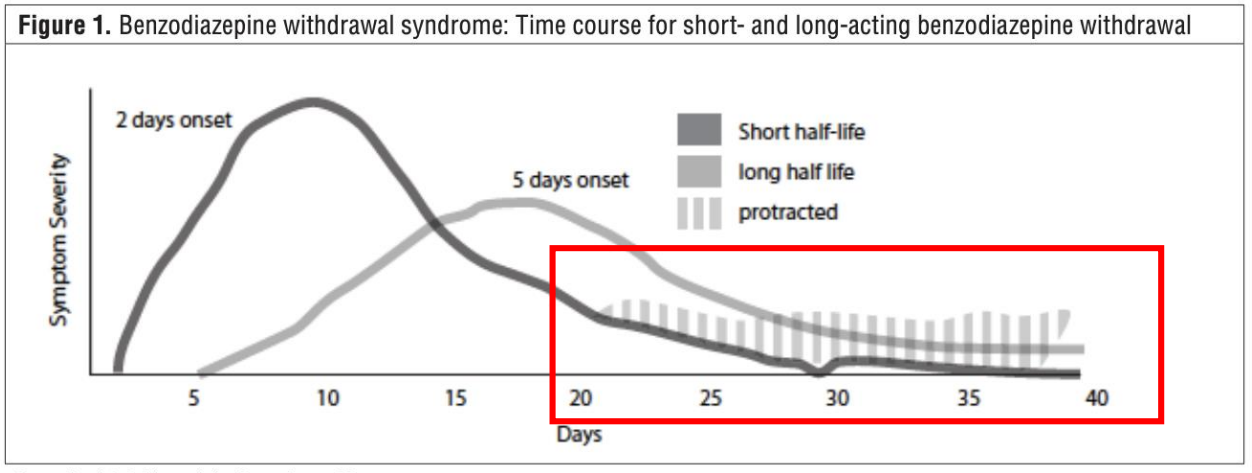
FIGURE 2 **Potential mechanism of tolerance to benzodiazepines.** Tolerance to the pharmacological effects of benzodiazepine may be mediated by: 1. A decrease in the number of postsynaptic $GABA_A$ receptors; 2. changes in $GABA_A$ receptor subunit composition; 3. uncoupling between GABA and benzodiazepine binding sites; 4. alterations in posttranslational modifications (e.g., phosphorylation, P) of $GABA_A$ receptors.

Gravielle M. Chapter 30: Effect of Chronic BZD Exposure on GABAa Receptors: Regulation of GABA/BZD Site interactions.
Tan KR, et al. *Trends Neurosci.* 2011 Apr;34(4):188-97.

- *Disinhibition of dopamine neurons* similar to OUD
- Decrease in the total number of GABAa receptors
- Selective changes in expression of GABAa receptor leading to internalization of the receptor
- Enhancement of excitatory glutaminergic receptors with abrupt cessation of chronic BZD use

Benzodiazepine Withdrawal Symptoms

Mild (2-3 days)	Moderate (2-14 days)	Severe (2-14 days)
Anxiety	Sleep Disturbances	Seizure
Insomnia	Irritability	Psychosis
	Anxiety/Panic Attacks	
	Palpitations	
	Tremor	
	Diaphoresis	



Peturrson H. *Addiction.* 1004;90*(11):1455.
Gold J. Approaches to Managing Benzodiazepines. Available from: https://www.pharmacytoday.org/article/S1042-0991(20)30219-X/pdf

Benzodiazepine Comparisons

Table 2. Commonly used benzodiazepines: anxiolytics[17,18]

Medication	Duration of action (hours)	Effect (ie, use)	Rate of onset	Administration
Alprazolam (Xanax)	6-12	Anxiolytic	Intermediate	Oral
Clonazepam (Klonopin, Rivotril)	18-50	Anxiolytic, anticonvulsant	Slow	Oral
Lorazepam (Ativan)	10-20	Anxiolytic, alcohol withdrawal, preanesthetic	Intermediate	Oral, IM, IV
Diazepam (Valium)	20-100	Anxiolytic, anticonvulsant (status epilepticus), muscle relaxant	Fast	Oral, IM, IV, rectal
Clorazepate (Tranxene)	36-200	Anxiolytic, anticonvulsant	NA	Oral
Prazepam (Centrax)	36-200	Anxiolytic	Slow	Oral
Oxazepam (Serax, Serenid, Serepax)	4-15	Anxiolytic, alcohol withdrawal	Slow	Oral
Chlordiazepoxide (Librium)	5-30	Anxiolytic, alcohol withdrawal, preanesthetic	Intermediate	Oral, IM, IV

Approximate Benzodiazepine Dose Equivalents[47]

Benzodiazepine	Approximate Dosage Equivalents	Elimination Half-Life (may include active metabolites)
Alprazolam	1 mg	12-15 hours
Chlordiazepoxide	25 mg	>100 hours
Clonazepam	1 mg	20-50 hours
Diazepam	10 mg	>100 hours
Lorazepam	2 mg	10-20 hours
Temazepam	15 mg	10-20 hours

Most frequently abused are the short-acting benzodiazepines with rapid onset of action:

- Alprazolam
- Diazepam

Wyatt, S. Understanding Benodiazepines: Commonly Prescribed but Caution Advised. Available from: https://www.psychiatrictimes.com/view/transgenerational-transmission-of-resilience-after-catastrophic-trauma
Gold J, et al. Pharmacist Toolkit: Benzodiazepine Taper. Available from: https://cpnp.org/guideline/benzo/pdf?view=link-0-1530209527&.pdf

Alprazolam and its Unique Properties

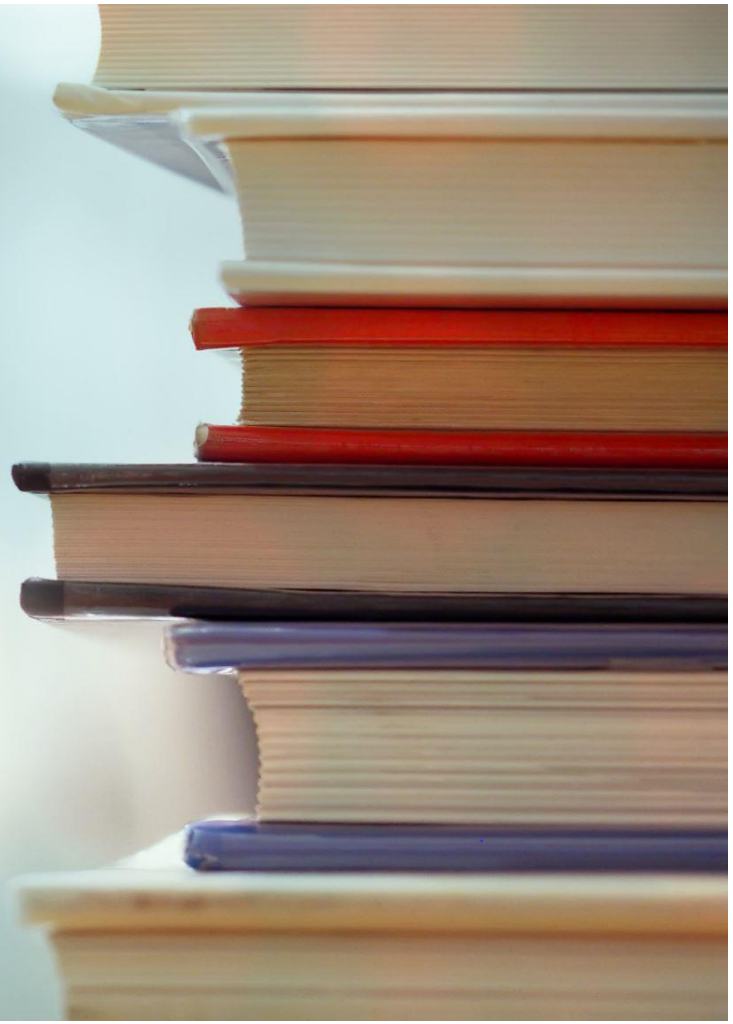
- Short half-life: 8-16 hours
- Triazolobenzodiazepine – changes in receptor binding affinity?
- Increased release of dopamine
- More intense withdrawal symptoms?
- Delirium and psychosis?
- Alpha-2 adrenergic effects

Alt-Daoud N, et al. *J Addict Med.* Jan/Feb 2018;12(1):4-10..

Adverse Effects with Long-Term Use

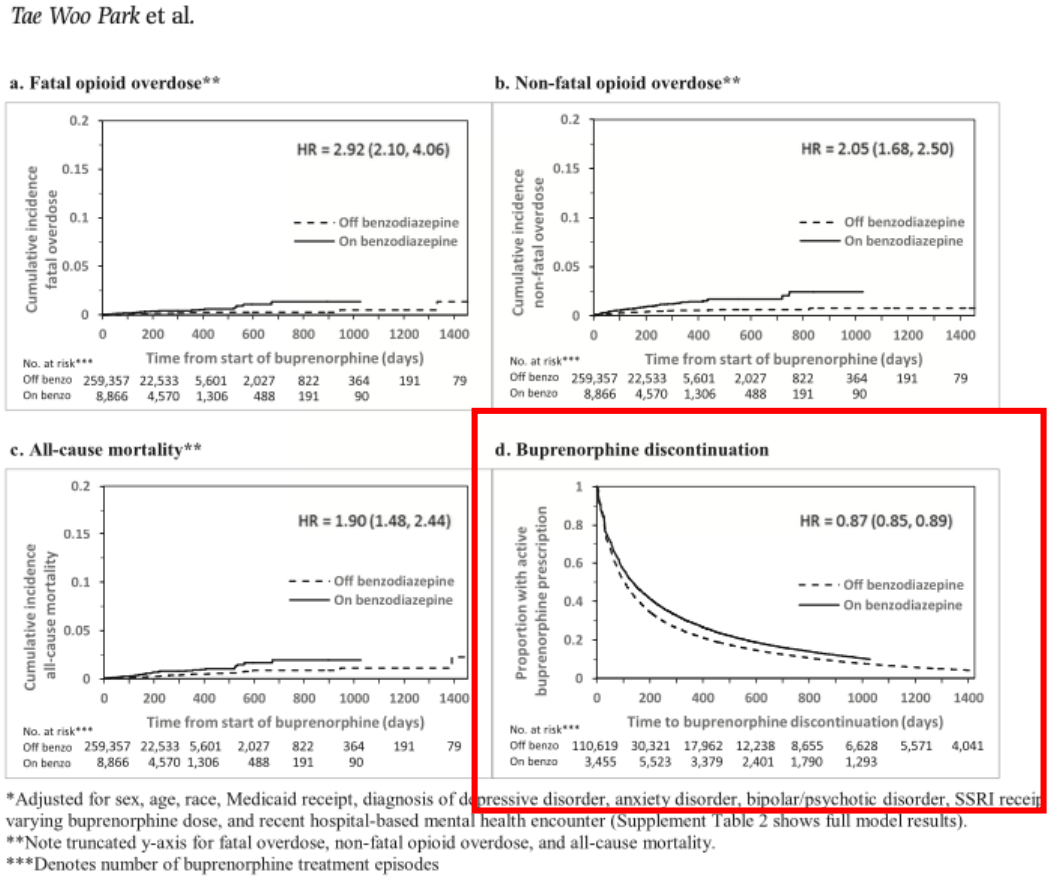
- Sedation
- Psychomotor impairment
- Cognitive Impairment
- Fractures
- Falls
- Overdose when added to other drugs that lead to sedation
- Addiction risk → SDOH

Literature in BZD Use in Patients with Opioid Use Disorder



Associations Between Prescribed BZDs, Overdose Death, and Buprenorphine Discontinuation

- Retrospective cohort study of 63,000 Massachusetts residents
- **Goal**: Identify association between BZD prescription and fatal opioid overdose,
- **Secondary**: non-fatal opioid overdose, all-cause mortality , and buprenorphine discontinuation
- **Conclusion**: BZD associated with harms but with decreased risk of buprenorphine discontinuation



Park TW, et al. *Addiction.* 2020 May;115(5):924-32.

Association Between BZD and Drug-Related Poisonings Among Patients on Buprenorphine

- Case-Crossover study –outcome of **non-fatal** drug-related poisoning

- **Results**: Buprenorphine treatment days associated with 40% reduction in risk of poisoning compared with non-treatment days
  - BZD treatment was associated with an 88% increase in risk
  - High-dose BZD associated with increased (odds ratio=1.64) poisonings in combination with buprenorphine co-treatment but lower than the odds risk associated with treatment WITHOUT buprenorphine
    - High-dose: (>30mg diazepam or equivalent)

- **Conclusion**: Risk of nonfatal drug-related poisonings associated with BZD is partially reduced by buprenorphine treatment
  - Dose reduction may be preferable to abruptly stopping BZDs

Xu KY, et al. *Am J Psychiatry*. 2021 Mar 3;appiajp202020081174.

Treatment Retention and Mortality Amongst BZD and Buprenorphine Patients

- Case-note review of 278 patients on MOUD
- BMT – diazepam up to 30mg/day; clonazepam up to 8mg/day

	BMT	BOP	NOB
Number of Patients	N = 127	N = 80	N = 71
Treatment Retention	72 months	51 months	34 months
In-Treatment Mortality	1.31/100 PY	0.33/100 PY	1.79/100 PY
Mortality after leaving care	5.90/100 YI	0.63/100 YI	2.24/100 YI
Rate of increase in mortality	450%	191%	125%

In BMT group, incidence of alcohol dependence, injecting, hep C was higher

BMT =BZD maintenance treatment;
BOP = briefly or occasionally prescribed BZD;
NOB: Never obtained BZD

Bakker A, et al. *J Psychopharmacol.* 2017 Jan;31(10:62-66.cc

BZD Use with MOUD in the Literature

Study	Intervention	Result
Weizman, et al. (2003) – observational study	CMT vs. CDTX in methadone patients	9/33 were BZD-free after 2 months in CDTX group; 28/33 refrained from abusing additional BZDs over entire year in CMT group.
Elliot, et al (2005)– observational study	Diazepam tapering of patients with mean dose of 27.8-29.8mg in methadone patients	75% of patients dropped out – after 6 months, only 10% dose reduction
Maremmani, et al (2014) – case series	Looking at feasibility of CMT with methadone and treatment retention	57.1% retained in treatment at 8 years; survival rate of 0.9 during the first year Methadone average dose 190 mg; clonazepam 21.36mg

Maremmani, et al. *Heroin Addict Relat Clin Probl* 2014;16(3):55-64.
Weizman T, et al. *Aust N Z J Psychiatry.* 2003;37:458-63.
Elliot, et al. *Drug Alcohol Rev.* 2005;24:25-31.

Assessment and Treatment

FDA Drug Safety Communication and Changes

FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks

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This provides updated information to the FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning issued on August 31, 2016.

Safety Announcement

[9-20-2017] Based on our additional review, the U.S. Food and Drug Administration (FDA) is advising that the opioid addiction medications buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS). The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks. Careful medication management by health care professionals can reduce these risks. We are requiring this information to be added to the buprenorphine and methadone drug labels along with detailed recommendations for minimizing the use of medication-assisted treatment (MAT) drugs and benzodiazepines together.

"While benzodiazepines are important therapies for many Americans, they are also commonly abused and misused, often together with opioid pain relievers and other medicines, alcohol and illicit drugs," said FDA Commissioner Stephen M. Hahn, M.D. "We are taking measures and requiring new labeling information to help health care professionals and patients better understand that while benzodiazepines have many treatment benefits, they also carry with them an increased risk of abuse, misuse, addiction and dependence."

https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-urges-caution-about-withholding-opioid-addiction-medications

Distinguishing Therapeutic vs. Abuse

- Treatment-seeking behavior with undertreated anxiety or insomnia vs. behaviors to obtain BZD for nonmedical use
  - Requests for dose increases
  - Running out of medication early
  - Resisting change in therapy despite adverse effects of medication
  - Non-adherence with monitoring
  - "Lost" or "stolen" prescriptions

Lintzeris, N, et al. *Am J Addict*. Jan-Feb 2010;19(1):59-72.

Assessment

- Assess for therapeutic use/abuse/dependence
  Severity of Dependence Scale (SDS)
- **Obtain UDS**
- Recent and previous BZD use
  - **Length of use**
  - Frequency
    - Historic binge or abuse patterns
  - Amount
  - Route of use
  - **Relationship with the BZD**
  - **Reason for use**
    - Help with opioid withdrawal?
    - "Counter" stimulant effects?
    - Therapeutic?
  - Source of BZD
- Address harms
  - Due to intoxication
  - Due to impairments on memory and cognition
    - "Emotional blunting"
  - Withdrawal symptoms (seizures, increased anxiety, sleep disturbances, "perceptual changes")
- Conduct both medical and psychiatric assessment
  - Underlying psychiatric disorder
  - Sleep apnea
  - Fall risk

Lintzeris, N, et al. *Am J Addict.* Jan-Feb 2010;19(1):59-72.

Benzodiazepine Metabolism

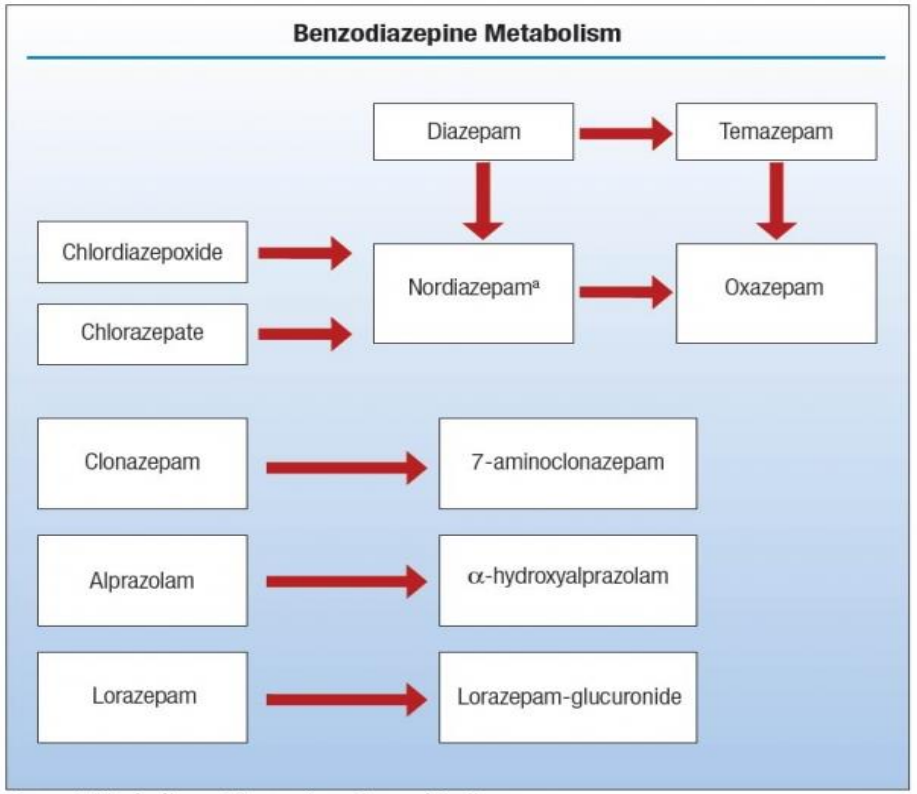


Figure 1: Illustrations of benzodiazepine metabolism.
Arrows indicate metabolic pathways
[a]Nordiazepam is also a metabolite of halazepam, medazepam, prazepam, and tetrazepam

Craven C , et al. Available from: https://www.practicalpainmanagement.com/treatments/addiction-medicine/drug-monitoring-screening/demystifying-benzodiazepine-urine-drug

Treatment Recommendations

Strategy
Utilize a patient-centered, "stepped-care" approach • Involvement of family • Education of goals of care
Avoid abrupt discontinuation can lead to worsening of substance use disorders and higher likelihood of relapse
For dependence, • Possible transfer to long-acting BZD (clonazepam) especially if reduction of a short-acting BZD leads to withdrawal symptoms (alprazolam) • **Stabilize patient** then taper over months Those chronically using over years (5+ years) have low chances of successfully tapering off • **Ensure optimal dose of MOUD!** • Limited use of adjuvant therapy (beta-blockers, TCAs) Carbamazepine? Gabapentin?
Use psychotherapy – cognitive behavioral therapy, motivational interviewing
Maximize first-line treatment options

Lintzeris, N, et al. *Am J Addict.* Jan-Feb 2010;19(1):59-72.

Sample Taper Guide

- Taper Guide
  - Goal: decrease withdrawal effects and manage rebound symptoms and recurrence of disease managed by BZD
  - 25% reduction every 1-2 weeks
    - 10-25% every 2-4 weeks lasting for 6 months
  - Longer, the better chance for success!

Pharmacist Toolkit: Benzodiazepine Taper. Available from: https://cpnp.org/guideline/benzo/pdf?view=link-0-1530209527&.pd

Strategies for a More Successful Taper

Overcoming Barriers to Tapering	Best Practices
Slow taper to avoid withdrawal	Discuss and provide clear instructions o for taper
Education on anxiety and insomnia being a part of withdrawal that will improve over time and if remain, there are alternative agents and psychotherapy	Avoid “as needed” BZD during taper
Highlight negative outcomes • Cognitive impairment/dementia • Fall risks • Motor vehicle accidents • Unintentional overdose	Converting to long-acting BZD
	Obtain UDS • Especially with aberrant behavior • Monitor for use of other substances • GGT for alcohol use • Understand that UDS to monitor adherence with BZD prescription or use of non-prescribed BZD is limited

Pharmacist Toolkit: Benzodiazepine Taper. Available from: https://cpnp.org/guideline/benzo/pdf?view=link-0-1530209527&.pd

Treatment Strategies

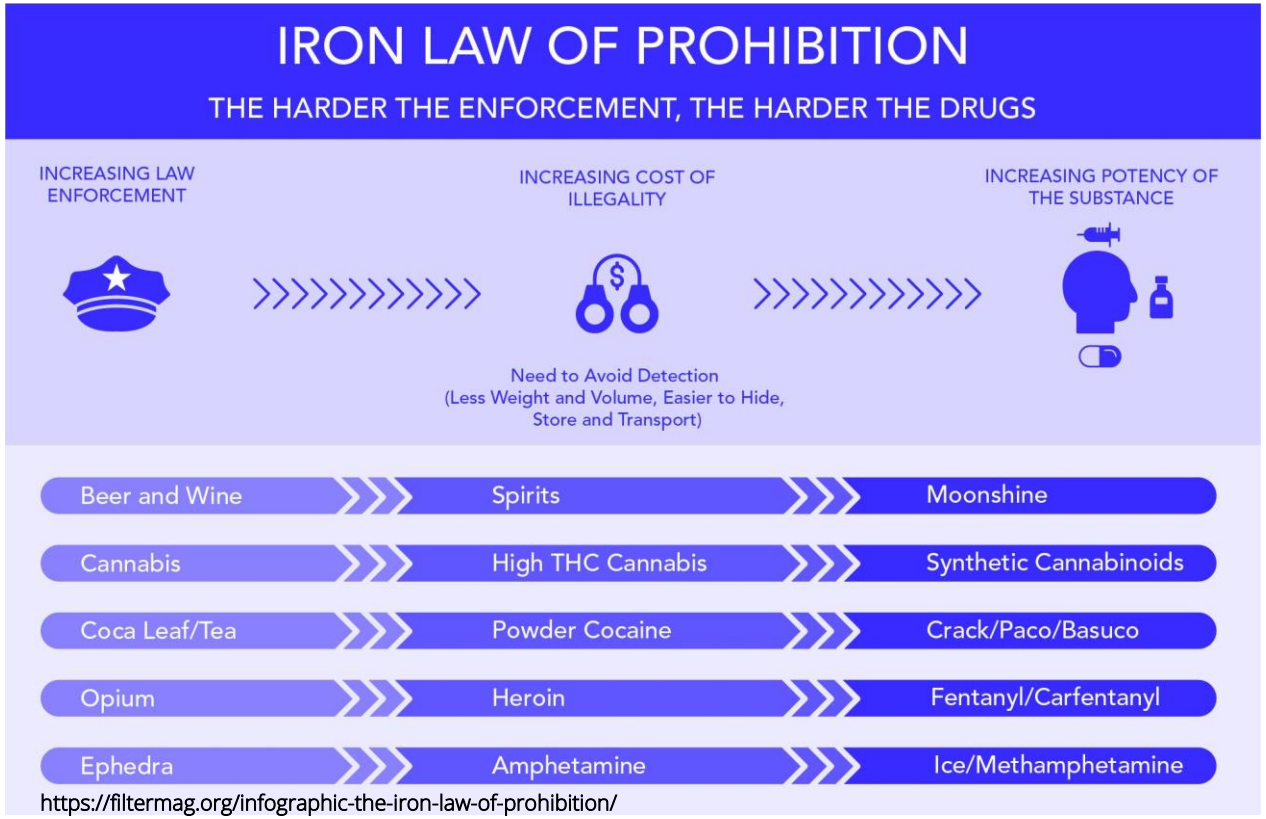
TABLE 2. Strategies for managing benzodiazepine dependence in OAT patients

1. Coordinate treatment providers
2. Address co-occurring medical and psychiatric disorders
3. Stabilize on a long-acting BZD
4. Attempt gradual reductions
5. Limit access to BZD medications
6. Identify and address aberrant drug behaviors in the treatment plan
7. Undertake regular monitoring, including clinical review, urine testing, and prescription monitoring systems
8. Utilize contingency management principles regarding treatment conditions
9. Develop a written treatment agreement
10. Document treatment decisions

Lintzeris, N, et al. *Am J Addict.* Jan-Feb 2010;19(1):59-72.

Harm Reduction

- Despite the aggressive interventions to reduce prescribing of controlled substances and illicit drug use, we must keep in mind that relapse is real: **"Meet the patient where they are at"**
- "Harder and harder" drugs continue to infiltrate the illicit drug supply
- Street benzodiazepines containing HPSOs unbeknownst to the person using the drugs
- Growth of other tranquilizers: Xylazine
- Ensure access to naloxone/clean syringes/test kits



https://filtermag.org/infographic-the-iron-law-of-prohibition/

End Goal: Prevention of overdose death

Summary

- Long-term BZD carries serious risks and there is no evidence-based pharmacological treatment available in those with use disorder
- Treatment retention is a major factor to consider when thinking about BZD management in those with OUD
- The rate of successfully tapering off BZDs in patients with chronic BZD use is low and ensuring a patient-centered, multidisciplinary approach is essential
- BZD prescribing in patients with substance use history should be done based on an evaluation of benefits and risks and with an individualized approach to ensure that the outcome is the prevention of overdose death
- Documentation of rationale to justify co-prescribing MOUD and BZDs is warranted in consideration of the risk of abruptly stopping these therapies

Thank you!

Questions & Discussion

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