

# Opioid Use Disorder Education and Treatment ECHO Series

## Session 11 – Benzodiazepines: Uses and Risks

April 19, 2022

Slides created by Charlie Reznikoff, MD, Hennepin Healthcare

Modified by Kurt DeVine, MD and Heather Bell, MD



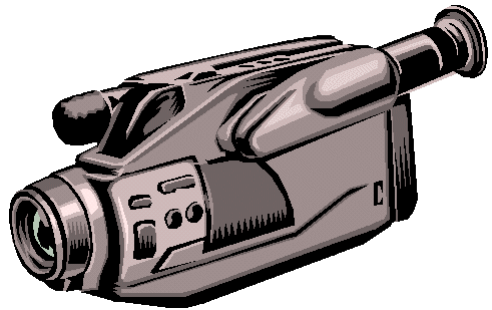
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# Announcements

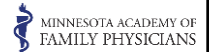


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## SESSIONS ARE RECORDED

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## YES, THERE'S *FREE* CME

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Minnesota Medical Association (MMA) through the joint providership of Stratis Health and the Minnesota Academy of Family Physicians. **Stratis Health is accredited by the MMA to provide continuing medical education for physicians.**

Stratis Health designates this educational activity for a maximum of **1 AMA PRA Category 1 Credits™**.

Physicians should claim credit commensurate with the extent of their participation in the activity.

### **Continuing Education Credits and Contact Hours for Other Health Professionals**

The OUD Education and Treatment ECHO Series may meet continuing education requirements for your focus. It is the responsibility of the individual to determine if this activity fulfills that requirement.



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## Attendance

- Please chat us the names of people on ECHO if there are multiple people in your room!
- “Re-name” your self so we know who’s here!
- Please turn your video on!
  - Human connection!
  - And we do NOT care if you are eating!



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## Case Presentations!

The ECHO model is based on case-based learning!  
The case presentation form is available on the MAFP website  
(<https://bit.ly/OUDCase>) and in the announcements email!  
\*\*\*BUT feel free to present in any de-identified format!\*\*\*

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## Upcoming Tuesday ECHO Sessions

- **Tuesday, May 3, 2022:** OUD and Ethanol Alcohol
- **Tuesday, May 17, 2022:** OUD and Stimulants
- **Tuesday, June 7, 2022:** OUD and Pregnancy
- **Tuesday, June 21, 2022:** OUD and Neonatal Opioid Withdrawal Syndrome (NOWS)
- **Tuesday, July 19:** Perioperative Management
- **Tuesday, August 2:** Community Collaboration Engagement
- **Tuesday, August 16:** Motivational Interviewing (MI) Lapse/Relapse

## Upcoming Wednesday ECHO Sessions

- **Wednesday, April 20, 2022**  
No ECHO
- **Wednesday, April 27, 2022**  
Minnesota SUD Reform, Direct Access, and Considerations for Placement – One Counselor’s Perspective, with Nate Erickson, LADC
- **Wednesday, May 4, 2022**  
Fentanyl Test Strips Part 3, with Charlie Reznikoff, MD
- **Wednesday, May 11, 2022**  
The Pharmacotherapy of Alcohol Use Disorder, with Ricardo Restrepo, MD, MPH

# “The Addiction Connection Podcast”

Weekly addiction  
topics- Tuesday  
release day!

[www.buzzsprout.com/954034](http://www.buzzsprout.com/954034)

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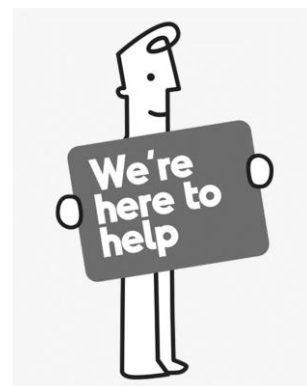
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## TECHNICAL ASSISTANCE

- **We are ALWAYS here for you!**
  - Program implementation
  - Inductions
  - Difficult cases
  - Trouble-shooting
  - Anything!
- **Call us anytime:**
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  - Heather Bell: 320-630-5607
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## Objectives

- Understand the indications for benzodiazepines
- Define the risks and contraindications of benzodiazepines
- Describe and recognize benzodiazepine withdrawal
- Understand implications of patients on buprenorphine being prescribed benzodiazepines

## Section One Benzodiazepines

## Overview Benzodiazepines

- Examples of benzodiazepines (benzos) and benzo-like drugs
- Indications for benzos
- Pharmacology of benzos
- Side effects and contraindications
- Benzo withdrawal
- Benzo tapers

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## Sedative/Hypnotics

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



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## Examples of Benzodiazepines

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



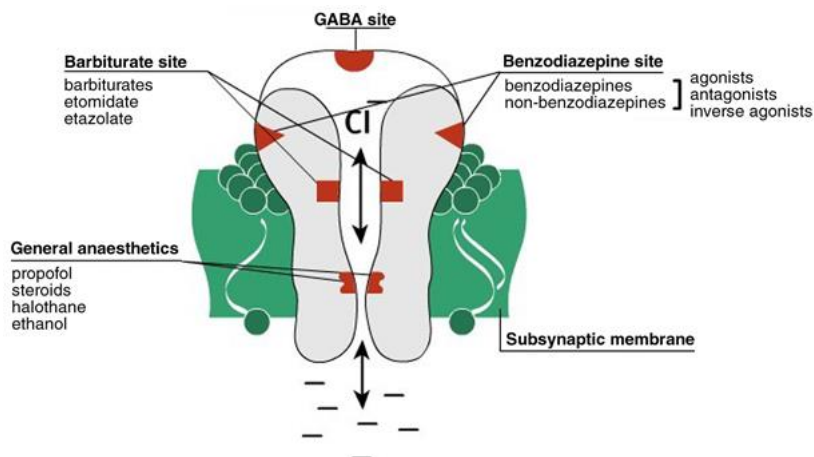
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## Sedatives: GABA-stimulating drugs have incomplete “cross tolerance”



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## Effects from Sedative (Benzo) Use

- Euphoria/bliss
- Suppresses seizures
- Amnesia
- Muscle relaxation
- Clumsiness, visuospatial impairment
- Sleep inducing
- Respiratory suppression
- Anxiolysis/disinhibition



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## Tolerance to Benzo Effects

- Effects quickly diminish with repeated use (weeks)
  - Euphoria/bliss
  - Suppresses seizures
- Effects incompletely diminish with repeated use
  - Amnesia
  - Muscle relaxation
  - Clumsiness, visuospatial impairment
  - Sleep inducing
- Durable effects with repeated use
  - Respiratory suppression
  - Anxiolysis/disinhibition

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## If you understand this pharmacology, you can figure out the rest.

- Potency
  - 1 mg diazepam <<< 1 mg alprazolam
- Duration of action
  - Half life differences
- Onset of action
  - Euphoria, clinical utility in acute situations
- Active metabolites
  - Liver safety, self-tapering properties

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## Duration

- High variability half life between benzos
  - Midazolam... <1 hour, good for anesthesia
  - Lorazepam... ~8 hours, good for panic attacks specific phobias and agitation
  - Diazepam... >1 day, good for alcohol detox and preventing alcohol withdrawal seizures

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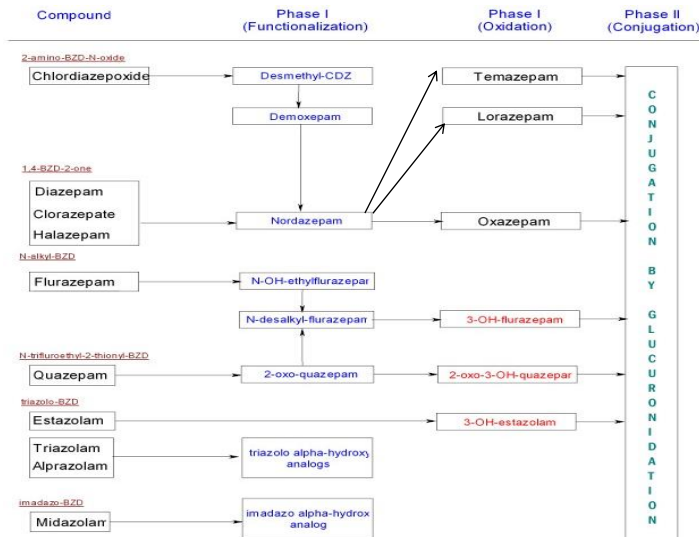
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# Active Metabolites

- Certain benzos (Valium, Librium) are metabolized to active compounds
- These “active metabolites” then also need to be broken down by the liver
- Active metabolites make the drug long acting and “self tapering,” a good thing for detox
- People with liver disease and elderly do not effectively clear the active metabolites and can be sedated for days/weeks
  - Diazepam (Valium) and chlordiazepoxide (Librium) have active metabolites



# Active Metabolites



## Onset of Action

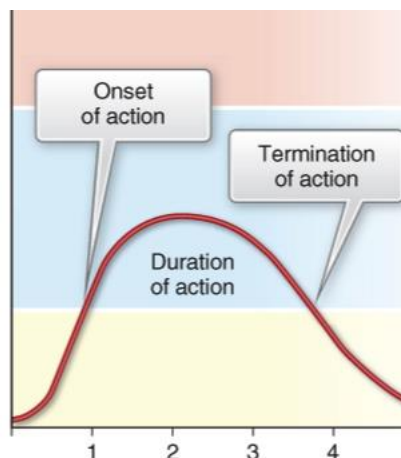
- Onset is different from duration or half life
  - Diazepam acts more quickly than lorazepam, but also has a longer duration
- Lorazepam (Ativan) kicks in fast if given IV but slow if taken orally
- Rapid onset is good for....
  - Breaking a seizure
  - Panic disorder
  - Getting high

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## Benzo Variables

- Potency differences
- Time of onset
- Duration
- Active metabolites



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# Commonly Used Benzos and Why

- Clonazepam for General/social anxiety, adjustment
  - Longer action, less euphoria
- Lorazepam for panic/phobias (PO), agitation (IV)
  - Medium onset, shorter half life, less euphoria
- Diazepam for alcohol detoxification
  - Self tapering, rapid onset, long half life– but off limits in patients with cirrhosis
- Midazolam for anesthesia
  - Very short half life, easy to titrate, IV
- Temazepam for sleep
  - Half life appropriate for 8-hour sleep, less euphoria

Table 2. Benzodiazepine Visit Rate by Indication

Indication <sup>a</sup>	Unweighted No. of Benzodiazepine Visits, 1 Million		Unadjusted Estimated Benzodiazepine Visit Rate, % (95% CI)		P Value <sup>b</sup>	Adjusted OR (95% CI) <sup>c</sup>
	2003 (n = 919)	2015 (n = 1672)	2003	2015		
Anxiety and depression	12.8	23.7	26.6 (22.6-31.0)	33.5 (28.8-38.6)	.003	1.43 (1.05-1.95)
Back and chronic pain	4.9	15.1	3.6 (2.6-4.9)	8.5 (6.0-11.9)	<.001	2.65 (1.65-4.26)
Insomnia	2.1	3.4	26.9 (19.3-36.0)	25.6 (15.3-39.6)	.72	0.94 (0.46-1.92)
Neurologic <sup>d</sup>	3.3	5.0	6.8 (4.8-9.5)	8.7 (6.2-12.1)	<.001	1.37 (0.85-2.22)
Other	9.1	24.5	1.8 (1.4-2.2)	4.4 (3.7-5.2)	<.001	2.50 (1.90-3.29)

Abbreviation: OR, odds ratio.

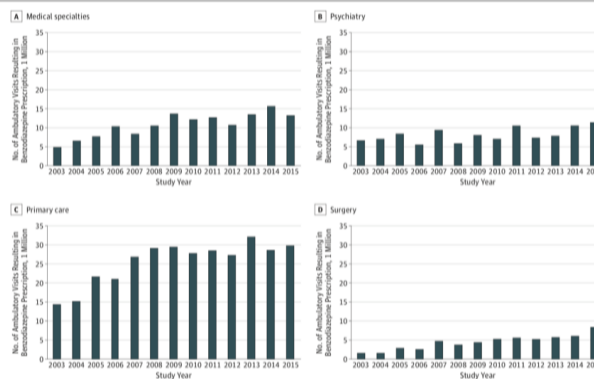
<sup>a</sup> A visit can be ascribed to multiple diagnoses.

<sup>b</sup> Calculated using  $\chi^2$  trend test.

<sup>c</sup> Adjusted for age, sex, race, insurance, region, and location.

<sup>d</sup> Includes headache, seizures, vertigo, and movement disorders.

Figure 2. Benzodiazepine Visits by Specialty



**BZD increase driven by primary care for back pain, anxiety and “other”**

## Benzos are Falling Out of Favor

- Don't use benzos long term for anxiety
- Don't use benzos long term for sleep
- Don't use benzos for alcohol detox outside of a controlled setting
- Don't use benzos chronically for seizures
- Don't use benzos for back pain
- Some never use benzos as an outpatient medicine
- Some use only rare doses (five/year), or daily doses over short periods

## Why are benzos falling out of favor?

- Benzos prevent learning coping skills, making you rely on a pill instead
  - You don't learn how to fall asleep on your own
  - You don't learn to manage your anxiety on your own
  - You get “stuck” in your pill use and don't progress

# The Most Important Contraindication to Benzodiazepine Use



## POLL QUESTION

What is the most important contraindication to benzodiazepine use?

- Opioid use
- Use with alcohol
- Elderly
- Pediatric

# POLL ANSWER

The most important contraindication to benzodiazepine use:

- **Elderly**
- Opioid use
- Respiratory insufficiency
- Pediatric
- Cognitively impaired
- Borderline personality disorder
- Addiction (use with caution)
- Learning or therapy
- Driving, using machinery
- Use with alcohol

**Use of benzos in older adults is associated with falls, hip fractures and death.**





# Benzos and Addiction

- Most patients with addiction who use benzos are not addicted to them
  - Benzos useful for mitigating other drugs' toxicity
    - Coming down from methamphetamine
    - Boosting opioids
    - Bridging WD between opioid intoxications
- Benzos are not that addictive
- A true benzo addiction is incredibly complex and challenging: the patient is a risk to themselves and others

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# Benzos and Addiction cont.

- Patients with benzo addiction are notoriously poor historians, and unreliable pill takers

They are not lying!  
They just don't remember.



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# Organ Toxicity From Benzos

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## POLL QUESTION

**Benzodiazepines have many organ toxicities**

- True
- False

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## POLL ANSWER

**False.** Benzos have almost NO organ toxicity.

- Contrast that to many of the “safer” alternatives (quetiapine olanzapine)

## Benzo Intoxication

## Which person is more likely on benzos?



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## What Else Dilates Pupils?

- Anticholinergics
- Opioid withdrawal
- Stimulants
- Dissociatives
- Darkness
- ... And some people just have large pupils

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## Mental Status - Benzo Intoxication

- Emotional lability
- Rambling tangential
- Overly disclosing
- Ataxia, clumsiness
- Slowed slurred speech
- Dilated pupils

## Facial bruises from falls are a sign of benzo intoxication



# POLL QUESTION

What is the most important responsibility you have when caring for a patient intoxicated on benzos?

- Oxygenation
- Hydration
- Safe transit
- Sleep

# POLL ANSWER

Assure **safe transit** home.

- Not just car keys:
  - Will they be vulnerable on a bus?
  - Car accidents, falls, victims of thefts or assaults, getting lost or losing something

## Benzo Intoxication cont.

- Interviews with patients on benzos can be frustratingly circular and nonproductive. You might find yourself repeating the same conversation every time and not “getting anywhere”.
- You may need to interrupt them and end the conversation.
- Write down anything important.
- You might have to be firm with the patient to end the visit.

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## Benzo Overdose Deaths

- These are probably mixed overdoses
- Opioid rates many times (>10X) higher

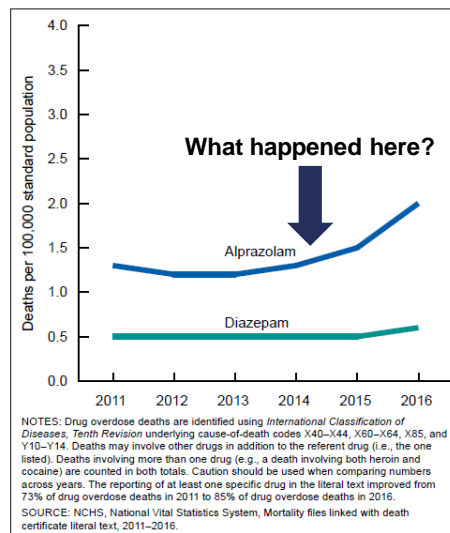


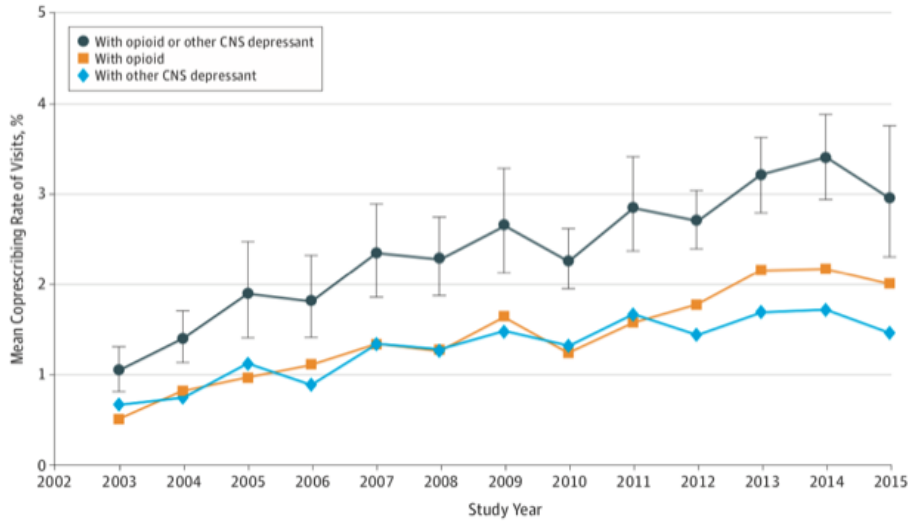
Figure 2. Age-adjusted rates for drug overdose deaths involving selected benzodiazepines, 2011–2016

National Vital statistic report, Vol 67, no 9 2018

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Figure 3. Coprescribing Rate for Benzodiazepines With Opioids and Other Central Nervous System (CNS) Depressants



## Benzo Overdose

Therapeutic index is very high

Main risk is trauma/accidents

Dangerous overdoses are co-ingestions (EtOH, opioids)

Support/monitor the patient

Intubate if necessary

Reversal of opioids with naloxone

Reversal of benzos with flumazenil



## Common Non-Benzo Sedatives

- Carisoprodol, “Soma” or pro-meprobamate.
  - Barbiturate
- Butalbatol, “Fiorinol”
  - Barbiturate
- Phenobarbitol
  - Long-acting non-euphoric barbiturate used for tapers
- Propofol– cross tolerant with benzos
- GHB “Xyrem”
  - Powerful short acting sedative
- “Z drugs”: zolpidem, eszopiclone, zaleplon
  - Ambien lunesta sonata
  - Mild benzo-like drugs for sleep
- Alcohol

## Cautions with Z-Drugs

- Falls in hospital
- Falls at home
- Hip fracture
- Car accidents the next morning
- Amnesia during the night

# POLL QUESTION

Most street “alprazolam” is actually

- Fentanyl
- Heroin
- Oxycontin
- Morphine

# POLL ANSWER

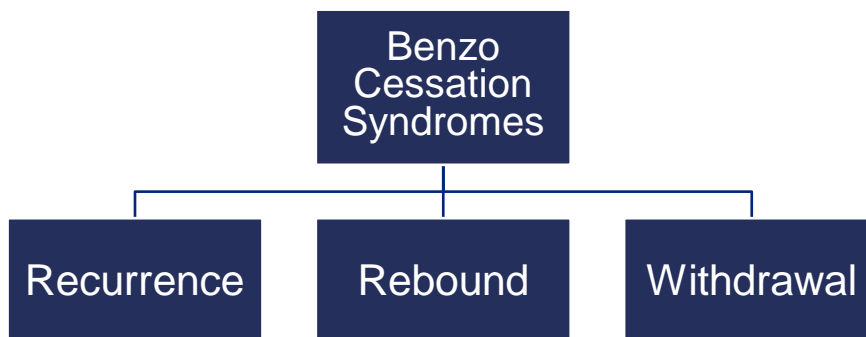
Most street “alprazolam” is actually **Fentanyl**.

## Online Synthetic Benzos

- Available on the dark web
  - Etizolam
  - Flubromazolam
  - Clonazolam
- Recall that much street “alprazolam” is actually fentanyl
- Some may not trigger a BZD screen

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## Benzo Withdrawal

- True benzo withdrawal is life threatening, requires close monitoring and detoxification
- Seizures, including status epilepticus
- Delirium and psychosis
- May start one week after last dose and continue for weeks
- Medical complications of withdrawal, like pneumonia

## Likelihood of True Withdrawal

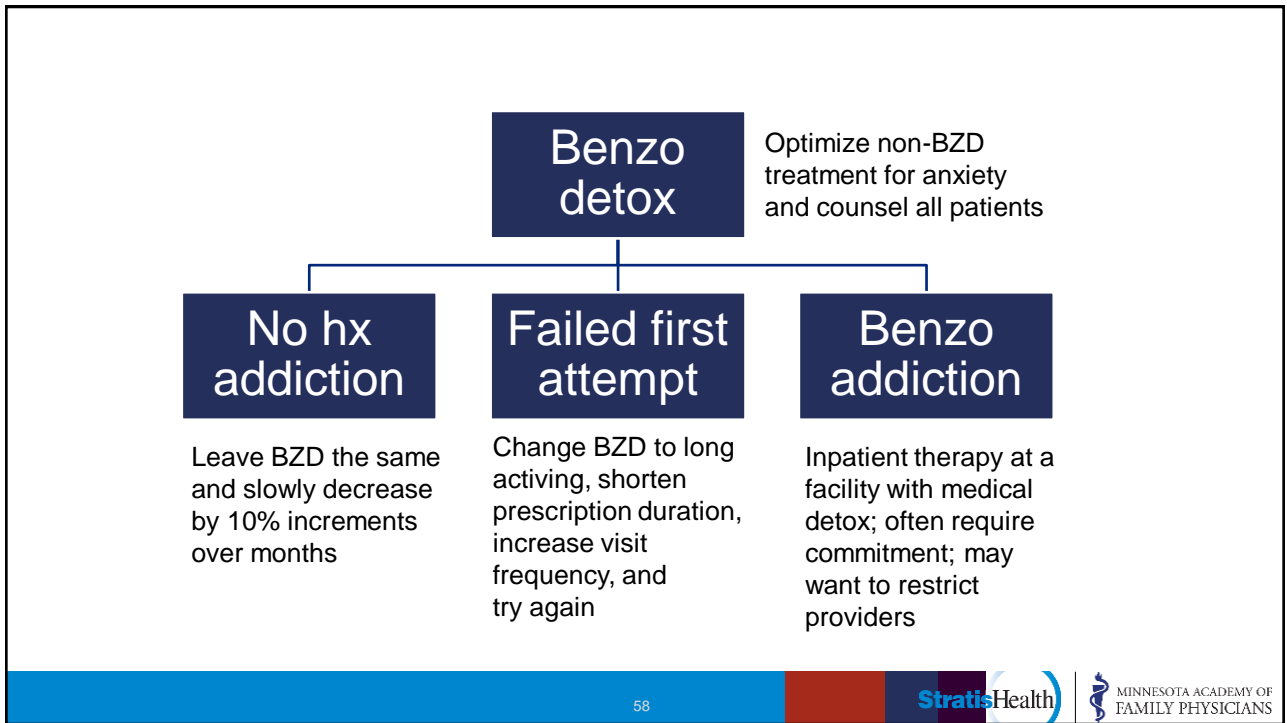
- Past withdrawal (including seizure)
- Short acting meds
- Concomitant heavy alcohol use
- Concomitant medical illness
- High dose

## Post-Cessation Anxiety Recurrence

- People who love benzos have anxiety disorders
- Benzos only hide the anxiety disorder– it is still there waiting to return after benzos
- While on benzos they don't learn appropriate coping mechanisms
- After benzos stopped, the insomnia and anxieties return
- This is universal and very distressing to benzo patients

## Benzo Rebound Anxiety

- Recurrence of anxiety symptoms with a vengeance
- If before benzos the patient had 1 panic attack a week, after benzos they will have panic attacks daily for a few weeks
- Reassure them that their anxiety will calm down in a few weeks



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## Summary of Section 1

- Benzos are sedative drugs with characteristic effect
- Benzos can be helpful for select conditions, but usually avoid for ongoing prescriptions
- Understand benzos based on their pharmacologic properties
- Identify benzo intoxicated patients
- Use special care with elderly and addicted patients
- Benzo withdrawal life threatening; benzo “rebound” troublesome and common

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## Section Two

# Benzodiazepine and Buprenorphine

## Benzodiazepine Use During Buprenorphine Treatment for Opioid Dependence: Clinical and Safety Outcomes\*

2013 Drug and Alcohol Dependence. October 2013. Oliver et al.

\*Retrospective study

## Oliver et al.

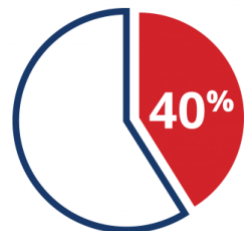
- Clinical outcomes they were looking for
  - 12-month treatment retention
  - Urine toxicology results
  - ED visits for OD or injury

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## Results Oliver et al.

- 12-month retention was 40%
- Benzodiazepine misuse nor benzodiazepine prescription use was related to retention or illicit opioid use
- Benzodiazepines were associated with a 73x increased risk of accidental injury and >4x in females



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## Findings Oliver et al.

- Slightly lower risk with long-acting benzodiazepines (than shorter)
- And...even lower risk with Z drugs
- So... switching patients to long-acting benzodiazepines or Z drugs is somewhat more safe

## Association Between Benzodiazepine or Z Drug Prescriptions and Drug Related Poisonings Among Patients Receiving Buprenorphine Maintenance: A Case Crossover Study

Xu et al.. American J. Psych. 2020

# Association Between Benzodiazepines and Z Drug Prescriptions and Drug-Related Poisonings

- 30% of patients with OUD on MOUD are on benzodiazepines
- 1/3 of these patients misuse
- It is unclear whether risk of benzodiazepines and MOUD outweighs benefits



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## Xu et al.

- Some findings suggest that retention is better when patients are on benzodiazepines in buprenorphine programs
- But benzodiazepines are related to many poisonings

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## Concerns

- The interaction with other benzodiazepines with different half-lives, potency, and so on relate to morbidity and mortality - not studied
- There is little research on drug related poisonings with Z drugs

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## Research Gap

- So... there is a research gap on OUD outcomes on patients taking buprenorphine, benzodiazepine, and Z drugs



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## Study – Xu et al.

- Analyzed non-fatal overdose/poisoning associated with specific benzodiazepines or Z drugs and dosing regimens in patients with OUD



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## Xu et al.

- Buprenorphine treatment days (days patients actually took medications) decreased poisoning by 40% on those days, but... benzodiazepine and Z drug treatment days doubled poisoning risk

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## Xu et al. cont.

- Benzo/Z drug + Buprenorphine < risk than Benzo/Z drug alone
- Buprenorphine dose did not change risk
- SSRIs did not change risk

## Findings Xu et al.

- Clear dose dependency for overdose risk and outcome of benzodiazepines and Z drugs
- Lower dose and decreased treatment duration decreased risk

# Association between benzodiazepines and opioid prescription and mortality among patients in a large healthcare system.

Mooney et al. J. Addiction Med. Jan/Feb 2022

## Mooney et al.

- Purpose of study - examines opioid and benzodiazepine co-prescription dosing and mortality in patients with and without OUD in large healthcare system
- Method - data from California State Prescription Drug Monitoring Program from 2010 to 2014
  - 5,202 patients
  - 1,978 with OUD
  - 3,224 controls

## Discussion Mooney et al.

- OUD patients had more “other” substances use disorders, as well as more issues with mental and physical comorbidities.
- OUD patients were prescribed higher doses of benzodiazepines and opioids than non-OUD patients
- Average daily dose of both was associated with all-cause mortality
- Significant interaction in co-prescribed patients on mortality in non-OUD patients.

## Mooney et al. cont.

- OUD vs non-OUD patients
  - OUD patients have
    - Higher all cause mortality
    - Higher dose of benzodiazepines prescribed
    - More physical and mental concerns
  - Previous research has shown:
    - More benzodiazepine prescriptions in chronic pain patients especially at high opioid doses

## Mooney et al. cont.

- Opioid and benzodiazepine prescription and mortality
  - Use of either as related to increased all cause mortality- and reported in other studies
  - All cause mortality is dose dependent
  - 36% of OUD patient deaths had benzodiazepine
  - 35% of non-OUD patient deaths had benzodiazepine
  - Benzodiazepine dosing is directly related to all cause mortality risk

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## Mooney et al. cont.

- Other factors associated with mortality
  - Self pay increases risk
  - Older age
  - Alcohol
  - Many significant medical diagnoses

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## Summary of Part 2

- Patients in treatment for OUD have significant increased risk of injury
- Z drugs are associated with fewer injuries
- Patients on buprenorphine have 2x the risk of overdose if on benzodiazepines
- Patients with OUD on benzodiazepines have increase in all cause mortality that is dose dependent

## Sources

- Schuman-Olivier Z, Hoepfner BB, Weiss RD, Borodovsky J, Shaffer HJ, Albanese MJ. Benzodiazepine use during buprenorphine treatment for opioid dependence: clinical and safety outcomes. *Drug Alcohol Depend.* 2013 Oct 1;132(3):580-6. doi: 10.1016/j.drugalcdep.2013.04.006. Epub 2013 May 18. PMID: 23688843; PMCID: PMC3916951.
- Xu KY, Borodovsky JT, Presnall N, Mintz CM, Hartz SM, Bierut LJ, Grucza RA. Association Between Benzodiazepine or Z-Drug Prescriptions and Drug-Related Poisonings Among Patients Receiving Buprenorphine Maintenance: A Case-Crossover Analysis. *Am J Psychiatry.* 2021 Jul;178(7):651-659. doi: 10.1176/appi.ajp.2020.20081174. Epub 2021 Mar 3. PMID: 33653119; PMCID: PMC8286284.
- Mooney LJ, Zhu Y, Yoo CK, Wolitzky-Taylor K, Hser YI. Association Between Benzodiazepine and Opioid Prescription and Mortality Among Patients in a Large Healthcare System. *J Addict Med.* 2022 Jan-Feb 01;16(1):65-71. doi: 10.1097/ADM.0000000000000828. PMID: 35120065; PMCID: PMC8817063.

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Podcast:  
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