Co-occurring Benzodiazepine and Opioid Use

Safety Concerns and Treatment Options

Bob Sise, MD, MBA, MPH, FASAM
CEO/Addiction Psychiatrist, 406 Recovery
Consultant, MPCA & CMS

A Primary Care Approach to Treating Substance Use Disorders
May 28, 2025

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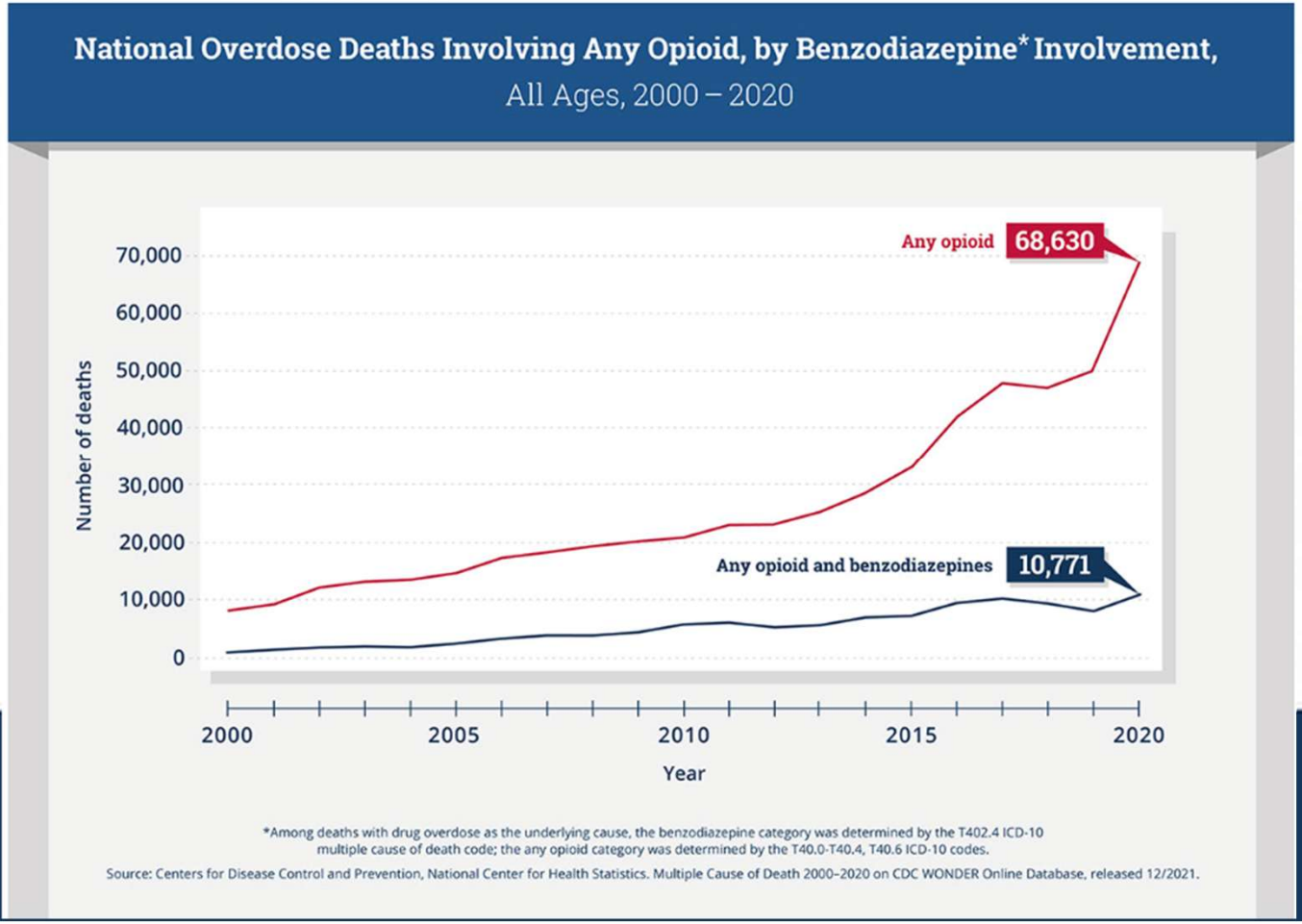
Why we care: co-use= 1/7 OD deaths



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Disclosures:

Nature of Relationship	*Name of Organization*
CEO/Co Founder	*406 Recovery (Nonprofit)*
Consultant	*MPCA (Nonprofit)*
Consultant	*Community Medical Services*

Preface: the Patient Case

Patient Case

AN is a 47-year-old women who presents to your clinic for “feeling overwhelmed by anxiety”. She currently works part-time at a nursery and is completing a BS degree online.

She is currently prescribed clonazepam 3 mg daily x 1 year that she takes regularly. In addition, AN is enrolled in an opioid treatment program (OTP) and receives methadone 110 mg PO daily for opioid use disorder. Denies taking further presciption medications noting “benzos are the only thing that works for me to help with anxiety.”

However, 3 weeks ago she started using diverted alprazolam, “Xanny Bars” that she buys from a friend or off the street. She reports rebound anxiety, stating “if I miss a dose of Xanax, I get bad anxiety…I often wakeup in the middle of the night with panic attacks.”

How do you proceed?

Select all that apply

1. Start a gradual benzodiazepine taper
2. Consider prescribing adjunctive medication to facilitate benzodiazepine dose reduction
3. Engage in motivational interviewing targeting benzodiazepine use reduction/cessation
4. Tolerate long-term benzodiazepine use so long as she is only taking clonazepam
5. Insist on abstinence from benzodiazepines prior to prescribing any additional medication
6. Proceed to treat PTSD and anxiety with evidence-based pharmacological treatment
7. Refer to a qualified therapist for Cognitive Behavioral Therapy

Objectives

1. Acknowledge how benzodiazepines work

2. Discuss the epidemiology of benzodiazepine use disorder (BZD UD) and the pertinent concerns

3. Discuss safety concerns of combined benzo and opioid use

4. Evaluate current forms of treatment for Benzodiazepine Use
   → The ASAM Guidelines

General Information

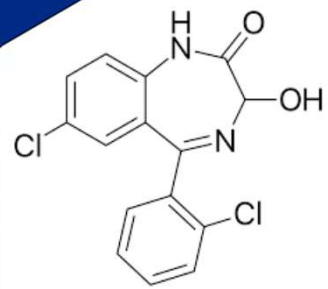
Benzodiazepines

- Act as CNS depressants, similar to alcohol
- BZDs specifically have effects on anxiety, sleep, seizure activity, muscle relaxation and memory

Clinical Use

- Overall safe when used for **short durations** (i.e., 2-4 weeks), but **dependence can occur in 50% of individuals who use for at least a month**

Titus-Lay, E. Substance-Related Disorders. CPNP Psychiatric Pharmacotherapy Review. 2022.



Benzodiazepines

Chemical structure = the fusion of benzene & diazepine rings

In 1955, Leo Sternbach accidentally discovered the first BZD, chlordiazepoxide (Librium)

Diazepam (Valium) debuted in 1963

By 1977, BZDs were the most prescribed medication class globally

BZDs remain some one of the most prescribed medication classes

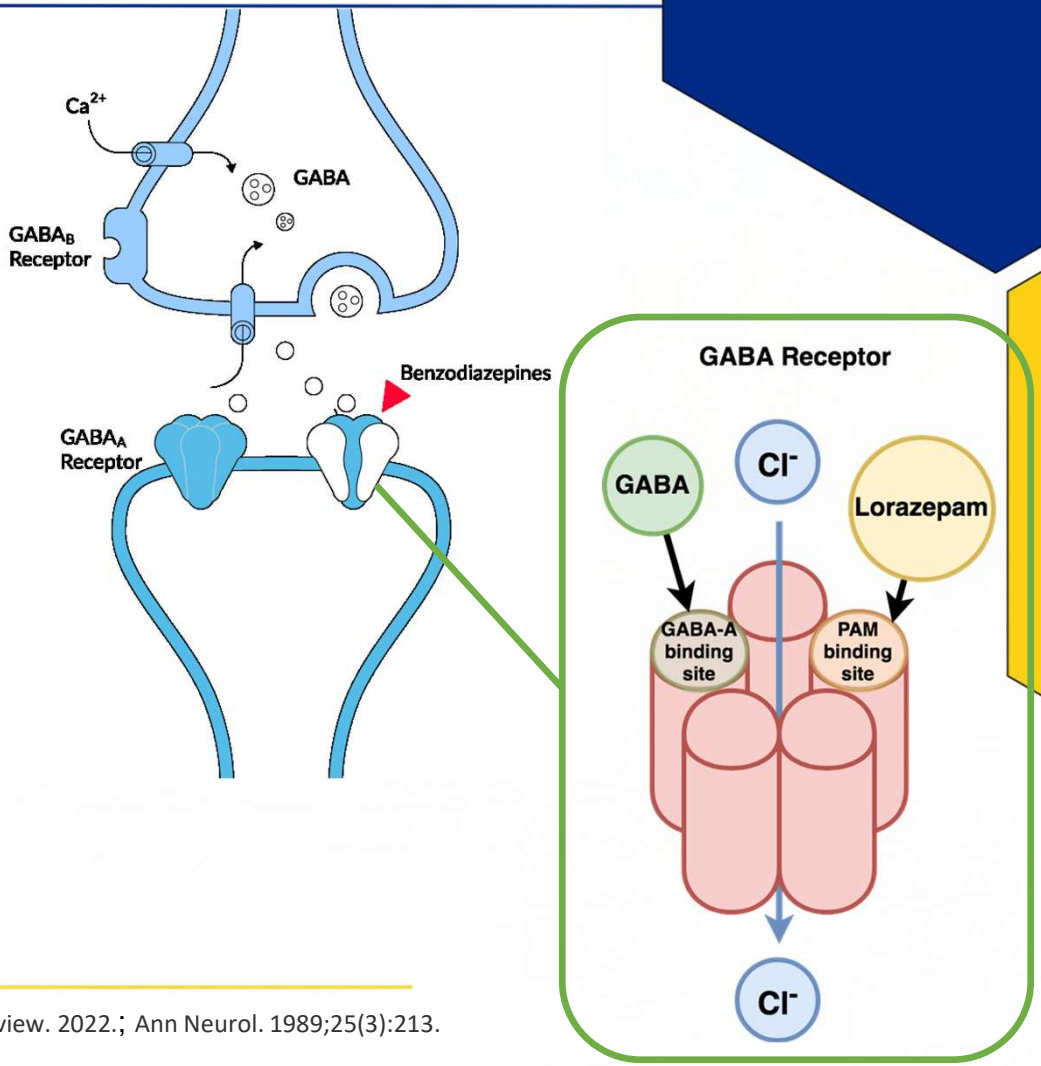
- Most commonly used CNS depressant in the US after alcohol

Common uses: treatment of anxiety, insomnia, catatonia, alcohol detox and seizures

Shorter E (2005). "Benzodiazepines". A Historical Dictionary of Psychiatry. Oxford University Press. pp. 41–2. ISBN 978-0-19-517668-1.

Mechanism of Action

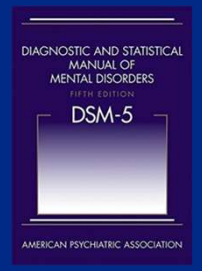
- BZDs affect a receptor in the brain called the **gamma-aminobutyric acid (GABA-A) receptor**
- By binding to GABA-A receptors, BZDs ↑ the receptor affinity for GABA & **lead to an enhancement of the inhibitory effects of GABA**
- This inhibitory effect leads to the anxiolytic, hypnotic, anticonvulsive, & muscle-relaxing properties of BZDs



Titus-Lay, E. Substance-Related Disorders. CPNP Psychiatric Pharmacotherapy Review. 2022.; Ann Neurol. 1989;25(3):213.

DSM 5 Diagnostic Criteria

Sedative, Hypnotic, or Anxiolytic (i.e. Benzodiazepine) Use Disorder



A problematic pattern of sedative, hypnotic, or anxiolytic use leading to clinically significant impairment or distress, as manifested by ≥2 of the following, occurring within a 12-month period:

1. Sedatives, hypnotics, or anxiolytics are often taken in larger amounts or over a longer period than was intended
2. There is a persistent desire or unsuccessful efforts to cut down or control sedative, hypnotic, or anxiolytic use
3. A great deal of time is spent in activities necessary to obtain, use or recover from the sedative, hypnotic, or anxiolytic
4. Craving, or a strong desire or urge to use the sedative, hypnotic, or anxiolytic
5. Recurrent sedative, hypnotic, or anxiolytic use resulting in a failure to fulfill major role obligations at work, school, or home
6. Continued use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the substance
7. Important social, occupational, or recreational activities are given up or reduced because of sedative, hypnotic, or anxiolytic use
8. Recurrent sedative, hypnotic, or anxiolytic use in situations in which it is physically hazardous
9. Use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
10. Tolerance, as defined by either of the following:
    a. A need for markedly ↑ amounts of the sedative, hypnotic, or anxiolytic to achieve intoxication or desired effect
    b. A markedly diminished effect with continued use of the same amount of the sedative, hypnotic, or anxiolytic
11. Withdrawal, as manifested by either of the following:
    a. The characteristic withdrawal syndrome for sedatives, hypnotics, or anxiolytics
    b. Sedatives, hypnotics, or anxiolytics (or a closely related substance, such as alcohol) are taken to relieve or avoid withdrawal symptoms

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.)

Epidemiology

Incidence & Prevalence

4.8 to 5.9 million people (1.8 to 2.1% of the U.S. population) ≥12 years old misused prescription BZDs, tranquilizers or sedatives in the past year

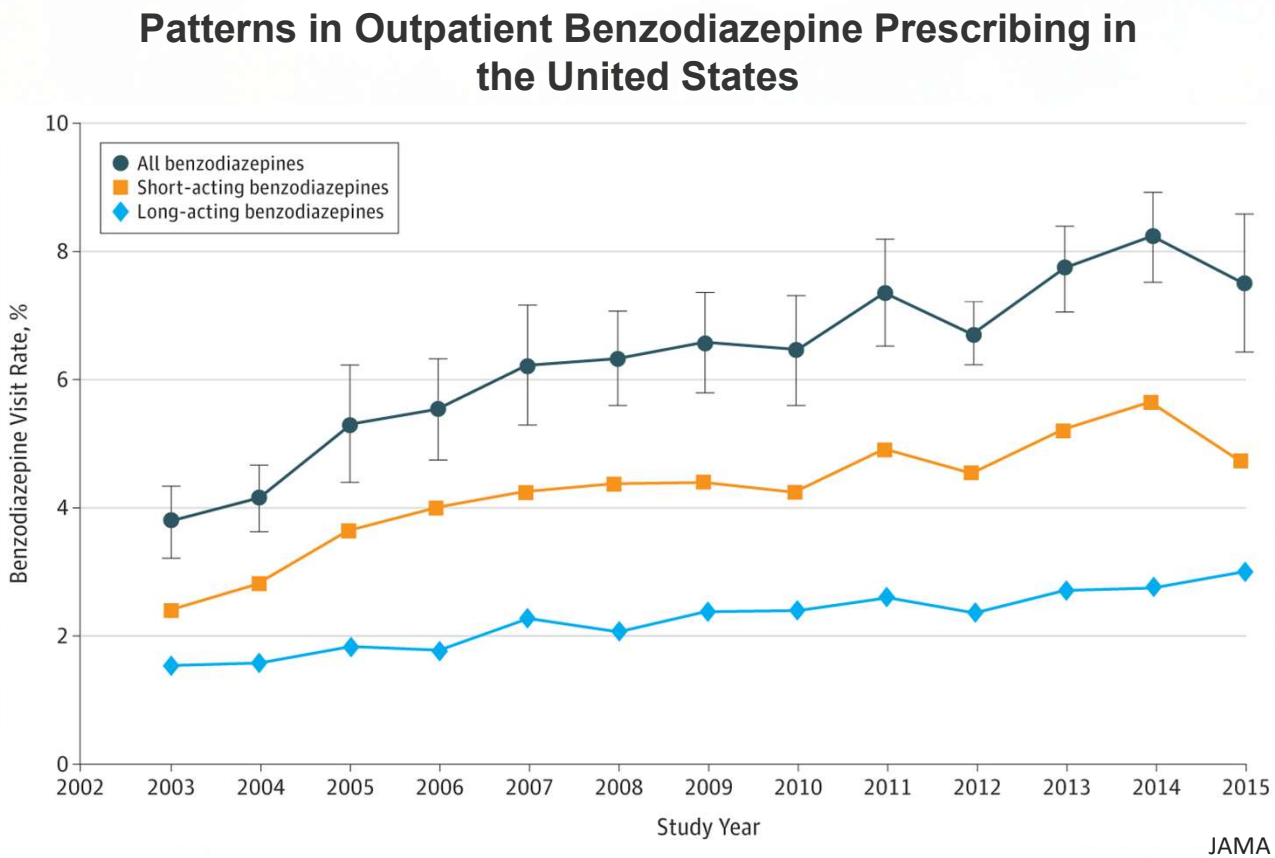
- Represents 9% of total illicit drug use

SUD treatment admissions for BZDs use has consistently risen

- In a 10-year period (2007-2017), rates doubled from 0.5% to 1%

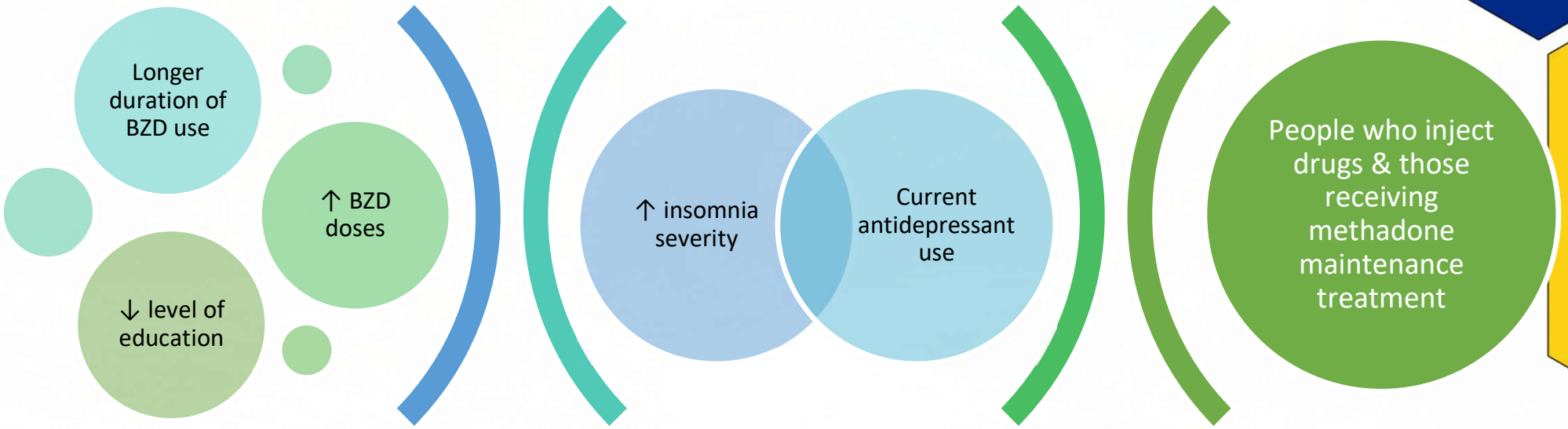
Substance Abuse and Mental Health Services Administration. 2019 National Survey on Drug Use and Health. Substance Abuse and Mental Health Services Administration; Department of Health and Human Services, Rockville, MD 2020.

How Frequently are BZDs Prescribed?



JAMA Netw Open. 2019;2(1):e187399.

Etiology & Risk Factors



Several risk factors for BZD UD have been identified:

Misuse of prescribed BZDs, which can contribute to or result from BZD UD, is associated with a:

↑ rates of misuse of BZDs have also been found among:

Compr Psychiatry 2004; 45:88.; Addiction 2012; 107:2173.; Addiction 1994; 89:379.; Drug Alcohol Depend 1999; 55:63.; Drug Alcohol Depend 1993; 32:257.

Clinical Course

Initial use and development of BZD UD often begin in teen years or early adulthood

Physiological dependence & impaired function ensue after prolonged use

Major concern for negative impact on cognition (e.g., memory, processing speed, attention) associated with long-term BZD use

Risk of fatal overdose with BZDs alone is low

Chance of **fatality ↑** when used concurrently with other respiratory depressants **(i.e., opioids)**

Titus-Lay, E. Substance-Related Disorders. CPNP Psychiatric Pharmacotherapy Review. 2022.

Co-occurrence

Benzodiazepine and Opioid Use

BZDs + Opioids = **Common Dangerous Cocktail**

- Co-administration of BZDs & opioids
  = ↑ rewarding effects than either agent alone

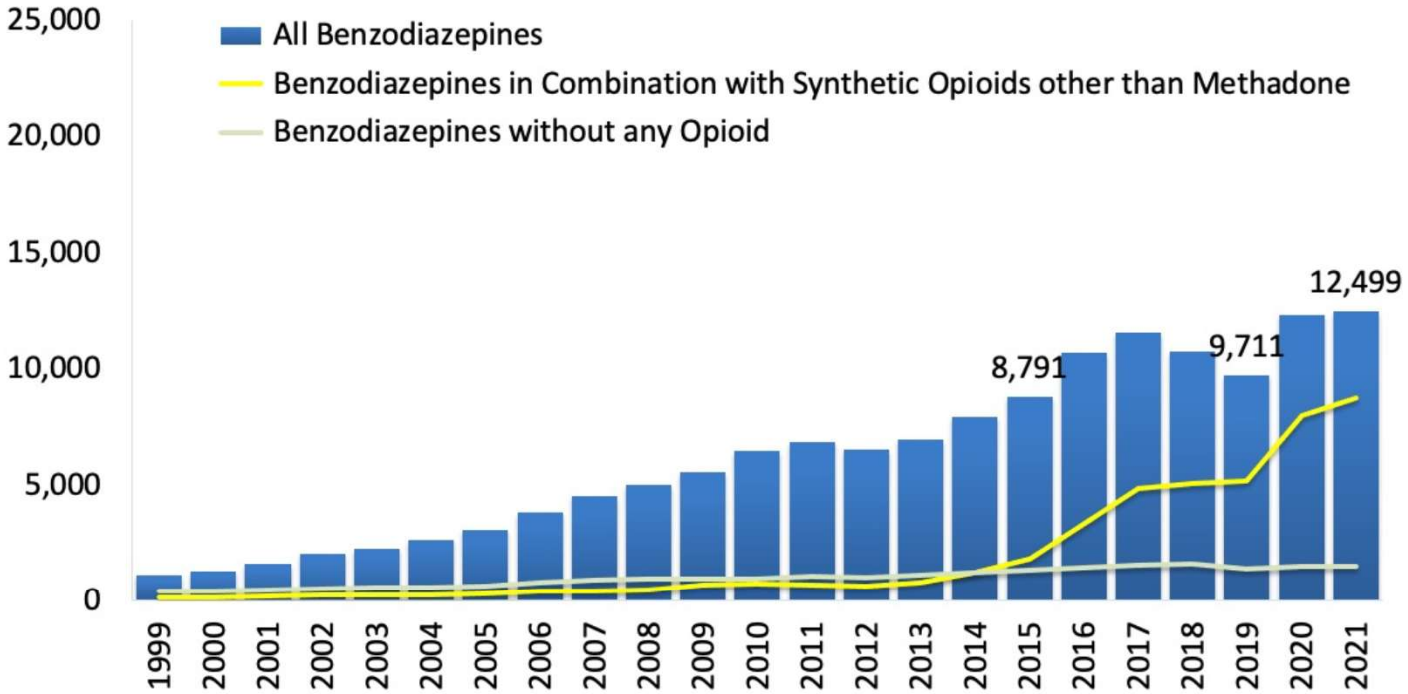
- Commonly abused BZDs w/ opioids include diazepam, midazolam, alprazolam (all have rapid onset 2/2 ↑ degree of lipophilicity)

- Prevalence of BZDs use among patients receiving methadone & buprenorphine
  = **51 -70%**

- In 2012: 73% of heroin users entering treatment report BZD use in the prior year

J Clin Psychiatry. 2006;67(7):1062.; Drug and alcohol dependence. 2012;125(1-2):8-18.

Figure 9. National Drug Overdose Deaths Involving Benzodiazepines*, by Opioid Involvement, Number Among All Ages, 1999-2021



*Among deaths with drug overdose as the underlying cause, the benzodiazepine category was determined by the T42.4 ICD-10 multiple cause-of-death code. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

Data shows an ↑ overdose mortality from benzodiazepines over the past decade secondary to concurrent opioid use

Co-occurrence

Benzos used w/ opioids ↑ ↑ ↑ risk of respiratory depression

Risk Index for Overdose or Serious Opioid-Induced Respiratory Depression (RIOSORD)

Description	Y/N	Score
In the past 6 months, has the patient had a health care visit (outpatient, inpatient, or ED) involving:		
Opioid dependence?		15
Chronic hepatitis or cirrhosis?		9
Bipolar disorder or schizophrenia?		7
Chronic pulmonary disease? (e.g., emphysema, chronic bronchitis, asthma, pneumoconiosis, asbestosis)		5
Chronic kidney disease with clinically significant renal impairment?		5
Active traumatic injury, excluding burns? (e.g., fracture, dislocation, contusion, laceration, wound)		4
Sleep apnea?		3
Does the patient consume:		
An extended-release or long-acting (ER/LA) formulation of any prescription opioid or opioid with long and/or variable half-life? (e.g.,OxyContin, Oramorph-SR, methadone, fentanyl patch, levorphanol)		9
Methadone? (Methadone is a long-acting opioid, so also write Y for "ER/LA formulation")		9
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Is the patient's current maximum prescribed opioid dose:		
>100 mg morphine equivalents per day?		16
50-100 mg morphine equivalents per day?		9
20-50 mg morphine equivalents per day?		5
In the past 6 months, has the patient:		
Had 1 or more ED visits?		11
Been hospitalized for 1 or more days?		8
Total Score		**115**

Opioid Induced Respiratory Depression (OIRD) Probability based on Calculated Risk Index

Risk index score	OIRD probability (%)
0-24	3
25-32	14
33-37	23
38-42	37
43-46	51
47-49	55
50-54	60
55-59	79
60-66	75
≥67	86

Adapted from: Zedler B, Xie L, Wang L et al. Development of a Risk Index for Serious Prescription Opioid-Induced Respiratory Depression or Overdose in Veterans' Health Administration Patients. Pain Medicine. Jun 2015. 16;1566-1579.

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Patients with **opioid dependence who regularly use long-acting opioids**, including methadone, Experience more than a **4-fold increase** in the risk of **severe respiratory depression when prescribed benzodiazepines concurrently.**

Non-Pharmacologic Treatment for BZD UD

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Non-Pharmacologic Treatment

Long-Term Treatment

Cognitive Behavioral Therapy (CBT)

- In Darker et. al 2015 meta-analysis that included nine trials:
  - CBT+ benzo taper resulted in higher rates of benzodiazepine discontinuation at 3 months vs. taper alone (relative rate of effect 1.51, 95% CI 1.15-1.98)

Psychodynamic Therapy & Motivational Interviewing

Group or family therapies

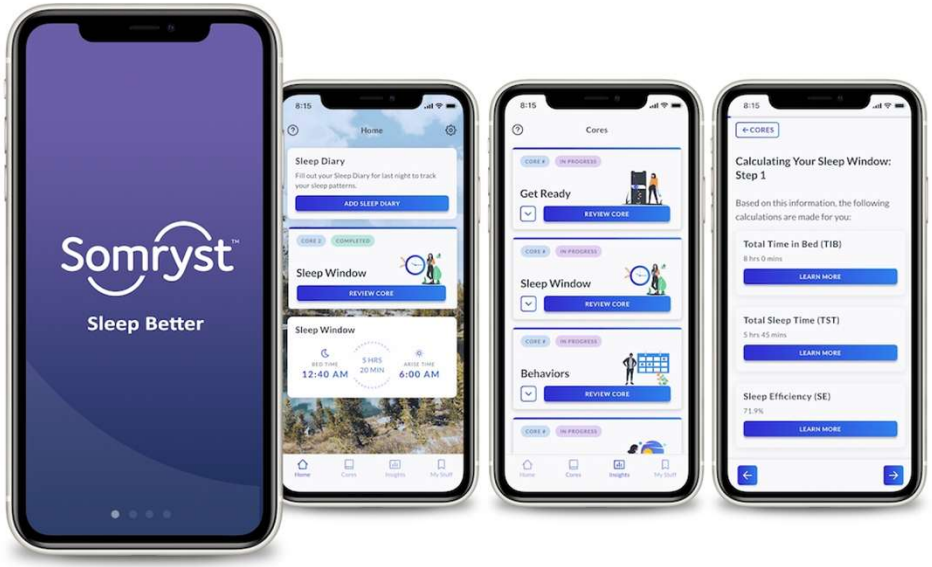
Sleep hygiene, stimulus control, relaxation techniques

Cochrane Database Syst Rev. 2015:(5):CD009652.

Somryst

Prescription Digital Therapeutic (PDT)

- The first and only FDA-approved PDT that uses CBTi for chronic insomnia



https://www.somryst.com/why-somryst/index.html

FDA Cleared Prescription Digital Therapeutics (PDTs)*

Six examples of DTx that have received FDA clearance for behavioral health treatment

Name	Used to Treat
EndeavorRx	Attention-deficit/hyperactivity disorder
Freespira	PTSD, panic disorder, panic attacks
NightWare	PTSD
reSET	Substance use disorders
reSET-O	Opioid use disorder
Somryst	Chronic insomnia

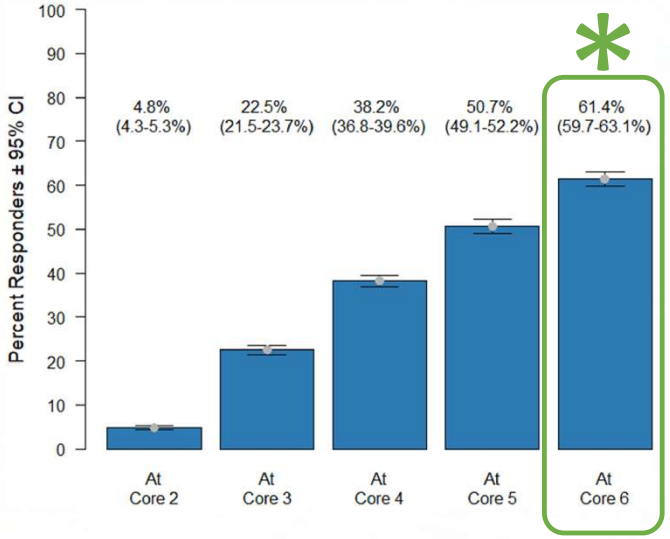
*Although all six have received FDA clearance, some have been more extensively researched, and long-term outcomes are still being examined.

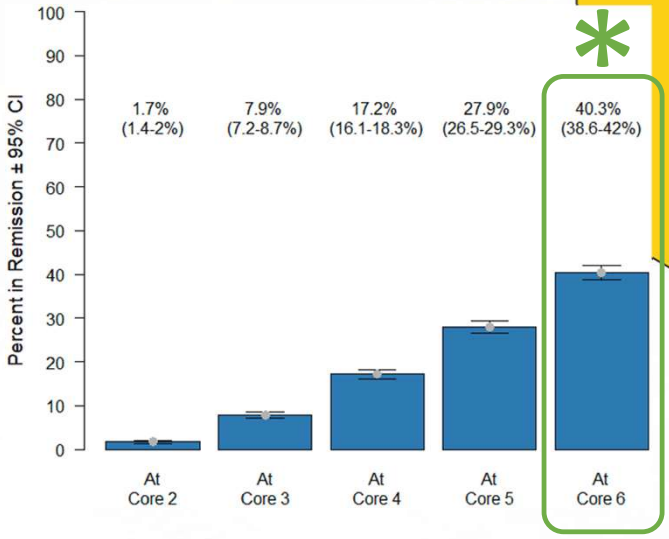
Real-world evidence from users of a behavioral digital therapeutic for chronic insomnia

Lee M. Ritterband [a,*], Frances P. Thorndike [b], Charles M. Morin [c], Robert Gerwien [b], Nicole M. Enman [b], Ray Xiong [b], Hilary F. Luderer [b], Samantha Edington [b], Stephen Braun [b], Yuri A. Maricich [b]

Highlights

- Although CBTi is first-line treatment for chronic insomnia, many do not receive the recommended treatment due to treatment barriers
- Digitally-delivered CBTi or Sleep Health Using the Internet (SHUTi) may expand treatment availability
- 7216 patients used SHUTi in the real-world (outside a clinical trial)
- **After treatment**:
  - **61.4% had meaningful response**
  - **40.3% met criteria for remission**





Behaviour Research and Therapy 2022. 153;104084.

Pharmacologic Treatment for BZD UD

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Treatment Guidelines

There are no medications FDA approved for BZD UD

General Approach	• Maintain patient safety & provide support during intoxication & withdrawal, & gradually taper BZDs
Co-existing Psychiatric Conditions	• Should be addressed & appropriately treated with first-line treatment options
BZD Intoxication/Overdose	• Patients should be appropriately monitored & treated symptomatically, as necessary • If co-ingestion is suspected, treat intoxication/overdose caused by the other substance (e.g., naloxone for opioid reversal)
Flumazenil	• FDA-approved for the treatment of BZD overdose • Use has been associated with serious adverse effects, including arrhythmias & seizures • Avoid routine use in the treatment of BZD overdose
BZD Withdrawal	• Gradually taper & discontinue BZDs to prevent withdrawal symptoms & ↓ seizure risk • Consider switching to long-acting BZD when tapering (i.e., clonazepam) • Gabapentin with 20-25% BZD dose ↓ per week

Titus-Lay, E. Substance-Related Disorders. CPNP Psychiatric Pharmacotherapy Review. 2022.

Team, A. S. A. M. "Joint Clinical Practice Guideline on Benzodiazepine Tapering: Considerations when Benzodiazepine Risks Outweigh Benefits."

ASAM American Society of Addiction Medicine

Now Available

The Joint Clinical Practice Guideline on Benzodiazepine Tapering: Considerations When Benzodiazepine Risks Outweigh Benefits

Risks of Co-Prescribing Benzodiazepines and Opioids

- Patients taking both **benzos and opioids** are at significantly **higher risk of respiratory depression.**
- Assess risks and benefits at every prescription renewal or clinical encounter, **at least every 3 months.**
- Increased risks include higher overdose rates, ED visits, and overall healthcare utilization.
- Patients co-prescribed these medications commonly have higher opioid doses and report increased pain and lower pain management self-efficacy.
- Additional risk factors: SUDs, bipolar disorder, schizophrenia, or use of potent opioids (e.g., fentanyl).

Team, A. S. A. M. "Joint Clinical Practice Guideline on Benzodiazepine Tapering: Considerations when Benzodiazepine Risks Outweigh Benefits."

ASAM American Society of Addiction Medicine

Now Available

The Joint Clinical Practice Guideline on Benzodiazepine Tapering: Considerations When Benzodiazepine Risks Outweigh Benefits

Clinical Recommendations for Managing Co-Prescription

- Offer or prescribe **naloxone** to all patients co-prescribed opioids and BZDs.
- Utilize the **lowest effective doses of both BZD and opioid medications.**
- Optimize **non-opioid** pain interventions, including exercise, CBT and mindfulness-based practices.
- Consider prescribing **buprenorphine**, a partial opioid agonist, for managing pain as lower risk.
- Coordinate care among all prescribing clinicians, using **Prescription Drug Monitoring Program.**

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Implementation and Risk Assessment Tools

- **Regularly reassess risks vs. benefits**, particularly when patients have additional risk factors.
- Employ the **Risk Index for Overdose or Serious Opioid-induced Respiratory Depression** (RIOSORD) to identify patients at highest risk.
  - → Evaluates co-occurring SUDs, psychiatric dx, biomedical factors, opioid formulations, and concurrent medication use.
- Maintain open communication with all healthcare providers involved; leveraging systems
- **Ensure shared decision-making** and clearly discuss tapering strategies when risks outweigh benefits.

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Appendix K. Adjunctive Pharmacological Interventions

Tables K.1 and K.2 were created to support Recommendation #11: Clinicians should first consider pausing or slowing the pace of the BZD taper when patients experience symptoms that significantly interfere with the taper (eg, sleep difficulty, anxiety), although clinicians can also

Table K.1. Medications for Anxiety-Related Symptoms*

Medication	Class/ Mechanism	Considerations for Use	Other Population Considerations
Acute Anxiety			
Clonidine†	Central alpha-2 agonist	Monitor blood pressure; avoid in hypotension If used as a scheduled medication, taper to discontinue	
Gabapentin†	GABA analogue	Risk for misuse Risk associated with combining with other medications, particularly opioids	Avoid in patients with history of sedative use disorder

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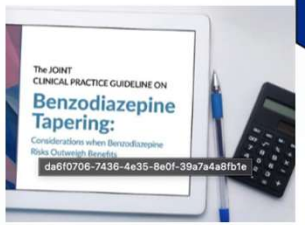

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Deprescribing benzodiazepine receptor agonists

Evidence-based clinical practice guideline

Kevin Pottie, Wade Thompson, Simon Davies, Jean Grenier, Cheryl A. Sadowski, Vivian Welch, Anne Holbrook, Cynthia Boyd, Robert Swenson, Andy Ma and Barbara Farrell

Canadian Family Physician May 2018, 64 (5) 339-351;

CFP MFC
CANADIAN FAMILY PHYSICIAN • LE MÉDECIN DE FAMILLE CANADIEN
The official journal of the College of Family Physicians of Canada

Recommendations*

- **Elderly adults (≥ 65 years)** - deprescribe (slowly taper) off BZDs, regardless of use duration
- **Adults (18 to 64 years)** - suggest describing (slowly taper) who have used BZDs for > 4 weeks
- These recommendations apply to patients who use BZDs:
  - To treat insomnia on its own (primary insomnia); or
  - Comorbid insomnia where potential underlying comorbidities are effectively managed

**This guideline does not apply to those with other sleep disorders or untreated anxiety, depression, or other physical or mental health conditions that might be causing or aggravating insomnia*

Canadian Family Physician May 2018. 64(5);339-351. Available at: https://www.cfp.ca/content/64/5/339

Practice Considerations

Example Prescribing Guidelines

I. Benzodiazepine Discontinuation Strategy:

1. **Confirm the patient has been on a benzodiazepine for ≥ 4 weeks** via prescription drug registry check and/or consistent urine drug screen results (please note that lower doses of clonazepam may not result in a positive result on a qualitative urine drug screen).
2. **Collaborative Engagement:** Ensure patients understand the tapering process and the reasons behind it. Involve them in decision-making to increase their commitment to the plan.
3. **If the patient is not taking Clonazepam, convert the patient's benzodiazepine to a dose equivalent amount of Clonazepam** to pursue gradual tapering. Dose conversion resources include:

   Benzodiazepine Conversion Calculator (mdcalc.com)

   https://www.mdcalc.com/calc/10091/benzodiazepine-conversion-calculator
4. **Gradual Tapering:** Implement a slow tapering strategy to minimize withdrawal symptoms and increase the likelihood of successful discontinuation.
   - **Initial Taper:** Aim for approximately 25% dose reduction of Clonazepam every two weeks. Monitor the patient for withdrawal symptoms and adjust the tapering schedule if needed. If the patient does not have renal insufficiency, consider using gabapentin during the benzodiazepine taper as an adjunct (dosed 300 mg PO TID with the option to increase to 600 mg PO TID as tolerated).
   - **Final Stages:** As the patient approaches the end of the taper, consider smaller reductions, such as 12.5% every two weeks, and/or incorporate benzo-free days.
5. **Monitoring and Support:** Regularly monitor patients throughout the tapering process. Provide support and counseling to help manage any withdrawal symptoms or anxiety related to discontinuation.

Practice Considerations

Example Prescribing Guidelines

Restricted Benzodiazepines

The following benzodiazepines are **not prescribed** unless approved by the CMO due to their high lipophilicity and associated risks:

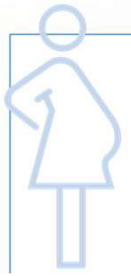
1. **Alprazolam**
2. **Diazepam**

Transition Strategy For patients currently taking short-acting and/or highly lipophilic benzodiazepines, the following transition strategy will be implemented:

1. **Supervised Transition:** Under the supervision of the CMO, patients will be transitioned to benzodiazepines with lower abuse potential, such as clonazepam. In the case of alprazolam, the patient may require a period of continued use of alprazolam at successively lower doses prior to transitioning to clonazepam.

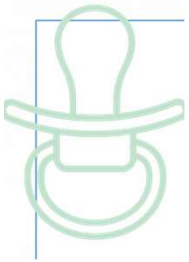
Special Populations

Pregnancy

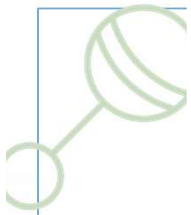


Pregnant women with BZD dependence should be gradually tapered off BZDs to avoid severe withdrawal symptoms

Abrupt cessation of BZDs should be avoided during pregnancy



Long-acting BZD agents are recommended for tapers during pregnancy



Inpatient management of withdrawal symptoms should be considered in pregnant patients

Titus-Lay, E. Substance-Related Disorders. CPNP Psychiatric Pharmacotherapy Review. 2022.

Return to the Patient Case

406Recovery.Care

Patient Case

AN is a 47-year-old women who presents to your clinic for “feeling overwhelmed by anxiety”. She currently works part-time at a nursery and is completing a BS degree online.

She is currently prescribed clonazepam 3 mg daily x 1 year that she takes regularly. In addition, AN is enrolled in an opioid treatment program (OTP) and receives methadone 110 mg PO daily for opioid use disorder. Denies taking further presciption medications noting “benzos are the only thing that works for me to help with anxiety.”

However, 3 weeks ago she started using diverted alprazolam, “Xanny Bars” that she buys from a friend or off the street. She reports rebound anxiety, stating “if I miss a dose of Xanax, I get bad anxiety…I often wakeup in the middle of the night with panic attacks.”

How do you proceed?

Select all that apply

1. Start a gradual benzodiazepine taper
2. Consider prescribing adjunctive medication to facilitate benzodiazepine dose reduction
3. Engage in motivational interviewing targeting benzodiazepine use reduction/cessation
4. Tolerate long-term benzodiazepine use so long as she is only taking clonazepam
5. Insist on abstinence from benzodiazepines prior to prescribing any additional medication
6. Proceed to treat PTSD and anxiety with evidence-based pharmacological treatment
7. Refer to a qualified therapist for Cognitive Behavioral Therapy

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Select all that apply

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7. **Refer to a qualified therapist for Cognitive Behavioral Therapy**

Objectives

1. Acknowledge how benzodiazepines work

2. Discuss the epidemiology of benzodiazepine use disorder (BZD UD) and the pertinent concerns

3. Discuss safety concerns of combined benzo and opioid use

4. Evaluate current forms of treatment for Benzodiazepine Use

   → The ASAM Guidlines

Objectives → *Takeaways*

1. Acknowledge how benzodiazepines work
   Bind GABAA receptors → enhance GABA activity → CNS Depression

2. Discuss the epidemiology of benzodiazepine use disorder (BZD UD) and the pertinent concerns
   BZD misuse = 9% of total illicit drug use and rising

3. Discuss safety concerns of combined benzo and opioid use
   ↑ ↑ ↑ *risk of respiratory depression and risk of death from overdose*

4. Evaluate current forms of treatment for Benzodiazepine Use
   → The ASAM Guidelines
   Gradually Taper BZD + CBT + treat co-occurring disorders

Questions?

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