Benzodiazepines

The Good, The Bad and The Ugly

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Addiction Medicine Network **May 2, 2024**

Objectives

1. Acknowledge how benzodiazepines work and their potential for abuse/misuse

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

3. Acknowledge current forms of treatment for BZD UD

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 only prescribed clonazepam 5 mg daily x 1 year that she takes regularly, no other psychotropic medications as “benzos are the only thing that works for me.”

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 wake up in the middle of the night with panic attacks.”

General Information

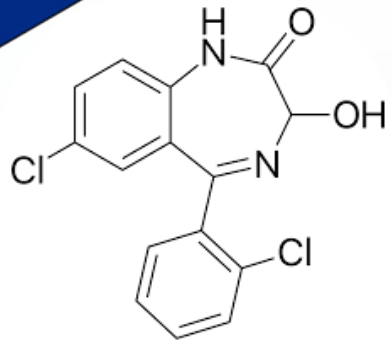
Terminology

- Benzodiazepines (BZDs)a ct as 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

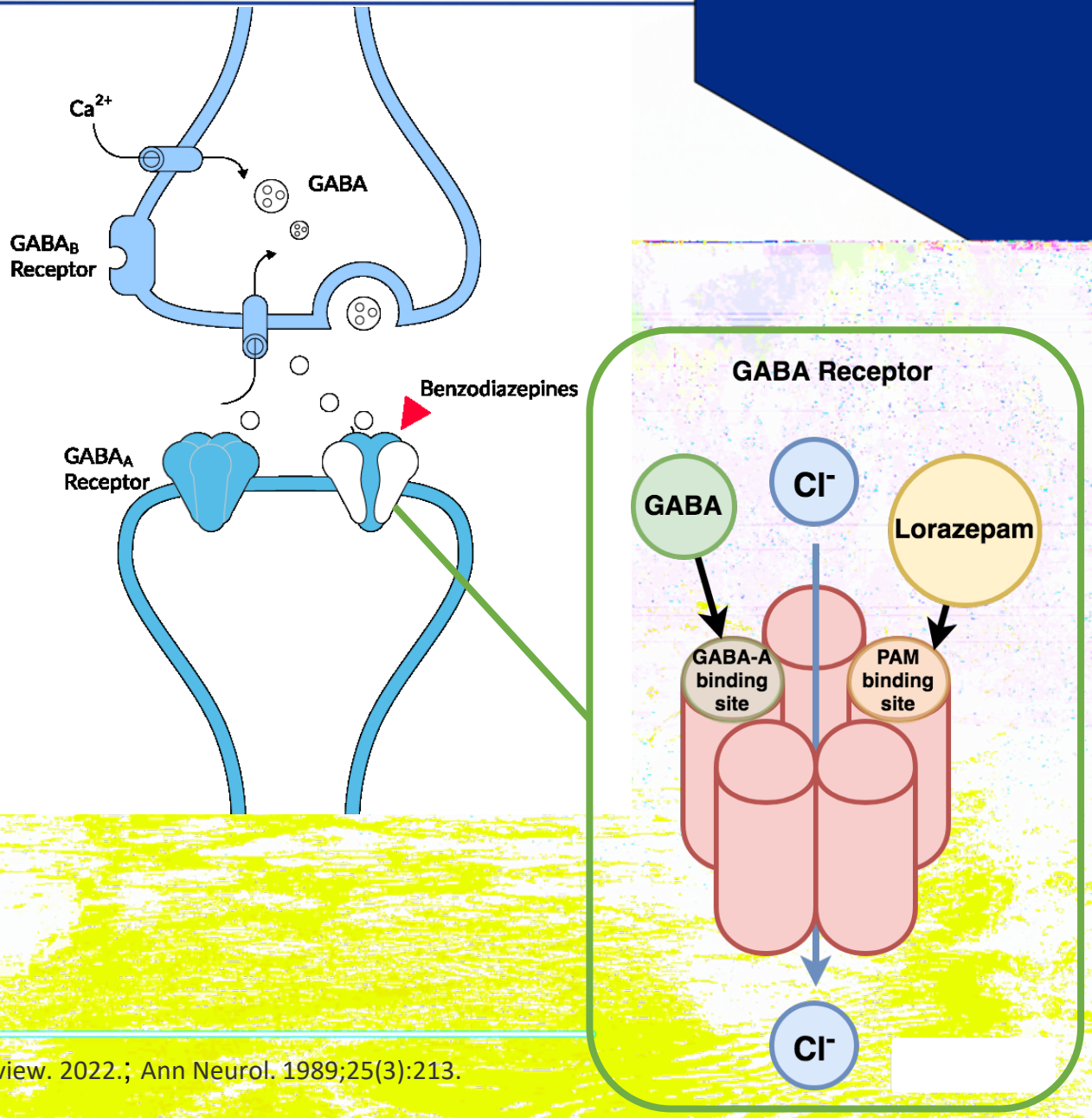
- Most commonly used CNS depressant in the US after alcohol

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.

Benzodiazepine receptor

- GABA is the major inhibitory neurotransmitter, and it operates in more than a third of CNS synapses
- Benzodiazepines enhance synaptic actions of GABA
- Benzodiazepine receptor is an allosteric recognition site on the GABA receptor

GABA-Benzodiazepine Receptor Complex

- Pentameric structure composed of 5 distinct glycoprotein subunits that span a lipid bi-layer and form a cylindrical structure with a chloride channel as a center
- Activation causes an influx of chloride ions and membrane hyperpolarization responsible for neuronal inhibition
- Benzodiazepines do not activate this process but facilitate the action of GABA by increasing the frequency of ion channel opening
- Barbiturates and high dose alcohol prolong the opening

Benzodiazepines

- Benzodiazepines all work in essentially the same way but vary in:
  - Dosage
  - Rate of onset of action
  - Duration of action
  - Tendency to accumulate
  - Potency

High abuse potential

- Alprazolam
- Diazepam
- Lorazepam
- Triazolam

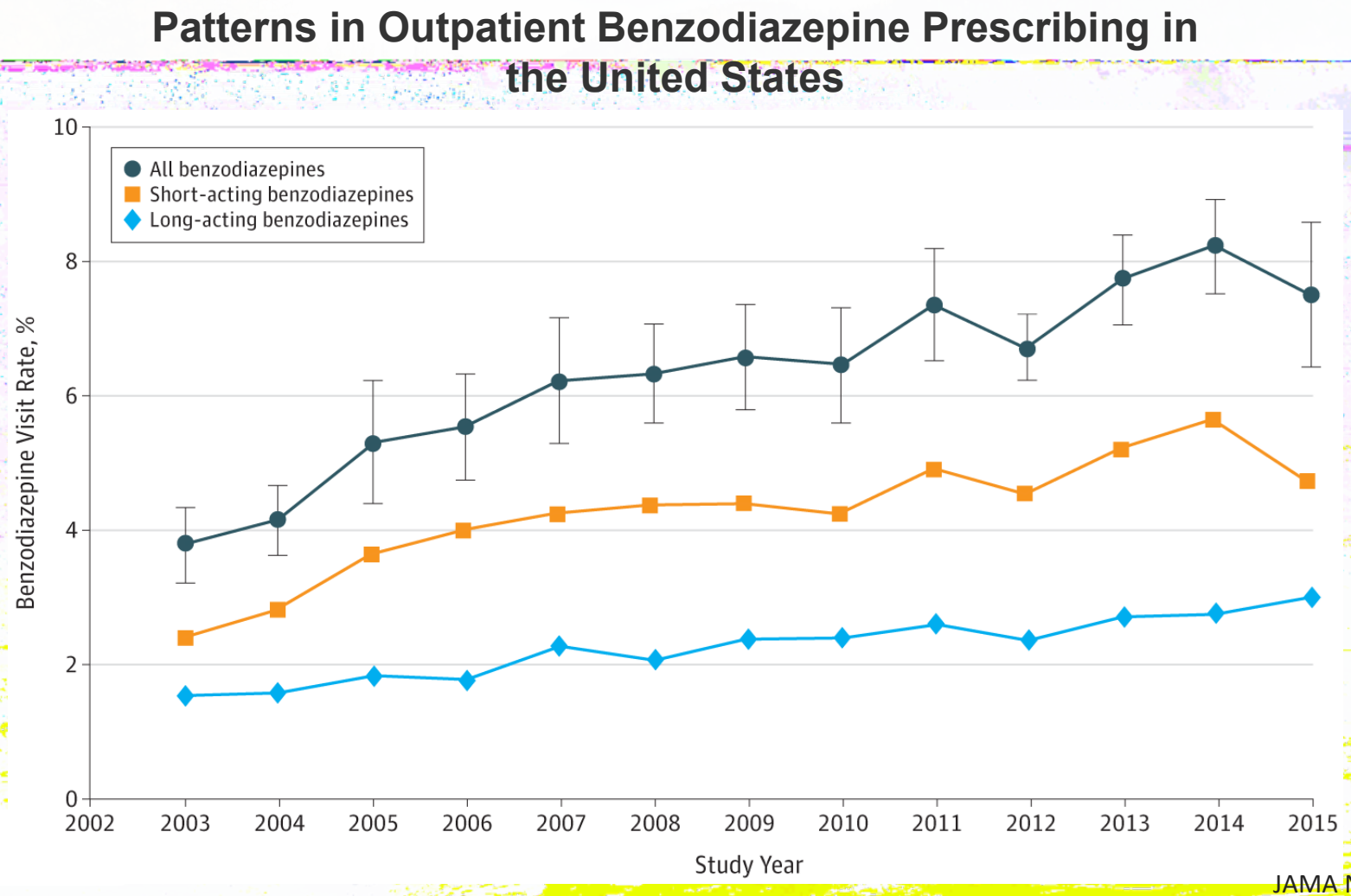
Lower abuse potential

- Oxazepam
- Halazepam
- Chlorazepate
- Chlordiazepoxide?
- Clonazepam

Benzodiazepine use

- 11% of population use benzodiazepine annually
  - 80% for < 4 months
  - 5% for 4-12 months
  - 15% > 12 months(about 1.6% of the population)

How Frequently are BZDs Prescribed?

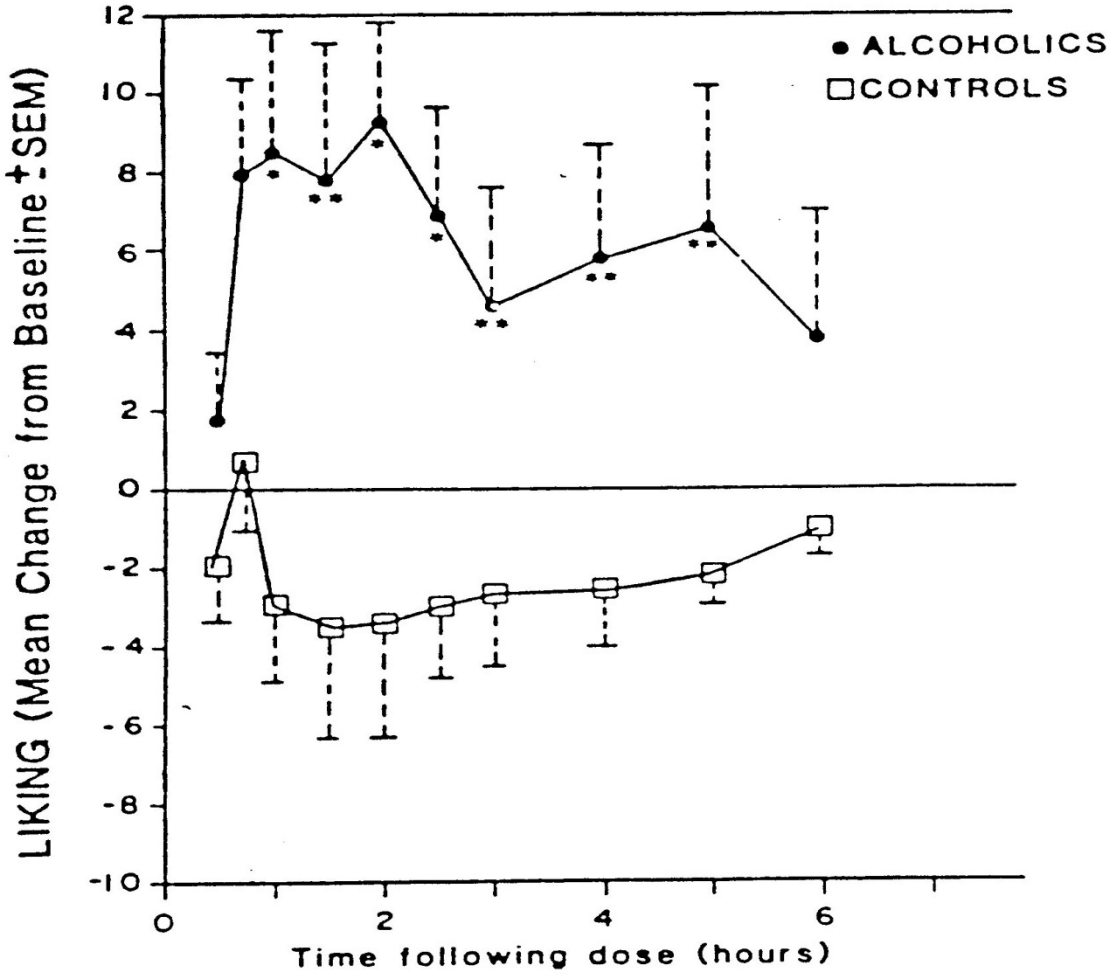


JAMA Netw Open. 2019;2(1):e187399.

Rates of Benzodiazepine Abuse

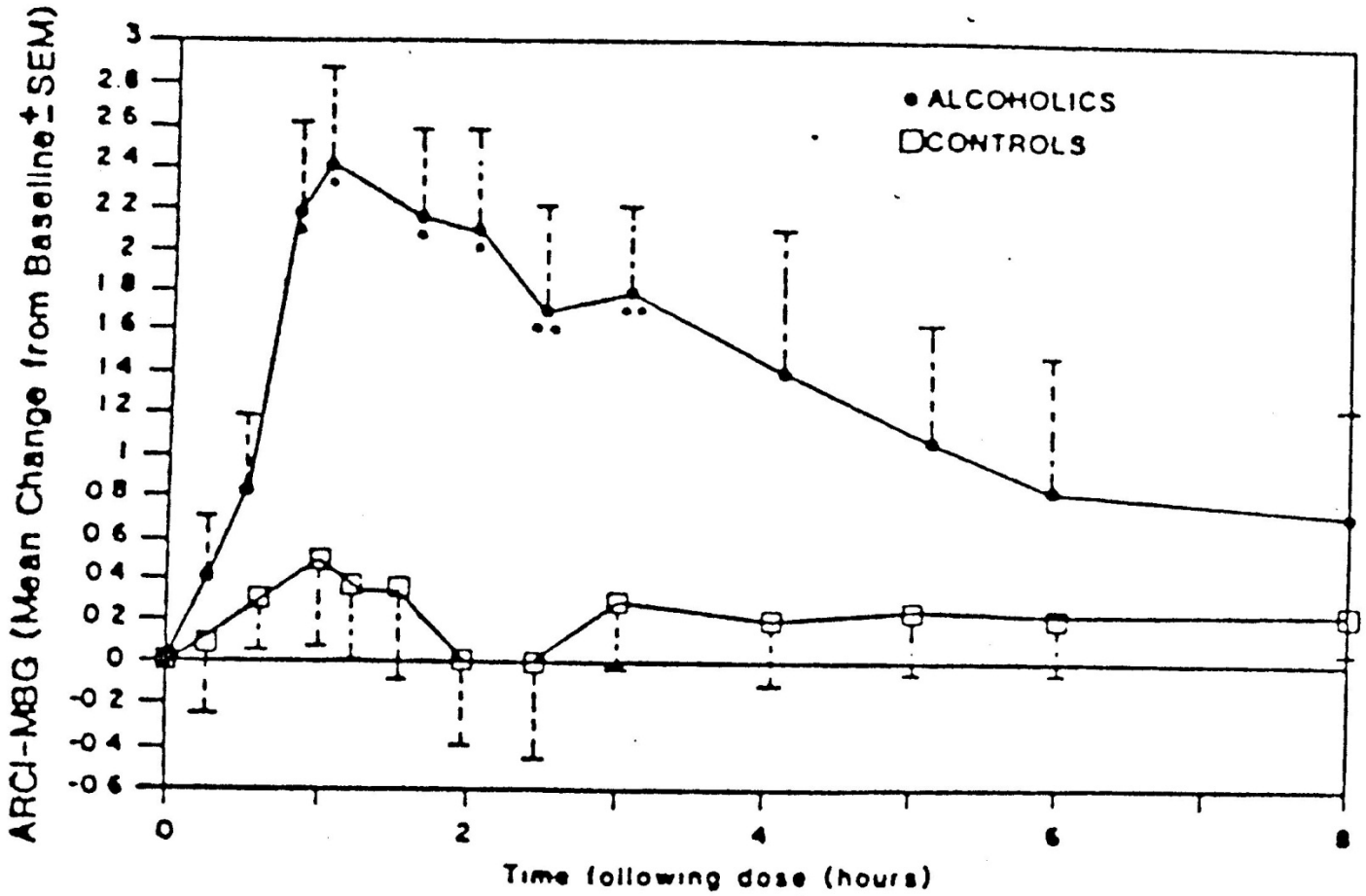
- General population variable
- Alcohol use disorders 30-75%
- Opioid use disorders up to 80%
- IP substance use disorders
  - Isolated BZD abusers 12%
  - Multiple substance dependent 80%

Figure 2. Comparison of Mean Drug-Liking Scale Scores After a Single 1-mg Oral Dose of Alprazolam to Alcoholics and Controls*



*Symbols: ** = $p \leq .05$; * = $p \leq .01$; T = standard error of the mean.

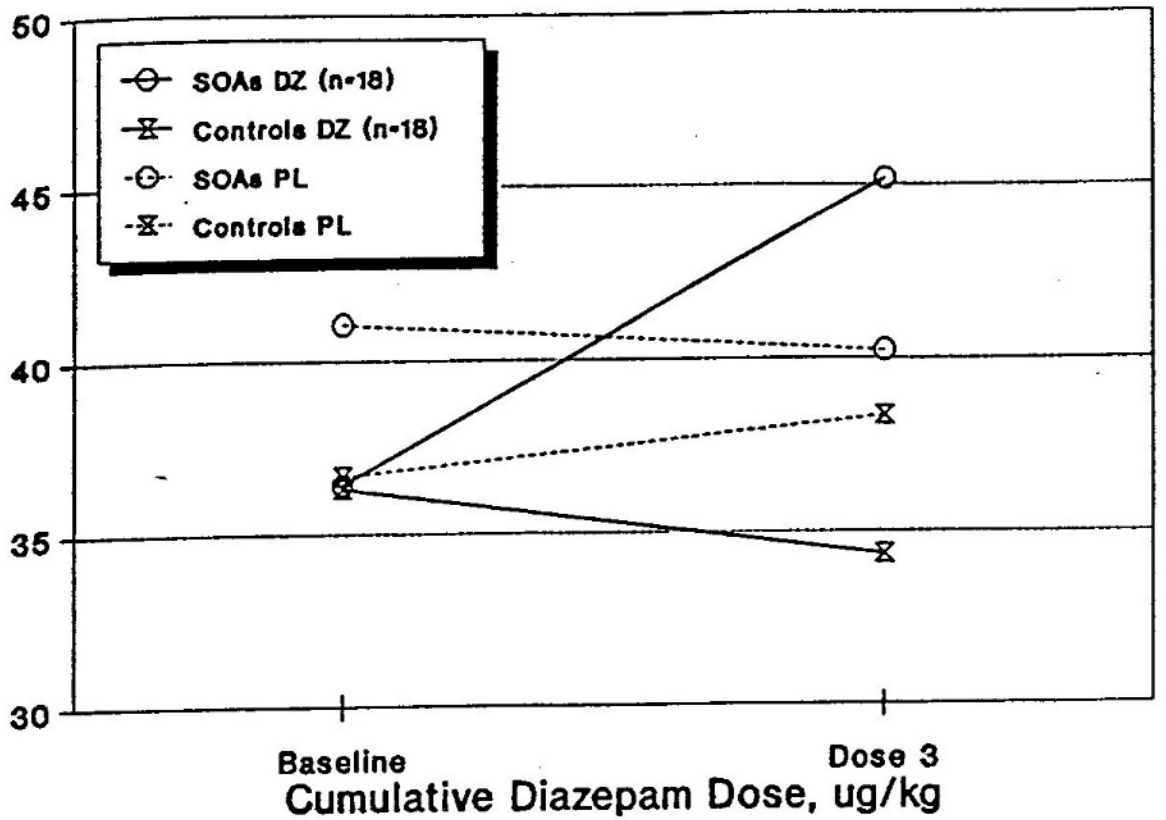
Figure 1. Comparison of Mean ARCI-MBG Scores After a Single 1-mg Oral Dose of Alprazolam to Alcoholics and Controls*



*ARCI-MBG = Addiction Research Center Inventory—Morphine/Benzedrine Group Scale. Symbols: ** = $p \leq .05$; * = $p \leq .01$; T = standard error of the mean.

RESPONSE TO DIAZEPAM IN SONS OF ALCOHOLICS

ARCI-MBG RATINGS



Separation from relapse and rebound may be difficult

- Relapse=re-emergence of original anxiety state
- Rebound=an increase in anxiety that is above original baseline levels
- Combination of relapse and withdrawal

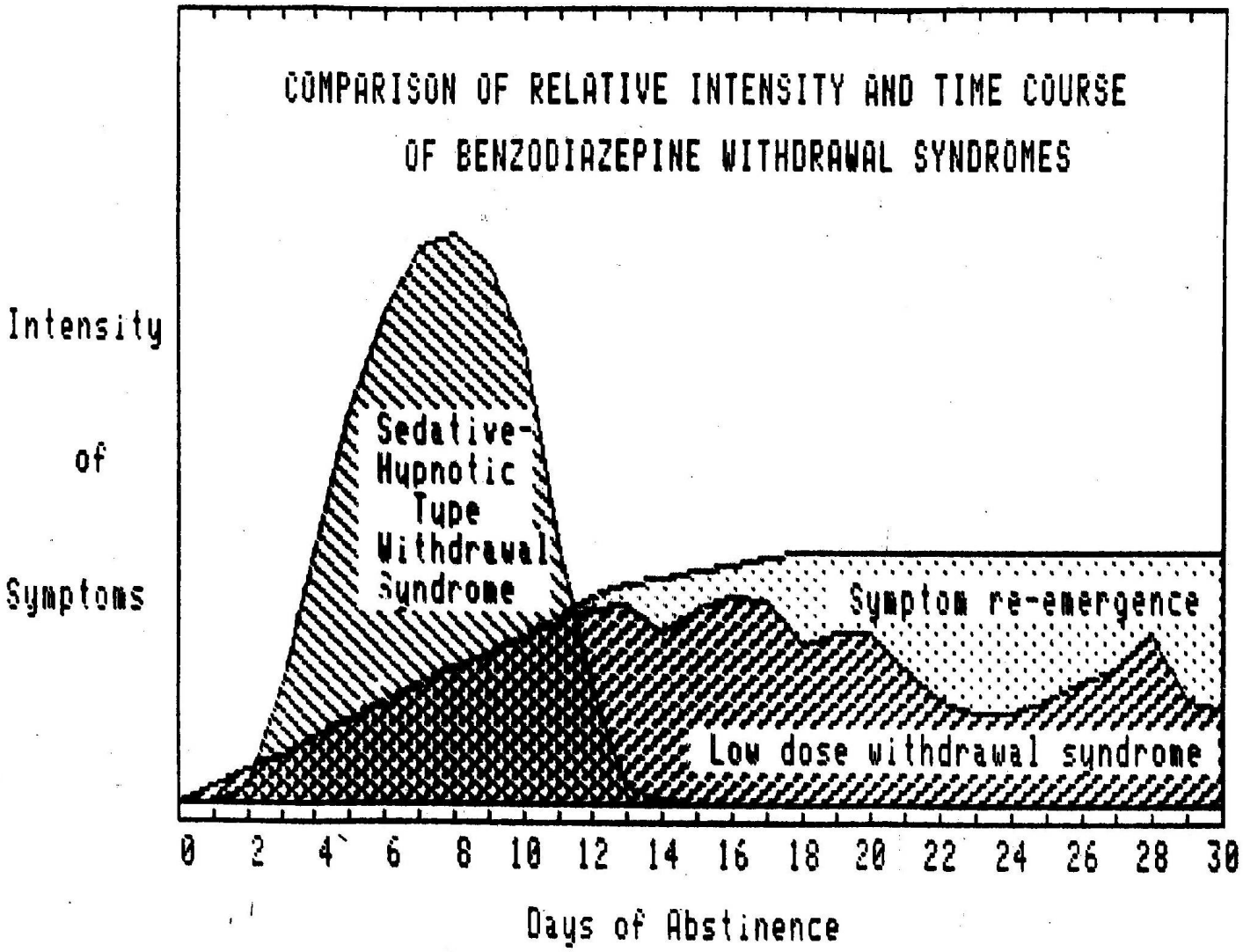
Cold Turkey

- Onset withdrawal day after with short and intermediate T1/2 drugs
- Onset within 3-8 days with long-acting BZD
- Withdrawal may last months

Withdrawal more probable or more severe if drug:

- Rapidly eliminated
- Highly potent
- Cold turkey
- High dose
- Chronic or prn basis vs. fixed
- More psychopathology
- With alcohol use
- Female
- Less educated
- Prior history alcohol and other substance use
- N.B. withdrawal less in short term users <6-8 months

FIGURE 1


COMPARISON OF RELATIVE INTENSITY AND TIME COURSE
OF BENZODIAZEPINE WITHDRAWAL SYNDROMES
Intensity
of
Symptoms
Sedative-
Hypnotic
Type
Withdrawal
Syndrome
Symptom re-emergence
Low dose withdrawal syndrome
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Days of Abstinence

63 panic patients
alprazolam 8 weeks, 2-10mg

- Median 8mg, tapered over 4 weeks
  - 35% rebound
  - 35% withdrawal with new somatic complaints
  - 10% co-existence of rebound and withdrawal
- Therefore, 50% had either withdrawal or rebound after only 8 weeks with a short T ½, high potency agent

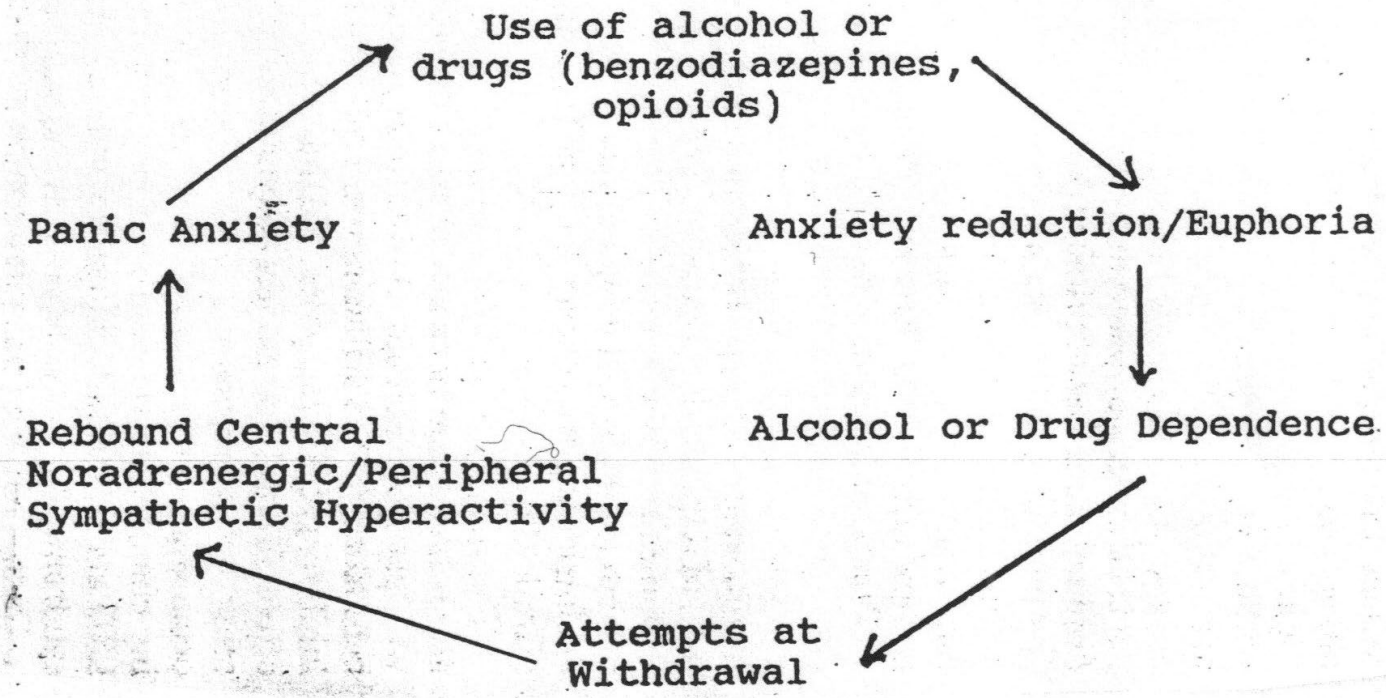
BZDs in insomnia

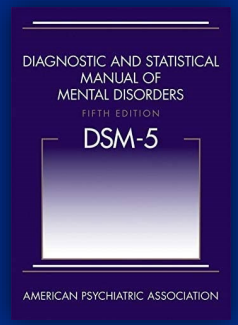
- Tolerance to sedation in 2-4 weeks
- Highest risk for abuse
  - Alcohol use disorder
  - Opioid use disorder

Adverse effects

- Impaired ability to learn new information
- Anterograde amnesia “blackouts”
- Triazolam, 40% of nights used, memory impairment
- In elderly:
  - More impairment of psychomotor function with long T1/2, than with short T1/2—increases risk of falling and hip fractures
- Depressive syndrome
  - 33% of 46 panic disorder patients receiving 3-10mg alprazolam
- Hostility
  - 10% of 80 patients given alprazolam

THE VICIOUS CYCLE OF ALCOHOL AND DRUG DEPENDENCE AND PANIC ANXIETY





DSM 5 Diagnostic Criteria

Sedative, Hypnotic, or Anxiolytic (i.e. Benzo) 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.

Comorbidity

Mental Health & SUD

BZD UD has been associated with a broad range of comorbid psychiatric disorders

In a survey of the United States general population, BZD UD was strongly associated with:

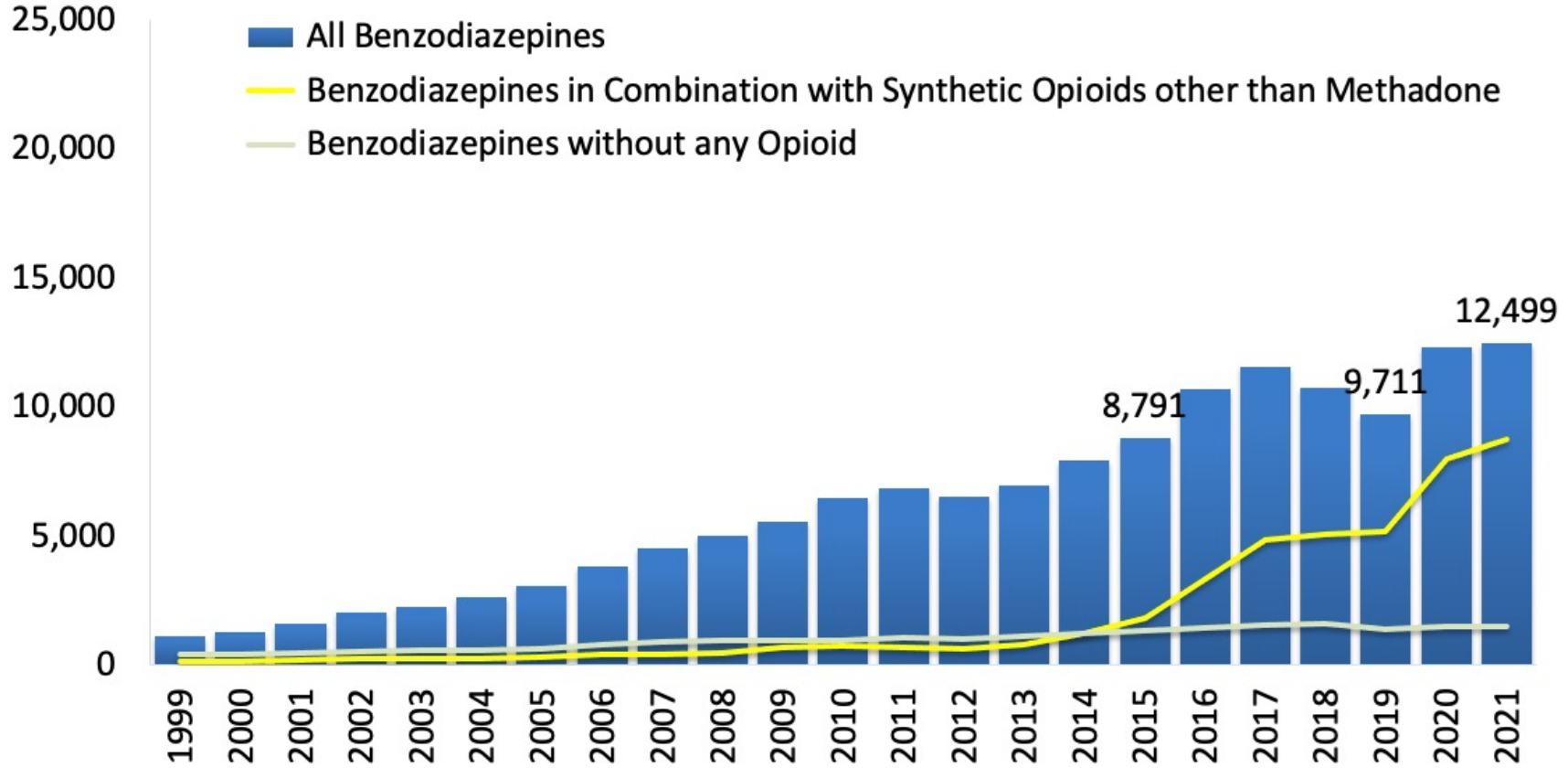
- Other substance use disorders
- Other prescription drug misuse
- Panic disorder with agoraphobia
- Bipolar I disorder
- Antisocial personality disorder

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 methadone & buprenorphine patients = **51 -70%**
- In 2012: 73% of heroin users entering treatment report BZD use in the preceding 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

Non-Pharmacologic Treatment for BZD UD

Non-Pharmacologic Treatment

Long-Term Treatment

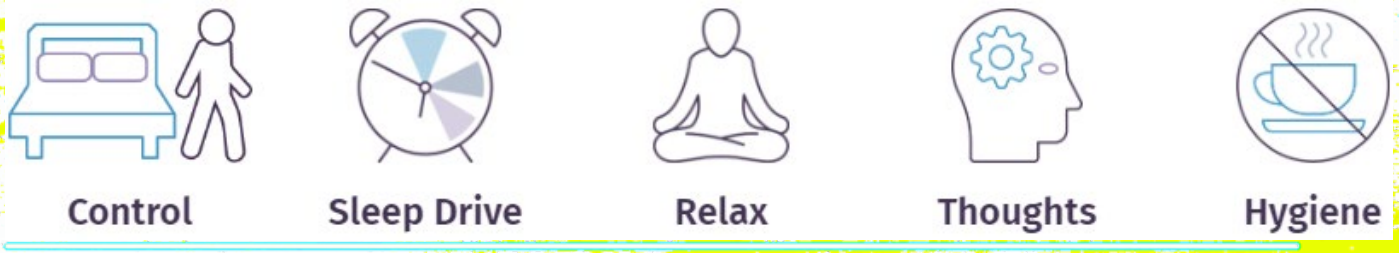
Cognitive Behavioral Therapy (CBT)

- 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

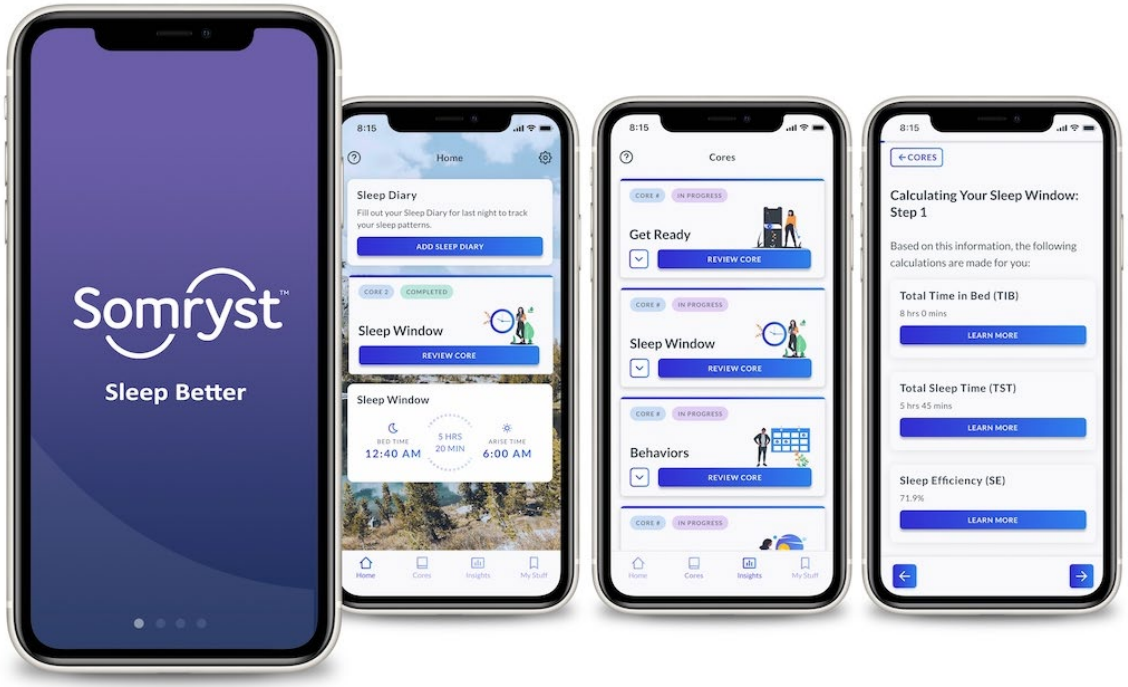


Cochrane Database Syst Rev. 2015:(5):CD009652.

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

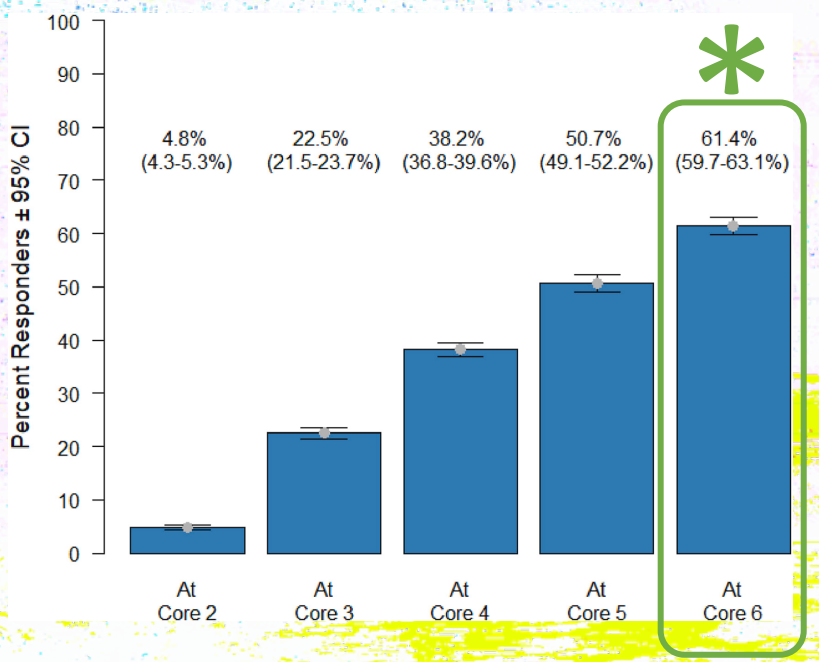
*Although all six have received FDA clearance, some have been more extensively researched, and long-term outcomes are still being examined.

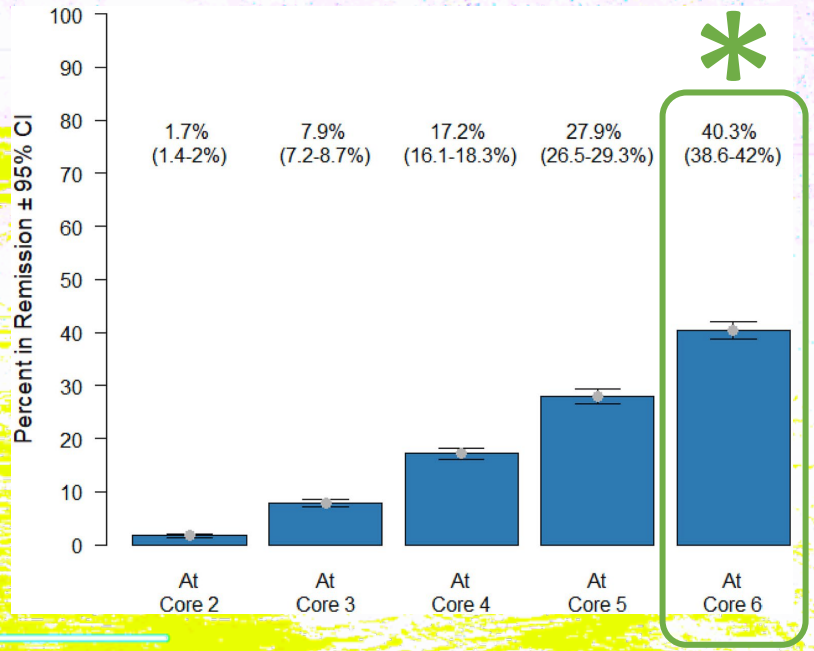
Real-world evidence from users of a behavioral digital therapeutic for chronic insomnia

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

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.

Withdrawal management

- Gradual reduction (+/- gabapentin)
- Switch to longer acting agent
- Switch to phenobarbital
- Carbamazepine(Tegretol) off label
- Psychological support
- May improve regarding anxiety and depression

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

deprescribing.org | Benzodiazepine & Z-Drug (BZRA) Deprescribing Algorithm

February 2019

Why is patient taking a BZRA?

If unsure, find out if history of anxiety, past psychiatrist consult, whether may have been started in hospital for sleep, or for grief reaction.

- Insomnia on its own OR insomnia where underlying comorbidities managed
  For those ≥ 65 years of age: taking BZRA regardless of duration (avoid as first line therapy in older people)
  For those 18-64 years of age: taking BZRA › 4 weeks

- Other sleeping disorders (e.g. restless legs)
- Unmanaged anxiety, depression, physical or mental condition that may be causing or aggravating insomnia
- Benzodiazepine effective specifically for anxiety
- Alcohol withdrawal

Engage patients (discuss potential risks, benefits, withdrawal plan, symptoms and duration)

Recommend Deprescribing

Continue BZRA

- Minimize use of drugs that worsen insomnia (e.g. caffeine, alcohol etc.)
- Treat underlying condition
- Consider consulting psychologist or psychiatrist or sleep specialist

Taper and then stop BZRA

(taper slowly in collaboration with patient, for example ~25% every two weeks, and if possible, 12.5% reductions near end and/or planned drug-free days)

- For those ≥ 65 years of age (strong recommendation from systematic review and GRADE approach)
- For those 18-64 years of age (weak recommendation from systematic review and GRADE approach)
- Offer behavioural sleeping advice; consider CBT if available (see reverse)

Monitor every 1-2 weeks for duration of tapering

Expected benefits:

- May improve alertness, cognition, daytime sedation and reduce falls

Withdrawal symptoms:

- Insomnia, anxiety, irritability, sweating, gastrointestinal symptoms (all usually mild and last for days to a few weeks)

Use non-drug approaches to manage insomnia

Use behavioral approaches and/or CBT (see reverse)

If symptoms relapse:

Consider

- Maintaining current BZRA dose for 1-2 weeks, then continue to taper at slow rate

Alternate drugs

- Other medications have been used to manage insomnia. Assessment of their safety and effectiveness is beyond the scope of this algorithm. See BZRA deprescribing guideline for details.

Pottie K, Thompson W, Davies S, Grenier J, Sadowski C, Welch V, Holbrook A, Boyd C, Swenson JR, Ma A, Farrell B. Evidence-based clinical practice guideline for deprescribing benzodiazepine receptor agonists. Can Fam Physician 2018;64:339-51 (Eng), e209-24 (Fr)

This algorithm and accompanying advice support recommendations in the NICE guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia, and medicines optimisation. National Institute for Health and Care Excellence, February 2019

deprescribing.org | Bruyère Research Institute | open

deprescribing.org | Benzodiazepine & Z-Drug (BZRA) Deprescribing Notes

February 2019

BZRA Availability

BZRA	Strength
Alprazolam (Xanax®) T	0.25 mg, 0.5 mg, 1 mg, 2 mg
Bromazepam (Lectopam®) T	1.5 mg, 3 mg, 6 mg
Chlordiazepoxide C	5 mg, 10 mg, 25 mg
Clonazepam (Rivotril®) T	0.25 mg, 0.5 mg, 1 mg, 2 mg
Clorazepate (Tranxene®) C	3.75 mg, 7.5 mg, 15 mg
Diazepam (Valium®) T	2 mg, 5 mg, 10 mg
Flurazepam (Dalmane®) C	15 mg, 30 mg
Lorazepam (Ativan®) T, S	0.5 mg, 1 mg, 2 mg
Nitrazepam (Mogadon®) T	5 mg, 10 mg
Oxazepam (Serax®) T	10 mg, 15 mg, 30 mg
Temazepam (Restoril®) C	15 mg, 30 mg
Triazolam (Halcion®) T	0.125 mg, 0.25 mg
Zopiclone (Imovane®, Rhovane®) T	5mg, 7.5mg
Zolpidem (Sublinox®) S	5mg, 10mg

T = tablet, C = capsule, S = sublingual tablet

BZRA Side Effects

- **BZRAs have been associated with:**
  - physical dependence, falls, memory disorder, dementia, functional impairment, daytime sedation and motor vehicle accidents
- **Risks increase in older persons**

Engaging patients and caregivers

Patients should understand:
- The rationale for deprescribing (associated risks of continued BZRA use, reduced long-term efficacy)
- Withdrawal symptoms (insomnia, anxiety) may occur but are usually mild, transient and short-term (days to a few weeks)
- They are part of the tapering plan, and can control tapering rate and duration

Tapering doses

- No published evidence exists to suggest switching to long-acting BZRAs reduces incidence of withdrawal symptoms or is more effective than tapering shorter-acting BZRAs
- If dosage forms do not allow 25% reduction, consider 50% reduction initially using drug-free days during latter part of tapering, or switch to lorazepam or oxazepam for final taper steps

Behavioural management

Primary care:
1. Go to bed only when sleepy
2. Do not use bed or bedroom for anything but sleep (or intimacy)
3. If not asleep within about 20-30 min at the beginning of the night or after an awakening, exit the bedroom
4. If not asleep within 20-30 min on returning to bed, repeat #3
5. Use alarm to awaken at the same time every morning
6. Do not nap
7. Avoid caffeine after noon
8. Avoid exercise, nicotine, alcohol, and big meals within 2 hrs of bedtime

Institutional care:
1. Pull up curtains during the day to obtain bright light exposure
2. Keep alarm noises to a minimum
3. Increase daytime activity & discourage daytime sleeping
4. Reduce number of naps (no more than 30 mins and no naps after 2 pm)
5. Offer warm decaf drink, warm milk at night
6. Restrict food, caffeine, smoking before bedtime
7. Have the resident toilet before going to bed
8. Encourage regular bedtime and rising times
9. Avoid waking at night to provide direct care
10. Offer backrub, gentle massage

Using CBT

What is cognitive behavioural therapy (CBT)?
- CBT includes 5-6 educational sessions about sleep/insomnia, stimulus control, sleep restriction, sleep hygiene, relaxation training and support

Does it work?
- CBT has been shown in trials to improve sleep outcomes with sustained long-term benefits

Who can provide it?
- Clinical psychologists usually deliver CBT, however, others can be trained or can provide aspects of CBT education; self-help programs are available

How can providers and patients find out about it?
- Some resources can be found here: https://mysleepwell.ca/

Pottie K, Thompson W, Davies S, Grenier J, Sadowski C, Welch V, Holbrook A, Boyd C, Swenson JR, Ma A, Farrell B. Evidence-based clinical practice guideline for deprescribing benzodiazepine receptor agonists. Can Fam Physician 2018;64:339-51 (Eng), e209-24 (Fr)

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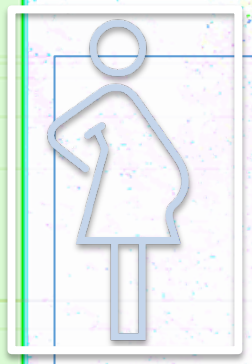
deprescribing.org | Institut de recherche Bruyère Research Institute | open

At risk populations

- Chronic medical illness, often older patients
- Chronic anxiety, dysphoria, and/or personality disorders
- Patients with panic disorder and/or agoraphobia
- Patients with chronic insomnia
- Patients with current or prior dependence on sedative hypnotics, including ALCOHOL

Special Populations

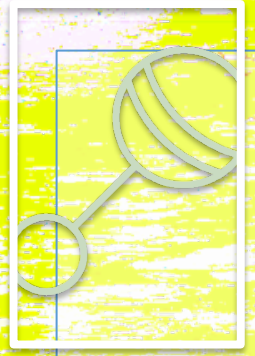
Pregnancy



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.

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 only prescribed clonazepam 5 mg daily x 1 year that she takes regularly, no other psychotropic medications as “benzos are the only thing that works for me.”

However, 3 weeks ago she started using diverted alprazolam, “Xanny Bars” that she buys from a friends 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. Prescribe gabapentin to facilitate benzodiazepine dose reduction
2. Engage in motivational interviewing targeting benzodiazepine use reduction/cessation
3. Tolerate long-term benzodiazepine use so long as she is only taking clonazepam
4. Insist on abstinence from benzodiazepines prior to prescribing any additional medication
5. Proceed to treat PTSD and anxiety with evidence-based pharmacological treatment
6. Refer to qualified therapist for Cognitive Behavioral Therapy

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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. Acknowledge current forms of treatment for BZD UD

   Taper BZD + CBT + treat co-occurring disorders