

Benzodiazepines

Christy Sutherland MD CCFP (AM) dABAM
Medical Director, PHS Community Services Society
Physician Education Lead, British Columbia Centre on
Substance Use
Clinical Assistant Professor, UBC Department of Family
Medicine

Faculty/Presenter Disclosure

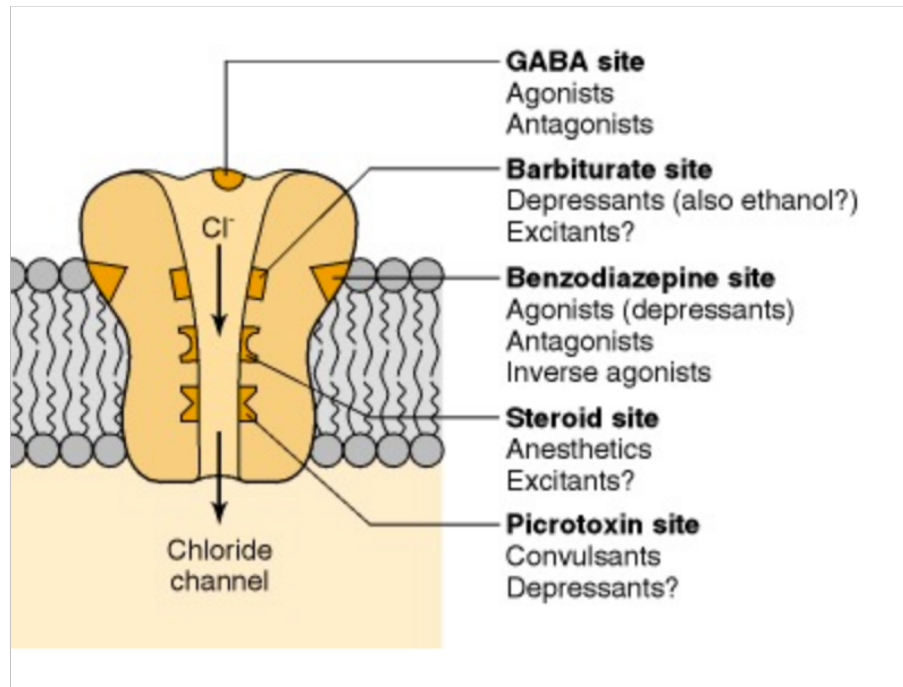
- **Faculty:** Christy Sutherland
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 - **Other:** Employee of =BC Centre on Substance Use
 - Medical Director PHS Community Services Society

Mitigating Potential Bias

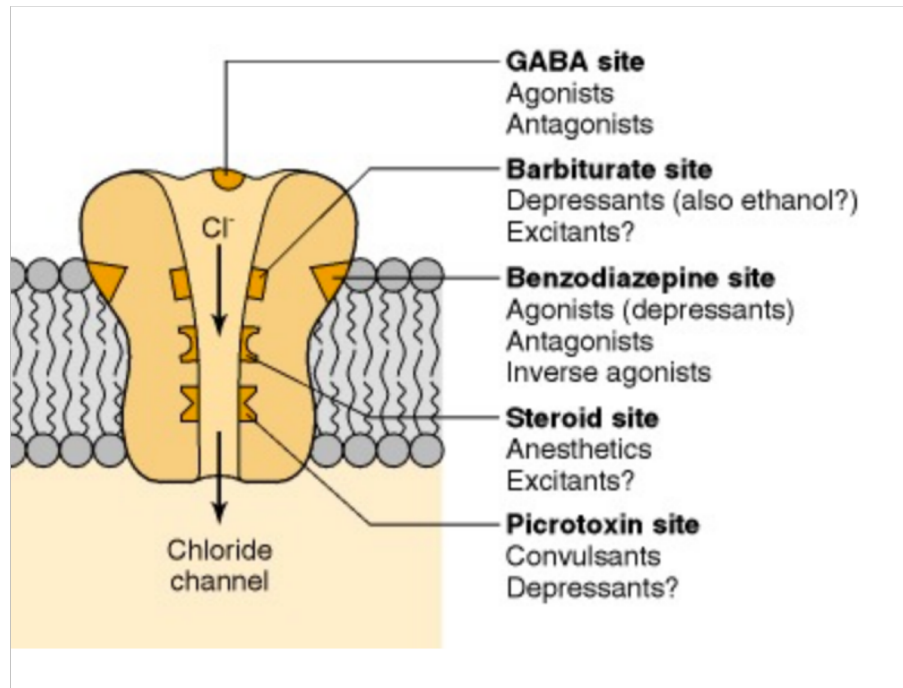
- I will present on what is the published literature
- I will note when there is no literature to guide practice.

Mechanism of Action

- Benzodiazepine receptor agonists attach to a site on the γ -aminobutyric acid type A receptor



- When the chloride channel opens, it causes inhibition



Examples of BZRA

BENZODIAZEPINES		
Duration of Action	Name	Brand Name
Long-acting (24-72 hours)	Chlordiazepoxide	Librium
	Clorazepate	<u>Tranxene</u>
	Diazepam	Valium
	Flurazepam	<u>Dalmane</u>
Intermediate-acting (6-24 hours)	Alprazolam	Xanax
	Bromazepam	<u>Lectopam</u>
	Clobazam	<u>Frisium</u>
	Clonazepam	<u>Rivotril</u>
	Lorazepam	Ativan
	Nitrazepam	<u>Mogadon</u>
	Oxazepam	<u>Serax</u>
	Temazepam	Restoril
Short-acting (<6 hours)	Midazolam	Versed
	Triazolam	Halcion

Examples of BZRA

NON-BENZODIAZEPINE HYPNOTICS (“Z-DRUGS”)	
Health Canada Approved Indication for Use – Insomnia	
Name	Brand Name
Zolpidem	Ambien
Zopiclone, <u>Ezopiclone</u>	Lunesta
Zaleplon	<u>Starnoc</u>

Other drugs that also work on GABA - A

- Barbiturates
 - Phenobarbital
 - Pentobarbital
- Alcohol
- Anesthetic steroids
- Anesthetic gasses

BZRA Prescribing in Community

- BZRA are widely prescribed and used in Canada.
- Nearly 4% of the population are currently prescribed BDRZ
- Up to 10% of Canadians over the age of 15 report use of prescribed or non-prescribed sedatives in the past year

Indication for Prescribing

Approved indications for benzodiazepines include short-term (e.g., 2-4 weeks) treatment of:

- Acute anxiety
- Panic disorder
- Insomnia
- Seizures
- Alcohol withdrawal

Z-drugs are approved for the short-term (e.g., 7-10 days) treatment of insomnia

BZRAs are often prescribed off-label:

- For more frequent use
- Longer time periods
- For other conditions, such as chronic insomnia and generalized anxiety

General Safety Information

- Short-term BZRA use is associated with a significant number of risks and adverse events

“These deserve special note because patients rely on health care professionals to provide them with this information.”

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;

Patients...commonly state they are reassured that BZRAs are safe because otherwise their physicians would not prescribe them.

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Potential Harms of BZRA Use

- Motor vehicle collisions, falls, accidents, and injuries
- Increased risk of mortality
- Risk of DSM-5 sedative use disorder and related withdrawal syndrome
- If taken long-term, worse overall severity of anxiety, insomnia, and post-traumatic stress disorder (PTSD)

Potential Harms of BZRA Use

- Increased risk of developing PTSD in those with recent trauma
- Confusion and disorientation, with potential persistent memory and other neurocognitive deficits
- Increased risk of respiratory failure in patients with chronic obstructive pulmonary disorder (COPD)

Patients can develop tolerance to the sedation effects, but not tolerance to the amnestic effects.

This can happen in as little as 4 weeks.



Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

[A-Z Index](#)



Morbidity and Mortality Weekly Report ([MMWR](#))

CDC



Changes in Opioid-Involved Overdose Deaths by Opioid Type and Presence of Benzodiazepines, Cocaine, and Methamphetamine — 25 States, July–December 2017 to January–June 2018

Weekly / August 30, 2019 / 68(34);737–744

R. Matt Gladden, PhD¹; Julie O'Donnell, PhD¹; Christine L. Mattson, PhD¹; Puja Seth, PhD¹ ([View author affiliations](#))

- The majority of opioid deaths (62.6%) co-occurred with one or more of the following drugs: benzodiazepines, cocaine, and methamphetamine.
- 32.5% of deaths had co-occurring benzodiazepine use

ER Visits

A 2014 U.S. study found that anxiolytic and sedative medications (primarily short-acting benzodiazepines) accounted for the largest proportion of emergency department visits involving psychoactive medications

BDRZ use is independently associated with a higher risk of hepatitis C, HIV, and mortality among people who use illegal drugs.

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Archives of Clinical Neuropsychology 33 (2018) 901–911

Archives
of
CLINICAL
NEUROPSYCHOLOGY

The Residual Medium and Long-term Cognitive Effects of Benzodiazepine Use: An Updated Meta-analysis

Simon F. Crowe*, Elizabeth K. Stranks

School of Psychology and Public Health, La Trobe University, Victoria, Australia

*Corresponding author at: School of Psychology and Public Health, La Trobe University, Victoria 3086, Australia. Tel.: +61 3 9479 1380;
fax: +61 3 9479 1956.

E-mail address: s.crowe@latrobe.edu.au

Editorial Decision 2 November 2017; Accepted 13 November 2017

Long-term benzodiazepine users were significantly impaired in:

- Sensory processing
- Psychomotor speed
- Non-verbal memory
- Visuospatial processing
- Speed of processing
- Problem-solving
- Attention/concentration
- Verbal memory
- General intelligence
- Motor control/performance
- Working memory
- Verbal reasoning

Diverted Benzos

Diverted or illicitly manufactured benzodiazepines are also readily available in the illegal drug market.

A recent survey of street-involved adults and youth in Vancouver found that the majority reported being able to obtain benzodiazepines on the street in less than 10 minutes.

BDRZ and Opioid Use Disorder

Concurrent use of BZRAs and opioids significantly increases the risk of respiratory depression, overdose, and death.

Due to the associated safety risks, prescribing OAT to patients also taking BZRAs has traditionally been contraindicated.

It is now recommended that OAT should not be delayed or withheld from patients who use BZRAs

Avoid Unnecessary and Off-Label Prescriptions of BZRAs

There are safer alternatives for clinical cases where a benzodiazepine or z-drug might initially be considered

[BMJ](#). 2011; 342: c7460.

PMCID: PMC3230126

Published online 2011 Jan 26. doi: [10.1136/bmj.c7460](https://doi.org/10.1136/bmj.c7460)

PMID: [21270081](https://pubmed.ncbi.nlm.nih.gov/21270081/)

Guidelines

Management of generalised anxiety disorder in adults: summary of NICE guidance

[Tim Kendall](#), director, visiting professor, consultant psychiatrist and medical director,¹²³ [John Cape](#), head, visiting professor,⁴² [Melissa Chan](#), systematic reviewer,¹ and [Clare Taylor](#), editor¹, On behalf of the Guideline Development Group

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“Do not offer a benzodiazepine to treat generalised anxiety disorder in primary or secondary care except as a short term measure during crises. (New recommendation.)”

Exceptions?

- Some specific clinical conditions may warrant ongoing benzodiazepine use, based on expert support.
 - Panic Disorder?
- Consider consultation with an anxiety specialist for anxiety disorders that are not responding to first line treatments.

- **Insomnia:**

- Psychosocial treatment interventions (e.g., sleep hygiene, cognitive behavioural therapy).
- BZRAs may be used short-term (i.e., <7 days) or intermittently for acute insomnia;
- **BDRZ not recommended** for the long-term management of chronic insomnia.

Treat the underlying cause

- Anxiety and insomnia can also be signs of an underlying issue:
 - Pain
 - Trauma
 - An undiagnosed mental health condition or
 - Substance use disorder

How long to be on Benzos?

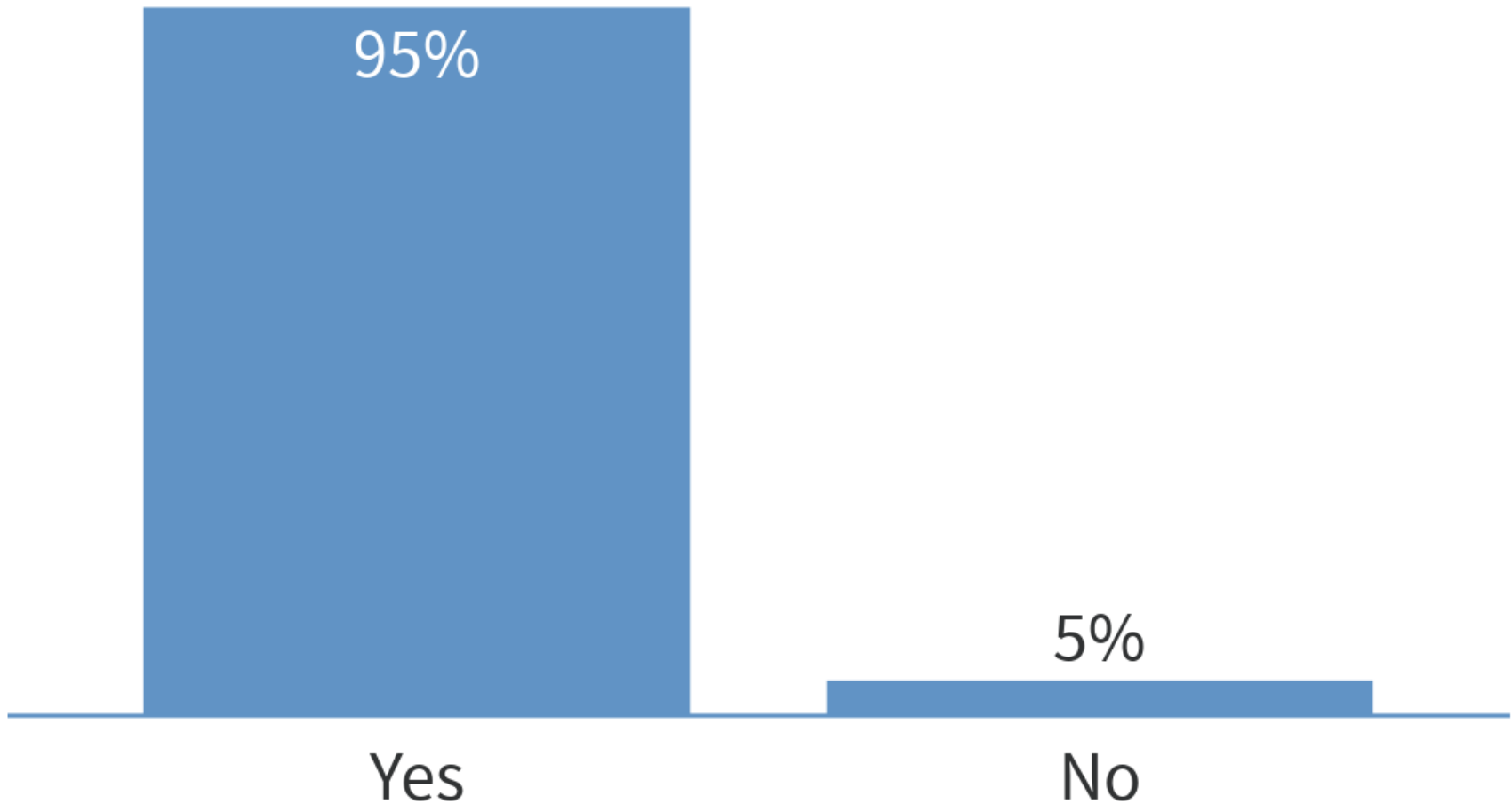
There is very limited evidence that long-term BZRA use (e.g., >2-4 weeks) is clinically effective.

Extra Caution

- Alcohol use
- Opioid Use
- TCA
- Elderly

Other than exceptional circumstances, with expert consultation, we should **Reduce or Discontinue Long-Term BZRA Prescriptions**

I struggle to taper benzodiazepines for some of my patients



When discussing a taper

- “Has anyone ever told you that you have a personality disorder?”
- “Do you find that you are tearful really easily?”
- “How is your concentration? Can you sit and read a book?”
- “How is your memory?”
- Ask about tolerance to frustration

Lack of Published Protocols for BDZA Tapers

Develop an individually tailored plan where benzodiazepine dose is reduced gradually, and patients are closely monitored and reassessed following each dose reduction.

There is a lack of research about how to do this!

Use a patient-centred approach – actively involve patients and families in developing a plan and decision-making at each stage of the taper

Create a clear plan for the taper

“I care about you”

Tapers for People with Opioid Use Disorder

Monitor patients closely for symptoms of opioid withdrawal, as breakthrough symptoms can emerge when BZRA dose is reduced

Screen for sleep-disordered breathing

When a taper is done

“Our systematic review found that there was no difference in overall BZRA withdrawal symptom scores for tapering compared with usual care or continuation of BZRAs.”

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Outpatient Alcohol Withdrawal

- Benzodiazepines are the gold standard for treatment of *severe* alcohol withdrawal in inpatient settings
- For *mild to moderate* alcohol withdrawal in outpatient settings consider
 - Gabapentin
 - Carbamazepine
 - Clonidine

Relapse during Alcohol Withdrawal

- BDRZ act synergistically with alcohol to increase respiratory depression
- Carbamazepine and Clonidine **do not** increase respiratory depression

Conclusion

- Be cautious and thoughtful about BZRA prescribing.
- Be especially cautious in patients with OUD, AUD, the elderly
- When doing tapers, go slowly and compassionately.
- Screen for OSA
- Exercise caution if using BZRA in outpatient alcohol withdrawal