



BRIDGES TO MENTAL HEALTH

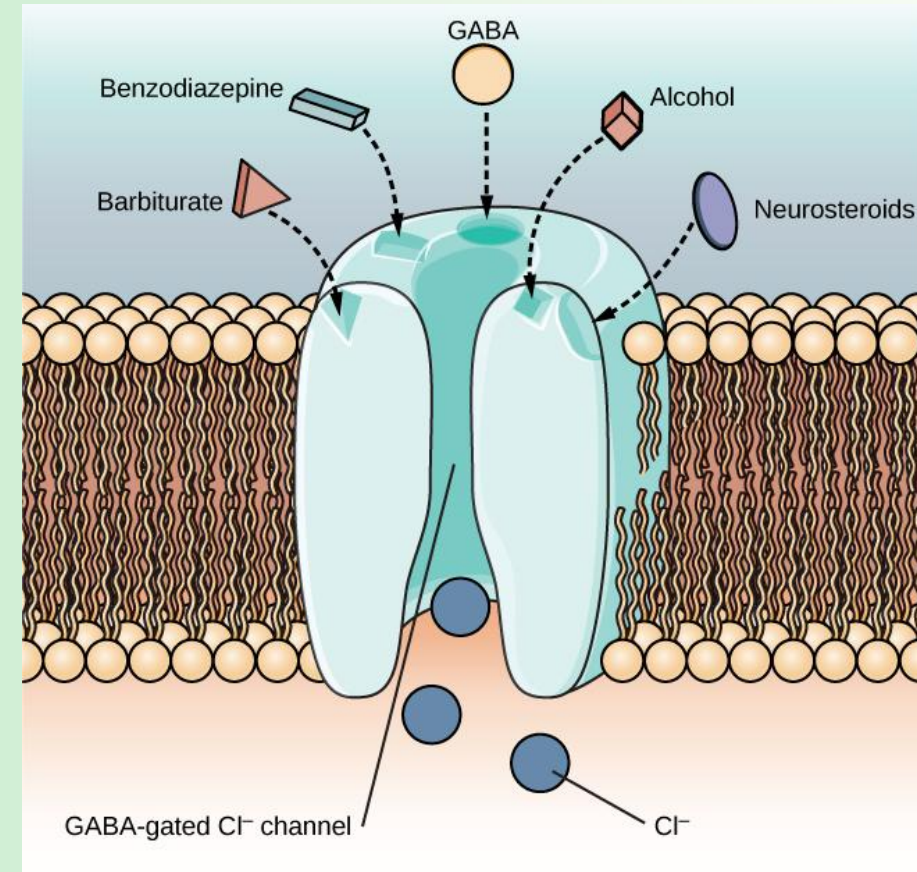
**Benzodiazepines:  
Are they all the same?  
Are they all bad?**



# Benzodiazepines (BZD) - How They Work



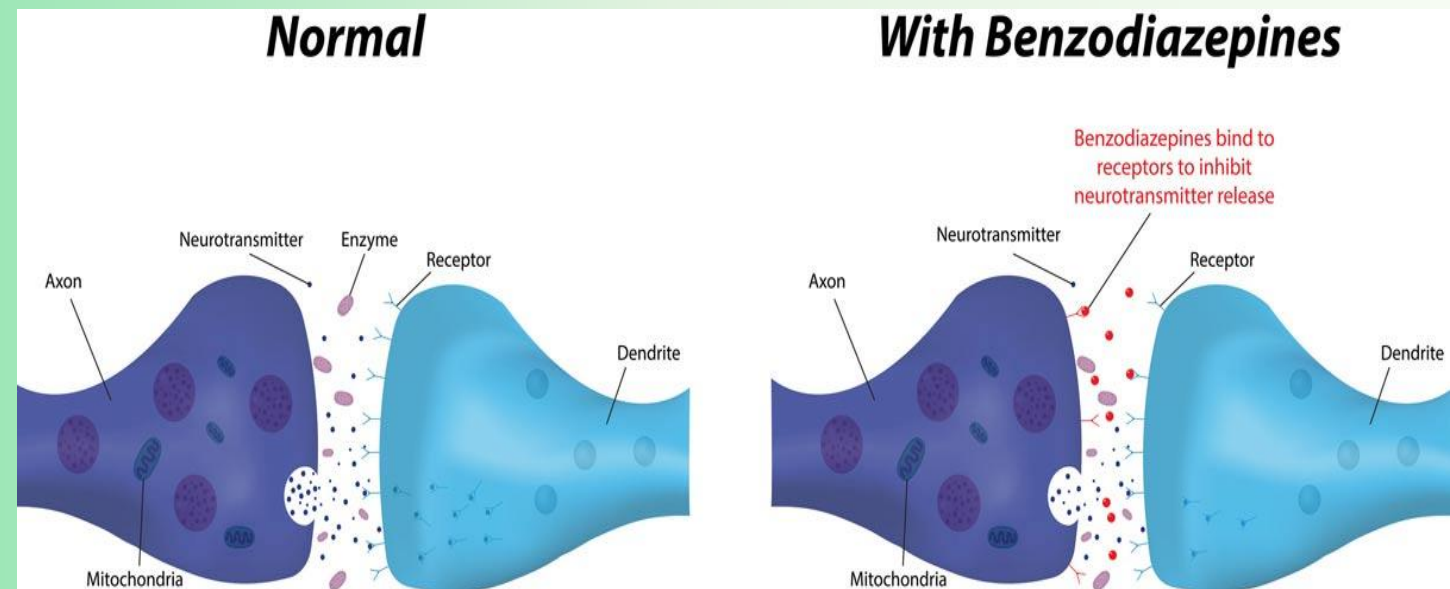
- Enhance inhibitory neurotransmission in the CNS
- BZD bind to a specific site on the GABA-A receptor that is distinct from where GABA binds
- BZD increase the affinity of GABA receptors for GABA, the effect of which increases  $\text{Cl}^-$  conductance, resulting in hyperpolarizing
- BZD **Do NOT** activate receptor directly (require presence of GABA ) acting as *indirect agonists* of the GABA receptor



# Benzodiazepines (BZD) Augment the Effects of GABA



- **GABA** is the main inhibitory neurotransmitter in the brain
- BZD potentiate (**amplify**) GABA's effect
  - ↓ anxiety
  - ↓ neuronal firing
  - ↑ sedation
  - ↑ muscle relaxation
  - ↑ anticonvulsant effects



[recoveryconnection.com/substance-abuse/drug-classes/benzodiazepine/](https://recoveryconnection.com/substance-abuse/drug-classes/benzodiazepine/)

# Primary Effect....

**Anxiolytic**

**Sedative**

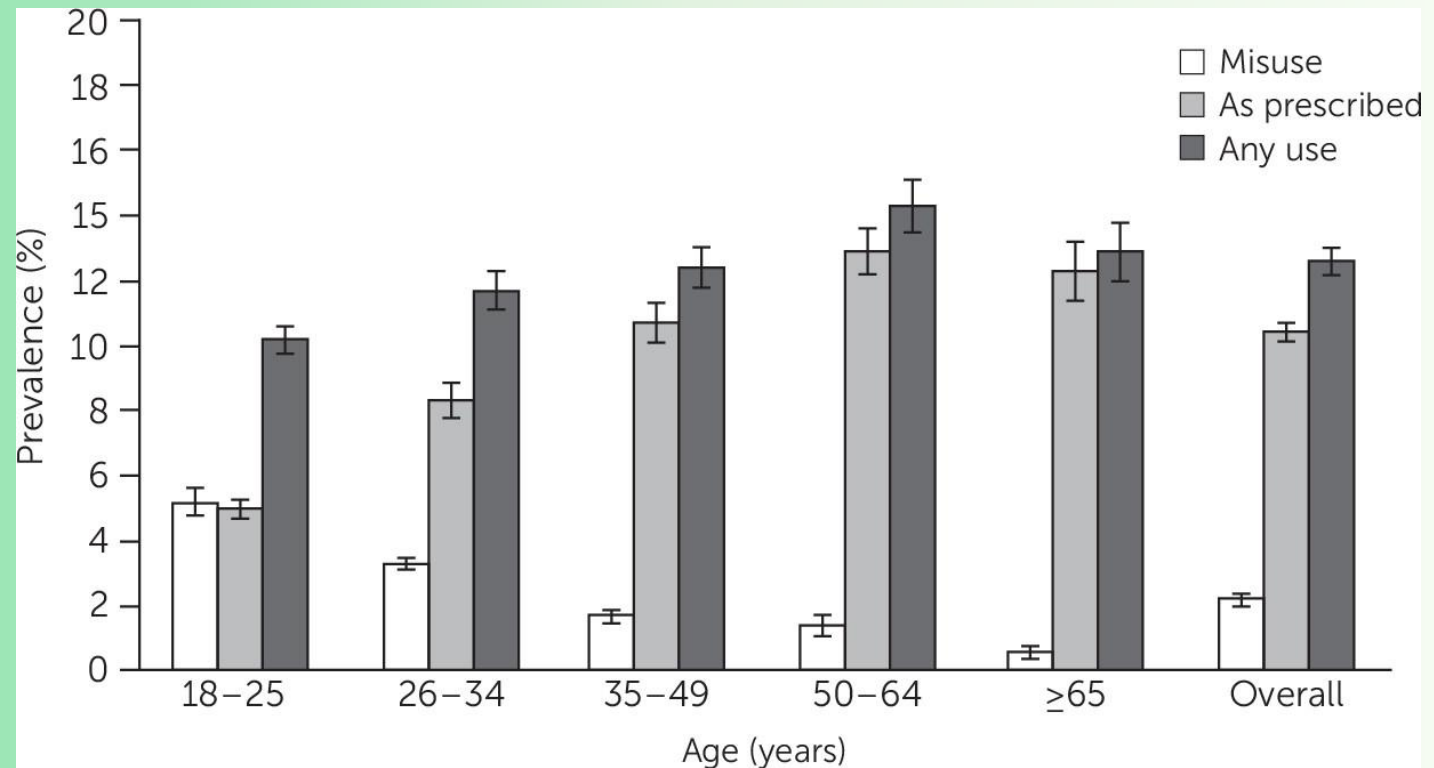
**Muscle relaxant**

**Anticonvulsant**

# Benzodiazepine – Use, Misuse, and Trends



- Use **↑ through the 2000s**, now plateauing/slightly declining
- **~12–13%** of U.S. adults report benzodiazepine use annually
- Higher Use;
  - Women > Men
  - Adults  $\geq 65$  years



Maust DT, Lin LA, Blow FC *Psychiatr Serv.* 2019;70(2):97-106.

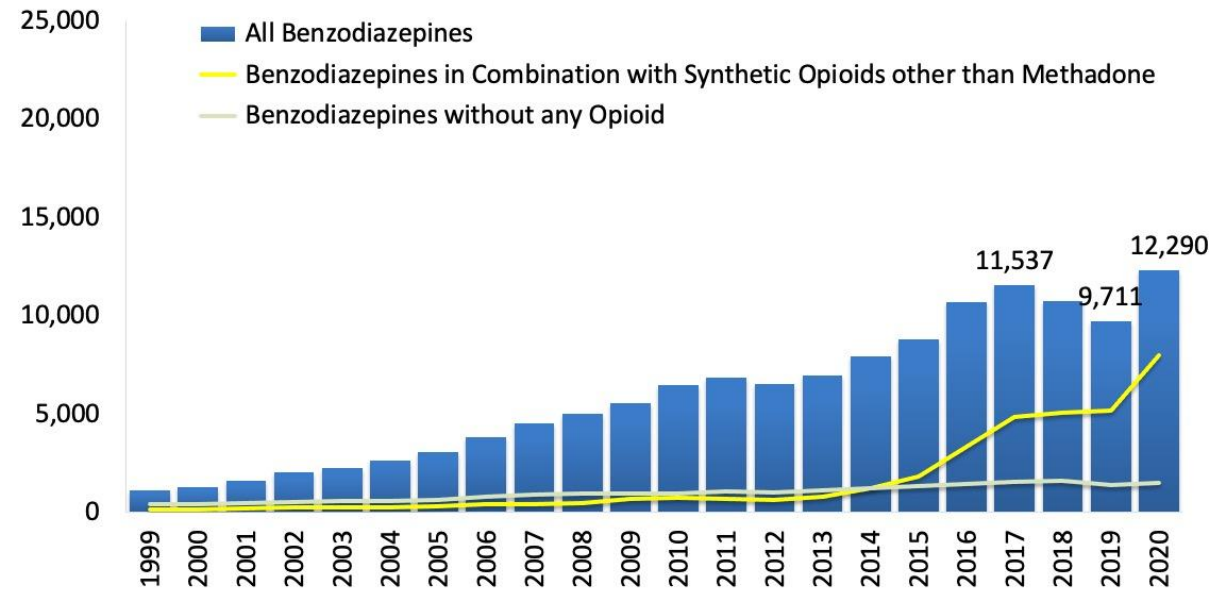
# Benzodiazepine – Use, Misuse, and Trends Cont'd



- **~15–20% of BZD users** report some form of misuse
  - Taking **higher doses than prescribed**
  - Taking **for longer or more often than prescribed**
  - Taking it in a way other than directed
  - Using **without a prescription**
  - Using for **non-medical reasons**
- Young adults (18-25) more likely to misuse
- Misuse declined with age
- **~2–3%** of users develop benzodiazepine use disorder

**Death often in combination with other drugs (opiates)**

**Figure 8. National Drug Overdose Deaths Involving Benzodiazepines\*, by Opioid Involvement, Number Among All Ages, 1999-2020**



\*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 1999-2020 on CDC WONDER Online Database, released 12/2021.

# Benzodiazepine – General Info

- **Schedule IV** DEA classification:
  - Abuse potential
  - Low potential for abuse (*relative to Schedule III*)
  - Prescriptions are regulated (limited refills/controlled)
- Approx 15 BZD FDA-approved in the United States (2,000 different bzd worldwide)



# Partial List - Benzodiazepines

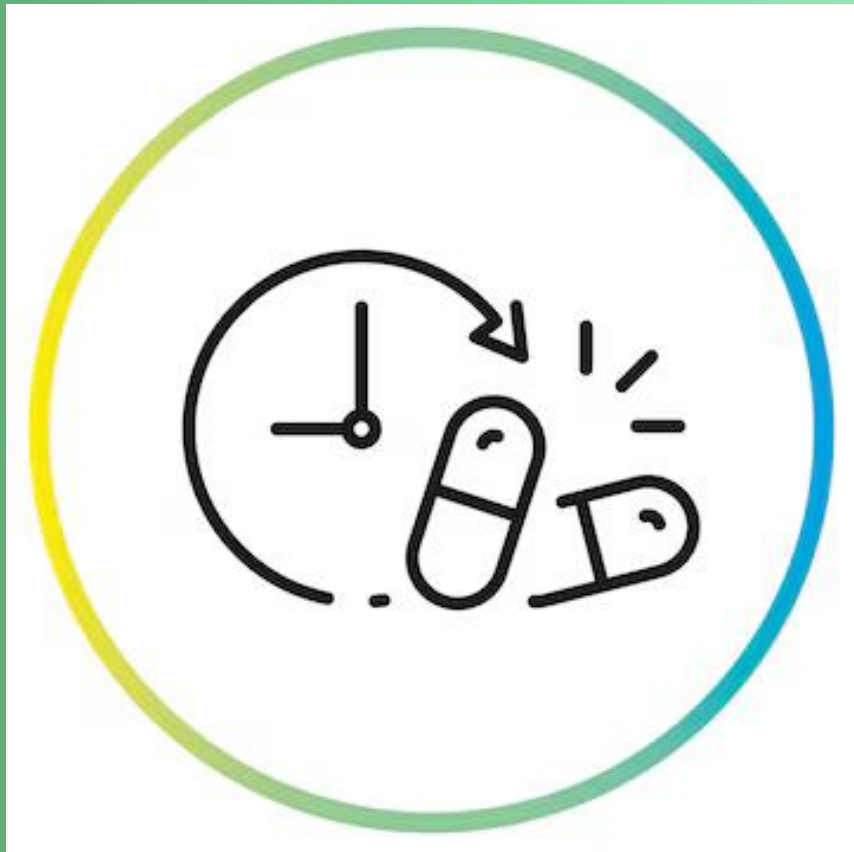
- **Valium**; generic name: diazepam
- **Prosom**; generic name: estazolam
- **Xanax (XR)**; generic name: alprazolam
- **Doral**; generic name: quazepam
- **Valium**; generic name: diazepam
- **Tranxene**; generic name: clorazepate
- **Librium**; generic name: chlordiazepoxide
- **Klonopin**; generic name: clonazepam
- **Serax**; generic name: oxazepam
- **Dalmane**; generic name: flurazepam
- **Halcion**; generic name: triazolam
- **Ativan**; generic name: lorazepam
- **Restoril**; generic name: temazepam
- **Versed**; generic name: midazolam

# Types of Benzodiazepines

- Ultra-short acting ( $t_{1/2} \sim 1.5-2.5$  hours):
  - midazolam (Versed), triazolam (Halcion)
- Short-acting ( $t_{1/2} \sim 6-20$  hours):
  - alprazolam (Xanax), lorazepam (Ativan)
- Long-acting ( $t_{1/2} \sim 20-70$  hours):
  - chlordiazepoxide (Librium), clonazepam (Klonopin), & diazepam (Valium)



# Long-Acting Benzodiazepines



- Smoother, prolonged effect
- Less frequent dosing
- Accumulates with repeated dosing
  - Sedation
  - Prolonged withdrawal
  - Hepatic impairment
  - Older adults
    - Falls
    - Delirium

# Benzodiazepines

Lorazepam (Ativan)

Alprazolam (Xanax)

Clonazepam (Klonopin)

Diazepam (Valium)



**Not first-line**

**Side-Effects**

- *Sedation/lethargy*
- *Cognitive blunting*
- *Disinhibition*
- *Memory loss*
- *Habit forming*
- *Addiction/Dependency/Abuse*
- *Respiratory depression*
- *Withdrawal*
- *Death*

# Benzodiazepines – Adverse Effects Cont'd



## Use in Pregnancy

- Risk factor for cleft lip or palate
- Lower muscle tone
- Withdrawal symptoms in the developing fetus

## May be safe in overdose (up to 30 times the normal daily dose)

- Usual symptoms of overdose include sedation, drowsiness, ataxia, and slurred speech
- May result in respiratory depression in combination with other CNS depressants
- **Management** includes gastric lavage, forced emesis, and assisted ventilation

## Medication Interactions

- Medications that increase benzodiazepine levels include P4503A4 inhibitors, ketoconazole, fluconazole, nefazodone.
- Medications that decrease benzodiazepine levels include P4503A4 inducers such as carbamazepine.

# Benzodiazepine FDA Indications



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Anxiety, muscle tension, insomnia, status epilepticus (diazepam), myoclonic epilepsy (clonazepam), preoperative anesthesia, and alcohol withdrawal.

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Two benzodiazepines, alprazolam and lorazepam, have FDA indication for **anxiety associated with depression**.

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Clonazepam and Alprazolam are indicated in the treatment of **panic disorder**.

# Benzodiazepine Use in Panic Disorder: Is Less More?



## Disadvantages PRN use:

- Reinforce panic = DANGER (must abort!)
  - → Greatest interference with ERP
- Increase attention to assessment of “need”
- Induction panic if “forget” to carry med
- May increase liability abuse (evidence from prn vs. standing dose drug reinforcement studies\*)
- PRN dosing alone = under treatment for panic disorder

## If monotherapy, dose daily to efficacy and tolerability

- Underdosing = risk without efficacy

\*Westra HA & Stewart SH. Curr Pharm Design. 2002.

# When Prescribing for the 1<sup>st</sup> Time



- Initiate with the lowest recommended dose, but this may need to be adjusted depending on patient's response.
- Usually prescribe for up to 4 weeks.
- Use phased dispensing where possible.
- Ensure that agreements between doctor and patient are documented.
- Record all details of medication prescribed and duration of treatment.
- Clear, effective and speedy communication concerning benzodiazepine usage should always take place between the prescribing professionals both within and between services.

# Patients Dependent on BZD or Patients in Receipt of Continuing Prescribing

- Issue small quantities at a time, review regularly – monthly
- Use a long acting BZD in dosages no higher than diazepam 5 mg three times daily (or equivalent)
- Make patients aware of the risks of long term BZD use and document this communication.
- Encourage dependent pts to withdraw, offer them a detoxification program at regular intervals (at least annually) and document
- A significant number of requests for repeat BZD prescribing are associated with addiction problems, primarily alcohol, or in urban areas, opiate misuse. A doctor who suspects this is the case should seek specialist advice

# Detection of Benzodiazepines



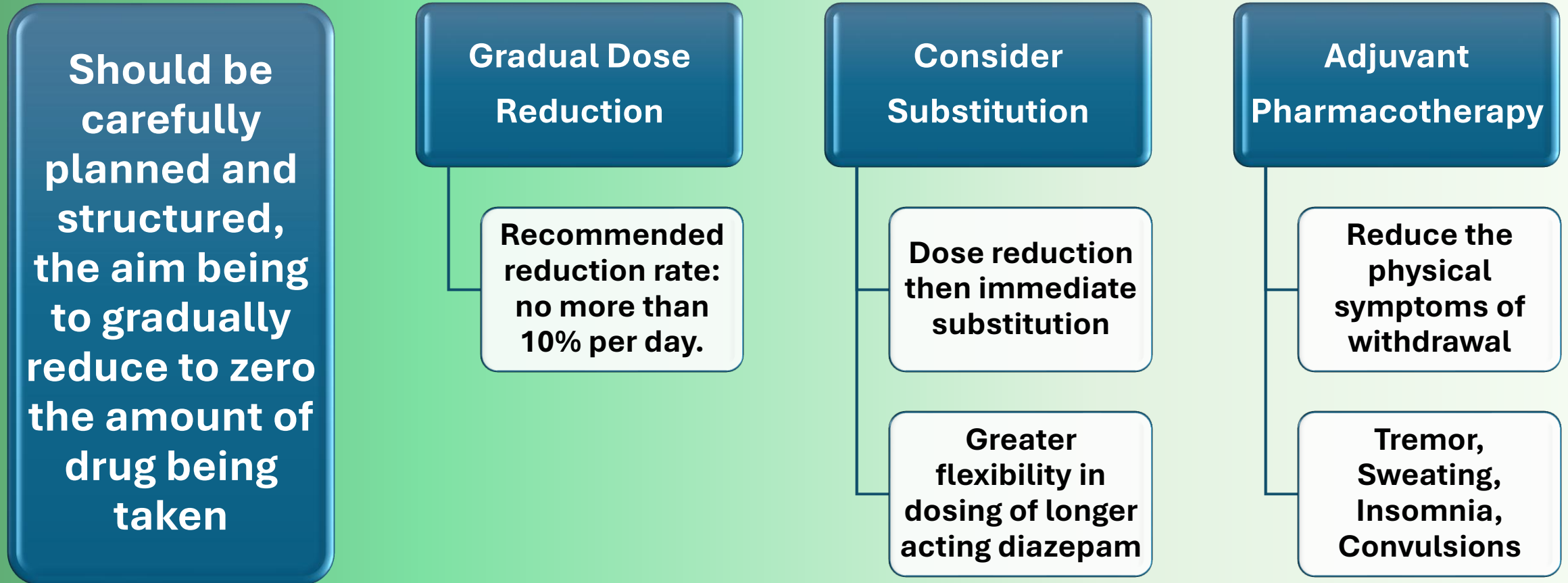
## Major metabolites detected in urine:

- Long acting- diazepam (10d)
- Intermediate acting - lorazepam/clonazepam (5 days)
- Short acting - triazolam (2d)

## Saliva testing 2 days

Weizman et al. Australian and New Zealand Journal of Psychiatry 2003; 37:458–463; O'Brient et al. J Clin Psych 2006; 66: 28-33)

# Tapering off Benzodiazepines



# Factors that **MAY** make BZD Withdrawal More Difficult Include

- Higher daily dose
- Shorter half-life, higher potency
- Longer duration of prior benzodiazepine therapy
- More rapid taper
- Patient Characteristics:
  - a diagnosis of panic disorder,
  - higher pre-taper levels of anxiety or depression,
  - characterological/relational challenges and/or personality disorder,
  - concomitant alcohol or substance abuse

# Potential Benefits of BZD



- Effective
- Rapid onset of therapeutic effect
- Well tolerated
- Rapid dose adjustment feasible
- Can be used “PRN” for situational anxiety (use sparingly and thoughtfully)
- Reduces antidepressant-induced activation
- Bridge until SSRIs/SNRIs take effect
- Available in multiple formulations (oral, sublingual, IV)
- Some meta-analyses (e.g. GAD\*) suggest:
  - greater effect size than serotonergic antidepressants (impact publication timeline?)
  - greater effect higher HAMA baseline scores & shorter studies

\*Gomez et al Exp Op Pharmacother 2018; Gale et al J Psychopharm 2019

# Potential Drawbacks of BZD



- Sedation, cognitive, and psychomotor impairment
- Interaction with alcohol
- Physiologic dependence with ongoing therapy
- Discontinuation-related difficulties: **TAPER VERY SLOWLY**
- Potential for abuse in predisposed individuals
- Not effective for comorbid depression
- \*May interfere with CBT exposure component

# Key Takeaways

- **Effective but high-risk** medications
- Best for **short-term, targeted use**
- Long-acting > short-acting
- Monitor
- Deprescribe
- Educate

