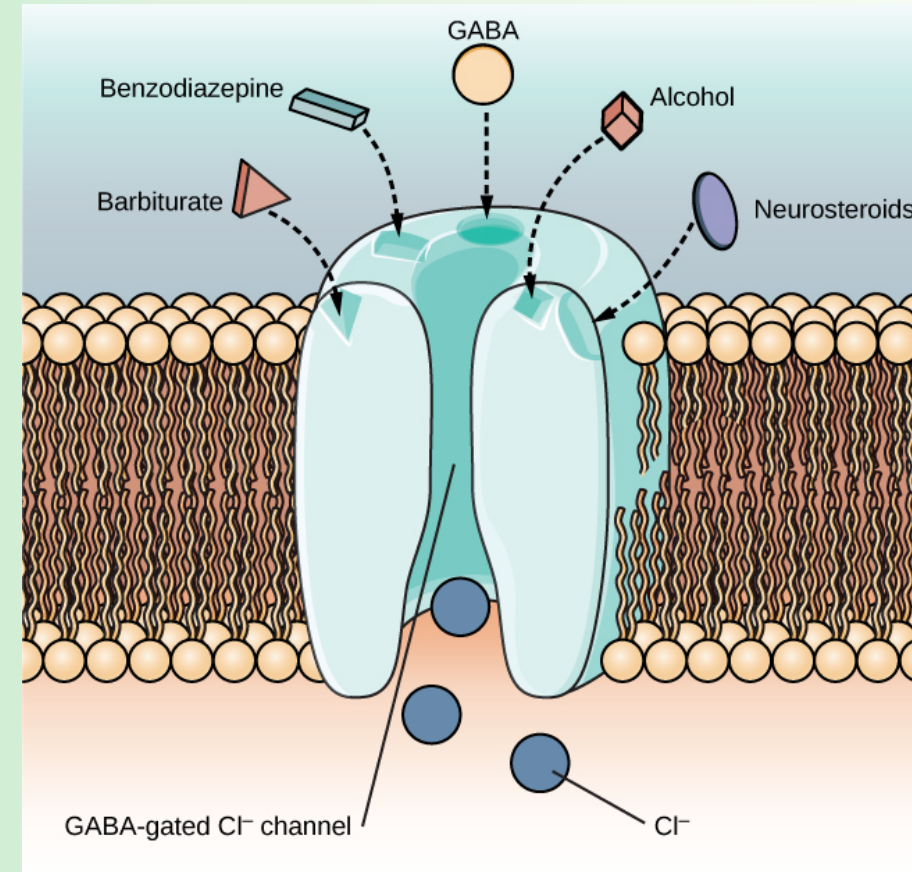


Benzodiazepines: Are they all the same? Are they all bad?



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 Cl^- conductance, resulting in hyperpolarizing
- BZD **Do NOT** activate receptor directly (require presence of GABA) acting as *indirect agonists* of the GABA receptor

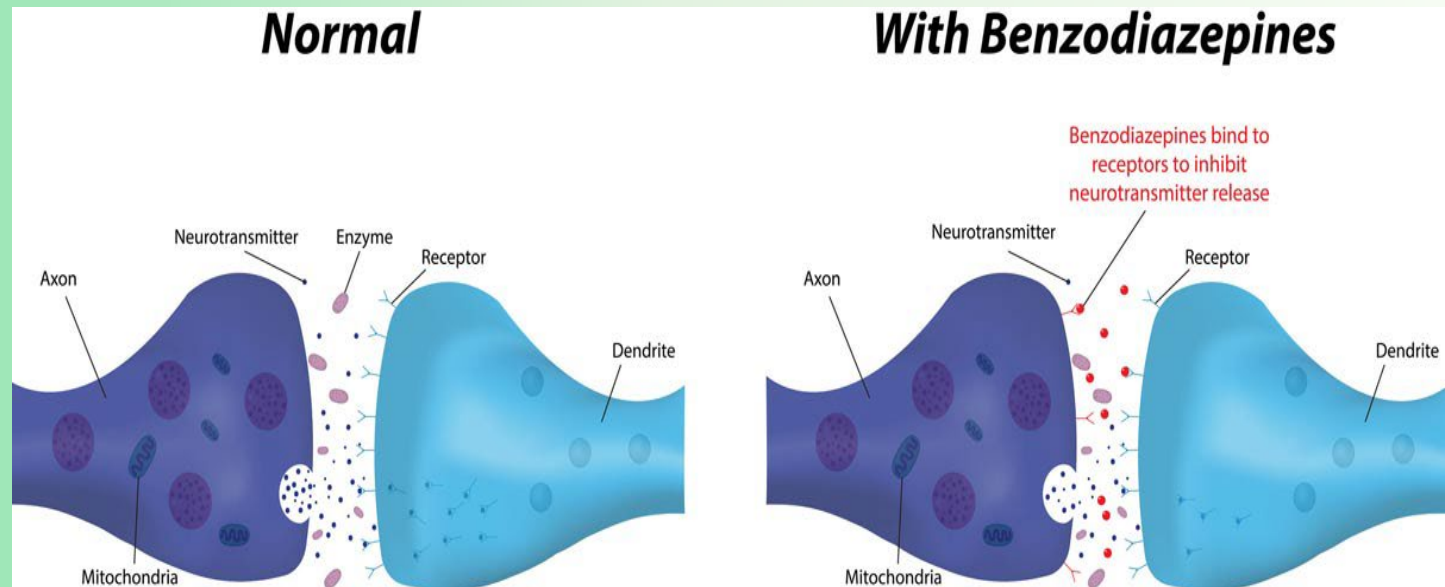


Benzodiazepines (BZD)

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/

Primary Effect....



Anxiolytic

Sedative

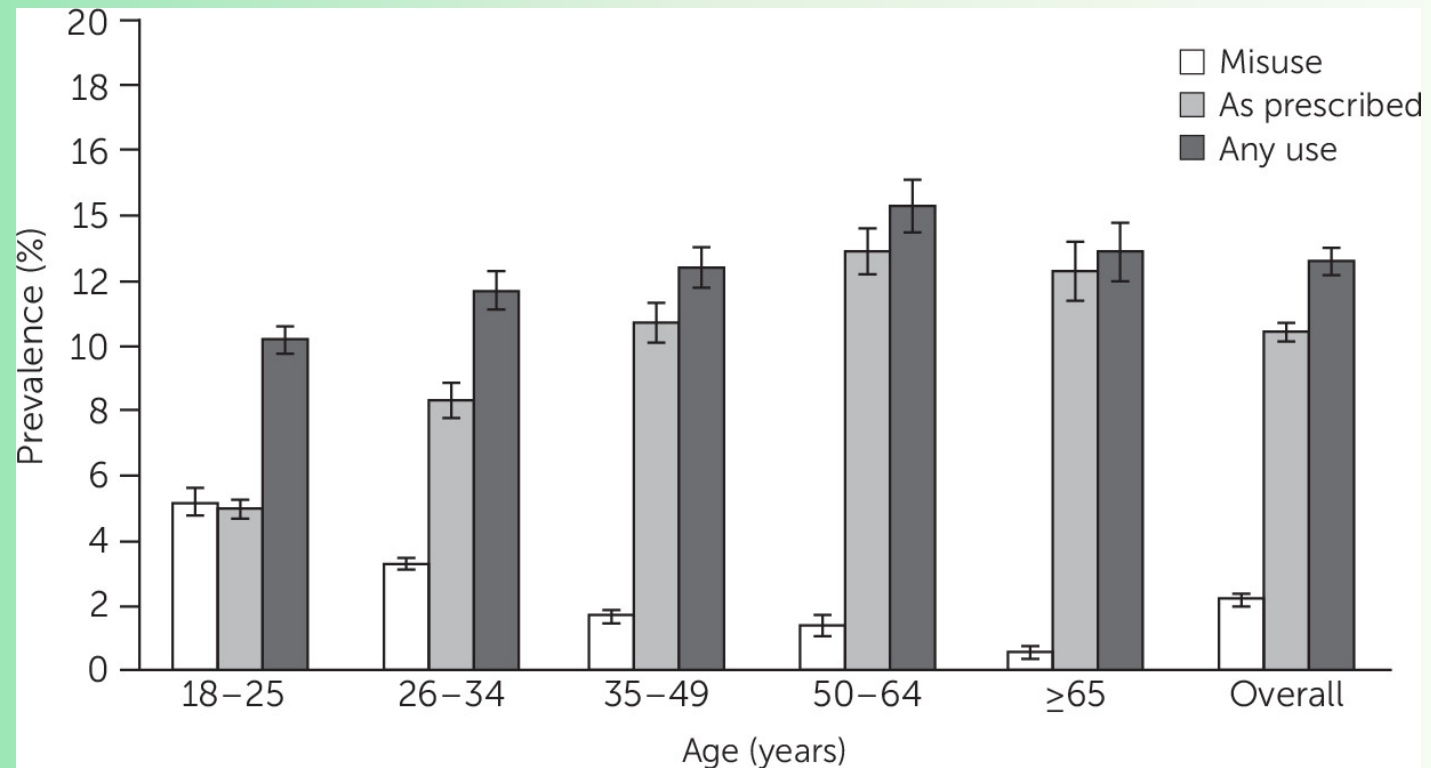
Muscle relaxant

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 ≥ 65 years



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

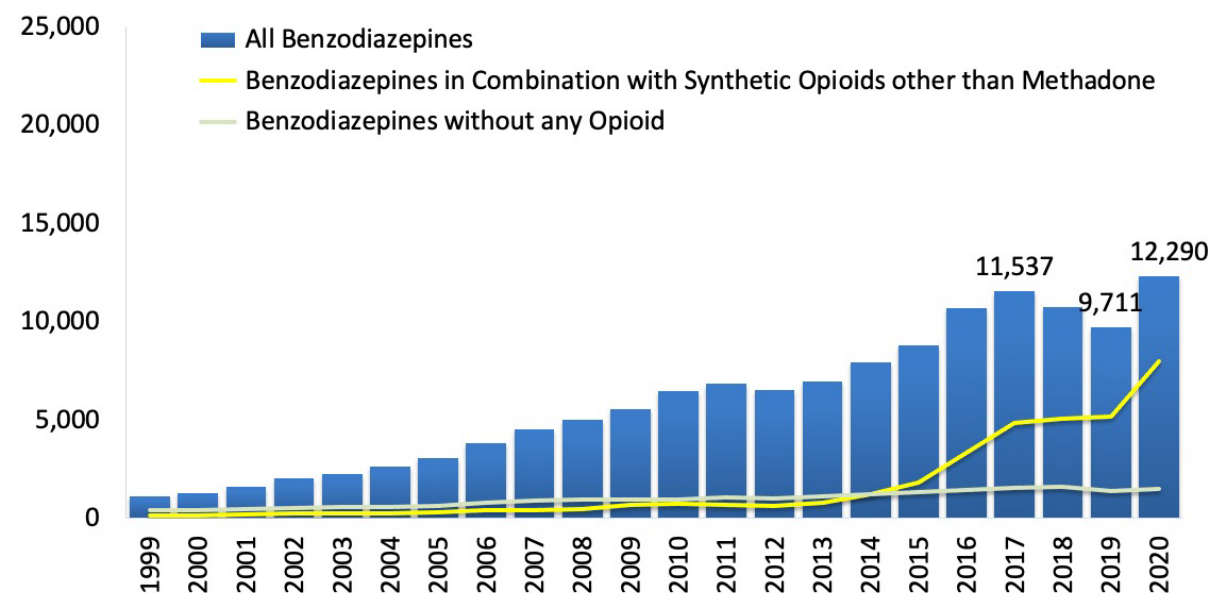
Benzodiazepine – Use, Misuse, and Trends Cont'd



- **~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.

CDC/ NIDA Vital Statistics Data: Dec 2021;
<https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>

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)

*Bachhuber, et al. American Journal of Public Health , [April 2016](#); 106;
[Jones and McAnich, Am J Prev Med. 2015 Oct;49\(4\):493-501. E-medicine health](#)*

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)

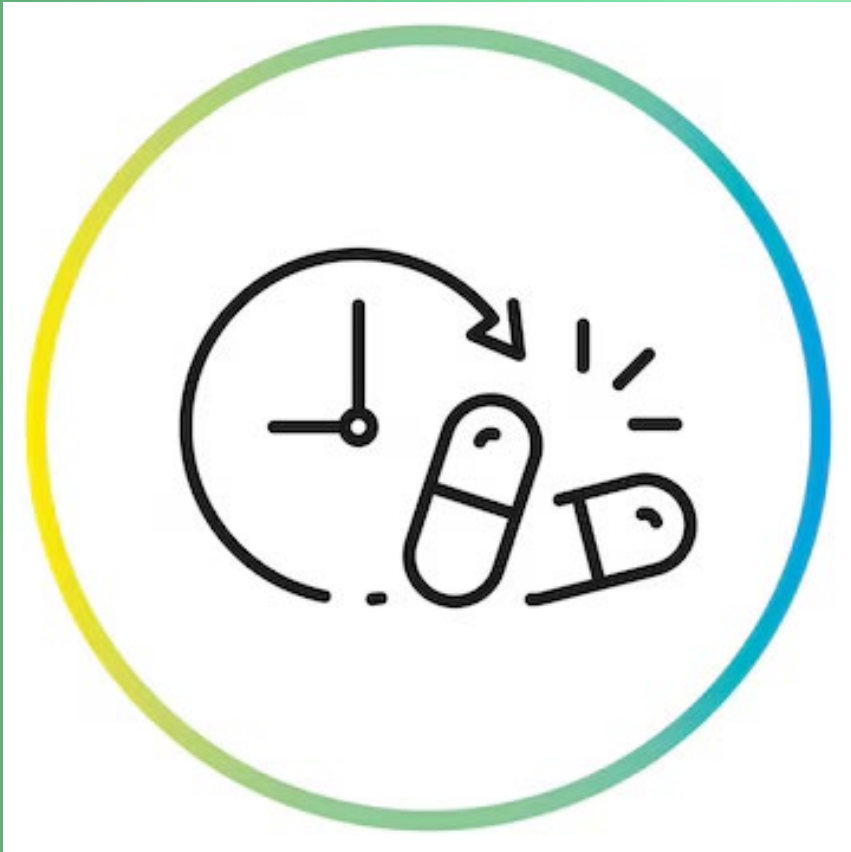


Pharmacokinetic and Pharmacodynamic Properties of Commonly Used Benzodiazepines

Generic Drug	Approximate Dosage Equivalents (mg)	Time to Peak Plasma Level (Hours)	Elimination Half-Life (Hours)	Metabolite Activity
Alprazolam	0.5	1–2	12–15	Inactive
Chlordiazepoxide	10–25	2–4	24–48 (>96*)	Active
Clonazepam	0.25–0.5	1–4	30–40	Inactive
Diazepam	5	1–2	44–48 (50–100*)	Active
Lorazepam	1	1–6	10–20	Inactive
Oxazepam	15	2–4	5–20	Inactive
Temazepam	15	2.5	10–20	Active

**Denotes prolonged half-life due to active metabolites. (Sources: Peng et al, 2022; Management of Substance Use Disorders Work Group. VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Washington, DC: Department of Veterans Affairs and Department of Defense; 2021.)*

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



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

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

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 1st 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.
- **Prescription Drug Monitoring Program (PDMP)/Prescription Monitoring Program (PMP)**

Prescription Drug Monitoring Program/Prescription Monitoring Program

- **Track History:** When and where controlled medications are dispensed to patients/picked-up.
- **Prevent Overdose:** Identify dangerous drug combinations (mixing opioids with benzodiazepines). Other/same benzos prescribed by another.
- **Stop Misuse:** Overlapping prescriptions from multiple doctors or pharmacies.

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 discontinue, 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



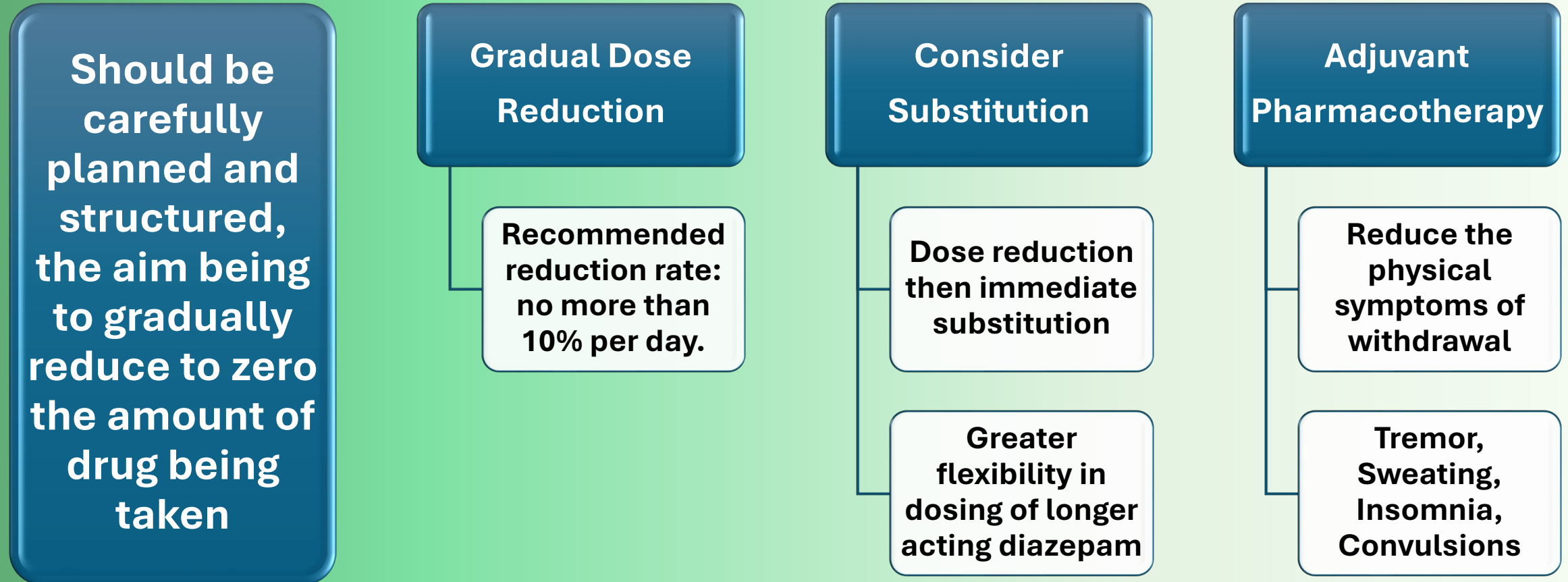
Major metabolites detected in urine:

- 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



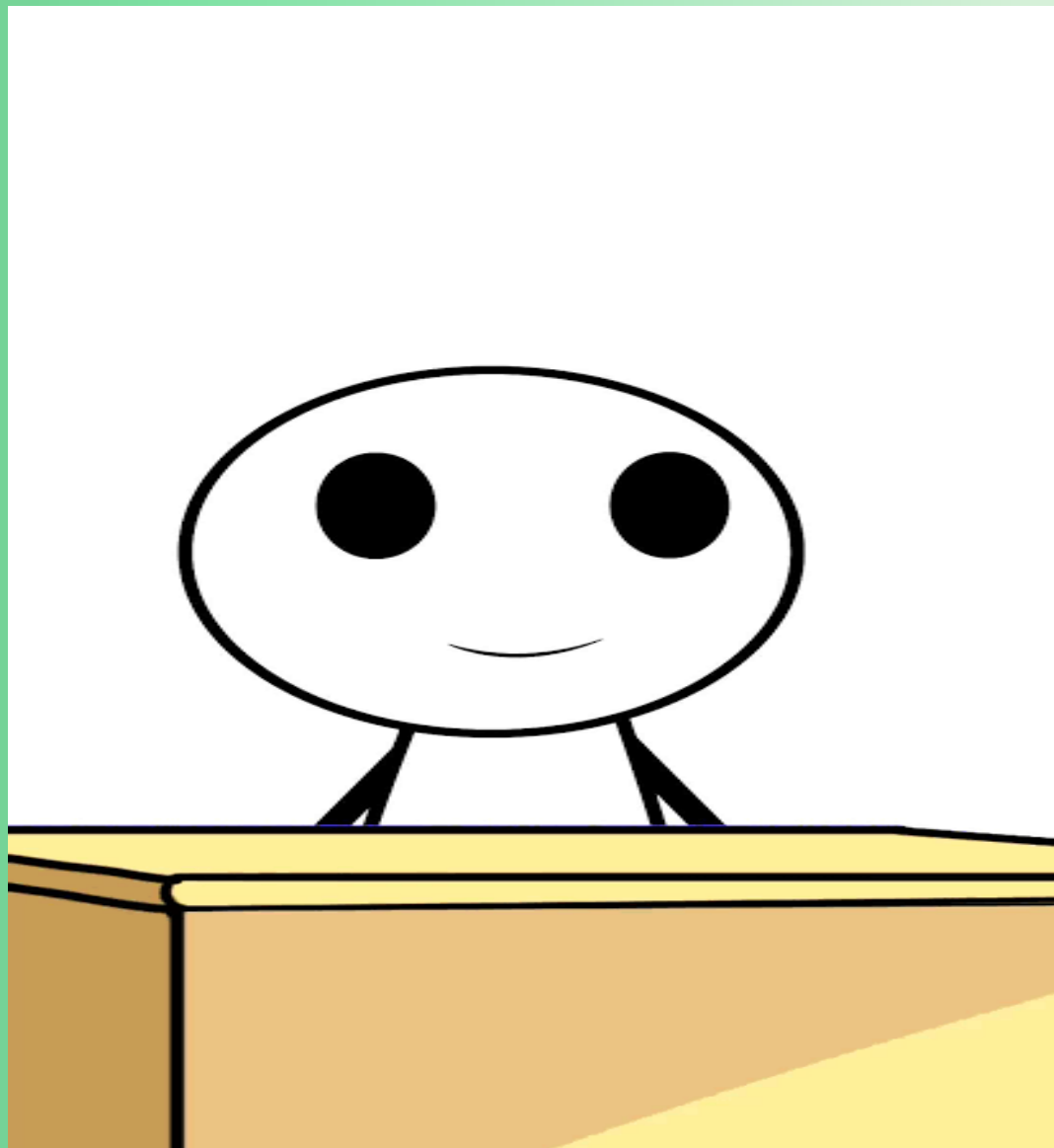
Factors that MAY make BZD Discontinuation More Difficult



- 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



BRIDGES TO MENTAL HEALTH



clarksonregional.com/bridges-to-mental-health

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

