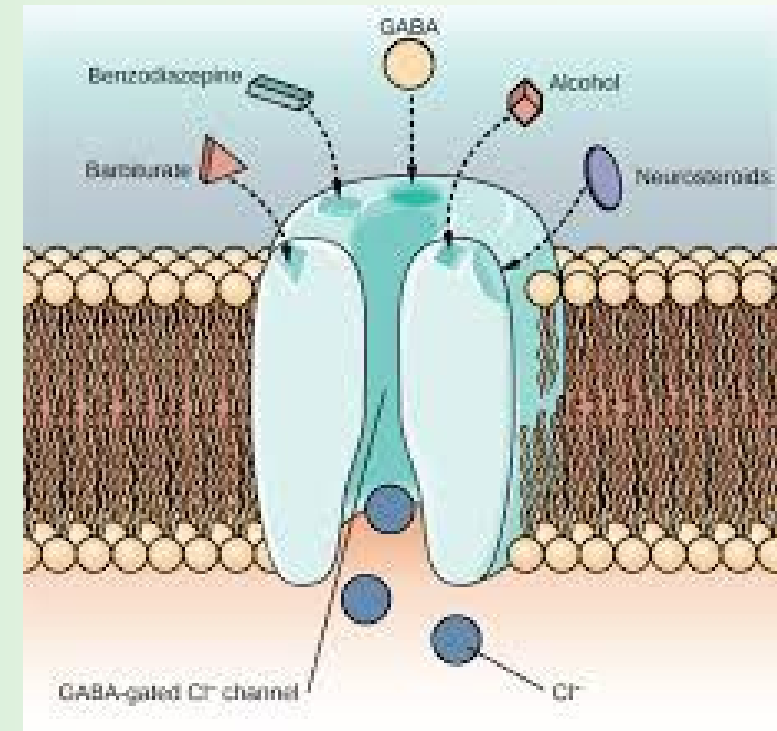


Benzodiazepines: Are they all the same, are they all bad?

Benzodiazepines Augment the Effects of GABA



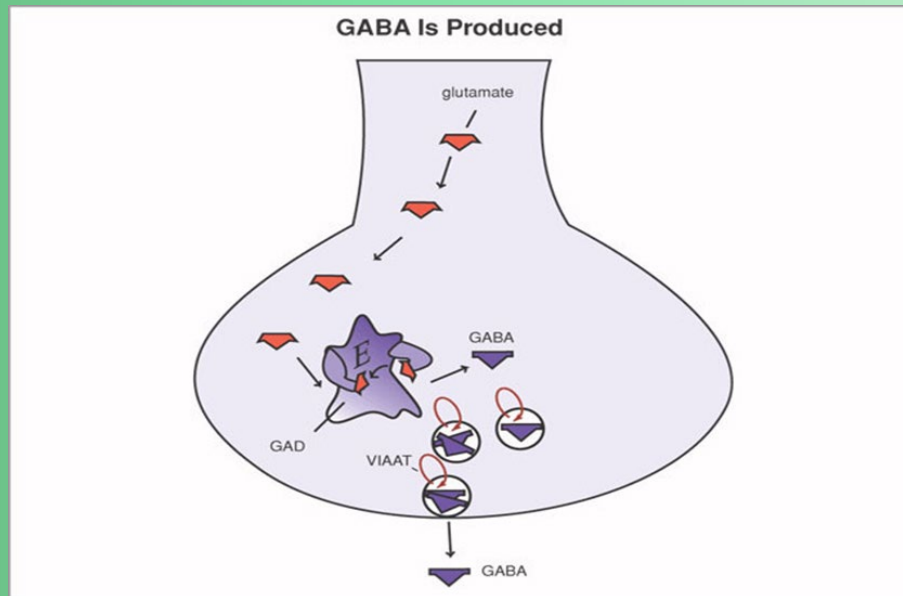
- GABA is the main inhibitory neurotransmitter in the brain (overall calming effect on the brain)
- Benzodiazepines bind to a specific site on the GABA-A receptor that is distinct from where GABA binds
- Benzodiazepines increase the affinity of GABA receptors for GABA, the effect of which increases Cl^- conductance, resulting in hyperpolarizing
- Benzodiazepines exert their action only in the presence of GABA – they are positive allosteric modulators (PAMs), acting as *indirect agonists* of the GABA receptor



Exogenous GABA Does Not Cross the Blood Brain Barrier (BBB)



GABA is produced in GABA-ergic neurons from the excitatory neurotransmitter glutamate by the enzyme GAD (glutamic acid decarboxylase)



Benzodiazepine FDA Indications



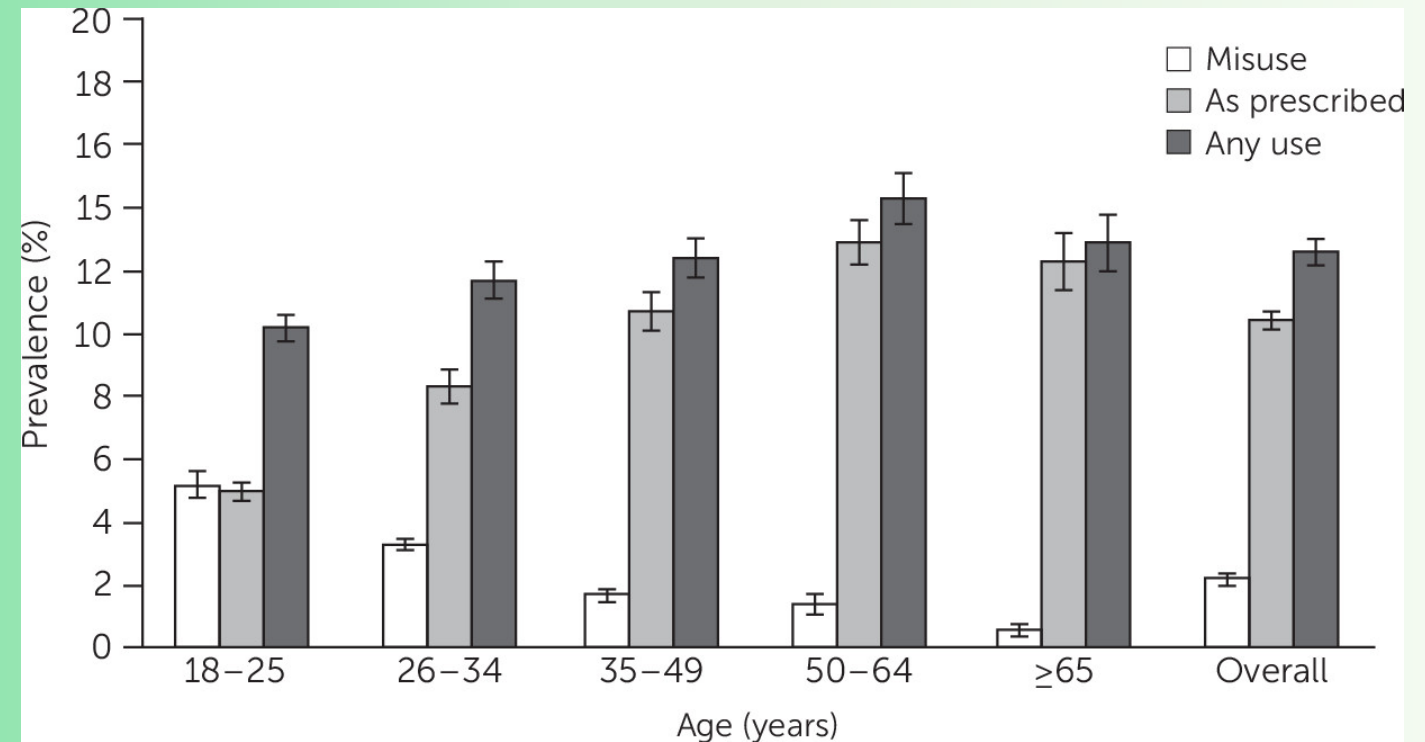
- Anxiety, muscle tension, insomnia (short-term use), seizure disorders, preoperative anesthesia, and alcohol withdrawal
- Alprazolam (Xanax) and lorazepam (Ativan) have FDA indication for **anxiety associated with depression**
- Clonazepam (Klonopin) and alprazolam (Xanax) have indication for the treatment of **panic disorder**

Schedule IV DEA classification: recognized medical use but also have a potential for abuse and dependence, so prescriptions are regulated

Benzodiazepine Use and Misuse

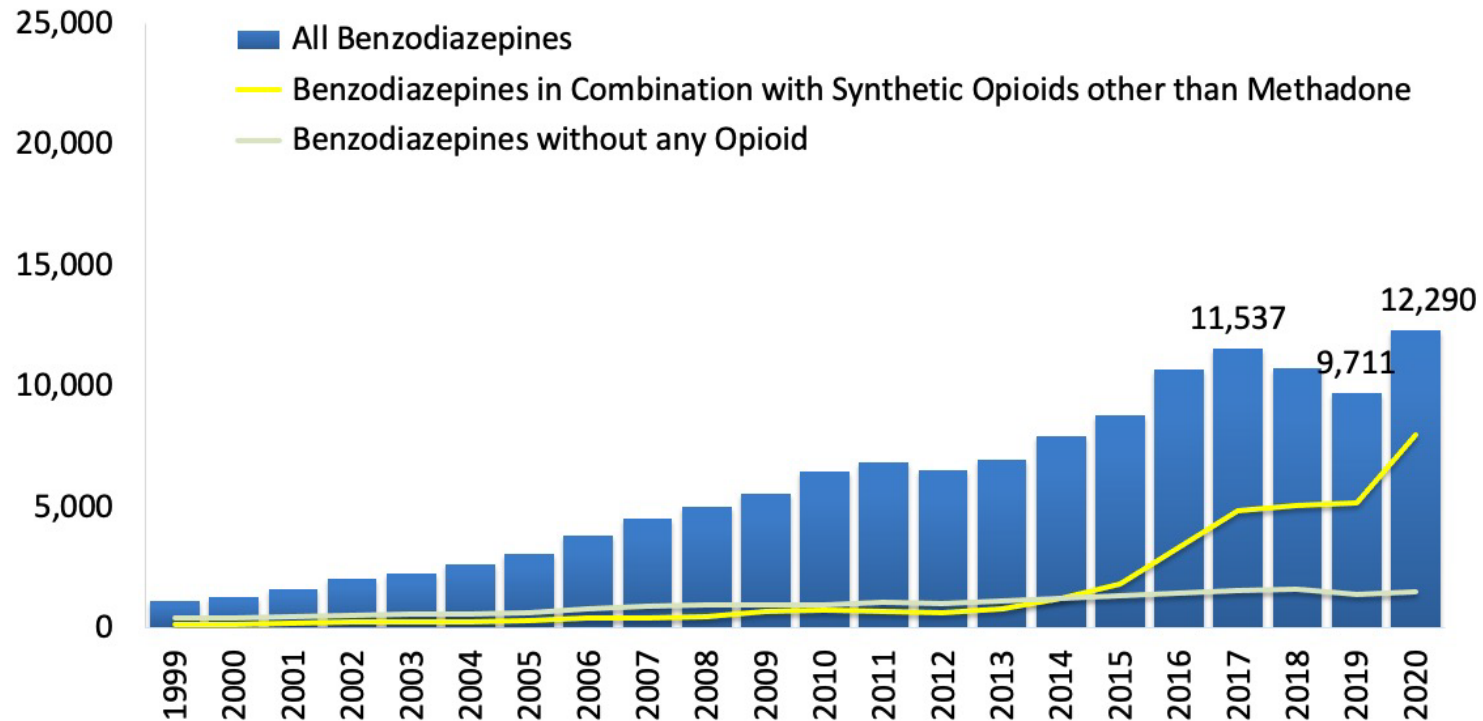


- There has been an overall increase in use; now used by 12.6% of U.S. adults.
- Rate of benzodiazepine misuse is 2.1%
- Rate of benzo use disorder is 0.2%
- Death often in combination with other drugs (opiates)



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

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.

May be safe in overdose up to 30 times the normal daily dose when solo

Some usual symptoms of overdose include sedation, drowsiness, ataxia, slurred speech

Dangerous with other CNS depressants (e.g., alcohol, opioids)
→ respiratory depression

Management of overdose includes gastric lavage, forced emesis, and assisted ventilation

Partial List of 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

Although more than 2,000 different benzodiazepines have been produced worldwide, only about 15 are currently FDA-approved in the US

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Key differentiators include **half life and potency**

- high-potency benzos have a greater affinity for GABA-A receptors; they generally require lower doses and have more intense withdrawal symptoms
- Potency does not always correlate with half-life

Pharmacology of Select Benzos



Benzodiazepine	Elimination half-life (hours)	Comparative potency (mg)	Adult oral total daily dose (mg)	Onset after oral dose (hours)	Metabolism
Alprazolam (Xanax)	6-15, prolonged in hepatic impairment and obesity	0.5	0.5-4 (max 6)	0.25-1 (rapid onset)	CYP3A4 to minimally active metabolites
Lorazepam (Ativan)	10-20	1	0.5-4 (max 6)	1-1.5 (intermediate onset)	Non-CYP glucuronidation in liver. No active metabolite
Clonazepam (Klonopin)	18-50	0.25-0.5	0.5-4	1-2 (slower onset)	CYP3A4. No active metabolites
Diazepam (Valium)	20-100, prolonged in older adults and renal or hepatic impairment	5	4-40	0.25-0.5 (rapid onset)	CYP2C19 and 3A4 to active metabolites
Chlordiazepoxide (Librium)	30-100, prolonged in older adults and hepatic impairment	10	5-100	1-2 (slower onset)	CYP3A4 to active metabolites

UpToDate: Benzodiazepines

Weigh the Pros and Cons: Potential Benefits



- Effective
- Rapid onset of therapeutic effect
- Rapid dose adjustment feasible
- Can reduce antidepressant-induced activation
- Useful for procedural anxiety, insomnia, catatonia
- Can be used “PRN” for situational anxiety (use sparingly and thoughtfully)

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

Weigh the Pros and Cons: Potential Drawbacks



- Tolerance and dependence
- Rebound anxiety/withdrawal
- Potential for misuse or addiction
- Discontinuation-related difficulties: taper slowly
- Sedation, cognitive slowing, psychomotor impairment
- Risk for respiratory depression (esp with alcohol or opioids)
- *May interfere with CBT exposure component

Use in Panic Disorder: Is Less More?



- Disadvantages PRN use:
 - Reinforce panic = DANGER (must abort!)
 - Interference with exposure and response prevention (ERP)
 - Increase attention to assessment of “need”
 - Induction of 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.

Additional Cautions



Avoid if

- History of substance use disorder
- PTSD with dissociation
- Chronic anxiety (consider SSRIs/SNRIs + CBT)
- Pregnancy (risk of teratogenicity and neonatal withdrawal)

Special Considerations

- Elderly: fall risk, cognitive impairment
- Hepatic dysfunction: avoid long-acting BZDs metabolized by liver
- Adolescents: limited indication, high risk for misuse

Interactions and Detection



- Medication interactions:
 - Many benzodiazepines (e.g., alprazolam, clonazepam, diazepam, chlordiazepoxide) are metabolized by CYP450 enzymes, particularly CYP3A4 and CYP2C19
- Major metabolites detected in urine:
 - Long acting 10d, intermediate acting 5 days, short acting 2d
 - Chronic use can extend the detection time
- Saliva testing detection 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)

Before Prescribing Benzodiazepines



- Take a full history including an alcohol and licit and illicit drug history
- Inform the patient of the side-effect profile of benzodiazepines, offer education about risks and benefits
- Consider and treat any underlying causes
- Consider referral to other/additional services
- Consider alternative sources of support for and with the patient

Prescribing Guidelines



- Use lowest effective dose for shortest possible duration
- Generally, <4 weeks recommended
- Document risks/benefits and patient education and agreements
- Record details of medication prescribed and duration of treatment
- Engage in regular follow-ups and avoid automatic refills

Benzodiazepine Dependent Patients or Patients on Chronic Dosing



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

Tapering off of Benzodiazepines



- Carefully plan and structure the taper
- Gradual Dose Reduction
 - Taper total daily dose by 20-25% every 2 weeks; hold at 50% of dose x 1 month, then decrease by 5-10% weekly to monthly
 - Monitor for withdrawal sx: insomnia, restlessness, irritability, anxiety, GI sx, diaphoresis
- Consider substitution for benzos with shorter half-lives
 - Greater flexibility in dosing of longer acting diazepam
 - Dose reduction then immediate substitution
- Consider adjuvant pharmacotherapy for withdrawal: buspirone, clonidine, gabapentin, hydroxyzine

Factors that MAY make Benzodiazepine Withdrawal more Difficult



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



Thank you!