Neuroscience Education Institute

THE WHEN, WHY, AND HOW OF USING BENZODIAZEPINES

Jeffrey R. Strawn, MD
Professor of Psychiatry, Pediatrics and Clinical Pharmacology, University of Cincinnati

Presented at 2021 NEI Congress

Learning Objectives

- Identify neurobiological mechanisms for modulating GABA neurotransmission to target anxiety symptoms
- Describe the effect of food and concomitant medications on benzodiazepine pharmacokinetics
- List clinical and pharmacologic factors that increase the risk of benzodiazepine withdrawal
- Describe pharmacologic strategies for discontinuing benzodiazepines

Selected Events in Benzodiazepine History

Chlordiazepoxide marketed as safer barbiturate alternative; along with newer benzodiazepines, promoted as lacking dependence-inducing properties

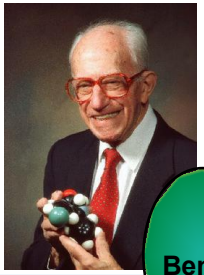
Rise in Diazepam

2016
FDA boxed warning re: combining BZDs with opiates

2018
Reports of concern re: cognitive risk in older adults

1950 1960 1970 1980 1990 2000 2010 2020

Discovery by Leo Sternbach



Benzo

1958
Diazepam introduced

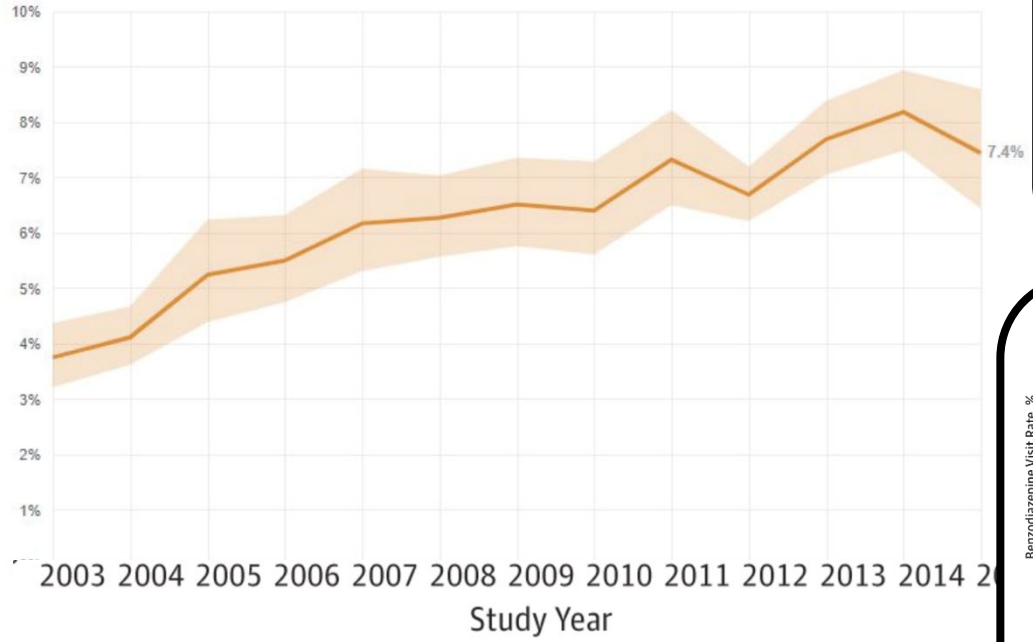
1973
Lorazepam introduced

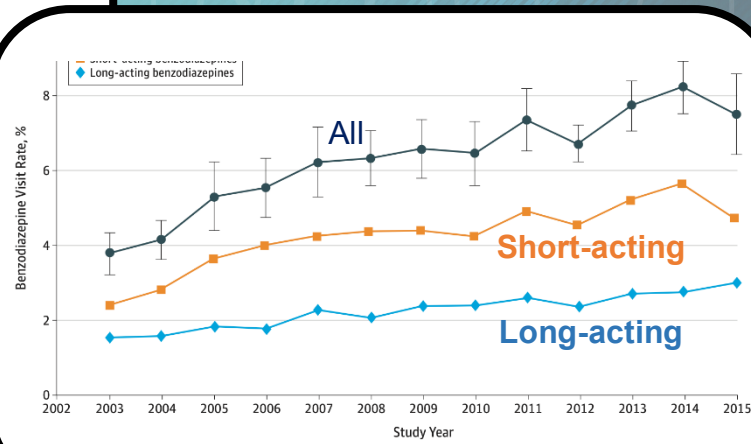
1975
Clonazepam introduced

1979
- Sen Ted Kennedy hearing into BZD risks
- Hearings dominated by narrative in which Valium played the fall guy
- Newer BZDs (Xanax, Klonopin, Ativan) were “heralded as good anxiolytics”

2020
FDA boxed warning: tolerance and abuse

Benzodiazepine Use in the United States





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

Benzodiazepines: Pros and Cons

Advantages

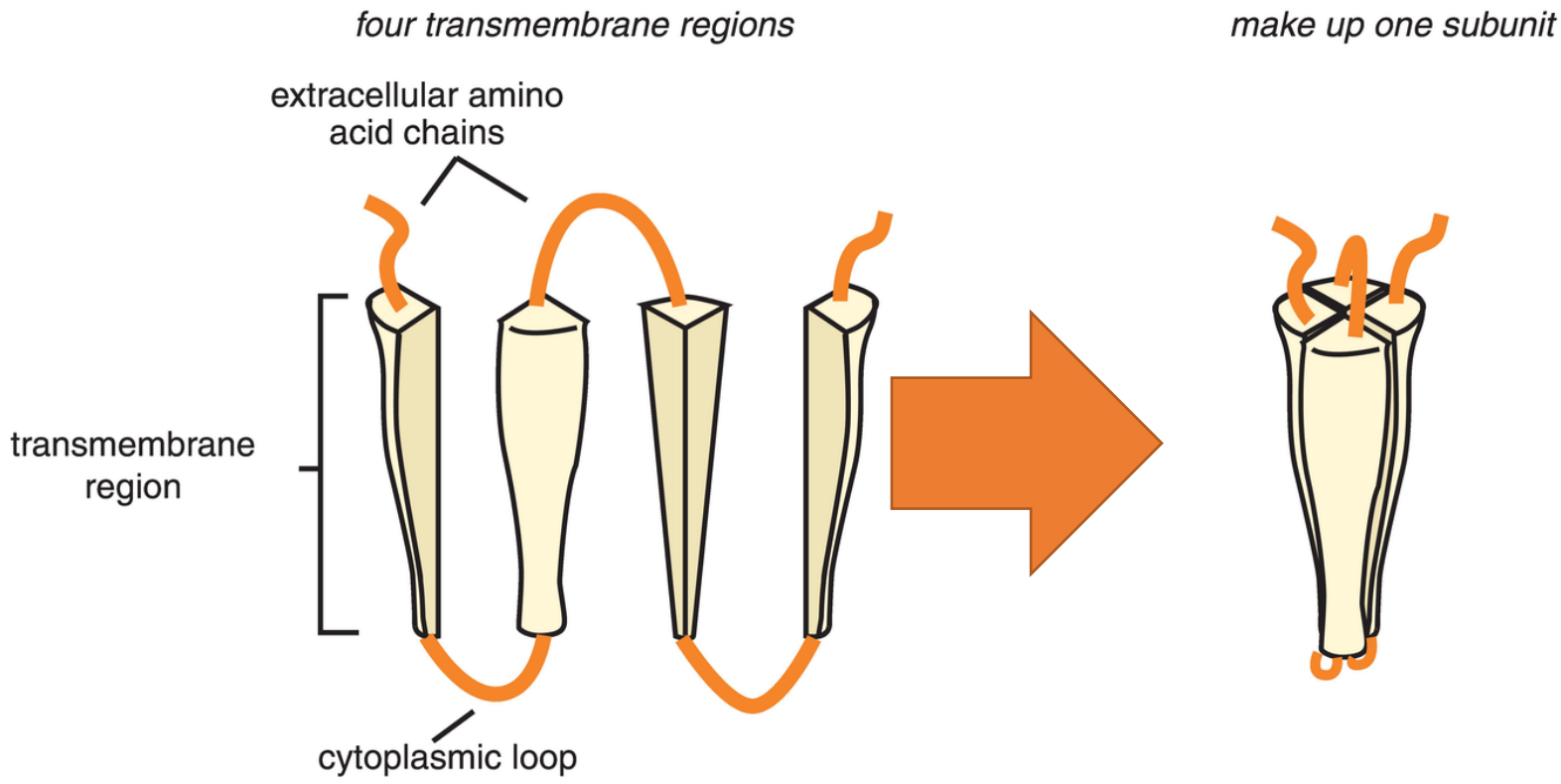
- Rapid onset
- Reasonable tolerability
- Useful for breakthrough symptoms
- May enhance adherences to Tx and alleviate activating Sx of SSRIs
- May use for acute and chronic anxiety

Disadvantages

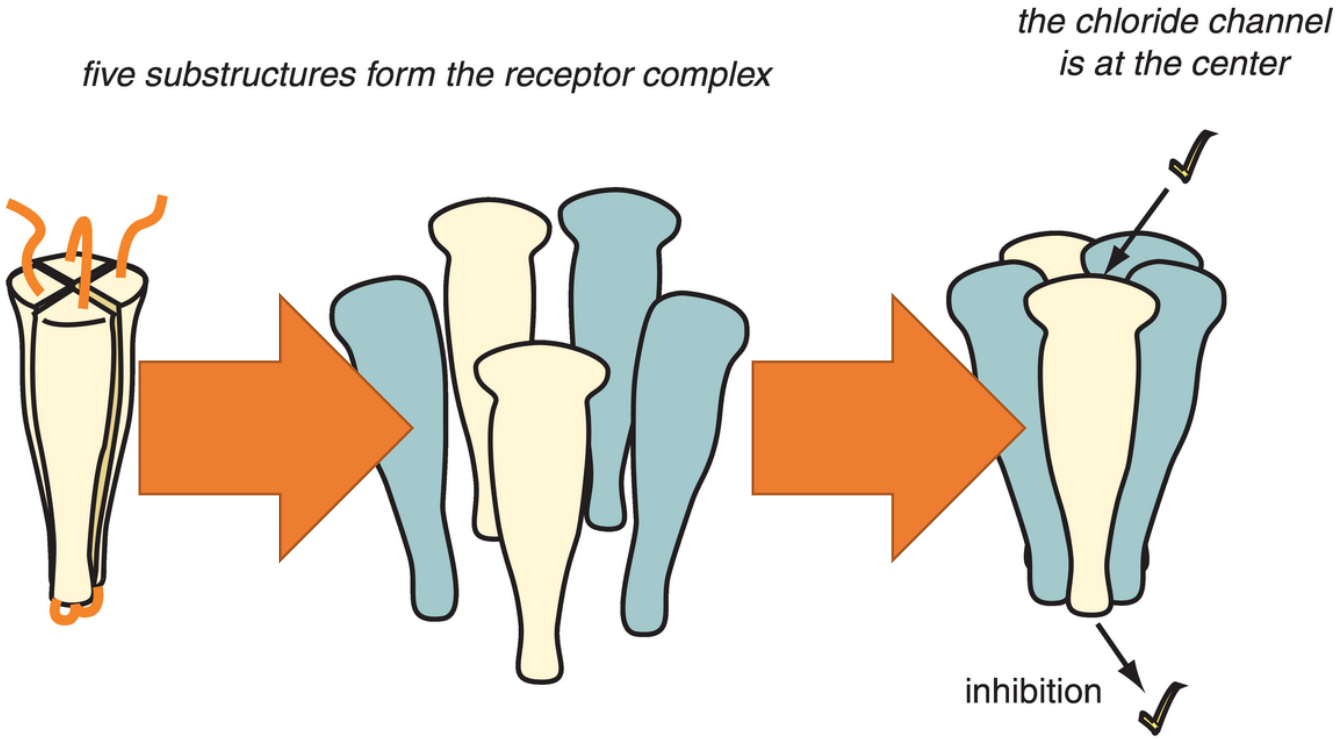
- Initial sedation
- Memory impairment
- Falls
- Possible increased risk of fracture
- Possibility of abuse dependence and withdrawal
    - Lower probability of abuse in anxious patients without substance abuse

Neuropharmacology of GABA and Benzodiazepines

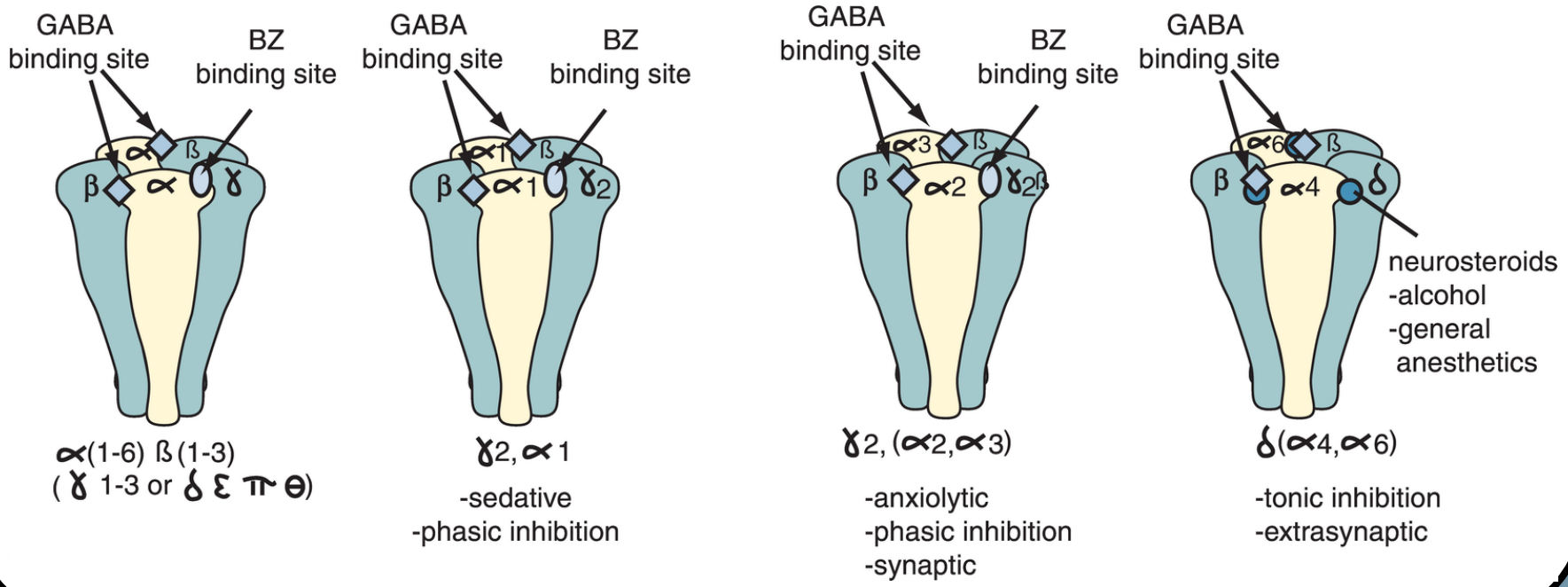
Structure of $GABA_A$ Receptor



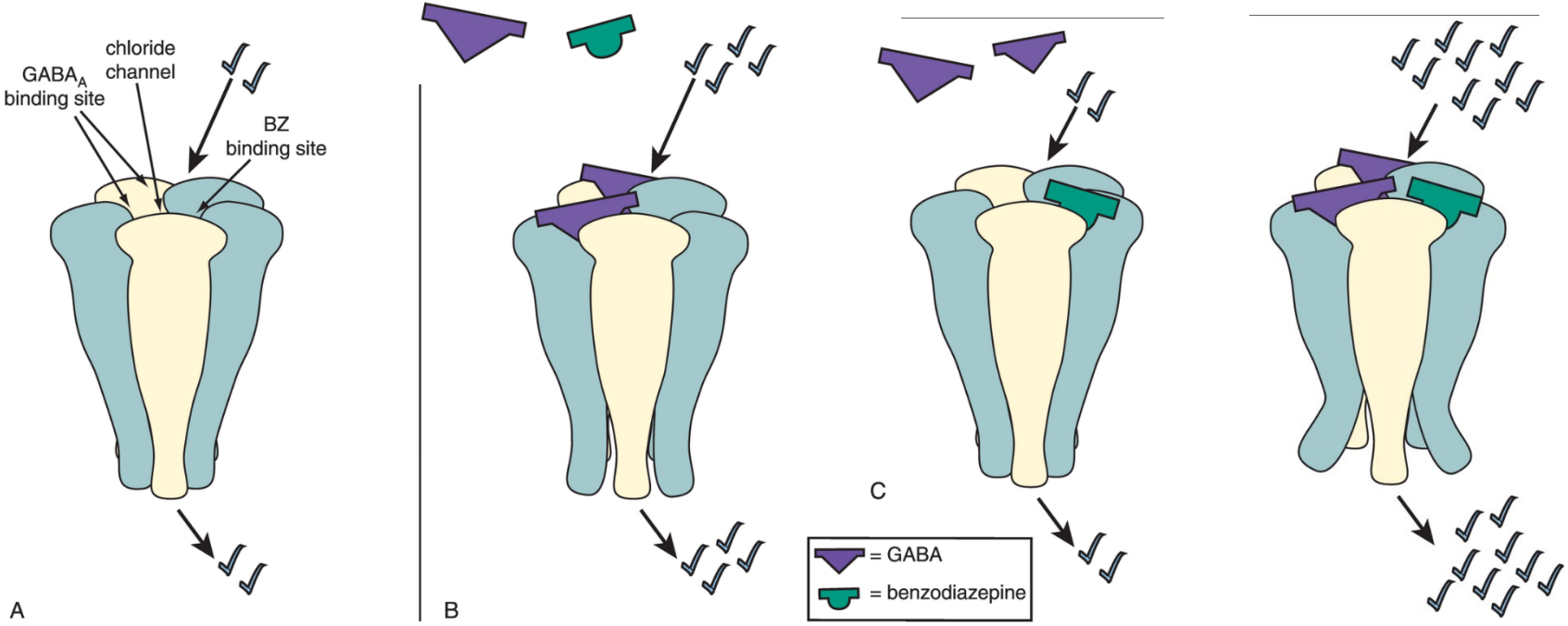
Structure of $GABA_A$ Receptor



Subtypes of GABA Receptors

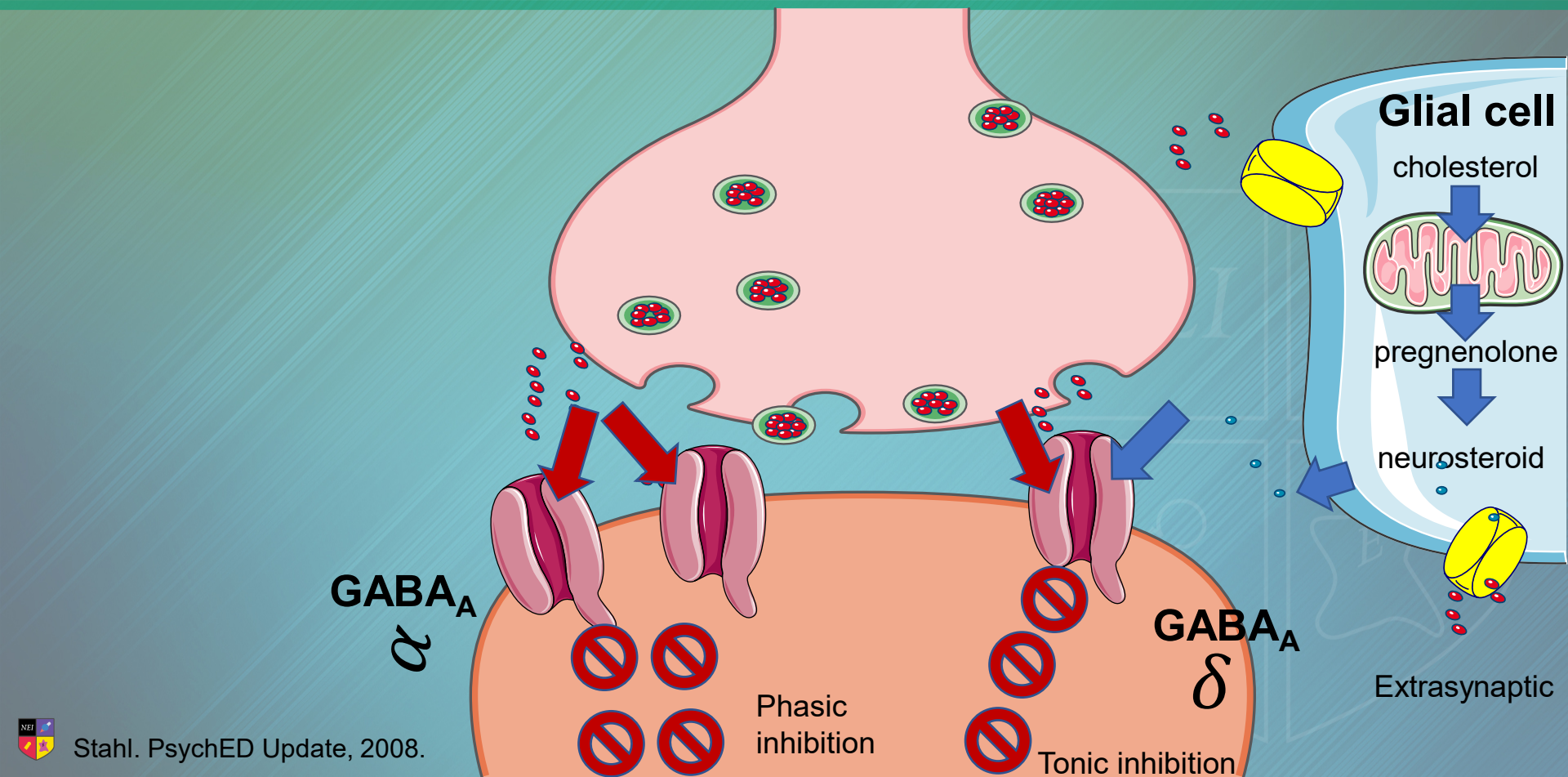


Positive Allosteric Modulation of $GABA_A$ Receptors



Stahl's Essential Pharmacology 4th Edition

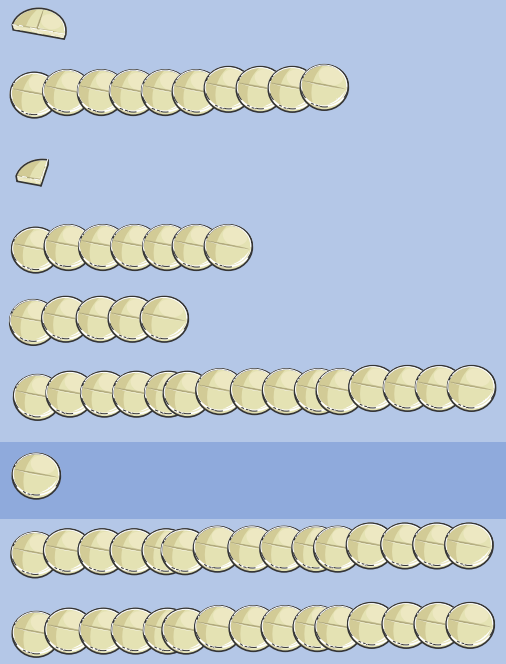
Types of $GABA_A$ Mediated Inhibition



Stahl. PsychED Update, 2008.

Benzodiazepine Equivalence

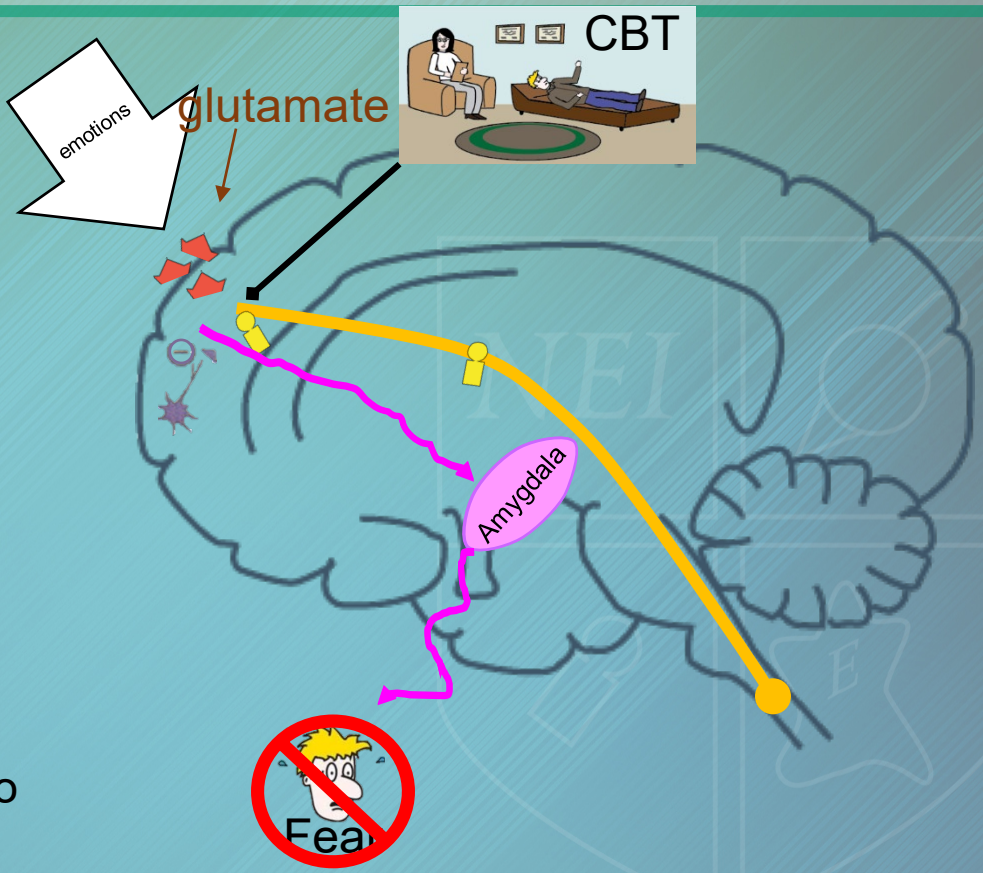
Benzodiazepine	Equivalent Dose (mg)
Alprazolam	0.5
Chlordiazepoxide	10
Clonazepam	0.25
Clorazepate	7.5
Diazepam	5
Flurazepam	15
Lorazepam	1
Oxazepam	15
Temazepam	15



Clinically-Relevant Neurobiology of Anxiety

Fear Conditioning & Extinction: Amygdala

- Emotional inputs to the amygdala frequently use glutamate to ring the alarm
  - GABA and 5-HT temper the alarm
- GABA interneurons in the cortex and hippocampus inhibit emotional input to the amygdala, as do serotonergic nerve terminals from the raphe
- CBT enhances inhibitory tone in the cortex by reprogramming the neurons there as they become desensitized and deconditioned to anxiety-provoking triggers



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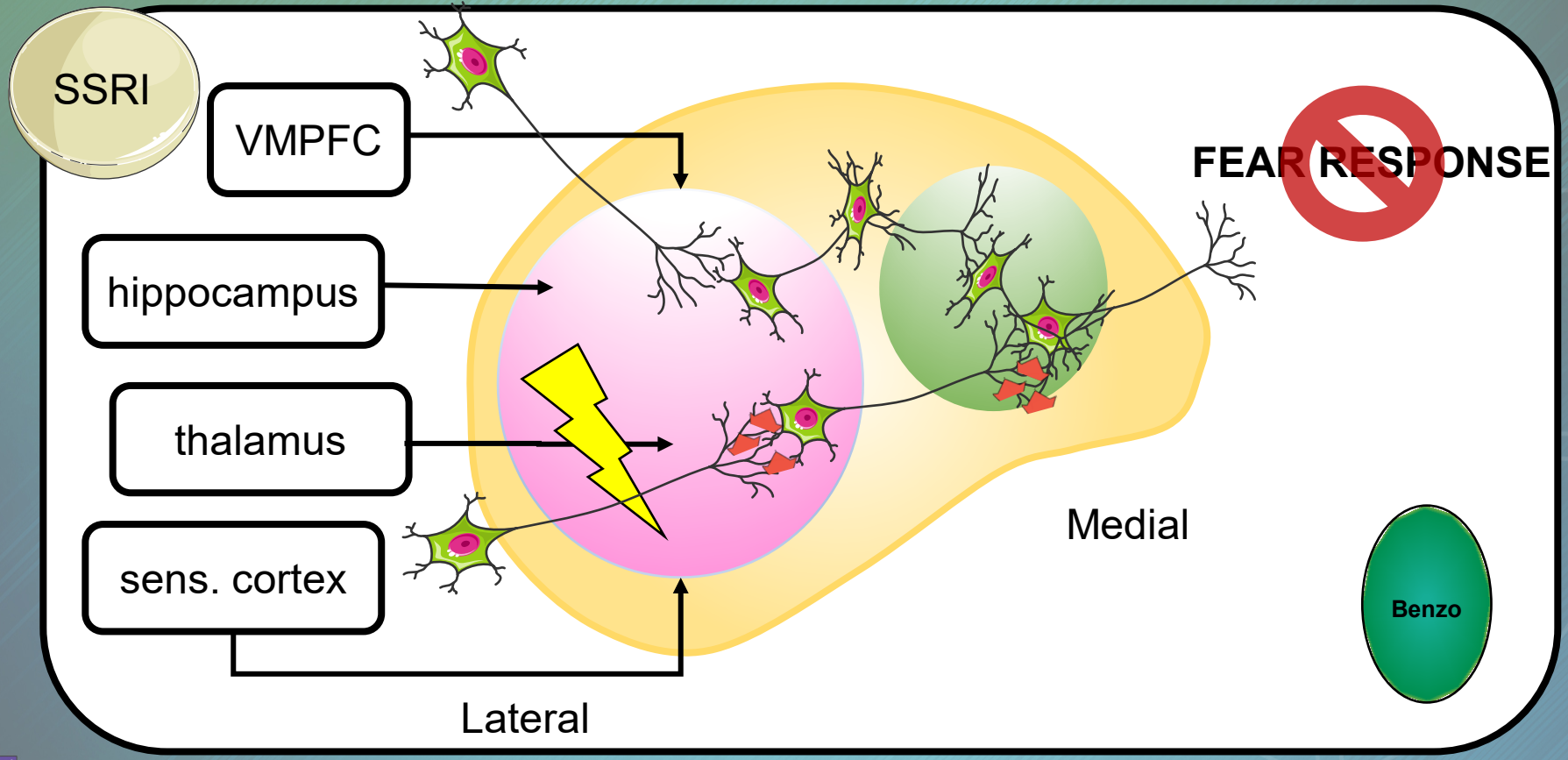
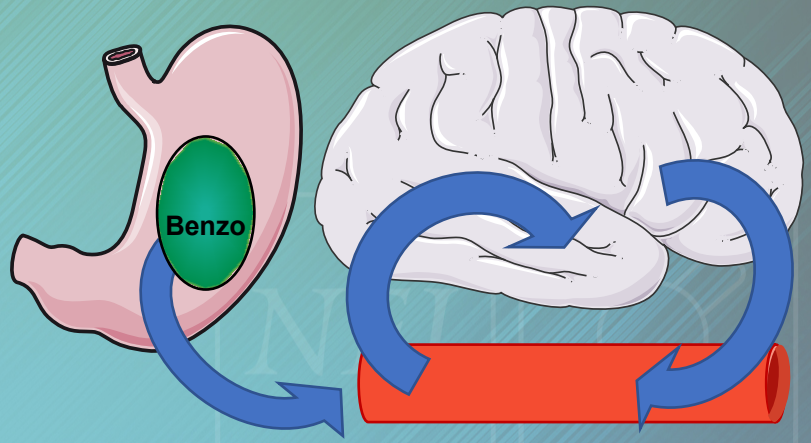


Janak PH, Tye KM. From circuits to behaviour in the amygdala. Nature 2015;517(7534):284-92.

Benzodiazepine Absorption and Metabolism

Benzodiazepine Absorption

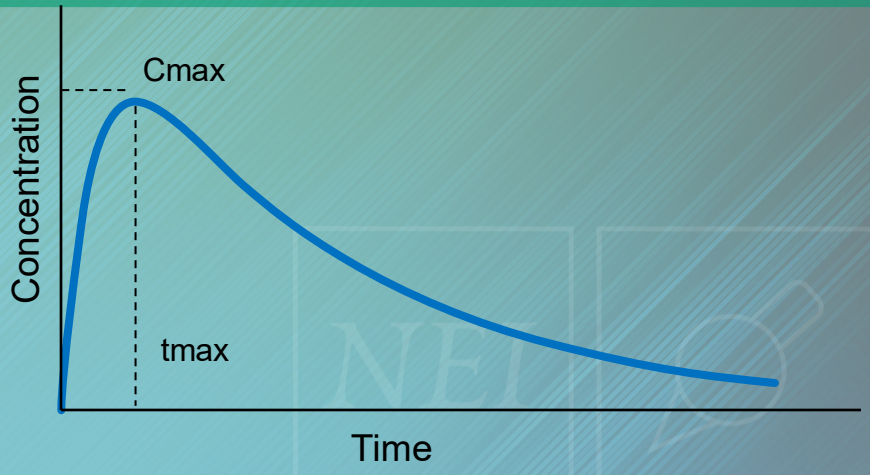
- Rapidly absorbed BZDs enter circulation quickly
  - GI absorption dictated by intrinsic properties of BZD
- Lipophilicity, at physiologic pH influences the rate at which it crosses the BBB by passive diffusion

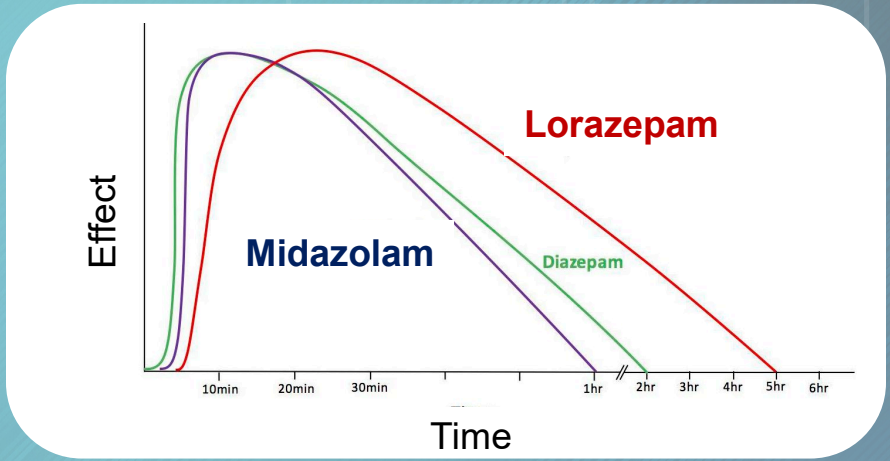


Highly Lipophilic	Less Lipophilic
• Enter the brain more quickly • "Turning on" the effect promptly • "Turn off" the effect more quickly as well, as they disappear into fat • More intense effect	• Less lipophilic BZDs (e.g., lorazepam) produce slower effect • Provide more sustained relief, despite a shorter half life • Less intense effect

Benzodiazepine Duration of Action

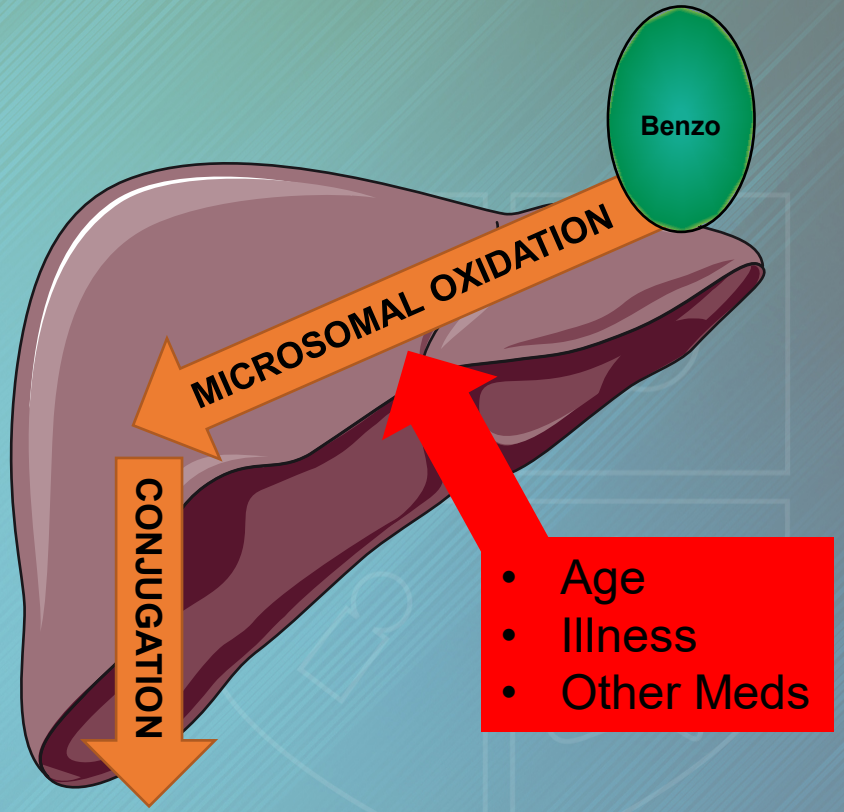
- Determined by **rate and extent of distribution rather than by the rate of elimination**
- Example
  - Diazepam has a longer half-life than lorazepam, BUT has a shorter duration of clinical action after a single dose
  - Reason: Because of its greater lipophilicity, diazepam is more extensively distributed to peripheral sites, particularly to fat tissue; consequently, it is more rapidly moved out of the blood and brain into inactive storage sites and its CNS effects end more rapidly
  - **Less lipophilic benzodiazepines maintain their effective CNS concentrations longer** because they are less extensively distributed to the periphery



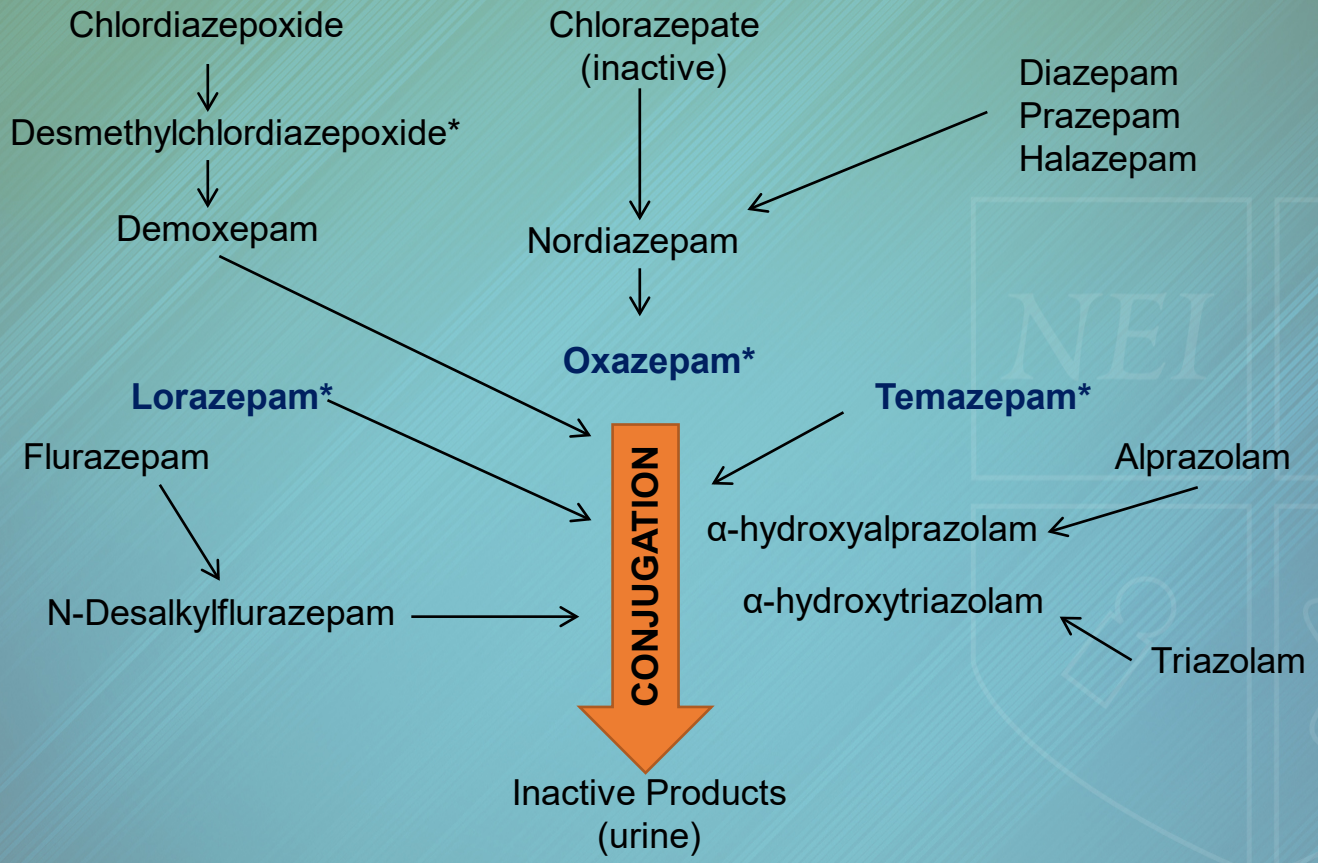


Benzodiazepine Biotransformation

- Metabolized by
  - microsomal oxidation or
  - glucuronide conjugation
- In the elderly, or in individuals with hepatic disease, **benzodiazepines that are conjugated are safer than those that are metabolized by oxidation**
- Specifically, and despite its short $t_{1/2}$, midazolam accumulates in patients with hepatic impairment

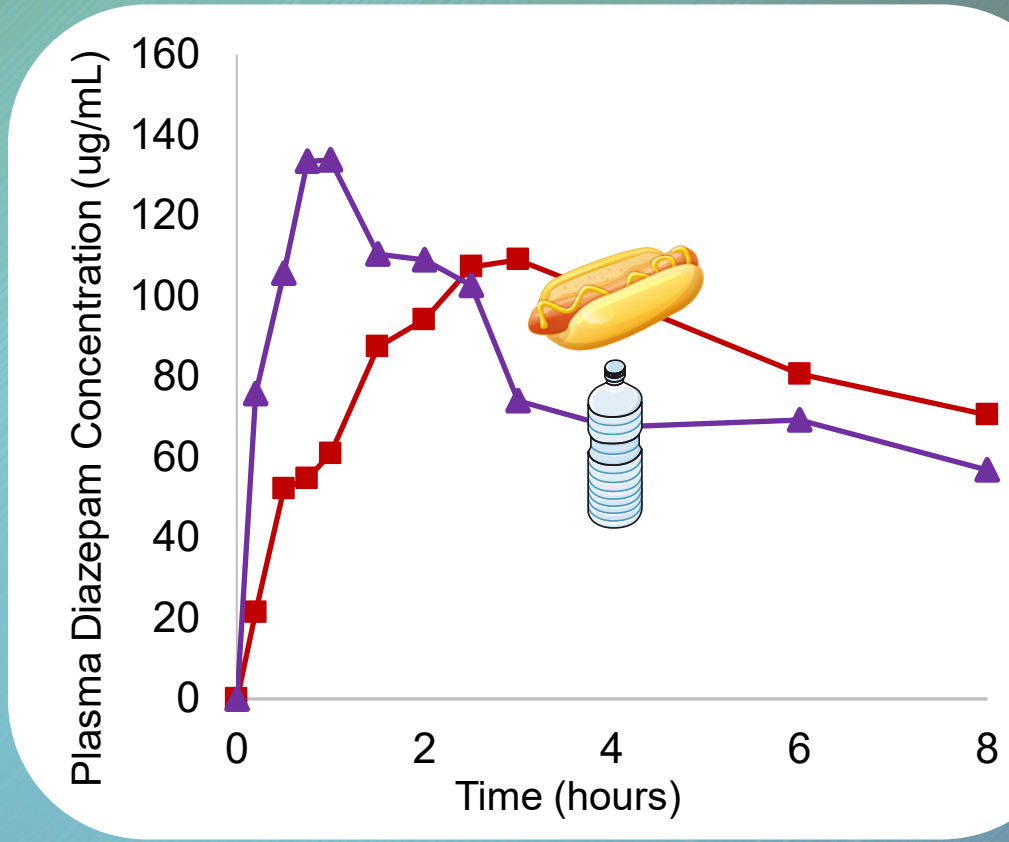


Benzodiazepine Biotransformation



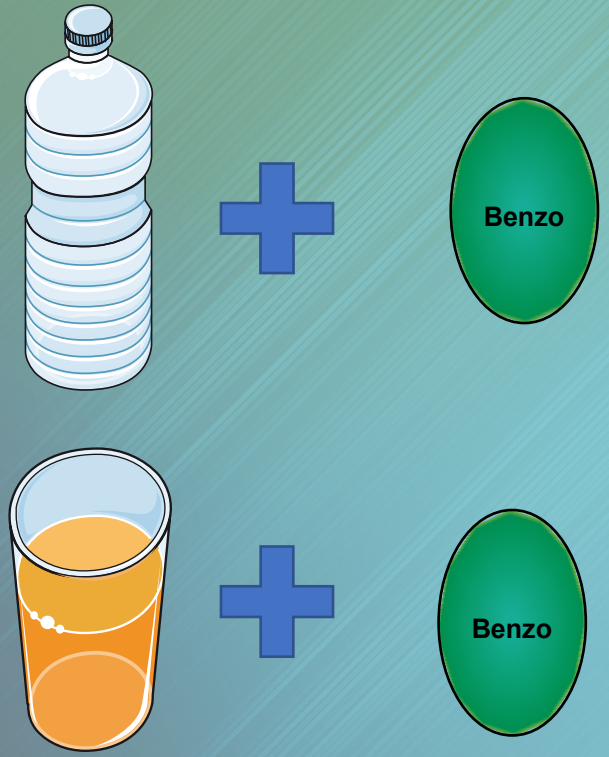
Clinically-Relevant Benzodiazepine Interactions

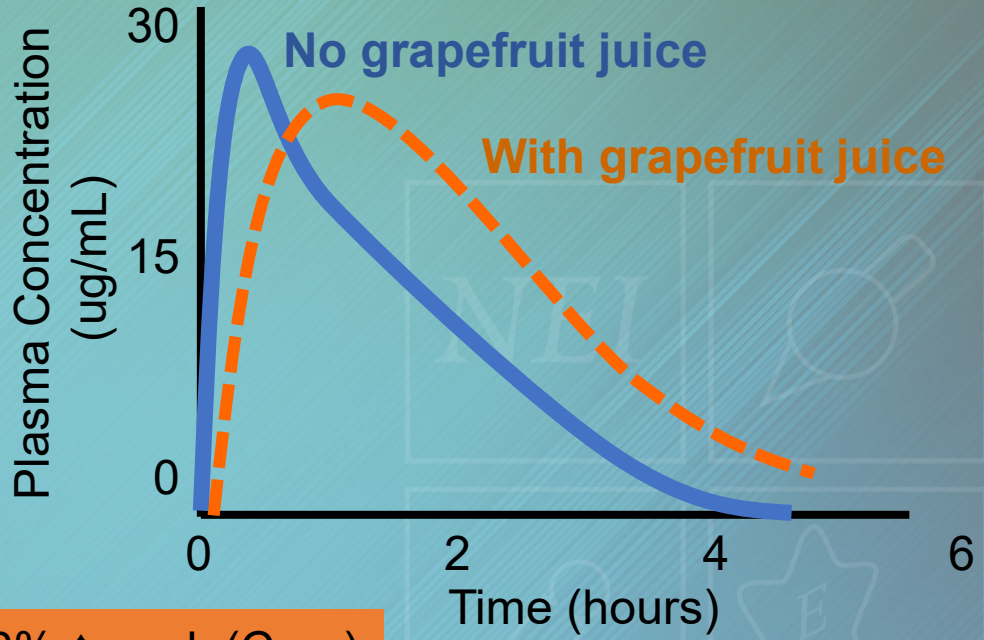
Benzodiazepine Interactions: Food



Greenblatt et al. Clinical Pharmacology & Therapeutics.

Benzodiazepine Interactions: Grapefruit Juice





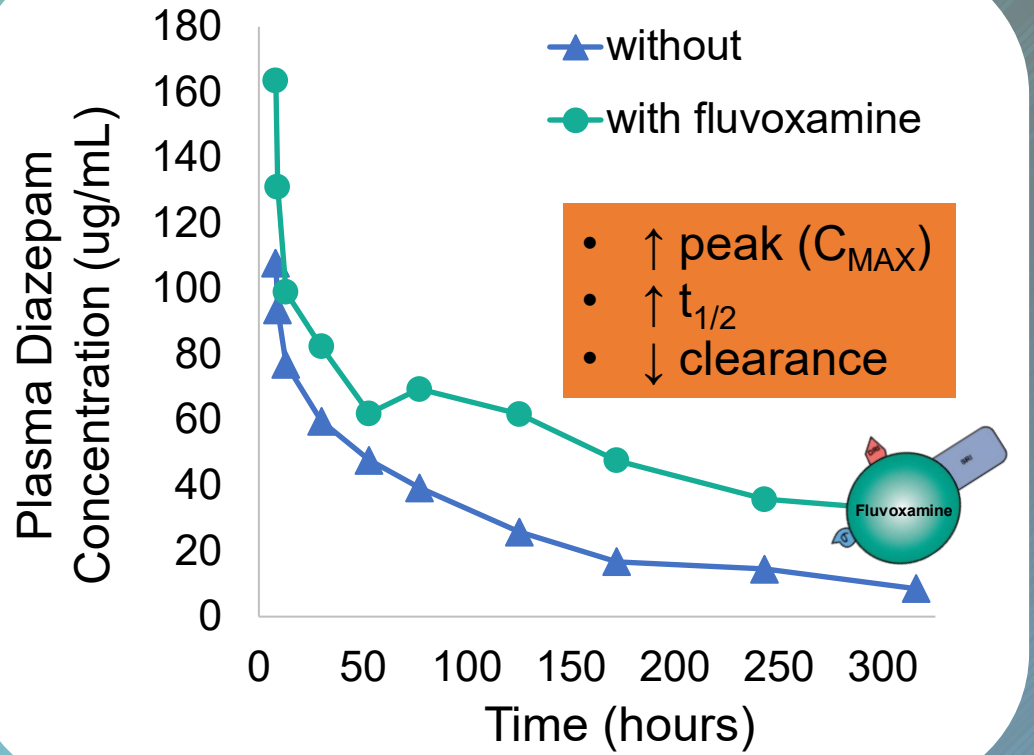
- 56% ↑ peak (C_{MAX})
- 80% ↑ t_{MAX}
- 50% ↑ absorption

Kupferschmidt et al. Clinical Pharmacology & Therapeutics 1995;58:20-8.

Benzodiazepine Interactions: Fluvoxamine

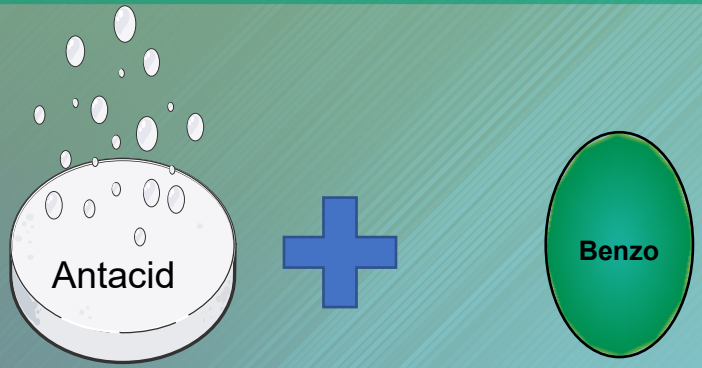
Other CYP3A4 inhibitors

- Antifungals (e.g., ketoconazole)
- Calcium channel blockers (e.g., verapamil/diltiazem)
- Nefazodone
- Protease inhibitors
- Macrolides

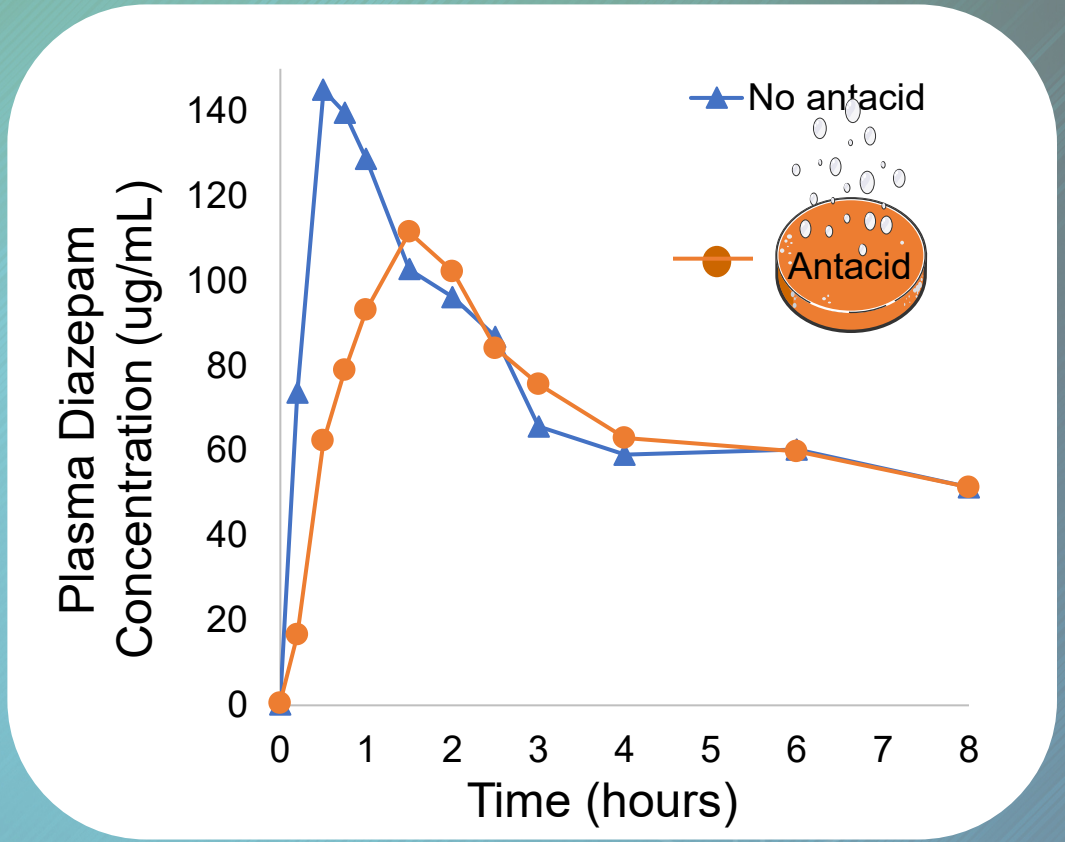


Perucca et al. Clinical Pharmacology & Therapeutics 1994;56:471-6.

Benzodiazepine Interactions: Antacids

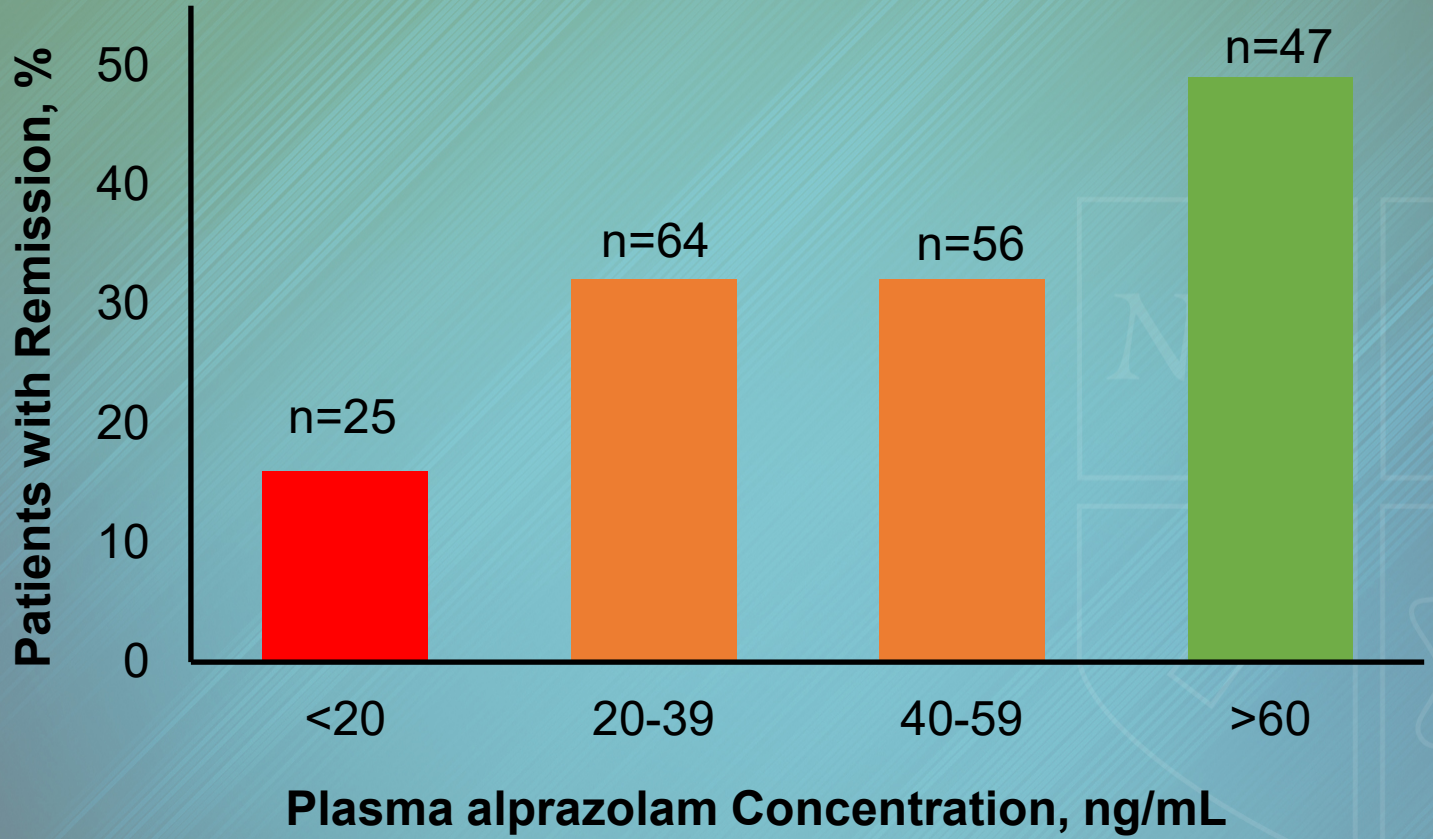


- ↓ peak (C_{MAX})
- ↑ t_{MAX}
- ↓ absorption rate



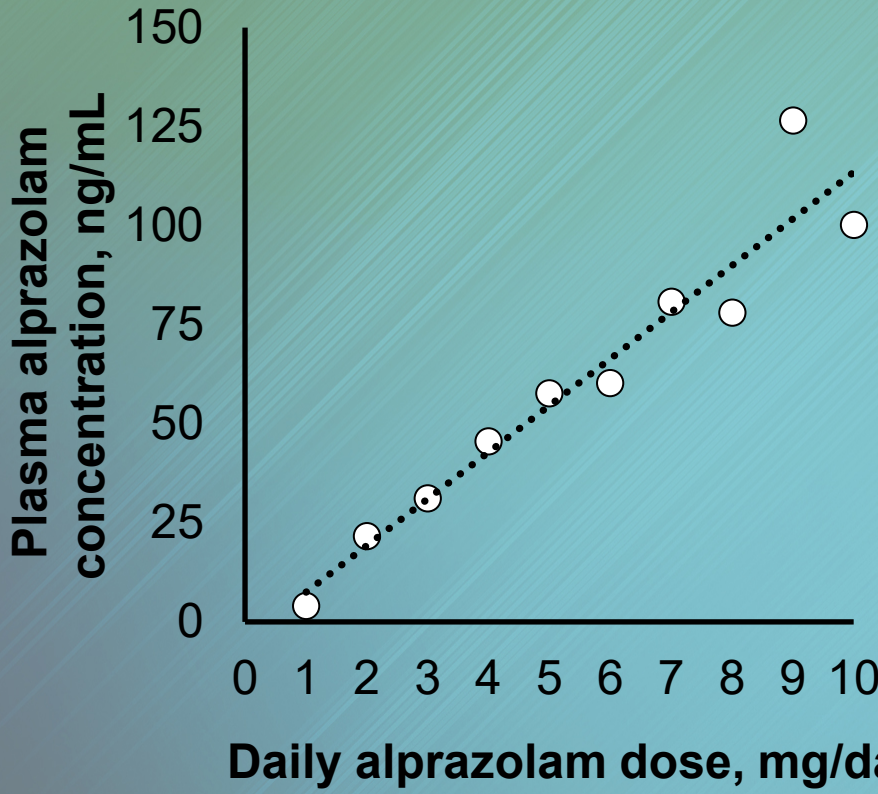
Greenblatt et al. Clinical Pharmacology & Therapeutics.

Benzodiazepine Levels in Anxiety Disorders



Greenblatt et al. Archives of General Psychiatry 1993;50:715.

Benzodiazepine Levels in Anxiety Disorders



Greenblatt et al. Archives of General Psychiatry 1993;50:715.

Benzodiazepine Tolerance and Tolerability

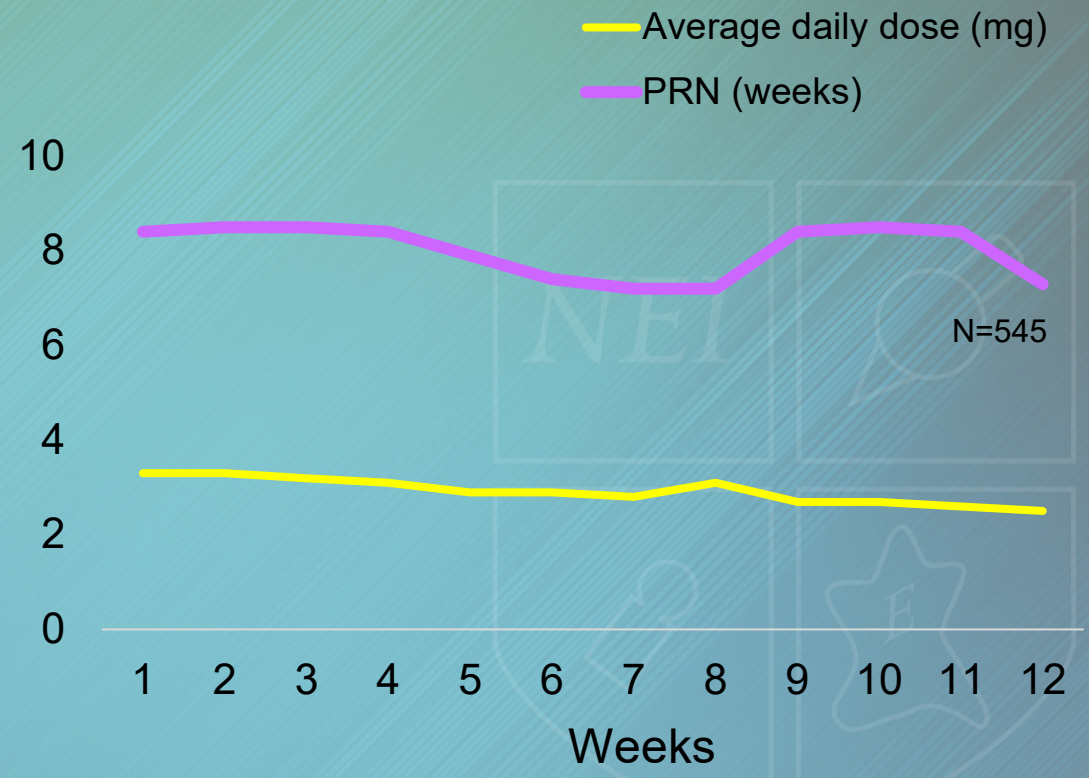
Benzodiazepine Dose and Use Over Time in Anxious Adults + Substance-Use Disorders

BZD use does not predict recovery or recurrence

- Did not predict likelihood of AUD disorder
  - recovery (RR = 1.31, 95% CI = 0.81 to 2.13) or
  - recurrence (RR = 0.82, 95% CI = 0.46 to 1.60).

BZD Use and Dose Over Time

- No statistically significant increases in dose or amount of PRN use (except for year 4 and 11 [small, <1 week])



Mueller et al. Long-Term Use of Benzodiazepines in Participants with Comorbid Anxiety and Alcohol Use Disorders. Alcohol Clin Exp Res 2005;29(8):1411-8.

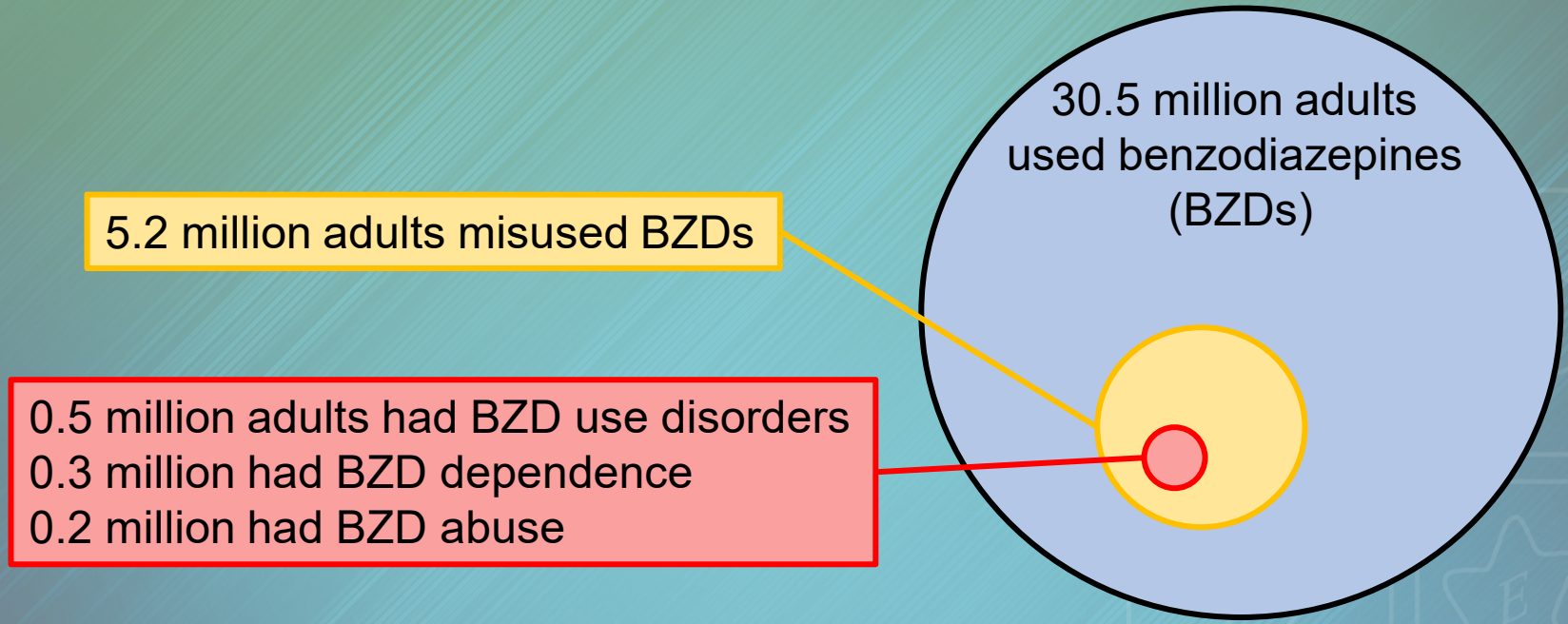
Benzodiazepines and Dementia Risk

- Among 171,287 patients with benzodiazepines or Z-drugs use, 9,776 (4%) patients developed dementia.
- **No association between benzodiazepines or Z-drugs and dementia**
  - Controls for number of prescriptions and cumulative benzodiazepine or Z-drugs use
- Higher odds ratio of dementia in patients with the lowest benzodiazepine or Z-drug use (OR=1.1) compared with no lifetime use
- Patients with the highest use had lowest risk of dementia (OR=0.83)
- **No relationships with short- or long-acting drugs**
- ”Some results compatible with a protective effect”

Osler et al. Associations of Benzodiazepines, Z-Drugs, and Other Anxiolytics With Subsequent Dementia in Patients With Affective Disorders: A Nationwide Cohort and Nested Case-Control Study. Am J Psychiatry 2020;177(6):497-505.

Gale et al. Influence of covariates on heterogeneity in Hamilton Anxiety Scale ratings in placebo-controlled trials of benzodiazepines in generalized anxiety disorder: systematic review and meta-analysis. J Psychopharmacol 2019;33(5):543-7.

Benzodiazepine Use, Misuse, and Use Disorders in the US



Blanco et al. Prevalence and Correlates of Benzodiazepine Use, Misuse, and Use Disorders Among Adults in the United States. J Clin Psychiatry 2018:79(6); e1-10.

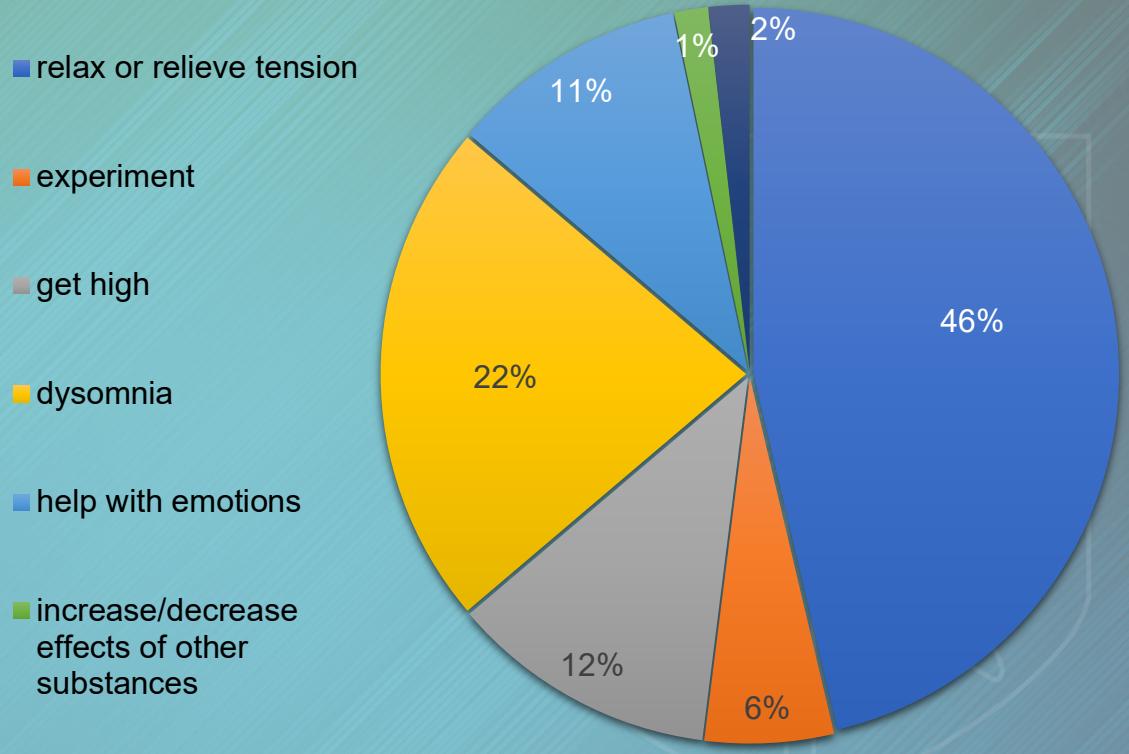
Maust et al. Benzodiazepine use and misuse among adults in the United States. Psychiatr Serv 2019;70(2):97-106.

https://www.fda.gov/drugs/drug-safety-and-availability/fda-requiring-boxed-warning-updated-improve-safe-use-benzodiazepine-drug-class

Use, Misuse, and Use Disorders in the US

- 1.5% met criteria for BZD use disorders, suggesting that “most patients are unlikely to become addicted to benzodiazepines”
- ↑ **risk for BZD misuse, use disorders, and harms:**
  - Younger, male, socioeconomically disadvantaged, substance use disorders, and divorced or separated or never married
- Persons with BZD use disorder → **more likely to report addiction-related motivations for benzodiazepine use**

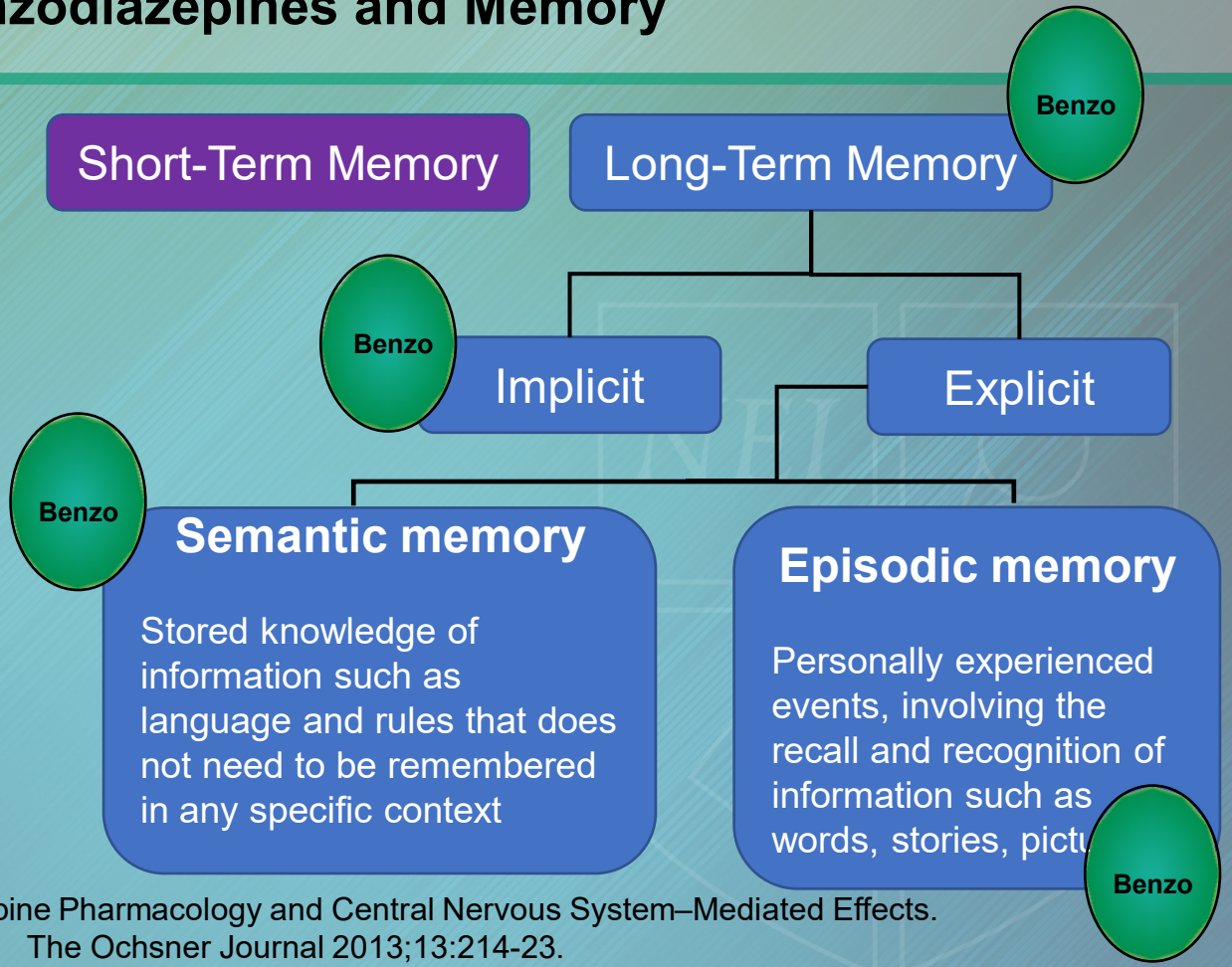
Main reason for BZD misuse, most recent time within the past year. 5.2 million with past year BZD use, N=2900.



Blanco et al. Prevalence and Correlates of Benzodiazepine Use, Misuse, and Use Disorders Among Adults in the United States. J Clin Psychiatry 2018: 79(6); e1-10.

Benzodiazepines and Memory

- **Implicit memory**
  - Impairment coincides with peak BZD plasma levels
  - Does not last as long as the impairments in explicit memory
- **Explicit memory**
  - Impairment earlier (in reference to dosing)
  - Persists longer than implicit memory impairment

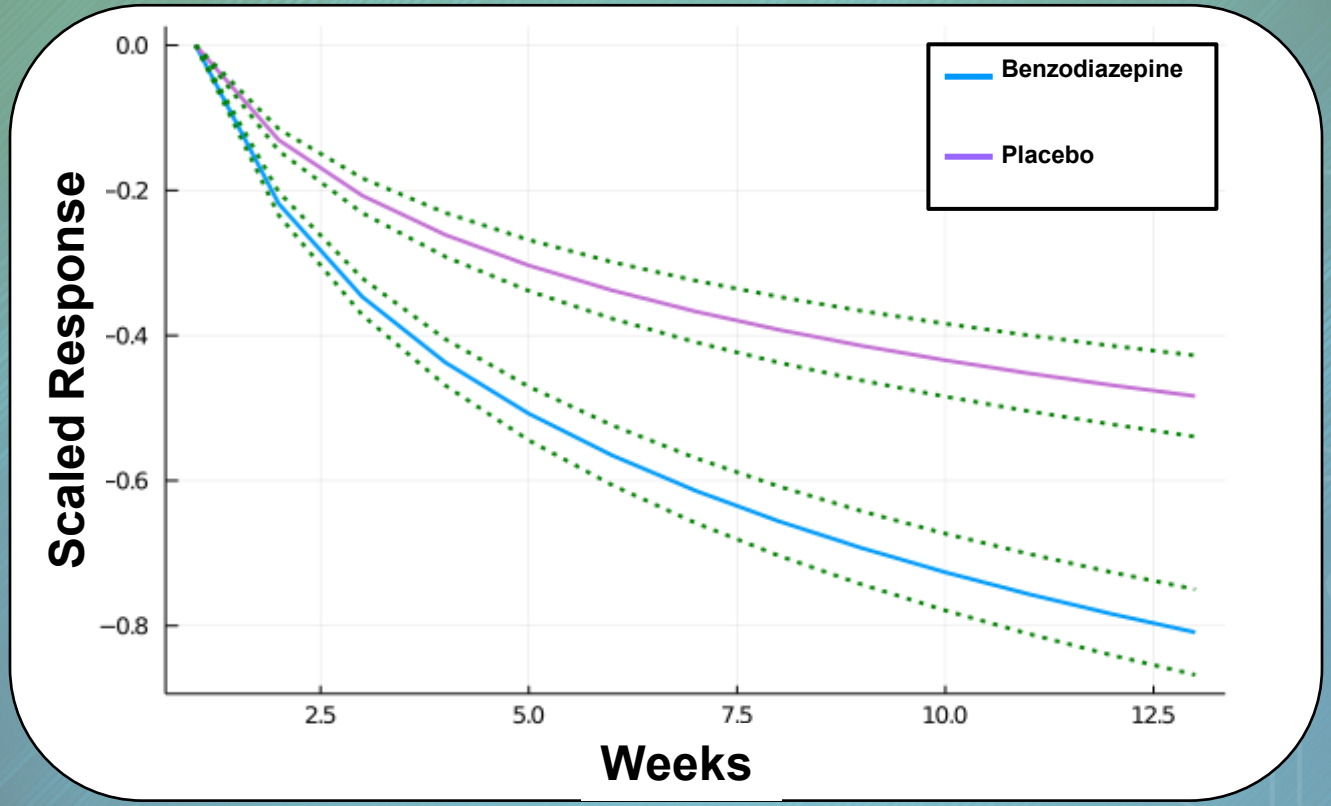


Griffin et al. Benzodiazepine Pharmacology and Central Nervous System–Mediated Effects. The Ochsner Journal 2013;13:214-23.

Roth et al. Benzodiazepines and memory. Br J Clin Pharmacol 1984;18 Suppl 1(Suppl 1):45S-49S.

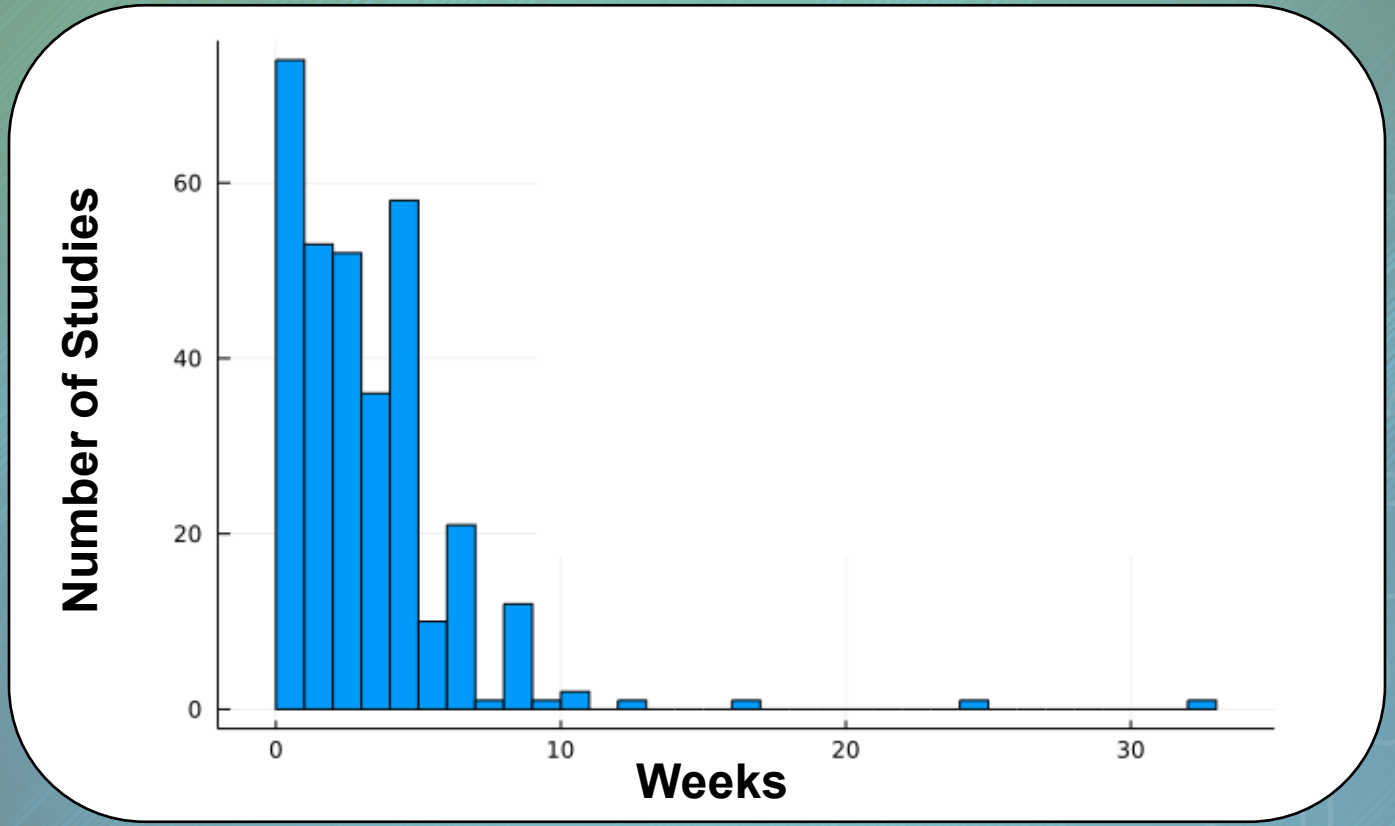
Benzodiazepines vs. other psychopharmacologic treatments for anxiety disorders

Efficacy: Benzodiazepines in Anxiety Disorders



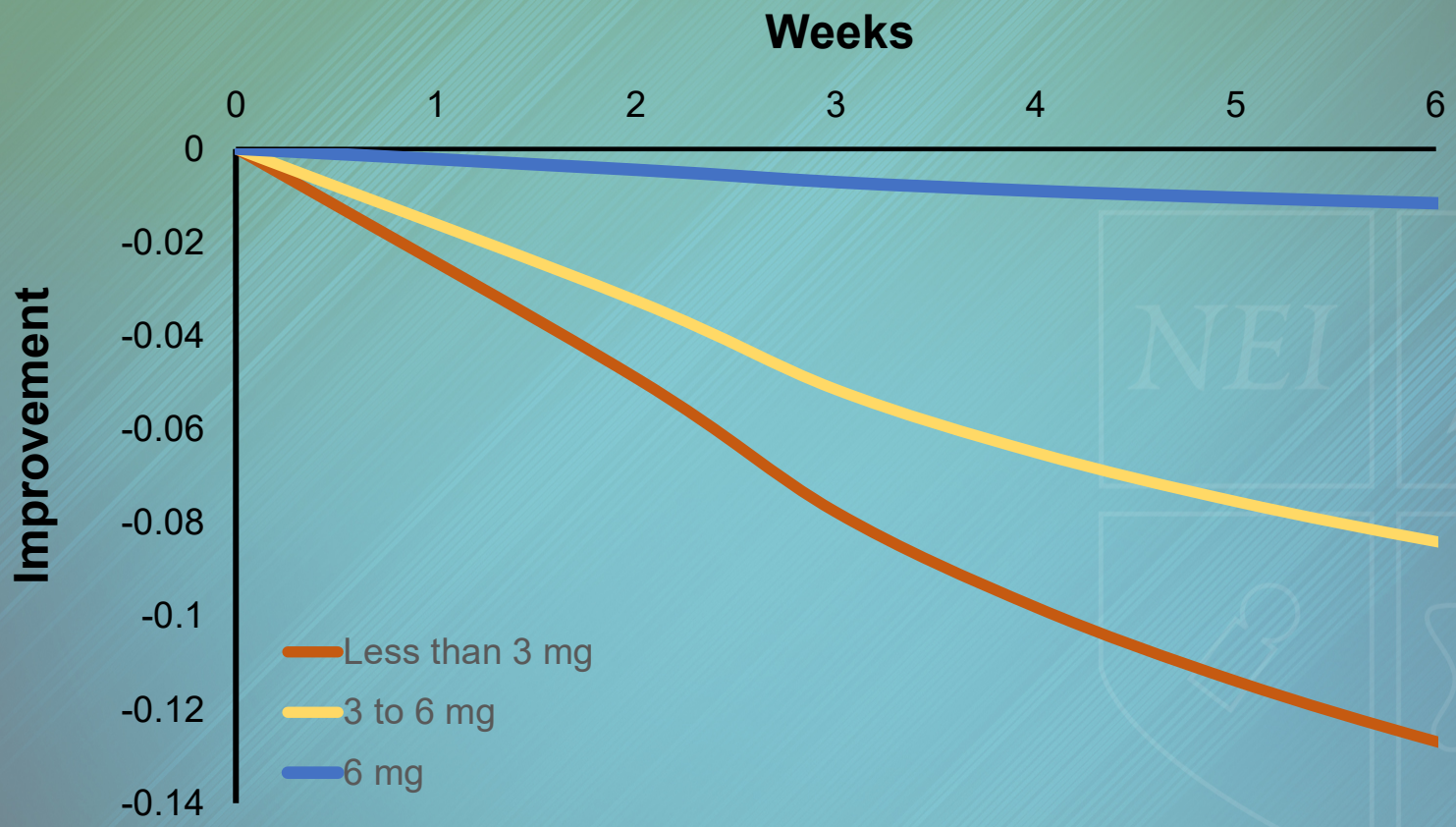
Strimpfl, Mills and Strawn. CNS Spectr 2021 (in press)

Benzodiazepine Studies in Anxiety Disorders: Most Are Very Short



Strimpfl, Mills and Strawn. CNS Spectr 2021 (in press)

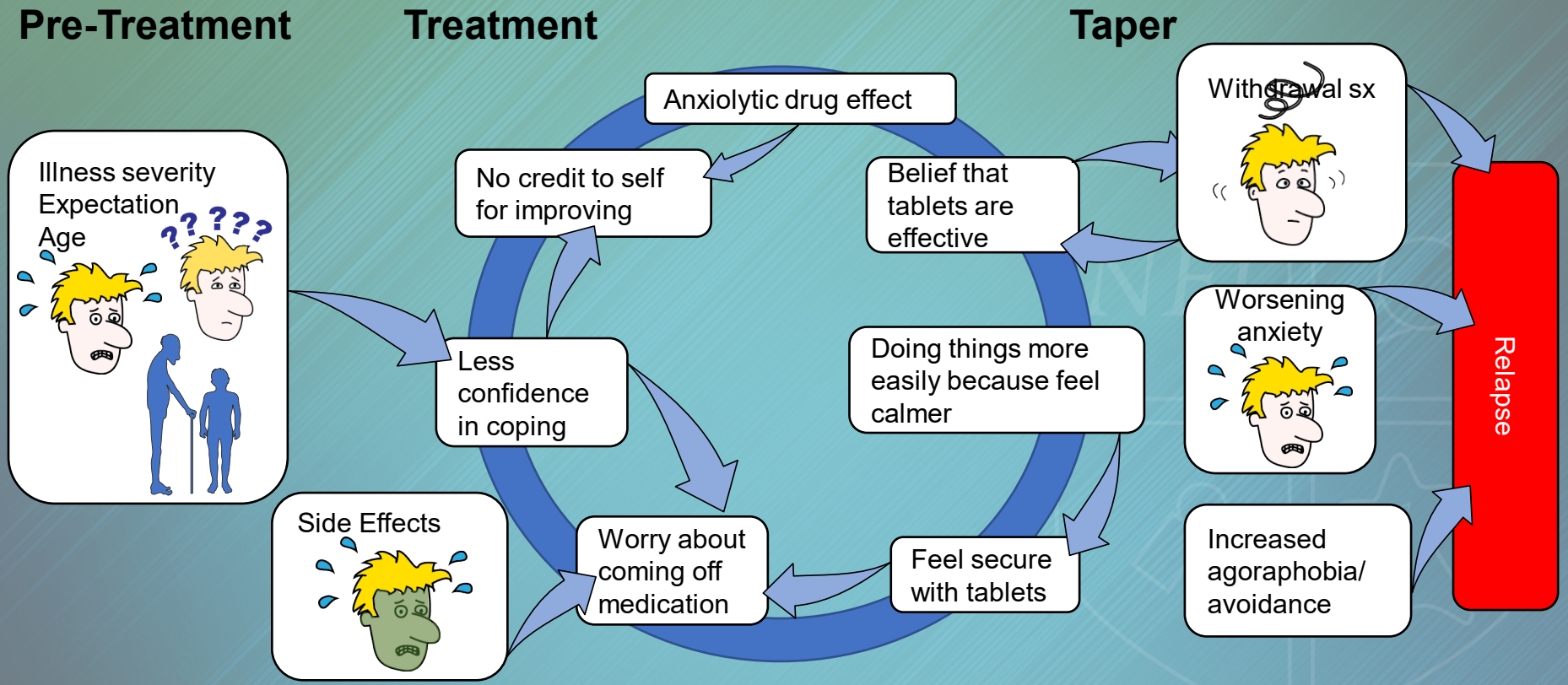
Benzodiazepine Dosing and Response in Anxiety Disorders



Strimpfl, Mills and Strawn. CNS Spectr 2021 (in press)

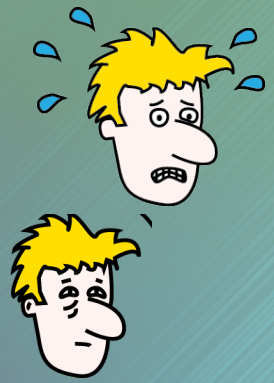
Benzodiazepine Tapering

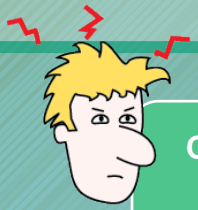
Benzodiazepines and Attribution



Metin et al. Alprazolam and Exposure for Panic Disorder with Agoraphobia: Attribution of Improvement to Medication Predicts Subsequent Relapse. The British Journal of Psychiatry 1994;164(5):652-9.

Symptoms of Benzodiazepine Withdrawal





Constitutional
Fatigue
Anorexia
Headaches
Weakness

Sensory
Paresthesia
Tinnitus
Numbness

Affective/Cognitive
Irritability
Tearfulness
Dread
Difficulty concentrating
Confusion
Anxiety/panic
Insomnia

Autonomic
Dizziness
Light-headedness
Sweating
Tachycardia
Tremor/myoclonus

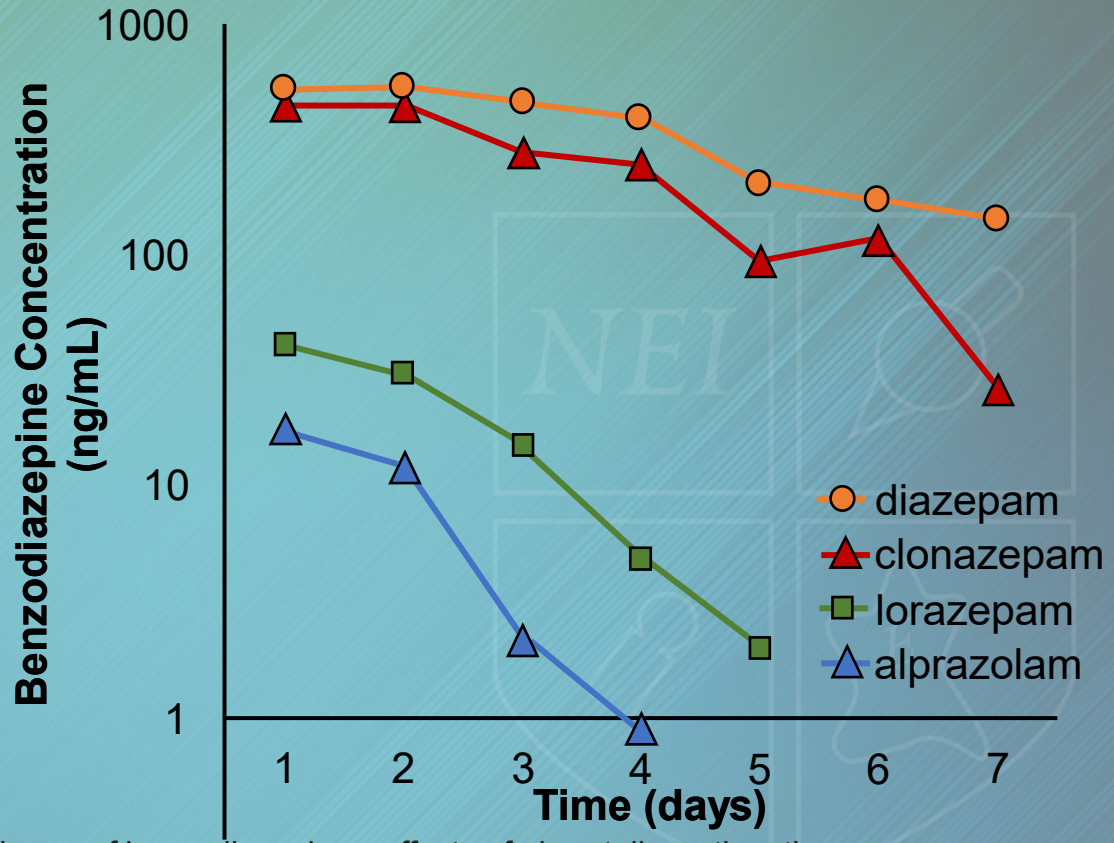
Benzo Withdrawal Syndrome

Gastrointestinal
Nausea
Vomiting

Nielsen et al. What is the difference between dependence and withdrawal reactions? A comparison of benzodiazepines and selective serotonin re-uptake inhibitors. Addiction 2012;107:900-8. | Rickels et al. Long-term therapeutic use of benzodiazepines: effects of abrupt discontinuation. Archives of General Psychiatry 1990;47:899-907

Benzodiazepine Withdrawal and Pharmacokinetics

- Half-life still matters regarding withdrawal
- Most important predictors of withdrawal are pharmacologic
  - Dose
  - Short vs. long half-life benzodiazepine
  - Inverse correlation between change in daily benzodiazepine plasma level and withdrawal severity → Greater decrease in blood level = more severe withdrawal ($r=0.63$, $p<0.01$).



Rickels et al. Long-term therapeutic use of benzodiazepines: effects of abrupt discontinuation. Archives of General Psychiatry 1990;47:899-907.

Predictors of Benzodiazepine Withdrawal

Pharmacologic Factors

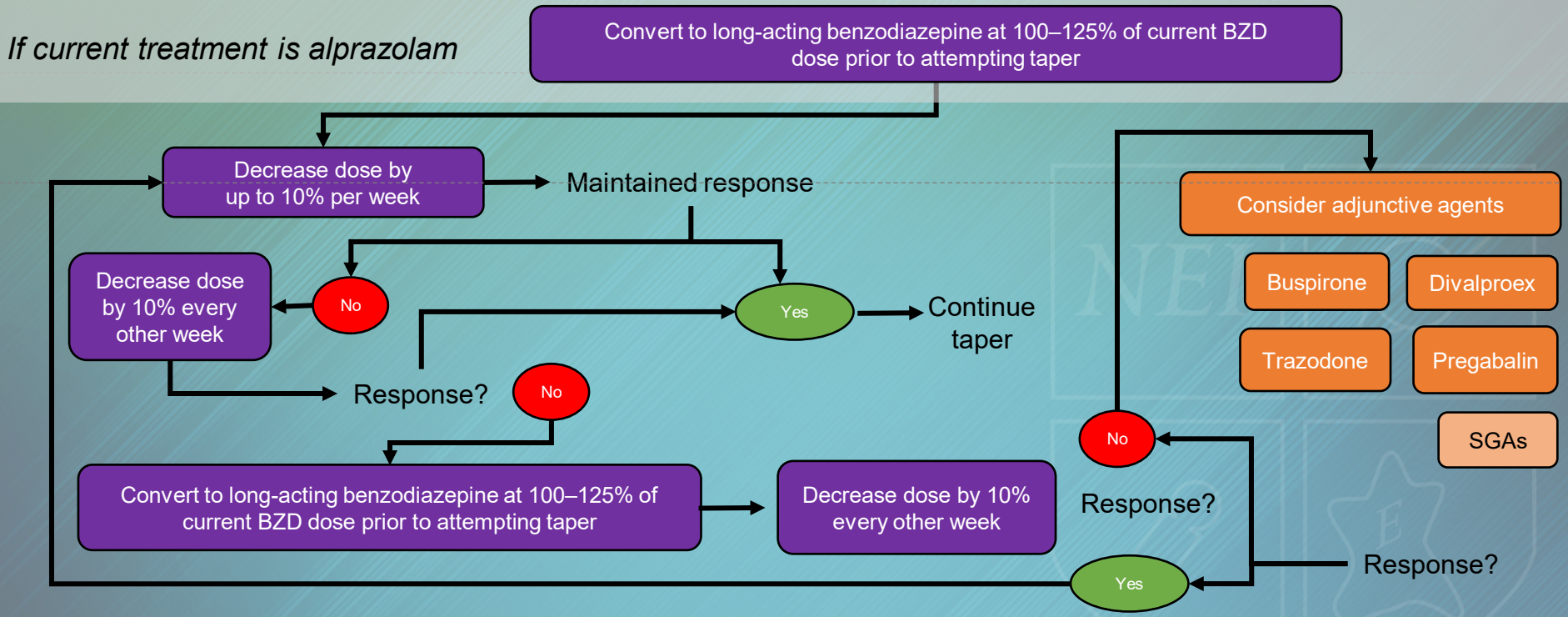
- Higher daily dose
- Shorter half-life
- Longer duration of therapy
- More rapid taper

Clinical Factors

- Panic disorder or higher pre-taper anxiety or depression
- Personality psychopathology
- Concomitant substance abuse/use

Noyes et al. American J Psychiatry 1991;148(4):517-23. | Murphy and Tyrer. Br J Psychiatry 1991;158:511-6. Rickels et al. Long-term therapeutic use of benzodiazepines. I. Effects of abrupt discontinuation. Arch Gen Psychiatry 1990;47:899-907. | Busto et al. NEJM 1986;315:854-9. | Hallfors and Saxe. The dependence potential of short half-life benzodiazepines: a meta-analysis. Am J Public Health 1993;83:1300-4. | Kales et al. Rebound insomnia. A potential hazard following withdrawal of certain benzodiazepines. JAMA 1979;241:1692-5.

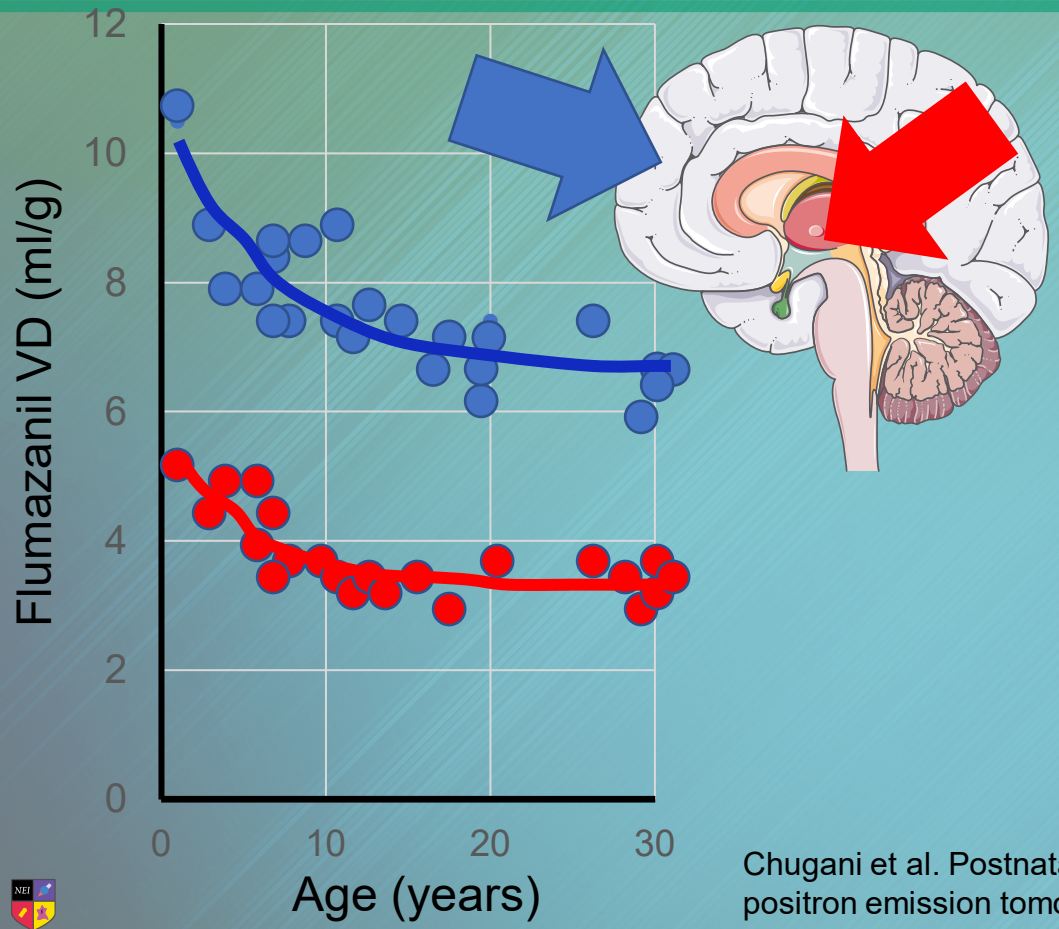
Tapering Benzodiazepines: After Optimizing SSRI/SNRI/Psychotherapy



Baandrup et al. Pharmacological interventions for benzodiazepine discontinuation in chronic benzodiazepine users. Cochrane Database Syst Rev 2018;3(3):CD011481. | Rickels et al. Imipramine and buspirone in treatment of patients with generalized anxiety disorder who are discontinuing long-term benzodiazepine therapy. Am J Psychiatry 2000;157(12):1973-9. | Rickels et al. Trazodone and valproate in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal symptoms and taper outcome. Psychopharmacology 1999;141:1-5.

Benzodiazepines in Pediatric Anxiety Disorders

$GABA_A$ Interventions in Children & Adolescents



- Subcortical regions reach adult V_D at 14–17.5 years
- Cortical regions reach adult V_D levels at 18–22 years
- Studies in pediatric anxiety disorders predominantly negative with poor tolerability

Chugani et al. Postnatal maturation of human $GABA_A$ receptors measured with positron emission tomography. Ann Neurol 2001;49(5)618–26.

Benzodiazepines: Who and When?

Potentially Beneficial

- Partial response to SSRI/SNRI or psychotherapy
- Patients with breakthrough symptoms
- Acute expected anxiety (phobias)
- When rapid onset is needed (e.g., panic attack)

Nuanced

- Prior to exposures or psychotherapy sessions
- Adjustment reactions/grief

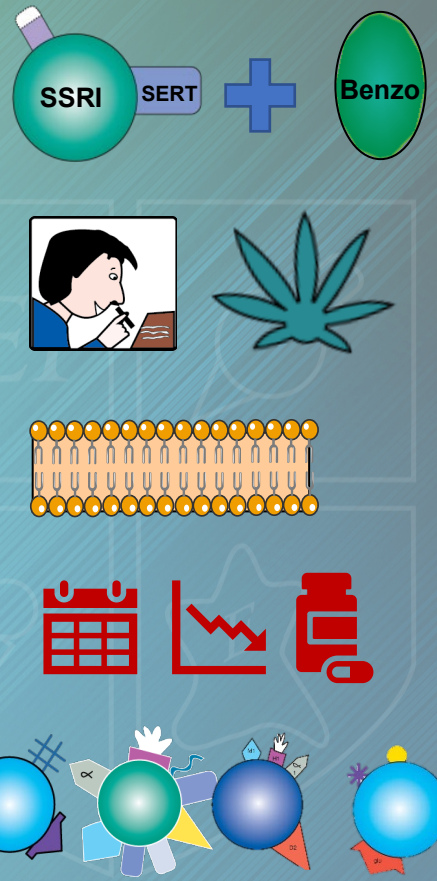
Increased Risk or Lower Likelihood of Benefit

- Elderly
- Children
- Concurrent opioid treatment
- Substance use disorders or history of BZD misuse
- Patients at risk of falling
- Heavy machinery operators, drivers, other occupations where cognitive effects could complicate job functioning.

Hirschtritt et al. Balancing the Risks and Benefits of Benzodiazepines. JAMA 2021;325(4):347-8. | Blanco et al. Prevalence and Correlates of Benzodiazepine Use, Misuse, and Use Disorders Among Adults in the United States. J Clin Psychiatry 2018;79(6):e1-10. | /www.fda.gov/drugs/drug-safety-and-availability/fda-requiring-boxed-warning-updated-improve-safe-use-benzodiazepine-drug-class

Conclusions

- Benzodiazepines **have a role in treating anxiety disorders**, but they **require monitoring** and consideration of risks/benefits
- **Tolerance data are mixed**, although BZDs should be used carefully in patients with a history of substance use
- **Abuse potential:** varies → related to high lipophilicity and short half-life
- Pharmacology
  - Consider **lipophilicity, NOT just half-life**
  - Interactions with food and medications are clinically important
- **Discontinuing BZDs**
  - Consider dose, type of BZD, and optimize pre-treatment anxiety/depression.
  - Potential adjunctive Rx: buspirone, valproate, pregabalin, and mixed dopamine serotonin receptor antagonists



Posttest Question 1

Highly lipophilic benzodiazepines:

1. Enter the brain more rapidly compared to less lipophilic benzodiazepines
2. Produce slower onset compared to less lipophilic benzodiazepines
3. Produce less intense effects compared to less lipophilic benzodiazepines
4. “Turn off slowly” by being slowly absorbed into fat

Posttest Question 2

In otherwise healthy adults, benzodiazepines' duration of action is most related to:

1. Cardiac output of the patient
2. Whether or not the benzodiazepine is oxidatively or non-oxidatively metabolized
3. Rate and extent of distribution rather than by the rate of elimination
4. Patient-specific variation in blood-brain barrier penetration

Posttest Question 3

Benzodiazepines impair:

1. Implicit memory
2. Explicit memory
3. Episodic memory
4. Semantic memory
5. All of the above