Sedative / Hypnotics

Robert Althoff, MD, PhD

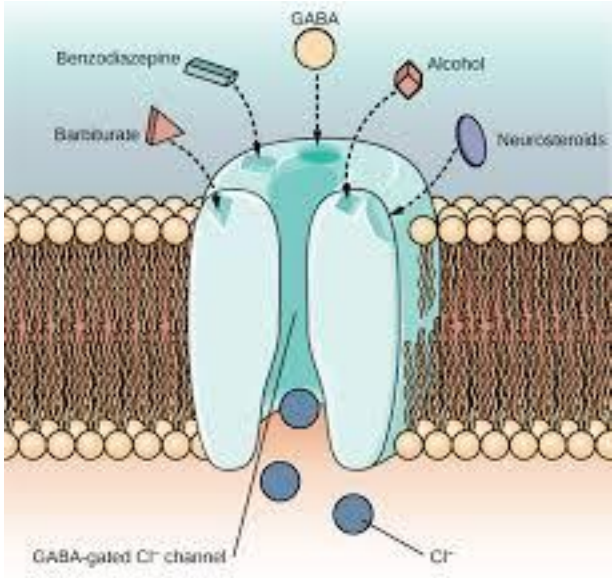
Disclosures

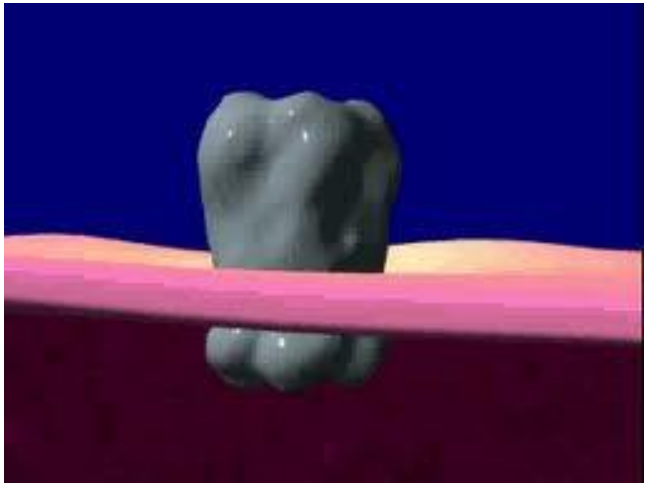
I have the following relevant financial relationship with a commercial interest to disclose:

- I receive or have received research support from NIMH, NIDA, and the Klingenstein Third Generation Foundation
- I have ownership equity in WISER Systems, LLC as a partner.

- Sedative / Hypnotics are a general class of agents
- Frequently refer to benzodiazepines (and like compounds) and barbiturates
- Many similarities in mechanisms of action, medical indications, behavioral effects, withdrawal considerations, and treatment

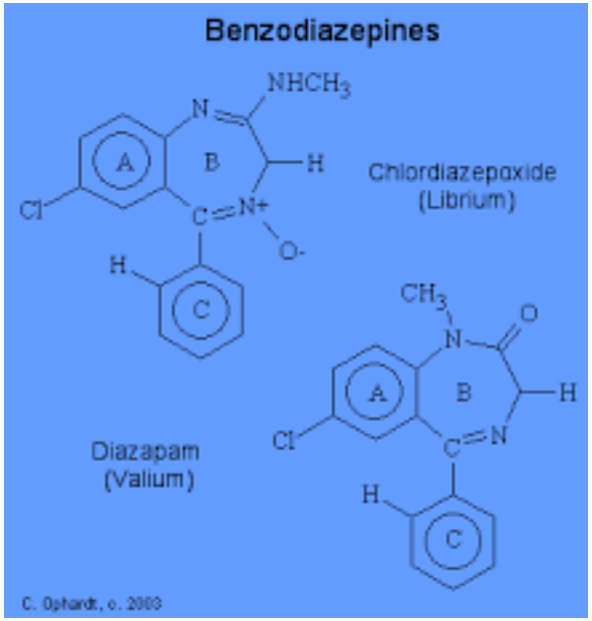
Benzodiazepine Mechanism of Action





Benzodiazepines are a class of agents that work on the central nervous system, acting selectively on gamma-aminobutyric acid-A (GABA-A) receptors in the brain. It enhances response to the inhibitory neurotransmitter GABA, by opening GABA-activated chloride channels and allowing chloride ions to enter the neuron, making the neuron negatively charged and resistant to excitation

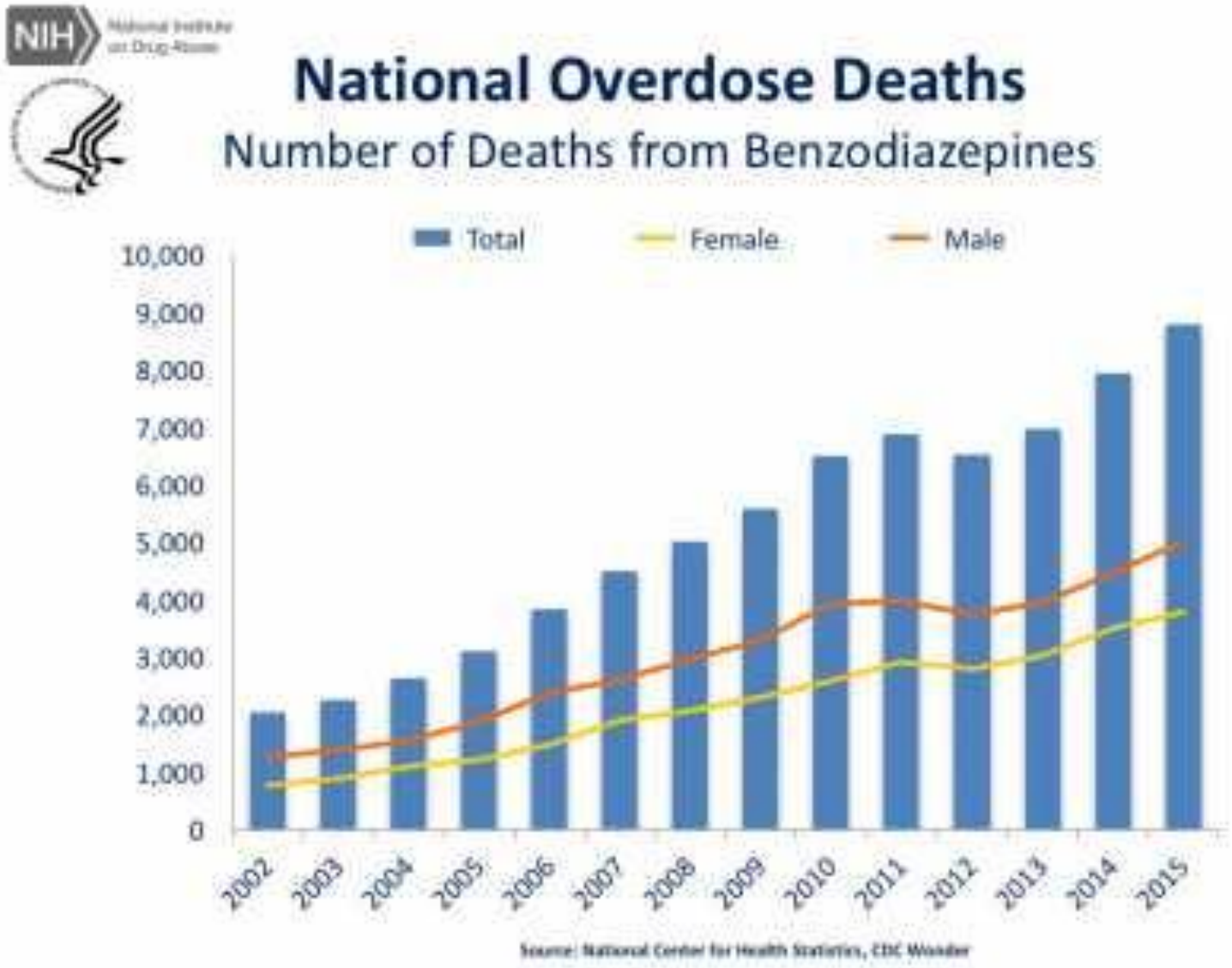
- Traditional benzodiazepines
  - Diazepam (Valium)
  - Clonazepam (Klonopin)
  - Others
- "Z" Drugs
  - Zaleplon (trade: Sonata)
  - Zolpidem (trade: Ambien, Edluar, Intermezzo)
  - Zopiclone (trade: Zimovane)



Benzodiazepine: General Info

- C IV DEA classification
- Although more than 2,000 different benzodiazepines have been produced worldwide, only about 15 are currently FDA-approved in the United States.
- Types of benzodiazepines therefore include those the following
  - Ultra-short acting: midazolam (Versed), triazolam (Halcion)
  - Short-acting: alprazolam (Xanax), lorazepam (Ativan)
  - Long-acting: chlordiazepoxide (Librium), diazepam (Valium)
- The use of benzodiazepines during pregnancy is a risk factor for cleft lip or palate, lower muscle tone, and withdrawal symptoms in the developing fetus

Bachhuber, et al. American Journal of Public Health , April 2016; 106;
Jone and McAnnich, Am J Prev Med. 2015 Oct;49(4):493-501. E-medicine health



CDC/ NIDA Vital Statistics Data: Jan 2017;
https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates

Benzodiazepine: General Info

- Increase in use (30% increase: 1996 [4%] to 2013 [5.6%])
- Dose of benzo's doubled during same period
- Rate of benzo use disorder in 2015 was 0.3% (SNDUH)
- The overdose death rate increased from 0.58 (95% CI = 0.55, 0.62) to 3.07 (95% CI = 2.99, 3.14) per 100 000 adults, with a plateau seen after 2010
- Deaths often in combination with other drugs
- Overall rise in benzodiazepine overdose deaths between 1999 and 2010 was greater than the rise in benzodiazepine prescribing- hence more risky use
- In recent research, 75% of benzodiazepine overdose deaths were found to also involve opioid use

Bachhuber, et al. American Journal of Public Health , April 2016; 106;
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Partial list of benzodiazepines

- **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
- **Klonopin;** generic name: clonazepam
- **Dalmane;** generic name: flurazepam
- **Halcion;** generic name: triazolam
- **Ativan;** generic name: lorazepam
- **Restoril;** generic name: temazepam
- **Versed**: generic name: midazolam

Benzodiazepine Indications

- Anxiety
- Panic/agoraphobia
- Insomnia
- Seizure control
- Muscle relaxation
- Anesthesia

Benzodiazepine toxicity

ACUTE

Drowsiness

Confusion

Dizziness

Blurred vision

Weakness

Slurred speech

Lack of coordination (ataxia)

Difficulty breathing

Coma

CHRONIC

Anxiety

Insomnia

Anorexia

Headaches

Weakness

Drug seeking behavior

Benzodiazepine: Links to SUD

- Rates of benzodiazepine use in patients with alcohol use disorder = psychiatric patients; both > general population
- Risk of benzodiazepine misuse in patients with alcohol use disorder > general population risk; however, not robustly different
- Important to differentiate between benzodiazepine tolerance, physiological dependence, and use disorder

Ciraulo et al., 145 (12), 1988, pp. 1501-1506

Benzodiazepine withdrawal (acute)

- Similar to alcohol withdrawal
- Management settings:
  - Outpatient (slow taper; exogenous benzodiazepines)
  - Inpatient (benzodiazepine or phenobarbital challenge and taper)
    - Suggest use of higher potency benzodiazepines
    - Suggest use of CIWA
- Chronic benzodiazepine withdrawal symptoms

Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)

- Validated 10 item scale, administered by a clinician with high inter-rater reliability
- Useful also for benzodiazepine and /or barbiturate withdrawal states
- Efficient and objective means of assessing alcohol/ sedative hypnotic withdrawal
  - decreased frequency of over-sedation with benzodiazepines in milder withdrawal
  - decreased frequency of under-treatment in patients with greater severity of withdrawal
- Score: mild < 15 ; moderate= 16 to 20; severe > 20

Sullivan et al. British Journal of Addiction 84:1353-1357, 1989.

Benzodiazepine withdrawal (chronic)

- Chronic benzodiazepine withdrawal symptoms
- Older RCT shows 4 weeks of mild withdrawal symptoms after discontinuation of therapeutic chronic benzodiazepines
- Anecdotal reports of withdrawal symptoms lasting to 26 weeks
- More withdrawal symptoms with shorter (alprazolam; Xanax) vs longer half-life (clonazepam; Klonopin) benzodiazepines

Busto et al, NEJM 1986 315:854-859

Treatment of Benzodiazepine Use Disorder

- Determination of level of care
- Detoxification from benzodiazepine (inpatient or outpatient)
- Evaluation of comorbidities (e.g. anxiety, depression, SUD, medical)
- Psychotherapies
  - Cognitive Behavioral Therapy
  - Supportive Care

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)

Treatment of Benzodiazepine Use Disorder

- Use of nonbenzodiazepines
  - Topirimate for core urges/cravings
  - Buspirone (pearl-use higher dose [e.g. 20 mg TID]
  - SSRI, SNRI
  - Beta blockers, alpha agonists
  - Gabapentin, pregabalin, low dose quetiapine (refractory cases)
- Benzodiazepines
  - RCT evidence of therapeutic clonzepam acceptable in past benzodiazepine use disorders (Weizman)
  - Use of lower abuse liability benzodiazepines (e.g. clorazepate; Tranxene)

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)

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Detection of Sedative/Hypnotics

- Benzodiazepines
  - Major metabolites detected in urine
  - Long acting-diazepam (10d), intermediate acting-lorazepam, clonazepam (5 days), short acting-triazolam (2d)
  - Saliva testing—2-3 days for all
  - Hypnotics (barbiturates)
  - Urine testing 3 – 14 days (depending on half-life)
  - 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)

Barbiturates—General Facts

- Street Names: Barbs, Phennies, Red Birds, Reds, Tooies, Yellow Jackets, Yellows
- Main types of barbiturates: pentobarbital (Nembutal®), phenobarbital (Luminal®)
- Form: Pill, capsule, liquid
- Administration: Swallowed, injected
- DEA Scheduling: II, III, IV**

www.nida.gov; Nat'l Survey on Drug Use and Heatlh; 2015)

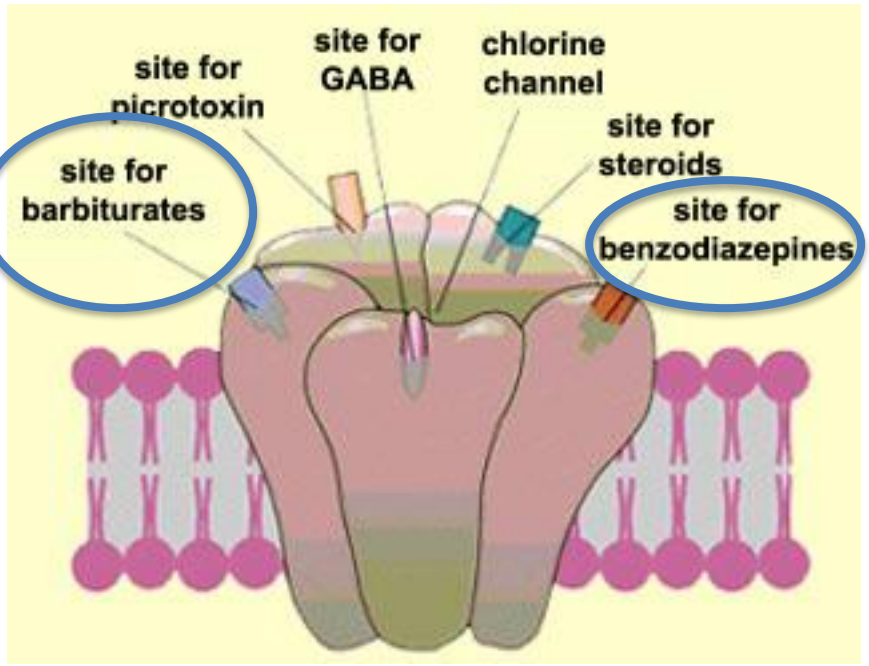
Barbiturates—General Facts

- 19 million prescriptions written yearly
- Phenobarbital most common barbiturate (78%)
- Cause of ca 400 deaths past year (40% by suicide)
- 9% of high school seniors have used barbiturates in past year
- Slight increase in nonmedical use; still lower than 1970's
- Past year sedative use disorder rate: 0.1%
- Adverse Effects: Drowsiness, slurred speech, poor concentration, confusion, dizziness, problems with movement and memory, lowered blood pressure, slowed breathing, respiratory depression.

www.nida.gov; Nat'l Survey on Drug Use and Heatlh; 2015; Health Funding Research.com 2016)

Effects of Barbiturates and Benzodiazepines on the GABA Receptor

-Both drugs bind to GABA-A receptor subunits at different sites
-Neither binds specifically to the agonist site
-Benzodiazepines INCREASE the frequency of channel opening but do not alter conductance or duration of opening
-Barbiturates PROLONG the duration of channel opening



McGill University:
http://thebrain.mcgill.ca/flash/i/i_04/i_04_m/i_04_m_peu/i_04_m_peu.html

Treatment of Sedative/Hypnotic Use Disorders

- Determination of level of care
- Detoxification from barbiturate (inpatient or outpatient)
- Evaluation of comorbidities (e.g. anxiety, depression, SUD, medical)
- Psychotherapies
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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)

Summary: Sedative/Hypnotics

- Similarities between benzodiazepines and barbiturates
- Cross tolerance with one another (and alcohol)
- Rapid development of tolerance, physiological dependence; sometimes addiction
- Withdrawal can be life threatening
- Often short and longer term withdrawal symptoms
- Treatment combines MI/CBT, pharm consideration, and treatment of underlying comorbidities

Thank you!