# Benzodiazepines

August 30, 2023
9:15 AM – 9:45 AM
CSAM Addiction Medicine Board Review Course

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Contents modified from Past Presentation by
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# CONFLICT OF INTEREST DISCLOSURE

I, *Dorothy DeGuzman,* have nothing to disclose, and I will not be discussing “off label” use of drugs or devices in this presentation.

# EDUCATIONAL OBJECTIVES

After attending this presentation, participants will be able to:

1. Discuss the neurobiology and pharmacology of benzodiazepines
2. Understand the prescribing history and epidemiology of benzodiazepine use
3. Discuss the management of intoxication and withdrawal, including benzodiazepine taper
4. Recognize drug-drug interactions, toxicity and drug testing discrepancies

# Benzodiazepines: Need to Know

- The basic **structure** of benzodiazepines and the Z-Drugs
- History of development – background in relation to barbiturates
- **Epidemiology** of unhealthy use; use in pregnancy
- **Pharmacokinetics** – relative potencies, time of onset, half-lives; the parent drug and elimination half-life and excretion; CYP450 hepatic **metabolism** versus glucoronidation, onset of action and active metabolites
- **Pharmacodynamics** – development of physiologic dependence; GABA receptor characteristics, activity at the GABA receptor and antagonism
- **Drug-Drug interactions** and concomitant opioid and alcohol use
- **Toxicity** and how to treat benzodiazepine overdose and withdrawal syndromes
- **Addiction** liability and how to **taper**

# Benzodiazepines

**Question 1:** Which Benzodiazepine is commonly not detected on urine immunoassay?

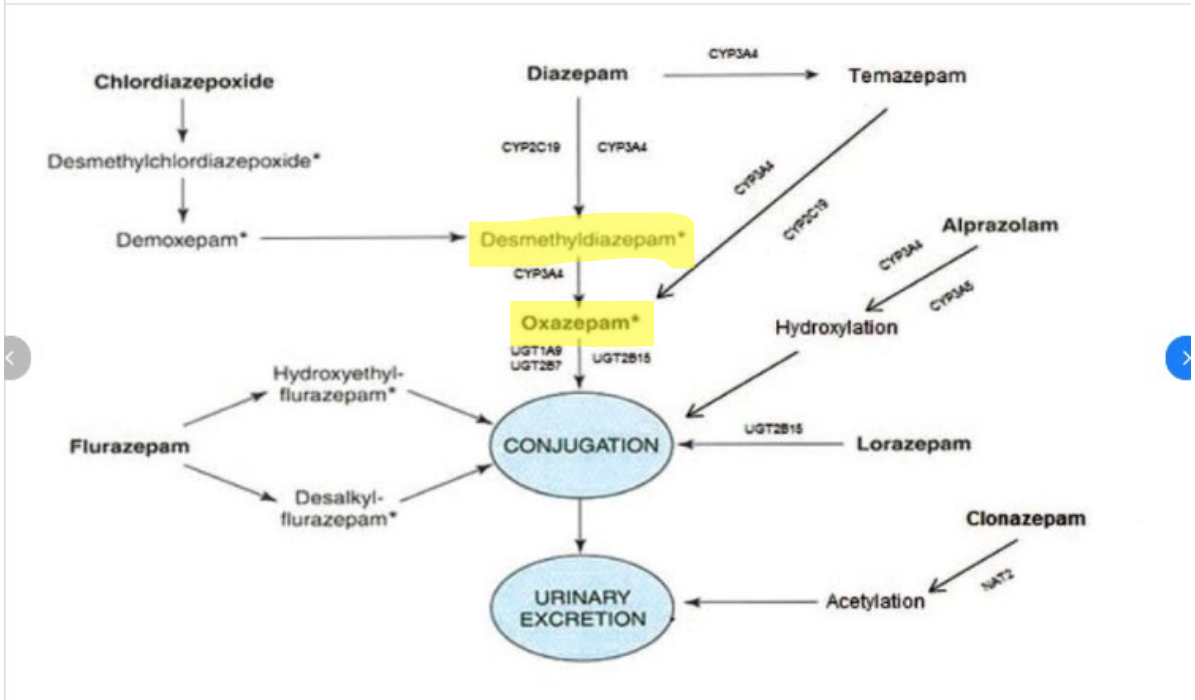
A. Temazepam

B. Clonazepam

C. Diazepam

D. Oxazepam

# 1) Answer B. Clonazapam




Behnoush B, Sheikhazadi A, Bazmi E, Fattahi A, Sheikhazadi E, Saberi Anary SH. Comparison of UHPLC and HPLC in benzodiazepines analysis of postmortem samples: a case-control study. Medicine (Baltimore). 2015 Apr;94(14):e640.

# Benzodiazepines

**Question 2:** Paul is a 32-year-old who has a fear of flying and requests their own alprazolam prescription for an upcoming transcontinental flight to visit an ailing father with end-stage liver disease and a history of alcohol use disorder. Pat recently "tried a friend's *Xanax (alprazolam)*" for his stress and depressed mood and thought it was more effective compared to the clonazepam or temazepam prescriptions previously prescribed. You are concerned with Pat's request based on which of the following properties of benzodiazepines?

A. Sedative properties
B. Pharmacokinetics
C. Anxiolytic effects
D. Hypnotic effects

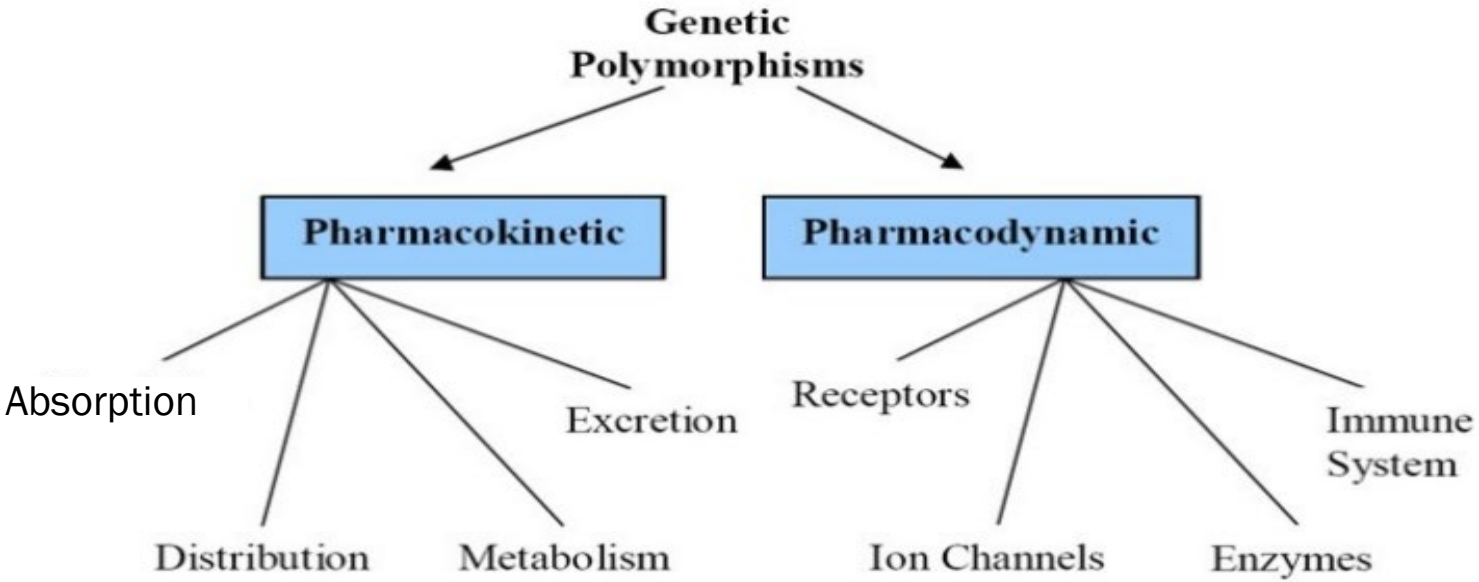
# 2) Answer: B. Pharmacokinetics

- Most benzodiazepines have comparable sedative, anxiolytic, hypnotic, cognitive, and psychomotor performance effects (considering relative potency), but onset of action and duration of effects vary.
- Alprazolam is highly potent, with a greater rate of absorption, a rapid onset contributing to increased euphoria, and a short half-life contributing faster withdrawal onset. These are all pharmacokinetic properties.

- Pharmacokinetics are affected by:
  - Routes of administration
  - Rates of absorption
  - Rates of elimination

- Pharmacokinetics determine drug onset and duration of effect.

Charles E. Griffin, III, MD, Adam M. Kaye, Pharm D, Franklin Rivera Bueno, MS,and Alan D. Kaye, MD, PhD, Benzodiazepine Pharmacology and Central Nervous System–Mediated Effects Ochsner J. 2013 Summer; 13(2): 214–223.




- **Pharmacokinetics** is the study of how the organism affects the drug
- **Pharmacodynamics** is the study of how a drug affects an organism

Charles E. Griffin, III, MD, Adam M. Kaye, Pharm D, Franklin Rivera Bueno, MS,and Alan D. Kaye, MD, PhD, Benzodiazepine Pharmacology and Central Nervous System–Mediated Effects Ochsner J. 2013 Summer; 13(2): 214–223.

# Benzodiazepines

**Question 3:** There is another aspect of Pat's history that you would like to explore. As you reflect on your conversation with Pat, which of the following statements regarding benzodiazepine use is true?

A. Benzodiazepine effects are pleasurable and reinforcing in a third of those who have anxiety disorder.

B. Benzodiazepines are common as primary drugs of misuse in 35% of the adult population.

C. Patients with alcohol use disorders and their offspring are more likely to experience mood elevations with benzodiazepines.

D. Buspirone is a safe and effective anxiolytic that is a preferred treatment for benzodiazepine withdrawal anxiety.

# 3) Answer: C. Patients with alcohol-use-disorder and their offspring are more likely to experience mood elevation with benzodiazepines.

- Studies have suggested a genetic risk for euphoric response to benzodiazepines in those with **alcohol use disorders and their offspring. Pat's father has a history of AUD.**

- Among benzodiazepine users, **17.1 % misuse** the drug and **2% have a use disorder**; and most people do not find their effects inherently reinforcing.
- Patients who have become physiologically dependent iatrogenically via adherence with medical treatment (e.g., for panic disorder, generalized anxiety) should not on that basis alone be considered to have a substance use disorder.

- **Buspirone** is a serotonin 5-HT1a partial agonist that is **ineffective** for benzodiazepine withdrawal and for most cases of anxiety in patients with a history of benzodiazepine use disorder.

Self-Assessment in Substance Abuse Treatment p. 46, APA 2005, Ross & Hayden

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# Benzodiazepines

**Question 4**: Which is **not** true of the interaction between BZDs and the GABA receptor?

A. BZD require the presence of GABA at the receptor

B. BZD increase the duration of the opening of the receptor

C. BZD bind at the cleft between the alpha and gamma subunits

D. BZD potentiate the inhibitory effects of GABA in the CNS

# 4) Answer: B. BZD increase the duration of the opening of the receptor

- The GABA receptor consists of 5 transmembrane glycoprotein subunits around a Chloride channel pore.
- BZD increase the frequency of the chloride-channel opening, Barbiturates increase the duration and do NOT require the presence of GABA
- They both potentiate the inhibitory effects of GABA in the CNS

Soyka. The Treatment of Benzodiazepine Dependence. NEJM 2017, 376;12

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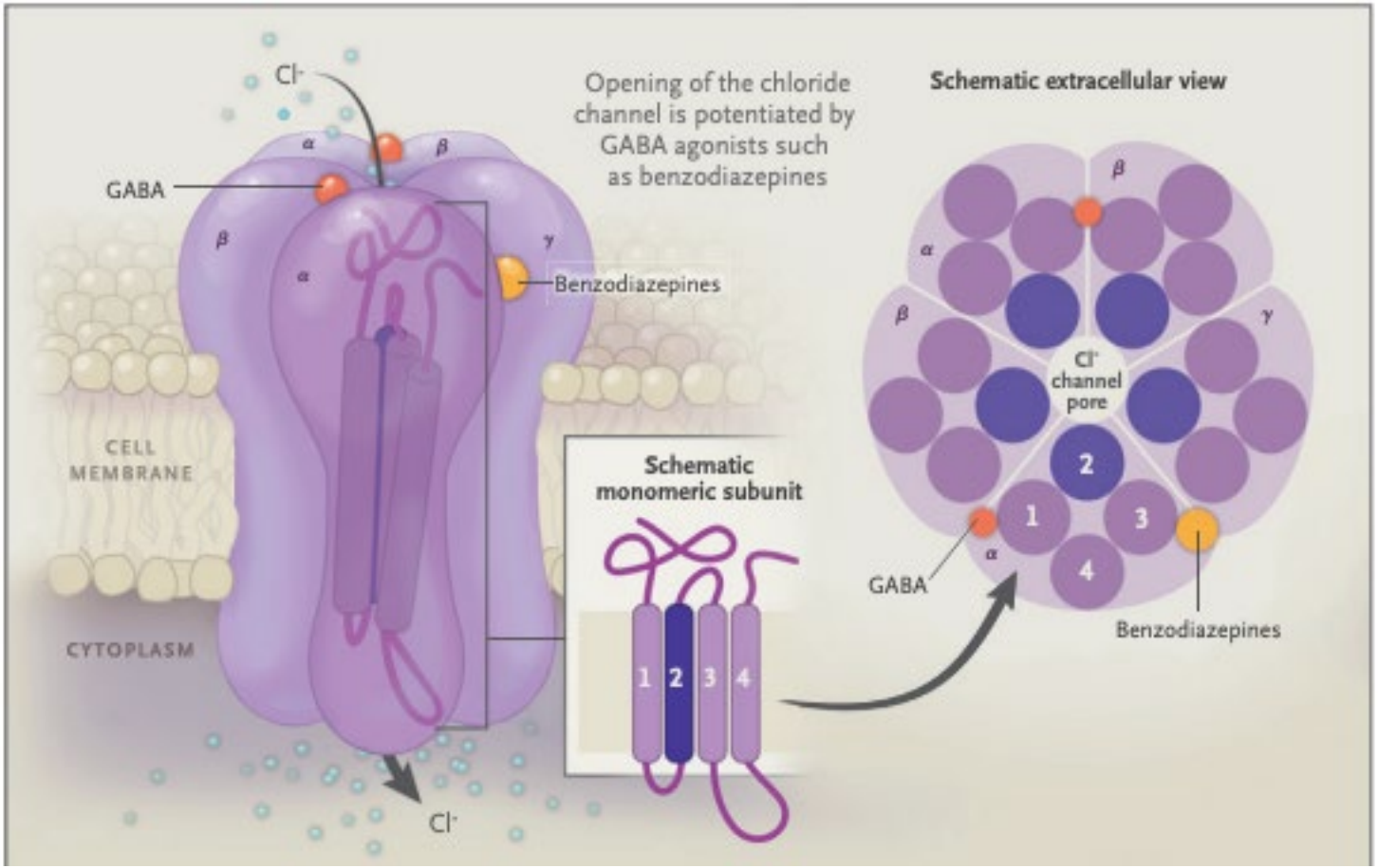


Soyka. The Treatment of Benzodiazepine Dependence. NEJM 2017, 376;12

# Benzodiazepines

**Question 5**: A 22-year-old college student, found unresponsive by his roommate, responded to naloxone opioid reversal administration en route to the ED. The patient's urine drug screen is positive for fentanyl, despite the patients reports of only using "Xanax bars". What percentage of benzodiazepine-involved deaths involved illicitly manufactured fentanyl (IMF) in 38 states from January to June 2020?

A. 25.2%
B. 33.3%
C. 66.7%
D. 82.5%

# 5) Answer: C. 66.7%

- From January-June, 2020, 92.7% of benzodiazepine-involved deaths involved any opioid and **66.7% involved illicitly manufactured fentanyl** (IMF) in 38 states and the District of Columbia.
- From 2019 to 2020, benzodiazepine overdose emergency department visits increased by 23.7%, both with (34.4%) and without (21.0%) opioid co-involvement.
- Patients with combined opioid and benzodiazepine use can experience synergistic effects for both reward and sedation.
- These trends highlight the need to (1) decrease co-prescribing of opioid and benzodiazepines, (2) expand naloxone availability, and (3) increase treatment access to persons co-using opioids and benzodiazepines who may be less likely to receive medications for opioid use disorder than persons using opioids only.

Liu S, O'Donnell J, Gladden RM, McGlone L, Chowdhury F. Trends in Nonfatal and Fatal Overdoses Involving Benzodiazepines — 38 States and the District of Columbia, 2019–2020. MMWR Morb Mortal Wkly Rep 2021;70:1136–1141. DOI: http://dx.doi.org/10.15585/mmwr.mm7034a2external icon


REAL
FAKE

# Benzodiazepines

**Question 6:** A 32 y/o female presents to your treatment program for help in getting off alprazolam. The patient been prescribed three to four 2 mg alprazolam tabs (6-8 mg) daily as needed for the past 6 years and gets anxiety with tremors when she tries to stop. After drug screens are negative for other substances besides alprazolam, all the following would be acceptable treatment options ***except***:

A. Assess for seizure risk and consider inpatient treatment
B. Switch to diazepam and taper off during 30-day residential treatment for closer medical monitoring
C. Continue with current alprazolam and begin gradual taper
D. Switch to chlordiazepoxide and taper slowly over several months

# 6) Answer: B. Switch to diazepam and taper off during 30-day residential treatment for closer monitoring

- A Cochrane Review in 2006 failed to find any convincing evidence for one treatment strategy over another. **However, a 30-day taper is too rapid and is rarely tolerated.**

- **Gradual taper of same benzodiazepine**, switching to a longer acting benzodiazepine and using other agents such as carbamazepine are probably all acceptable methods of taper, given current limited state of knowledge.

- **Tapering will usually take months**. One possibility: Reduce dose initially by 5-10% every 2-4 weeks (even longer). Anticipate rebound anxiety and insomnia

- Additional **psychosocial support and education** are the most helpful things you can offer patients.

VA National Center for PTSD, 2013
Malcolm Lader, Andre Tylee, John Donoghue, Withdrawing Benzodiazepines in Primary Care, CNS Drugs, 2009, Volume 23, Number 1, Page 19

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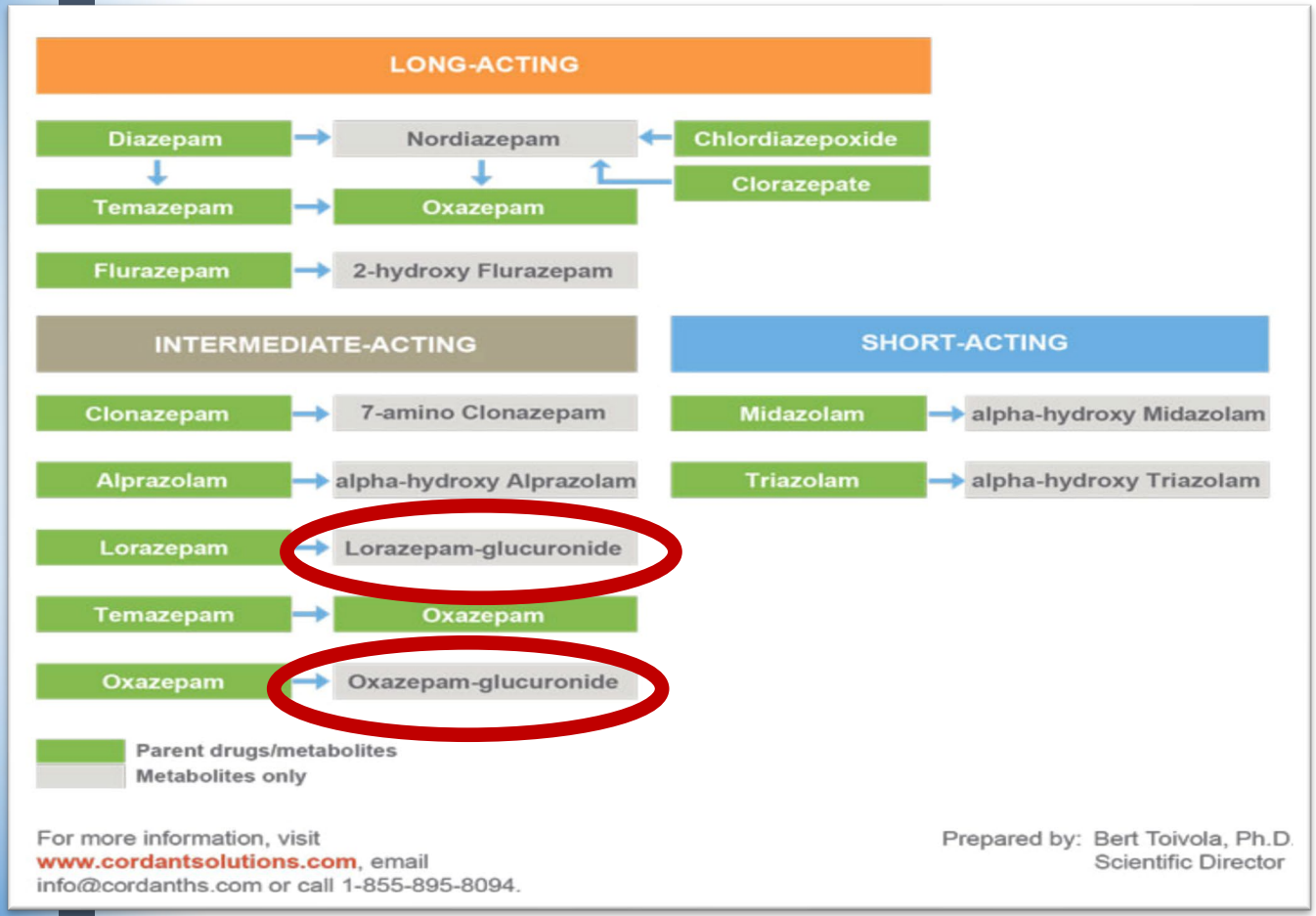
# Benzodiazepines

**Question 7**: Which benzodiazepine would be safest to use in treating alcohol withdrawal in someone with liver disease and why? Choose the best pair of agent and reason.

A. Temazepam– because it has no active metabolite(s)
B. Chlordiazepoxide—because an end metabolite is oxazepam
C. Oxazepam– because it is glucuronidated
D. Lorazepam – because of its half-life

# 7) Answer: C. Oxazepam-because it is glucuronidated




- Lorazepam and Oxazepam have no active metabolites that could accumulate in the presence of liver disease.
- The other benzodiazepines all have active metabolites.
- **"LOT"**: Lorazepam, Oxazepam are glucuronidated; temazepam metabolizes to oxazepam.

# Benzodiazepines

**Question 8:** During withdrawal from benzodiazepines which symptom/symptoms would you ***not*** expect?

A. Tachycardia/Hypertension

B. Agitation/Hallucinations/Seizures

C. Nausea/Diarrhea

D. Cold sweats/Chills

# 8) Answer: D Cold sweats/Chills

- Patients may experience fever during withdrawal, but you would not expect a cold sweat or chills, this is experienced during opioid withdrawal.
- Many patients may experience symptoms for up to 4 weeks after abstinence.
- Additional sxs are anxiety, delirium, insomnia, irritability, sensory disturbances, anorexia

# 8) Answer: D Cold sweats/Chills

- Symptoms of benzodiazepine discontinuation fall into 4 categories
  - *Symptom recurrence or relapse* – recurrence of symptoms such as anxiety or insomnia for which the BZD was initially intended to treat.
  - *Rebound* – symptoms within hours to days of medication discontinuation that are similar but more intense than before treatment
  - *Psychological withdrawal (Pseudowithdrawal)* – occurs when the expectations of withdrawal lead to the experience of withdrawal symptoms, without any reduction in the medicine (fear, anticipation)
  - *Physical withdrawal* – occurs when a BZD is stopped in an individual with physical dependence on the medication, symptoms are psychological and somatic, can use CIWA – Ar scale to monitor/follow symptoms

ASAM Essentials, Chap 52

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# Benzodiazepines

**Question 9**: A 43 y/o female presents to the ED after a seizure. Her CT head is within normal limits and urine immunoassay is negative. A few days later her confirmatory test detects 7-amino-clonazepam at 215 ng/ml. The patient admits to taking 7-9 mg clonazepam daily, self-obtained. What is the next best step?

A. Prescribe alprazolam and refer to residential treatment
B. Coordinate outpatient care for chlordiazepoxide taper along with psychotherapy services.
C. Add levetiracetam (Keppra®) 500 mg twice a day to clonazepam taper
D. Add quetiapine 50 mg as needed for anxiety

## 9) Answer: B. Coordinate outpatient care for chlordiazepoxide taper along with psychotherapy referral.

- The patient's urine clonazepam metabolite levels are low which accounts for the seizure. One option is to begin taper with a long-acting agent such as chlordiazepoxide. Changing from a long-acting to short-acting agent such as alprazolam offers no advantage, only potential complications for inter-dose rebound withdrawal.
- **Patients with Sedative, Hypnotic or Anxiolytic Use Disorders should receive additional psychosocial intervention and treatment in addition to medically supervised tapers.**
- The seizure is most likely due to known benzodiazepine withdrawal; therefore, **anti-epileptic and antipsychotic medications are not usually standard of care in acute benzodiazepine withdrawal**. However, the use of other anti-convulsive medications such as carbamazepine could be used for PAWS.

Darker CD, Sweeney BP, Barry JM, Farrell MF, Donnelly-Swift E. Psychosocial interventions for benzodiazepine harmful use, abuse or dependence. Cochrane Database Syst Rev. 2015;(5):CD009652. doi: 10.1002/14651858.CD009652.pub2. PMID: 26106751.

# Benzodiazepines

**Question 10:** Phil is a 73-year-old male retiree who takes care of his school-aged grandchildren and is establishing care with you, requesting that you continue his previous lorazepam 0.5 mg bedtime prn dose that he only uses on rare occasions and may only need #30 tabs every 6 months. What aspect of Phil's history is typical for a patient who uses benzodiazepines?

A. His sex
B. His age
C. Lorazepam use
D. His long-term use

# 10) Answer: B. His age

- Approximately **5.2% of adults** in the United States use benzodiazepines. The prevalence of use increases as people age.
- Use ranged from:
  - *2.6% (18-35)*
  - *5.4% (36-50)*
  - *7.4% (51-64)*
  - ***8.7% (65-80)***
- Benzodiazepine use is twice as prevalent in **women** >> as in men.
- In the oldest age group (65-80), **31.4%** of those using benzodiazepines are using them long term (>120 days).
- History break – In 1970 BZD accounted for 10 % of all prescriptions written in the US.

Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. JAMA Psychiatry. 2015 Feb;72(2):136-42. doi: 10.1001/jamapsychiatry.2014.1763. PMID: 25517224.

# Benzodiazepines

**Question 11**: Jane is a 27 year-old G1P0 who is 10 weeks pregnant and has been referred to you by high-risk OB, because she is taking diazepam 20mg daily for back spasms and insomnia, along with buprenorphine 10mg sublingual daily. All of the following are true ***except***:

A. Prenatal benzodiazepine use can exacerbate neonatal abstinence syndrome (NAS) in the presence of opioid use disorder and can cause seizures in the newborn.
B. Diazepam is the most dangerous benzodiazepine for pregnancy – switch to temazepam.
C. While medically assisted opioid withdrawal is contraindicated in pregnancy, sedative–hypnotic–anxiolytic withdrawal can be accomplished with caution and regular monitoring.
D. Possible neonatal benzodiazepine effects include neonatal withdrawal symptoms and floppy infant syndrome.

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## 11) Answer: B. Diazepam is the most dangerous benzodiazepine for pregnancy – switch to temazepam.

- In the DEA's previous pregnancy risk categories most benzodiazepines were **Category D** rating (positive evidence of human fetal risk), more current recommendations state to weigh risk versus benefit. However, four benzodiazepines (flurazepam, estazolam, **temazepam**, and quazepam) had a Category X rating and are contraindicated in pregnancy. **Do Not switch her to temazepam – at best the risk is not lessened.**
- Prenatal benzodiazepine use can exacerbate neonatal abstinence syndrome (NAS) **in the presence of opioid use disorder** and can cause seizures in the newborn.
- While medically assisted opioid withdrawal is contraindicated in pregnancy, one could perform sedative–hypnotic–anxiolytic tapering slowly and regular monitoring.

Pg. 731 Principles of Addiction Medicine 6th Edition

## 11) Answer: B.

- Newborns exposed to benzodiazepines in utero in the 3rd trimester or during delivery may present with floppy infant syndrome (low Apgar score, poor sucking, hypotonia, diminished reflexes, and/or apnea). Neonatal withdrawal syndromes have also been described.
- Severe benzodiazepine withdrawal symptoms during pregnancy can place the fetus in distress, potentially causing miscarriage, and may induce preterm labor.
- All classes of benzodiazepines (and phenobarbital) cross the placenta and are excreted in breast milk

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# Benzodiazepines

**Question 12**: Tiffany is a 26-year-old post-graduate student from Singapore who comes to you during a student health clinic visit asking for zolpidem because of insomnia and alprazolam for panic attacks. The risks of this request for zolpidem and alprazolam include all of the following ***except***:

A. Suicide
B. Mortality
C. Motor Vehicle Accidents
D. Myocardial infarction

# 12) Answer: D. Myocardial infarction

- Benzodiazepines appear to cause an overall **increase in the risk of attempting or completing suicide**. Possible mechanisms of pro-suicidal effects may include increases in impulsivity or aggression, rebound or withdrawal symptoms, and toxicity in overdose.

- **Subgroup analyses showed that the exposure to zolpidem consistently increased the OR of suicide and suicide attempt** in different age groups, sex, urbanization level, occupation, mental disorders, and comorbidity index levels and in groups of people with or without the presence of insomnia.

Dodds TJ. Prescribed Benzodiazepines and Suicide Risk: A Review of the Literature. Prim Care Companion CNS Disord. 2017
Sun Y, et al Association Between Zolpidem and Suicide: A Nationwide Population-Based Case-Control Study. Mayo Clin Proc. 2016
Weich S, et al. Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: retrospective cohort study BMJ 2014
Brandt J, et l Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. Drugs R D. 2017
https://www.mdcalc.com/charlson-comorbidity-index-cci

# 12) Answer: D. Myocardial infarction

- ***BMJ study, published in 2014, retrospective cohort study of over 100 K patients***
- Patients were followed for a mean **of 7.6 years**
- Age adjusted hazard ratio for **mortality** during the entire follow-up period for use of any benzodiazepine or Z drug in the first year
  - *after adjusting for potential confounders* ***3.32*** *(3.19 to 3.45).*

Weich S, et al. Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: retrospective cohort study BMJ 2014
Dodds TJ. Prescribed Benzodiazepines and Suicide Risk: A Review of the Literature. Prim Care Companion CNS Disord. 2017
Sun Y, et al Association Between Zolpidem and Suicide: A Nationwide Population-Based Case-Control Study. Mayo Clin Proc. 2016
Brandt J, et l Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. Drugs R D. 2017

# 12) Answer: D. Myocardial infarction

- There is an **overwhelming degree of evidence, both experimental and epidemiological, implicating benzodiazepines and Z-drugs, with fatal and non-fatal motor vehicle accidents.**

Weich S, et al. Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: retrospective cohort study BMJ 2014
Dodds TJ. Prescribed Benzodiazepines and Suicide Risk: A Review of the Literature. Prim Care Companion CNS Disord. 2017
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- **Drug-Drug interactions** and concomitant opioid and alcohol use
- **Toxicity** and how to treat benzodiazepine overdose and withdrawal syndromes
- **Addiction** Liability and how to **taper**

Thank you and Best Wishes!