SEDATIVE HYPNOTICS

August 24, 2022

9:15 AM – 9:45 AM

CSAM Addiction Medicine Board Review Course

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CONFLICT OF INTEREST DISCLOSURE

I, *Warren Yamashita*, 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. Identify the important concepts of sedative hypnotics (benzodiazepines) that one must know to be prepared to take the Addiction Medicine Board Exam
2. Have an overview of the neurobiology and pharmacology of sedative hypnotics, primarily benzodiazepines
3. Understand the addiction liabilities of sedative hypnotics (particularly benzodiazepines) and the principles of tapering these agents
4. Understand drug-drug interactions, toxicity, and epidemiology of sedative hypnotic use

Sedative Hypnotics: 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**

Sedative Hypnotics

Question 1: A 54-year-old female has been on 60 mg of hydrocodone daily for chronic low back pain. When she has migraines, she may take more hydrocodone than prescribed. A year ago, she began taking lorazepam 0.5 mg for anxiety. She now takes 1 mg three times daily. She comes to you to establish care. What would be the most important thing to do this first visit?

A. Follow Benzodiazepine Risk Evaluation and Mitigation Strategy (REMS)
B. Reduce harm by starting opioid and benzodiazepine tapering
C. Co-prescribe naloxone
D. Check Prescription Drug Monitoring Program (PDMP) before refilling lorazepam and hydrocodone

1) Answer: C. Co-prescribe naloxone

Co-prescribing is the practice of prescribing naloxone with opioid medications.

- (e.g., in California AB 2760 was signed into law 2018 and effective 1/1/2019 now requires prescribers to offer a prescription for naloxone for reversal of opioid depression if a patient receives >90 MMED*, has an opioid overdose history, or is at high risk for opioid overdose, such as this patient receiving benzodiazepines.)

Risk Evaluation and Mitigation Strategy (REMS)

- The FDA can require a **REMS** drug safety program if the agency determines that safety measures are needed beyond the professional labeling to ensure that a drug's benefits outweigh its risks. REMS practices reinforce medication use behaviors and actions to support safe use.
- Drug sponsors develop REMS programs, FDA reviews and approves them.
- **Benzodiazepines do not required REMS**.

Checking the **PDMP** is important as would broaching the topic of **tapering** the opioid and benzodiazepines, one at a time, however co-prescribing naloxone takes priority at this initial visit.

*MMED – Morphine Milligram Equivalents per Day
AMA Opioid Task Force Aug 2017
"Naloxone Prescription Requirements." *Medical Board of California*, https://www.mbc.ca.gov/Resources/Medical-Resources/Naloxone.aspx.

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Sedative Hypnotics

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

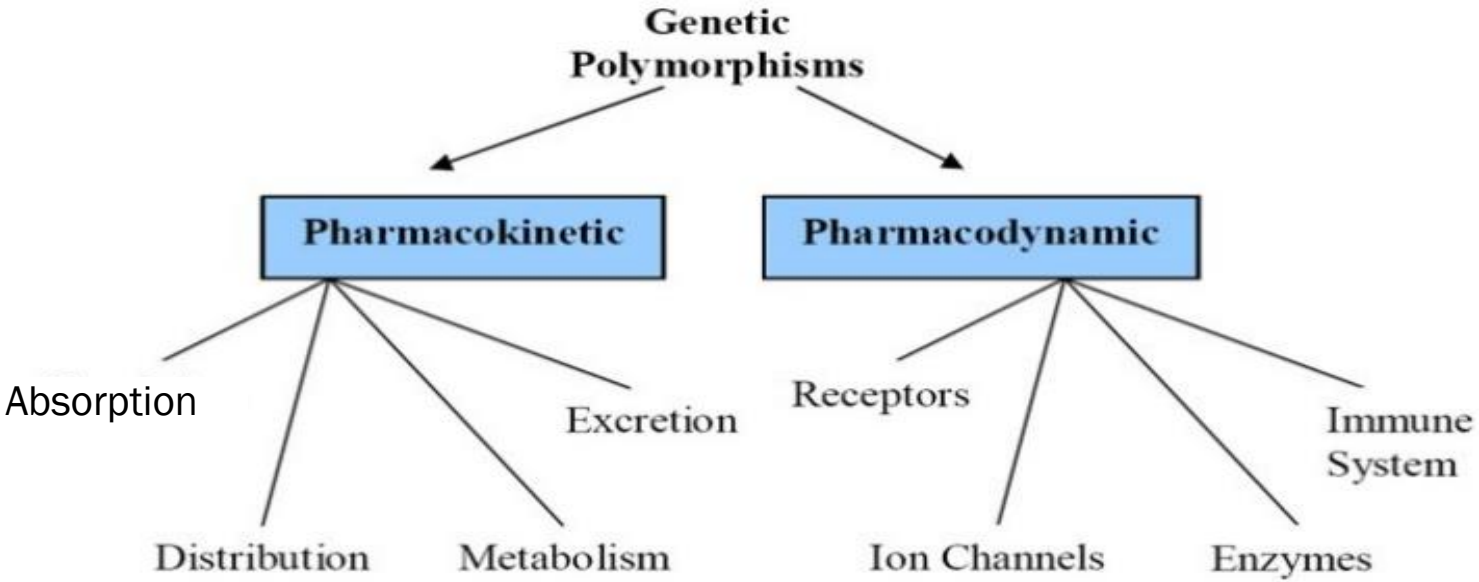
2) Answer: B. Pharmacokinetics

- 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.



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

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.

Sedative Hypnotics

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. Alcohol-use-disordered patients 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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Question 4: A 65-year-old Asian American female with generalized anxiety disorder, coronary artery disease and insomnia will likely develop a dependence to all the following drugs except:

A. Temazepam
B. Zaleplon
C. Clorazepate
D. Hydroxyzine

4) Answer: D. Hydroxyzine(Vistaril)

- **Hydroxyzine is an antihistamine** with its effect is due to its metabolite, cetirizine, a potent H1 receptor antagonist and selective inhibitor of peripheral H1 receptors and does not usually cause dependence with tolerance and withdrawals.
- **Temazepam (Restoril®) and Clorazepate (Tranxene®)** are benzodiazepines that act on the GABA-A receptor and over time cause dependence exhibited by tolerance and withdrawal.
- **Zaleplon (Sonata®)** is a Z-drug like **zolpidem** (**Ambien®**) and acts on the GABA-A receptor, is subject to misuse and known to cause anterograde amnesia confusion, daytime drowsiness, agitation, and hallucinations.

Pollmann, A. S., Murphy, A. L., Bergman, J. C., & Gardner, D. M. (2015). De-prescribing benzodiazepines and Z-drugs in community-dwelling adults: a scoping review. *BMC Pharmacology & Toxicology*, *16*, 19

Sedative Hypnotics

Question 5: A 22-year-old college student found unresponsive by his roommate, responded to naloxone opioid reversal administration on 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
XANAX
FAKE
XANAX

Sedative Hypnotics

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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benzo.org.uk

Newcastle University

The Institute of Neuroscience

Professor Heather Ashton

ASHTON MANUAL INDEX PAGE

BENZODIAZEPINES: HOW THEY WORK AND HOW TO WITHDRAW

(aka The Ashton Manual)

- PROTOCOL FOR THE TREATMENT OF BENZODIAZEPINE WITHDRAWAL
- Medical research information from a benzodiazepine withdrawal clinic

Professor C Heather Ashton DM, FRCP
Revised August 2002

www.benzo.org.uk

ASHTON METHOD

Schedule 1. Withdrawal from high dose (6mg) alprazolam (Xanax daily with diazepam (Valium) substitution. (6mg alprazolam is approximately equivalent to 120mg diazepam)

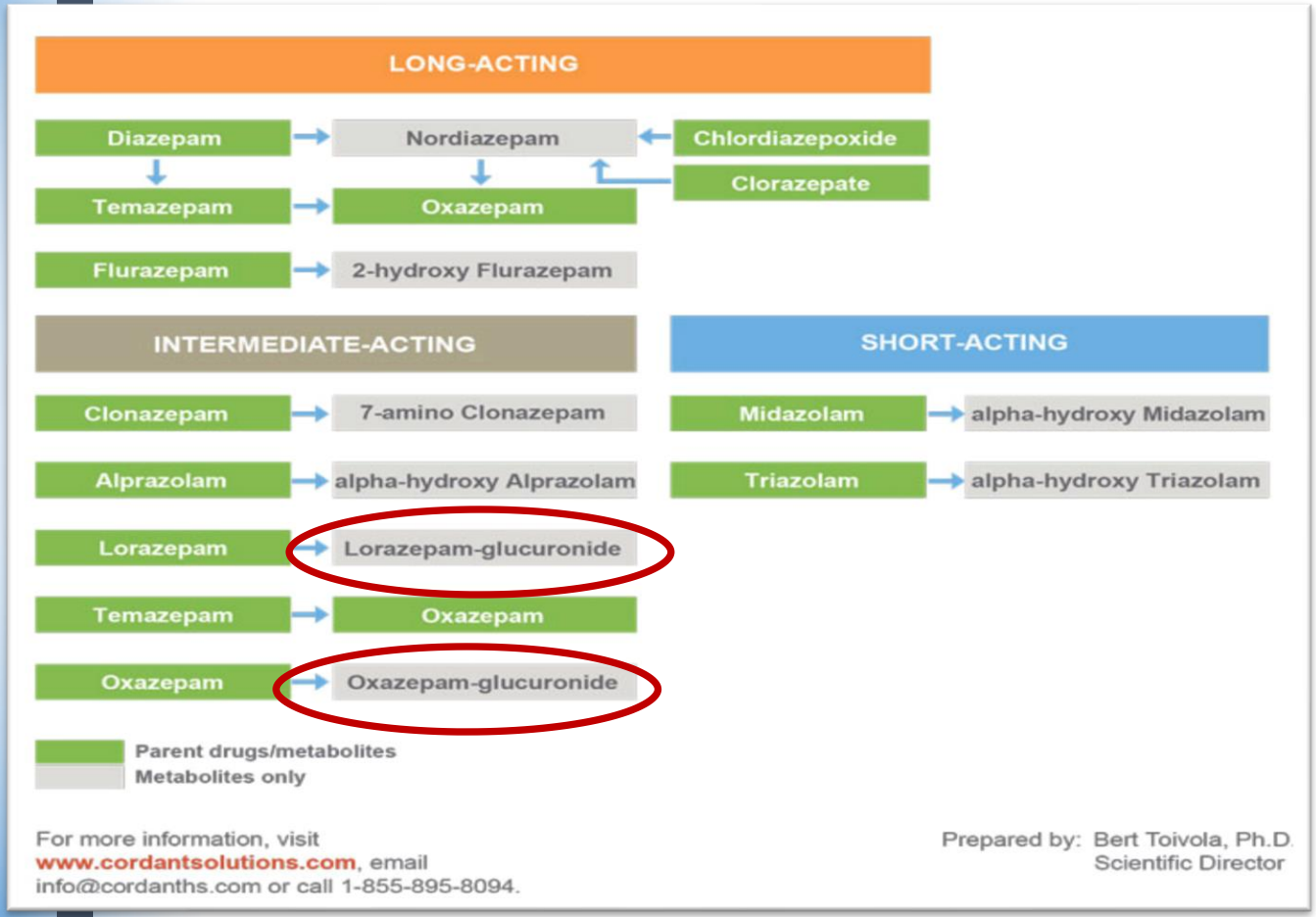
	Morning	Midday/Afternoon	Evening/Night	Daily Diazepam Equivalent
Starting dosage	alprazolam 2mg	alprazolam 2mg	alprazolam 2mg	120mg
Stage 1 (one week)	alprazolam 2mg	alprazolam 2mg	alprazolam 1.5mg diazepam 10mg	120mg
Stage 2 (one week)	alprazolam 2mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 3 (one week)	alprazolam 1.5mg diazepam 10mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 4 (one week)	alprazolam 1mg diazepam 20mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 5 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	alprazolam 1mg diazepam 20mg	110mg
Stage 6 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	alprazolam 0.5mg diazepam 20mg	100mg
Stage 7 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	Stop alprazolam diazepam 20mg	90mg
Stage 8 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	alprazolam 1mg diazepam 10mg	diazepam 20mg	80mg
Stage 9 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	alprazolam 0.5mg diazepam 10mg	diazepam 20mg	80mg
Stage 10 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	Stop alprazolam diazepam 10mg	diazepam 20mg	60mg
Stage 11 (1-2 weeks)	Stop alprazolam diazepam 20mg	diazepam 10mg	diazepam 20mg	50mg
Stage 12 (1-2 weeks)	diazepam 25mg	Stop midday dose; divert 5mg each to morning and night doses	diazepam 25mg	50mg
Stage 13 (1-2 weeks)	diazepam 20mg	--	diazepam 25mg	45mg
Stage 14 (1-2 weeks)	diazepam 20mg	--	diazepam 20mg	40mg

Sedative Hypnotics

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.

Sedative Hypnotics

Question 8: A 27 y/o male you are treating for opioid use disorder has a urine drug screen positive for benzodiazepines. He says he took his mother's zolpidem which probably caused the positive result. Your next best step is to:

A. Ask him for permission to call his mother to confirm his report.

B. Order a confirmatory urine for benzodiazepines

C. Counsel him not to use his mother's zolpidem, because it can cause false positive results for benzodiazepine immunoassays.

D. Counsel him that a false positive is unlikely, and ask if he is taking any benzodiazepines.

8) Answer: D. Counsel him that a false positive is unlikely, and ask if he is taking any benzodiazepines.

- Although sleep aids such as zolpidem and eszopiclone act on the GABA A receptor, they are not detected on typical immunoassays.
- Concurrent benzodiazepine with buprenorphine carries an increased risk of overdose. It is important to determine if the patient is taking benzodiazepines while treating his opioid use disorder.
- Confirmatory drug tests should be if additional testing will impact clinical decision making and management. Providing the patient a space to share about his benzodiazepine use will improve the therapeutic alliance while obtaining the needed information for his care.
- If he says, he's not using benzodiazepines, consider ordering a confirmatory test.

Pg. 353 Principles of Addiction Medicine 6th Edition

8) Answer: D. Counsel him that a false positive is unlikely, and ask if he is taking any benzodiazepines.

- Benzodiazepines have poor cross-reactivity on immunoassays which leads to greater likelihood of false negative and less false positive results.
- The interpretation of standard urine immunoassays for benzodiazepines is affected by their diverse metabolic pathways with different parent compounds. Detection is affected by their diverse metabolites and variable potencies.
- Urine specimens usually contain little of the parent benzodiazepine.
- **Many tests are designed to detect nordiazepam and oxazepam only**, and will less likely detect clonazepam, lorazepam or triazolam unless at high doses.

Ries, Richard, et al. “Chapter 23: Laboratory Assessment.” *The Asam Principles of Addiction Medicine*, Wolters Kluwer Health, Philadelphia, 2014, pp. 348–358.

Sedative Hypnotics

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. See Dr. Heather Ashton taper methods for guidance. Changing from a long-acting to short-acting agent such as alprazolam offers no advantage, only potential complications for inter-dose rebound withdrawal.
- Benzodiazepine dependence may be treated with tapering doses of a long-acting benzodiazepines along with additional psychotherapeutic support.
- **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.

Sedative Hypnotics

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. Phil's history is typical for a patient who uses benzodiazepines because of?

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 use varies with age and with increasing use 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).

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.

Sedative Hypnotics

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.

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

- In the DEA's previous pregnancy risk categories (no longer used) most benzodiazepines were **Category D** rating (positive evidence of human fetal risk), but the benefits from use in pregnancy may outweigh the risks. 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.
- However, there is no evidence of increased seizure risk with buprenorphine and benzodiazepines.
- While medically assisted opioid withdrawal is contraindicated in pregnancy, one could perform sedative–hypnotic–anxiolytic tapering with caution and regular monitoring.

Pg. 731 Principles of Addiction Medicine 6th Edition

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

- 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

Pg. 731 Principles of Addiction Medicine 6th Edition

Sedative Hypnotics

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 Charlson 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

- ***34, 727*** **patients aged 16 years and older first prescribed anxiolytic or hypnotic drugs, or both, between 1998 and 2001**
- ***69, 418*** **patients with no prescriptions** (controls) matched by age, sex, and practice
- Followed for a mean **of 7.6 years**
- Age adjusted hazard ratio for **mortality** during the entire follow-up period for use of any drug in the first year
  - *after recruitment was* ***3.46*** *(95% confidence interval 3.34 to 3.59) and*
  - *after adjusting for other 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
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12) Answer: D. Myocardial infarction

- **Dose-response** associations were found for all classes of study drugs (benzodiazepines, Z drugs (zaleplon, zolpidem, and zopiclone).
- **After excluding deaths in the first year, there were approximately four excess deaths linked to drug use per 100 people**.

- There is an **overwhelming degree of evidence, both experimental and epidemiological, implicating benzodiazepines, but Z-drugs as well, 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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- **Addiction** Liability and how to **taper**

Thank you and Best Wishes!