OPIOIDS & PAIN

August 30, 2023

CSAM Review Course in Addiction Medicine

Prepared by Katherine Pier, MD

Addiction Psychiatrist, Kaiser Permanente, San Francisco

Assistant Clinical Professor of Psychiatry, University of California, San Francisco

Substitute Presentation by Chwen-Yuen Angie Chen, MD
Internal and Addiction Medicine
Clinical Associate Professor of Medicine
Stanford University

CSAM

CONFLICT OF INTEREST DISCLOSURE

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

Speaker's Bureau & Consultant - AbbVie, Gilead Sciences (both ended 2021)

Advisory Board Member – Alkermes

EDUCATIONAL OBJECTIVES

After attending this presentation, participants will be able to:

1. Master relevant pharmacology related to the therapeutic and addictive properties of opioids
2. Describe the pharmacological properties of specific opioids
3. Review treatment options for opioid use disorder and drug-drug interactions
4. Describe epidemiology & illness course of opioid use disorder
5. Apply treatment guidelines to the management of chronic pain in the setting of opioid use disorder

CSAM

Question 1

Endogenous opioid peptides include the families of dynorphin, endorphin, and _____. These peptides are expressed in brain regions associated with reward, motivation, and pain perception.

A. enkephalin
B. oxytocin
C. peptidoglycan
D. thebaine

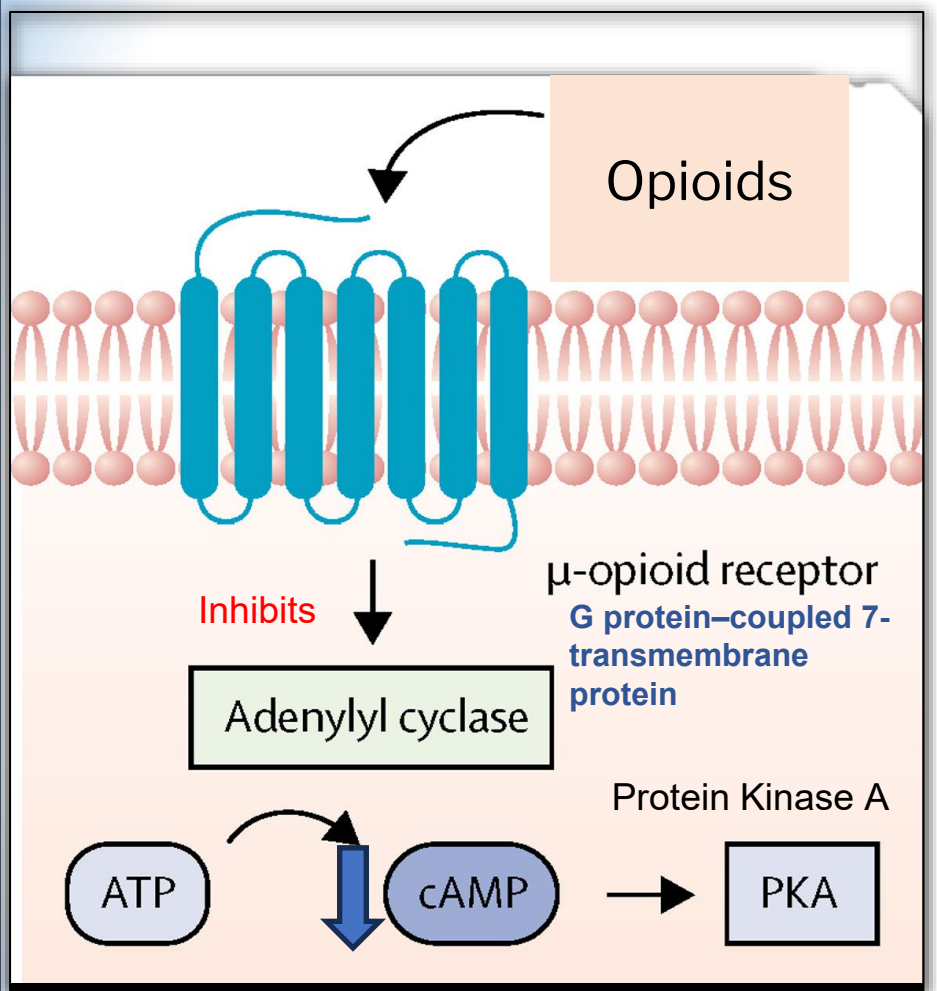
Question 1

Endogenous opioid peptides include the families of dynorphin, endorphin, and _____. These peptides are expressed in brain regions associated with reward, motivation, and pain perception.

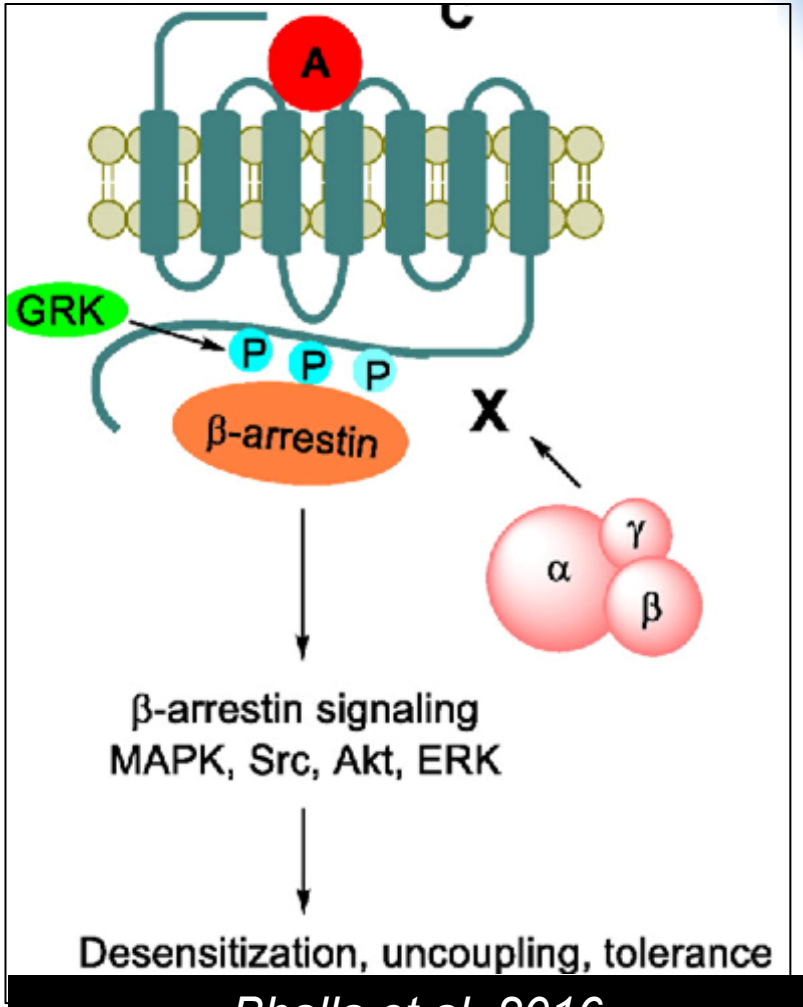
A. enkephalin
B. oxytocin
C. peptidoglycan
D. thebaine

Type	Effects	Notable agonists	Notable antagonists
μ	Analgesia, euphoria, respiratory depression , physiologic dependence	Morphine, fentanyl, methadone **Endomorphins, β-endorphins**	Naltrexone, naloxone
δ	Analgesia, nociception, convulsions, antidepressant, respiratory depression	**Enkephalins, β-endorphins**	Naltrexone, naloxone
κ	Analgesia, nociception, **dysphoria,** anticonvulsant, dissociative/hallucinogen	Salvia, ibogaine **Dynorphins**	Naltrexone, naloxone, buprenorphine

CSAM



Srivastava et al, 2020



Bhalla et al, 2016

QUESTION 2

Which of the following is *incorrectly* paired with one of its purported mechanisms of action?

A. Methadone—NMDA glutamate antagonist

B. Mitragynine—Mu-opioid receptor partial or full agonist

C. Salvinorin—Kappa-opioid antagonist

D. Tramadol—Serotonin reuptake inhibitor

QUESTION 2

Which of the following is *incorrectly* paired with one of its purported mechanisms of action?

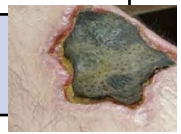
A. Methadone—NMDA glutamate antagonist

B. Mitragynine—Mu-opioid receptor partial or full agonist

C. Salvinorin—Kappa-opioid antagonist

D. Tramadol—Serotonin reuptake inhibitor

Name	Receptor effects	Highlights
Salvinorin (Salvia)	κ receptor agonist 	• Dissociative/hallucinogen via κ agonism • Hallucinations, analgesia • No respiratory depression
Methadone	μ opioid receptor agonist	
	NMDA receptor antagonist	• Attenuates tolerance, analgesia
Mirtragynine (Kratom)	Partial or full agonism at μ and most likely competitive antagonism of δ opioid receptors	• Very high potency at μ receptor • Low doses→ stimulation, Higher→ opioid effects • Used by patients to “attenuate” opioid withdrawal
Tramadol	μ opioid receptor partial agonist; SNRI	• Serotonin syndrome • Not detected on drug screens
Desomorphine (Krokodil)	High potency μ opioid agonist	• Easily synthesized from codeine • extensive skin necrosis



QUESTION 3

Which of the following is a potential benefit of low-dose buprenorphine initiation for the treatment of opioid use disorder?

A. Rapid onset of opioid withdrawal symptoms

B. Buprenorphine can be initiated concurrent with continued fentanyl use

C. Buprenorphine can be initiated once a COWS score reaches 5

D. It allows health care providers to use the lowest effective dose of buprenorphine

QUESTION 3

Which of the following is a potential benefit of low-dose buprenorphine initiation for the treatment of opioid use disorder?

A. Rapid onset of opioid withdrawal symptoms

B. Buprenorphine can be initiated concurrent with continued fentanyl use

C. Buprenorphine can be initiated once a COWS score reaches 5

D. It allows health care providers to use the lowest effective dose of buprenorphine

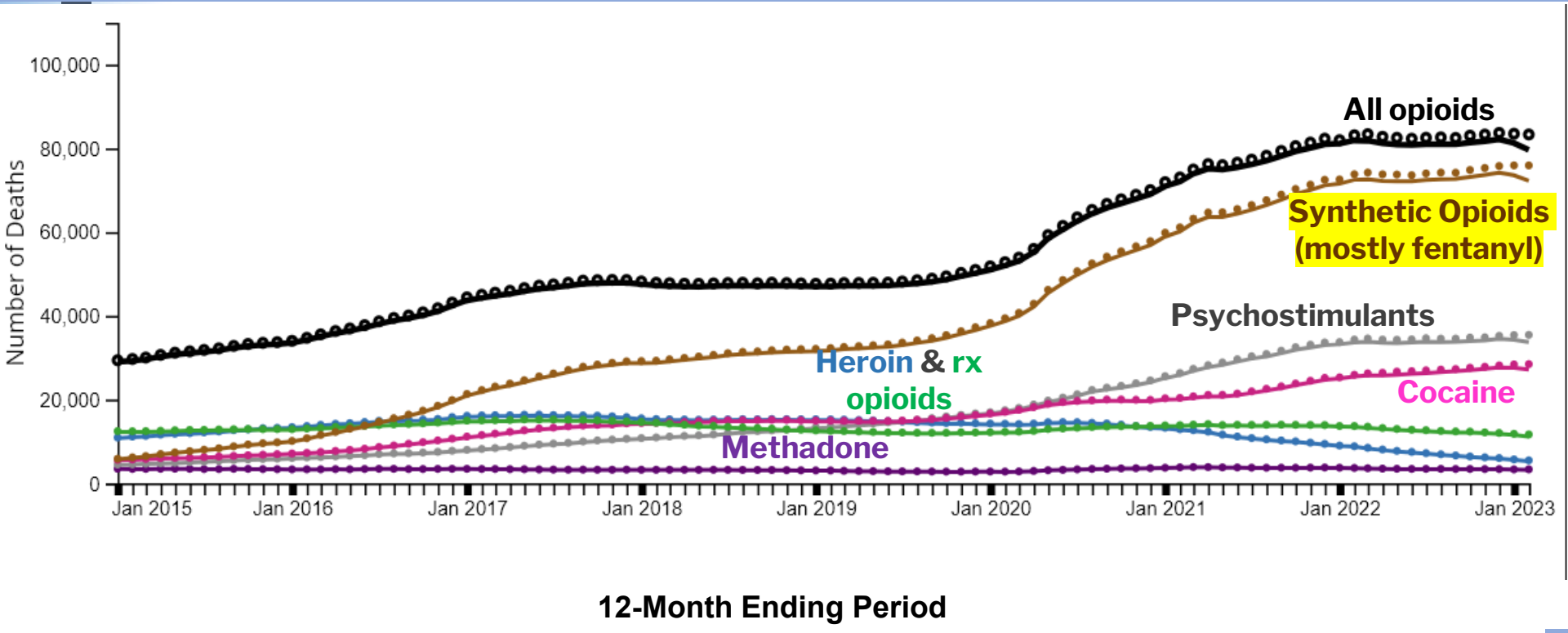
A Plea From People Who Use Drugs to Clinicians: New Ways to Initiate Buprenorphine are Urgently Needed in the Fentanyl Era

Kimberly L. Sue, MD, PhD, Shawn Cohen, MD, Jess Tilley, and Avi Yocheved

- Rationale for alternative buprenorphine initiation strategies
  - *Precipitated withdrawal (>22.19% in one sample when initiated within 24 hours of last fentanyl use)*
  - *Inability to stop using full agonist opioids for a required period*
  - *Difficulty initiating this medication that could confer stability and life-saving treatment*

Sue et al, 2022
Varshneya NB et al, 2022

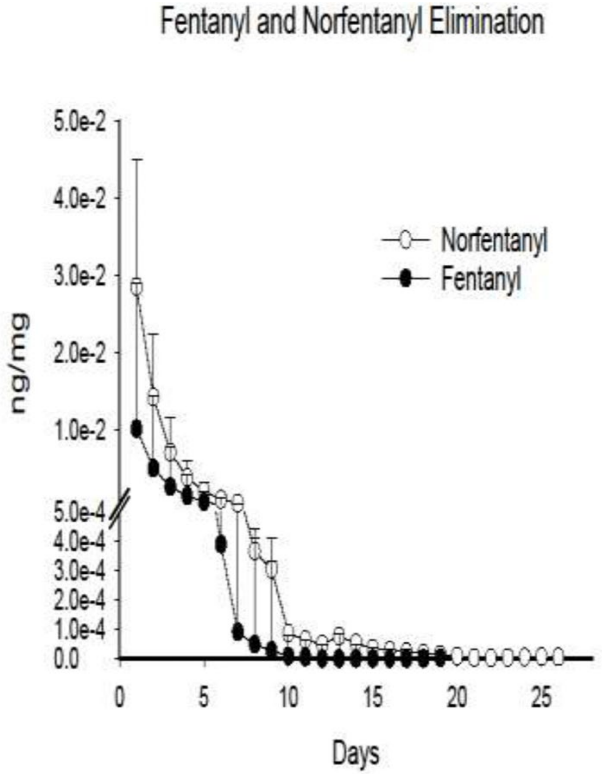
12 Month-ending Provisional Number of Drug Overdose Deaths by Drug or Drug Class: United States



Products - Vital Statistics Rapid Release - Provisional Drug Overdose Data (cdc.gov)

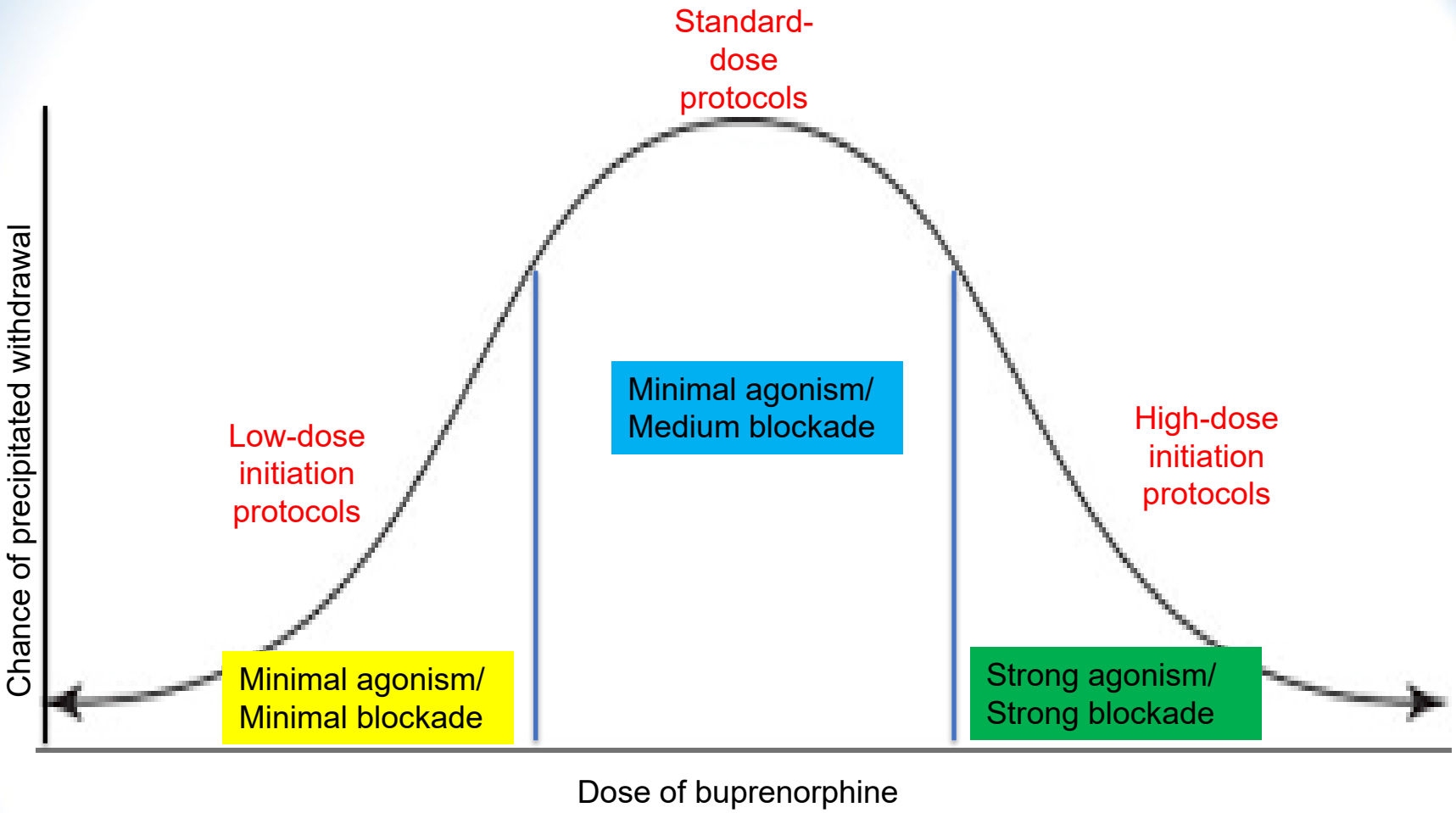
Pharmacological Properties of Fentanyl

- Fast onset and high potency
  - *50-100x more potent than morphine*
  - *high lipid solubility increases potency*
- Short duration of action due to redistribution in body fat
- Chronic use causes accumulation in adipose tissue and protracted renal clearance
  - *Might partly explain heterogeneous response to traditional buprenorphine induction strategies*



Herron & Brennan, 2019

Huhn et al, 2020



Greenwald et al, 2022

	Low-Dose	Standard-Dose	High-Dose
Optimal time since last use of fentanyl	Concurrent use is acceptable	>72 hrs * patients may not wait that long	Depends on protocol; generally, >6 hours OR use naloxone
Typical starting dose	<2mg	4mg	8-24mg
Time until target dose	2-7 days * risks lost to follow up	2-3 days	1-2 days
Precipitated withdrawal risk	Low	Moderate	Low (<2%) and resolves quickly

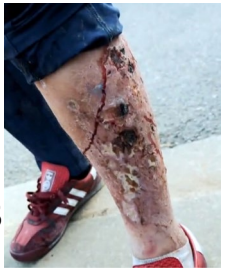
Cohen et al, 2021

Herring AA et al, 2021

Randall A et al, 2023

QUESTION 4

A patient is brought in by ambulance to a Philadelphia emergency room after being found unresponsive with pinpoint pupils and a RR of 4. Naloxone restores breathing and normalizes other vital signs, but the patient remains sedated. Two additional doses of naloxone are given without change in mental status. Physical exam is notable for the wounds pictured here on his legs. Urine toxicology is positive for fentanyl only. Which of the following is true about the likely culprit of these skin findings



A. Severe necrotic skin infections appear only where the drug is injected

B. As a contaminant of other drugs, it does not produce its own withdrawal syndrome

C. It is typically diverted from the veterinary pharmaceutical supply chain and added locally to other intoxicants

D. The pharmacology of this substance resembles that of benzodiazepines

QUESTION 4

A patient is brought in by ambulance to a Philadelphia emergency room after being found unresponsive with pinpoint pupils and a RR of 4. Naloxone restores breathing and normalizes other vital signs, but the patient remains sedate. Two additional doses of naloxone are given without change in mental status. Physical exam is notable for the wounds pictured here on his legs. Urine toxicology is positive for fentanyl only. Which of the following is true about the likely culprit of these skin findings?

A. Severe necrotic skin infections appear only where the drug is injected

B. As a contaminant of other drugs, it does not produce its own withdrawal syndrome

C. It is typically diverted from the veterinary pharmaceutical supply chain and added locally to other intoxicants

D. The pharmacology of this substance resembles that of benzodiazepines

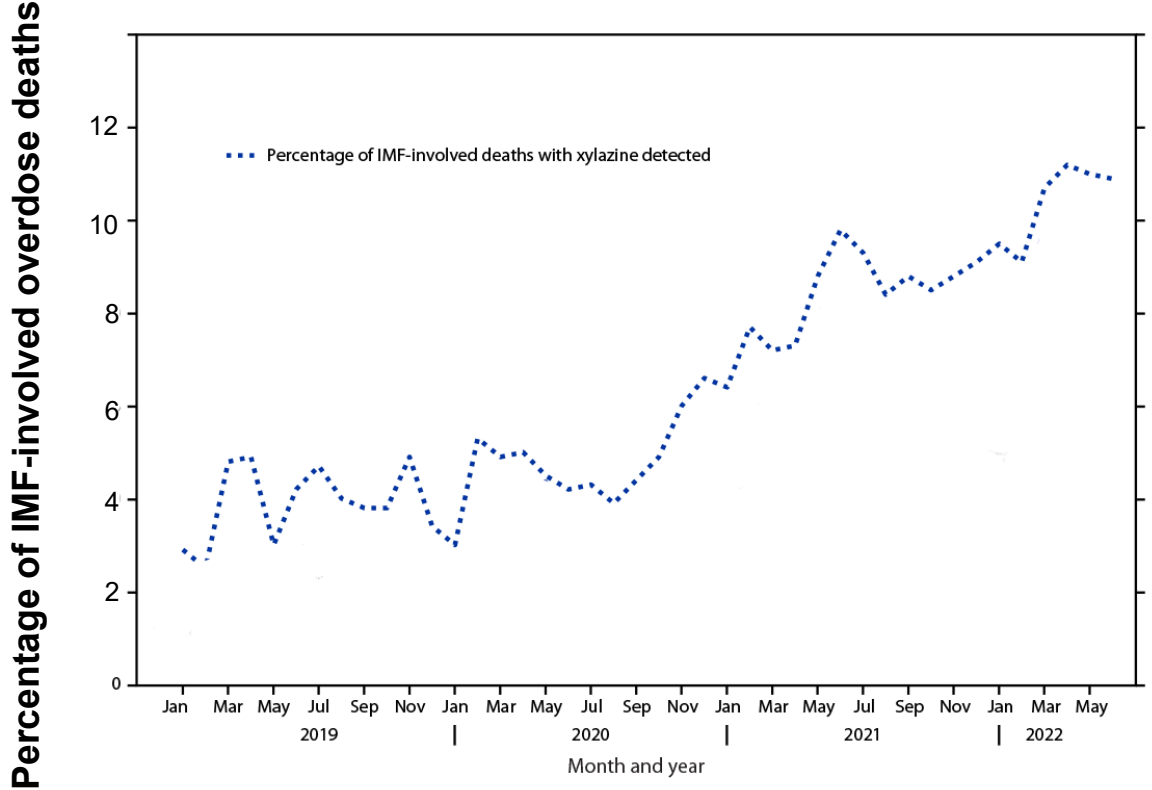
CSAM

XYLAZINE (AKA “TRANQ”)

- Non-opioid, veterinary pharmaceutical agent
- Not controlled under the Controlled Substance Act and not approved for human use
  - *Typically diverted from veterinary pharmaceutical supply chain and added to fentanyl*
- α2-agonist in the same class as clonidine (not benzodiazepines)
- Intoxicating effects include **sedation**, **analgesia**, **euphoria**, **hypotension**, **bradycardia**
- Withdrawal syndrome after prolonged use and abrupt discontinuation does occur - **irritability, anxiety, restlessness and dysphoria**

Ehrman-Dupre et al, 2022
Gupta et al, 2023
Lowry, Brown, 2014
https://www.deadiversion.usdoj.gov/drug_chem_info/Xylazine.pdf

%age of Drug-Overdose Deaths involving illicitly-manufactured fentanyls (IMF) with xylazine detected, 21 jurisdictions 2019-June 2022



Kariisa et al, 2023

Xylazine-Induced Skin Lesions

- Associated with severe necrotic skin ulcerations
- Injury may occur at or remote from an injection site, irrespective of the mode of use
- Pathophysiology is unclear and likely multifactorial
- Can require amputation

Malayala et al, 2022

QUESTION 5

A 55 year-old woman with opioid use disorder, diabetes mellitus type 2, uncontrolled hypertension, congestive heart failure and HIV is being treated for her opioid use disorder with methadone. The following medications were added in the past 6 months: metformin, carvedilol, efavirenz, and verapamil. She reports new onset episodes of gait instability and slurred speech, and her daughter later found her unresponsive on the floor of her home. Which of the following drug interactions is the *MOST LIKELY* explanation for her symptoms?

A. carvedilol-methadone interaction at cardiac beta-adrenergic receptors

B. efavirenz-methadone interaction at cytochrome P450 2B6 enzyme

C. verapamil-methadone interaction at cytochrome P450 3A4 enzyme

D. metformin-methadone interaction at cytochrome P450 2D6 enzyme

CSAM

QUESTION 5

A 55 year-old woman with opioid use disorder, diabetes mellitus type 2, uncontrolled hypertension, congestive heart failure and HIV is being treated for her opioid use disorder with methadone. The following medications were added in the past 6 months: metformin, carvedilol, efavirenz, and verapamil. She reports new onset episodes of gait instability and slurred speech, and her daughter later found her unresponsive on the floor of her home. Which of the following drug interactions is the *MOST LIKELY* explanation for her symptoms?

A. carvedilol-methadone interaction at cardiac beta-adrenergic receptors

B. efavirenz-methadone interaction at cytochrome P450 2B6 enzyme

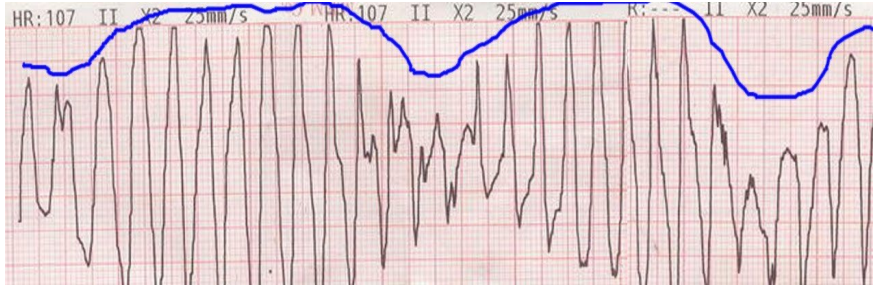
C. verapamil-methadone interaction at cytochrome P450 3A4 enzyme

D. metformin-methadone interaction at cytochrome P450 2D6 enzyme

CYP3A4 INDUCERS	CYP3A4 INHIBITORS
CarbAMAZEpine	Grapefruit + cranberry juice
RifAMPin	azole antifungals (ketoconazole, itraconazole > fluconazole)
St. Johns wort	Macrolide antibiotics: clarithromycin> erythromycin
Phenobarbital	Protease inhibitors: ritonavir, indinavir
Phenytoin	Thyroid hormones
Efavirenz	Calcium channel blockers (verapamil, diltiazem)
Psych: risperidone, modafinil	Cimetidine, omeprazole
Griseofulvin 	Psych: fluoxetine, fluvoxamine, valproic acid

Other tested methadone interactions

- **QTc prolongation & torsade de pointes**
  - Repeat EKG after other QTc prolonging medications are added including TCA antidepressants like imipramine, clomipramine and citalopram
  - *Block K+ efflux from cardiac myocytes during cardiac repolarization*



Kranz et al, 2009

CSAM

QUESTION 6

A healthy 23-year-old man last used pure heroin 34 hours ago. Which of the following is most likely to be the result from a confirmatory gas chromatography/mass spectroscopy urine test?

A. 1200 ng/mL 6-monoacetyl-morphine and 8750 ng/mL of morphine

B. 5430 ng/mL of 6-monoacetyl-morphine

C. 1420 ng/mL of hydromorphone and 4315 ng/mL of morphine

D. 3130 ng/mL of morphine

QUESTION 6

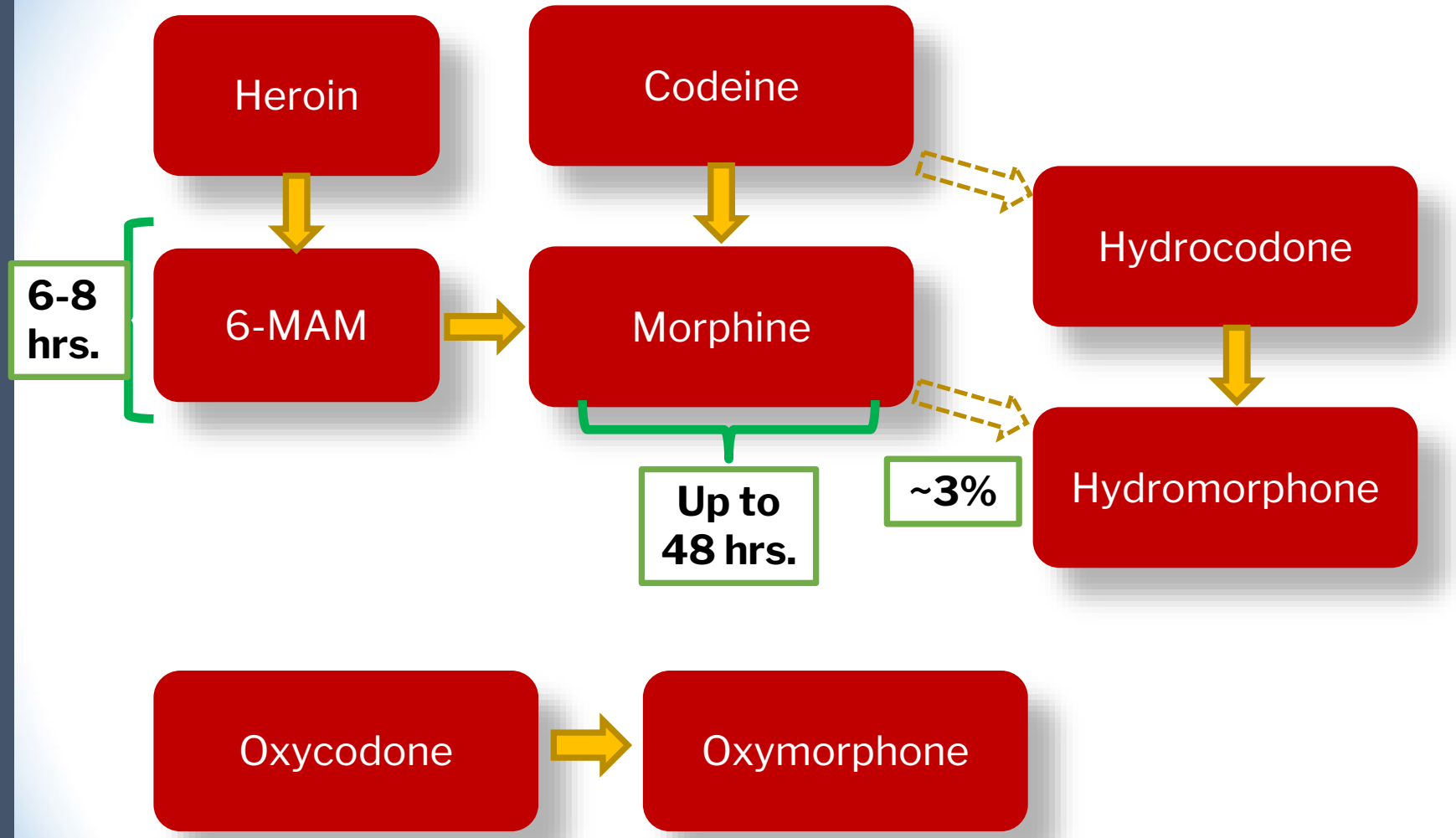
A healthy 23-year old man last used pure heroin 34 hours ago. Which of the following is the most likely to be the result from a confirmatory gas chromatography/mass spectroscopy urine test?

A. 1200 ng/mL 6-monoacetyl-morphine and 8750 ng/mL of morphine

B. 5430 ng/mL of 6-monoacetyl-morphine

C. 1420 ng/mL of hydromorphone and 4315 ng/mL of morphine

D. 3130 ng/mL of morphine


Heroin
Codeine
Hydrocodone
6-8 hrs.
6-MAM
Morphine
Up to 48 hrs.
~3%
Hydromorphone
Oxycodone
Oxymorphone

QUESTION 7

Changing prescription opioids from Schedule III to Schedule II under the Controlled Substance Act is an attempt of what kind of prevention?

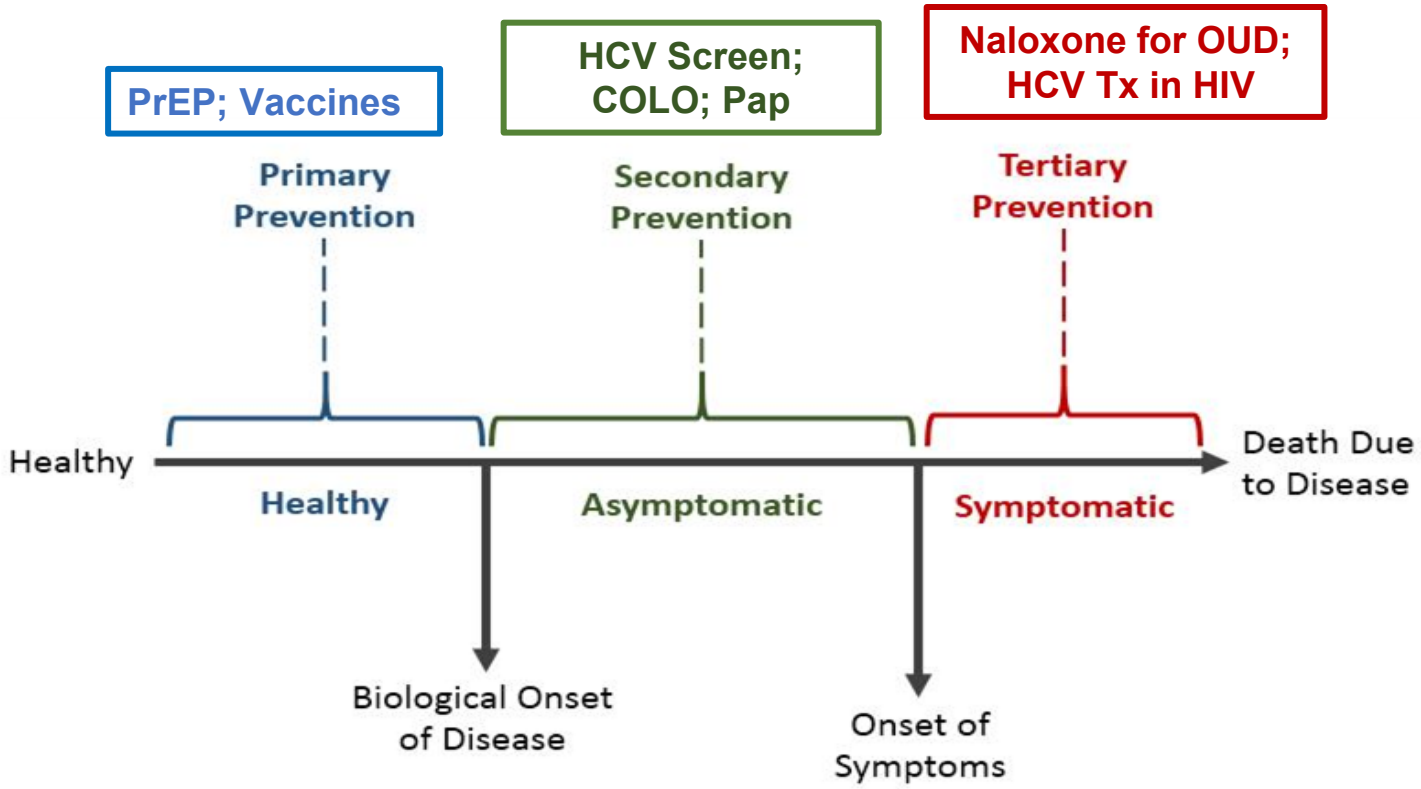
A. Indicated
B. Secondary
C. Selective
D. Universal

QUESTION 7

Changing prescription opioids from Schedule III to Schedule II under the Controlled Substance Act is an attempt of what kind of prevention?

A. Indicated
B. Secondary
C. Selective
D. Universal

Prevention


PrEP; Vaccines
HCV Screen; COLO; Pap
Naloxone for OUD; HCV Tx in HIV
Primary Prevention
Secondary Prevention
Tertiary Prevention
Healthy
Death Due to Disease
Healthy
Asymptomatic
Symptomatic
Biological Onset of Disease
Onset of Symptoms

	Universal prevention	Selective prevention	Indicated prevention
Population targeted	An entire population or subpopulation	A specific group or subpopulation	Individuals
Risk Factors	Not applicable	Increased risk by virtue of belonging to this group	Increased risk by virtue of individual traits/behaviors
Examples	***Direct***: Education/resilience program for 5th graders ***Indirect***: Environmental or legal regulations that lower substance access (e.g. more restrictions on Rx opioid access)	***Demographic*** Drug education for LGBTQ youth ***Biological*** Alcohol education for children of parents with AUD ***Psychosocial*** SUD screening for persons with adverse childhood events	***Risky use w/o SUD*** SBIRT for a person with a positive AUDIT-C ***Risky behaviors associated w/ SUD*** SUD screening for an adolescent expelled from school for conduct problems

QUESTION 8

All the following are risk factors for the development of opioid use disorder among those prescribed long-term opioids for pain, *except:*

A. Adolescence
B. African-American race
C. Major depressive disorder
D. Tobacco use

QUESTION 8

All the following are risk factors for the development of opioid use disorder among those prescribed long-term opioids for pain, *except:*

A. Adolescence
B. African-American race
C. Major depressive disorder
D. Tobacco use

Risk factors for developing OUD when rxed long-term opioids for chronic pain

- Personal substance use history (including alcohol & tobacco)
- Younger age (especially adolescents)
- Co-occurring psychiatric conditions (including mood & anxiety disorders)
- Higher risk for Whites

QUESTION 9

In 2016 the Center for Disease Control (CDC) published guidelines for the use of opioids in the management of chronic, non-cancer pain. Which of the following was among their recommendations?

A. Acute pain usually requires 3 months or less of opioids
B. Consider prescribing naloxone when daily opioid doses reach 50 morphine milligram equivalents or more
C. New opioid starts should use long-acting formulations when possible
D. Urine drug testing should be performed at least monthly when prescribing long-term opioids

QUESTION 9

In 2016 the Center for Disease Control (CDC) published guidelines for the use of opioids in the management of chronic, non-cancer pain. Which of the following was among their recommendations?

A. Acute pain usually requires 3 months or less of opioids

B. Consider prescribing naloxone when daily opioid doses reach 50 morphine milligram equivalents or more

C. New opioid starts should use long-acting formulations when possible

D. Urine drug testing should be performed at least monthly when prescribing long-term opioids

CDC guidelines on the use of long-term opioids for pain unrelated to cancer, palliative care, and end-of-life care:

- Initial opioid prescriptions should use **short-acting** formulations
- Consider naloxone for **≥50 morphine mg equivalents/day**
- Acute pain usually requires 3 days or fewer; **rarely > 7 days**
- Perform baseline urine drug testing and **at least annually** thereafter
- Check PDMP at baseline and at least every 3 months thereafter

QUESTION 10

A 53-year-old man with severe hip osteoarthritis is planning to undergo an elective total hip arthroplasty. He has a history of opioid use disorder, in sustained remission on buprenorphine treatment (total daily dose 16 mg). Which of the following *best* presents the expert consensus?

A. Continue buprenorphine and treat postoperative pain with short-acting full agonist opioid doses
B. Continue buprenorphine and treat postoperative pain with multimodal analgesia
C. Taper off buprenorphine 3 days prior to surgery and start full agonist opioids postoperatively
D. Taper off buprenorphine 1 week prior to surgery and treat with non-opioid pain treatments postoperatively

QUESTION 10

A 53-year-old man with severe hip osteoarthritis is planning to undergo an elective total hip arthroplasty. He has a history of opioid use disorder, in sustained remission on buprenorphine treatment (total daily dose 16 mg). Which of the following *best* presents the expert consensus?

A. Continue buprenorphine and treat postoperative pain with conventional short-acting opioid doses
B. Continue buprenorphine and treat postoperative pain with multimodal analgesia
C. Taper off buprenorphine 3 days prior to surgery and start full agonist opioids postoperatively
D. Taper off buprenorphine 1 week prior to surgery and treat with non-opioid pain treatments postoperatively

Management of Perioperative Pain for Patients on MOUD

Buprenorphine

- Blocks many effects of additive opioids, but additive analgesia is maintained
- Consider TID dosing
- Some argue for dropping <16mg below full μ-receptor occupancy

Methadone

- α –elimination reaction is about 8 hours and affects analgesia, split to TID dosing

Naltrexone

- 10-hour half-life, oral should be discontinued 48 hours prior to surgery
- Recommend stopping XR-NTX 4th weeks ahead of surgery; reports of analgesic blockade within 1st 2 weeks holding NTX

Several multimodal pain management options, depending on the specific procedure, are possible perioperatively:

- non-opioid medications (gabapentinoids, IV acetaminophen, alpha-2 agonists, ketamine, ketorolac, bupivacaine/lidocaine)
- regional anesthesia (e.g., peripheral nerve catheters, epidural medications)
- psychosocial supports, and…
- …when these options fail, adding full agonist opioids.
  - *While conventional short-acting opioids may benefit some people, others might require higher than normal doses and high potency agents such as fentanyl or hydromorphone.*
  - *When the latter approach is used, care should be in a unit with quick access to emergency airway management in the event of overshooting the full agonist dose*[11]

NEED TO KNOW

- Treatment guidelines for medication treatment of OUD
- The role of opioids in the management of chronic pain
- The pharmacokinetics & pharmacodynamics of common opioids
- The epidemiological trends in OUD and opioid overdoses
- OUD treatment in special populations
- Principles of preventive medicine as applied to persons with OUD

REFERENCES

1) Srivastava AB, Mariani JJ, Levin FR. New directions in the treatment of opioid withdrawal. Lancet 2020: 1938-1948. **Question 1**

2) Bhalla S, Andurkar SV, Gulati A. Neurobiology of opioid withdrawal: Role of the endothelin system. Life Sci 2016: 159;34-42. **Question 1**

3) Hawk K, Kirrane BM, D, Onofrio G. “Psychoactive Substances: Their Recognition, Pharmacology, and Treatment." The ASAM Essentials of Addiction Medicine, edited by Herron A & Brennan TK, Wolters Kluwer, 2019, 116-117. **Question 2**

4) Products - Vital Statistics Rapid Release - Provisional Drug Overdose Data (cdc.gov) **Question 3**

5) Parks KDL, Domingo C, Kosten TR. “The Pharmacology of Opioids.” The ASAM Essentials of Addiction Medicine, edited by Herron A & Brennan TK, Wolters Kluwer, 2020, 55-59. **Question 3**

6) Huhn AS, Hobelmann JG, Oyler GA, Strain EC. Protracted renal clearance of fentanyl in persons with opioid use disorder. Drug Alcohol Depend 2020; 214:108-147. **Question 3**

7) Sue KL, Cohen S, Tilley J, Yocheved A. A Plea From People Who Use Drugs to Clinicians: New Ways to Initiate Buprenorphine Are Urgently Needed in the Fentanyl Era. J Addict Med. 2022; 16(4):389-391. **Question 3**

8) Varshneya NB, Thakrar AP, Hobelmann JG, Dunn KE, Huhn AS. Evidence of Buprenorphine-precipitated Withdrawal in Persons Who Use Fentanyl. *J Addict Med*. 2022;16(4):e265-e268. **Question 3**

CSAM

REFERENCES

9) Greenwald MK, Herring AA, Perrone J, Nelson LS, Azar P. A Neuropharmacological Model to Explain Buprenorphine Induction Challenges. *Ann Emerg Med*. 2022;80(6):509-524. **Question 3**

10) Cohen SM, Weimer MB, Levander XA, Peckham AM, Tetrault JM, Morford KL. Low Dose Initiation of Buprenorphine: A Narrative Review and Practical Approach. *J Addict Med*. 2022;16(4):399-406. **Question 3**

11) Herring AA, Vosooghi AA, Luftig J, et al. High-Dose Buprenorphine Induction in the Emergency Department for Treatment of Opioid Use Disorder . JAMA Netw Open. 2021;4(7):e2117128 **Question 3**

12) Randall A, Hull I, Martin SA. Enhancing Patient Choice: Using Self-administered Intranasal Naloxone for Novel Rapid Buprenorphine Initiation. *J Addict Med*. 2023;17(2):237-240. **Question 3**

13) Ehrman-Dupre R, Kaigh C, Salzman M, Haroz R, Peterson LK, Schmidt R. Management of Xylazine Withdrawal in a Hospitalized Patient: A Case Report. *J Addict Med*. 2022;16(5):595-598. **Question 4**

14) Gupta R, Holtgrave DR, Ashburn MA. Xylazine - Medical and Public Health Imperatives. *N Engl J Med*. 2023;388(24):2209-2212. **Question 4**

15) Lowry JA, Brown JT. Significance of the imidazoline receptors in toxicology. Clin Toxicol 2014. 52(5):454-69. **Question 4**

16) https://www.deadiversion.usdoj.gov/drug_chem_info/Xylazine.pdf Nov 2022. **Question 4.**

REFERENCES

17) Kariisa M, O'Donnell J, Kumar S, Mattson CL, Goldberger BA. Illicitly Manufactured Fentanyl–Involved Overdose Deaths with Detected Xylazine — United States, January 2019–June 2022. MMWR Morb Mortal Wkly Rep 2023;72:721–727. **Question 4.**

18) Malayala SV, Papudesi BN, Bobb R, Wimbush A. Xylazine-induced skin ulcers in a person who injects drugs in Philadelphia, Pennsylvania, USA. Cureus 2022;14(8):e28160. **Question 4**

19) McCance-Katz EF, Sullivan LE, Nallani S: Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. Am J Addict 2010; 19(1):4-16. **Question 5**

20) Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. QTc interval screening in methadone treatment. *Ann Intern Med* 2009: 150(6):387-95. **Question 5**

21) Kale N: Urine Drug Tests: Ordering and interpreting results. *Am Fam Physician* 2019;99(1):33-39. **Question 6**

22) Bertholf RL, Johannsen LM & Reisfield GM: Sensitivity of an opiate immunoassay for detecting hydrocodone and hydromorphone in urine from a clinical population: analysis of subthreshold results. *J Anal Toxicol* 2015; *39*(1), 24–28. **Question 6**

23) LeNoue SR, Riggs PD: Substance Abuse Prevention. *Child Adolesc Psychiatr Clin N Am* 2016;25(2): 297-305. **Question 7**

CSAM

REFERENCES

17) Kariisa M, O'Donnell J, Kumar S, Mattson CL, Goldberger BA. Illicitly Manufactured Fentanyl–Involved Overdose Deaths with Detected Xylazine — United States, January 2019–June 2022. MMWR Morb Mortal Wkly Rep 2023;72:721–727. **Question 4.**

18) Malayala SV, Papudesi BN, Bobb R, Wimbush A. Xylazine-induced skin ulcers in a person who injects drugs in Philadelphia, Pennsylvania, USA. Cureus 2022;14(8):e28160. **Question 4**

19) McCance-Katz EF, Sullivan LE, Nallani S: Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. Am J Addict 2010; 19(1):4-16. **Question 5**

20) Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. QTc interval screening in methadone treatment. *Ann Intern Med* 2009: 150(6):387-95. **Question 5**

21) Kale N: Urine Drug Tests: Ordering and interpreting results. *Am Fam Physician* 2019;99(1):33-39. **Question 6**

22) Bertholf RL, Johannsen LM & Reisfield GM: Sensitivity of an opiate immunoassay for detecting hydrocodone and hydromorphone in urine from a clinical population: analysis of subthreshold results. *J Anal Toxicol* 2015; *39*(1), 24–28. **Question 6**

23) LeNoue SR, Riggs PD: Substance Abuse Prevention. *Child Adolesc Psychiatr Clin N Am* 2016;25(2): 297-305. **Question 7**

CSAM

REFERENCES

24) Kaye AD, Jones MR, Kaye AM, et al: Prescription opioid abuse in chronic pain: an updated review of opioid abuse predictors and strategies to curb opioid abuse: part 1. *Pain physician* 2017; *20*(2S), S93-S109. **Question 8.**

25) Dowell D, Haegerich TM, Chou R: CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. *MMWR Recomm Rep* 2016;65(No. RR-1):1–49. **Question 9.**

26) Goel A, Azargive S, Weissman JS, Shanthanna H, et al. Perioperative pain and addiction interdisciplinary network (PAIN) clinical practice advisory for perioperative management of buprenorphine: results of a modified Delphi process. *Br J Anaesth* 2019; 23(2):e333-e342. **Question 10**

27) Harrison TK, Kornfeld H, Aggarwal AK & Lembke A: Perioperative considerations for the patient with opioid use disorder on buprenorphine, methadone, or naltrexone maintenance therapy. *Anesthesiol Clin 2018; 36:3.* ***Question 10.***

28) Grinnell SG, Ansonoff M, Marrone GF, Lu Z, Narayan A, Xu J, Rossi G, Majumdar S, Pan YX, Bassoni DL, Pintar J, Pasternak GW. Mediation of buprenorphine analgesia by a combination of traditional and truncated mu opioid receptor splice variants. Synapse. 2016 Oct;70(10):395-407. doi: 10.1002/syn.21914. Epub 2016 Jul 12. PMID: 27223691; PMCID: PMC4980214.

REFERENCES

29) Signaling diversity of mu- and delta- opioid receptor ligands: Re-evaluating the benefits of β-arrestin/G protein signaling bias, Cellular Signaling, Volume 80, 2021

Thank you and
Good Luck!