OPIOIDS & PAIN

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CSAM Review Course in Addiction Medicine

Katherine Pier, MD

Addiction Psychiatrist, Kaiser Permanente, San Francisco

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

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 Scienes (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

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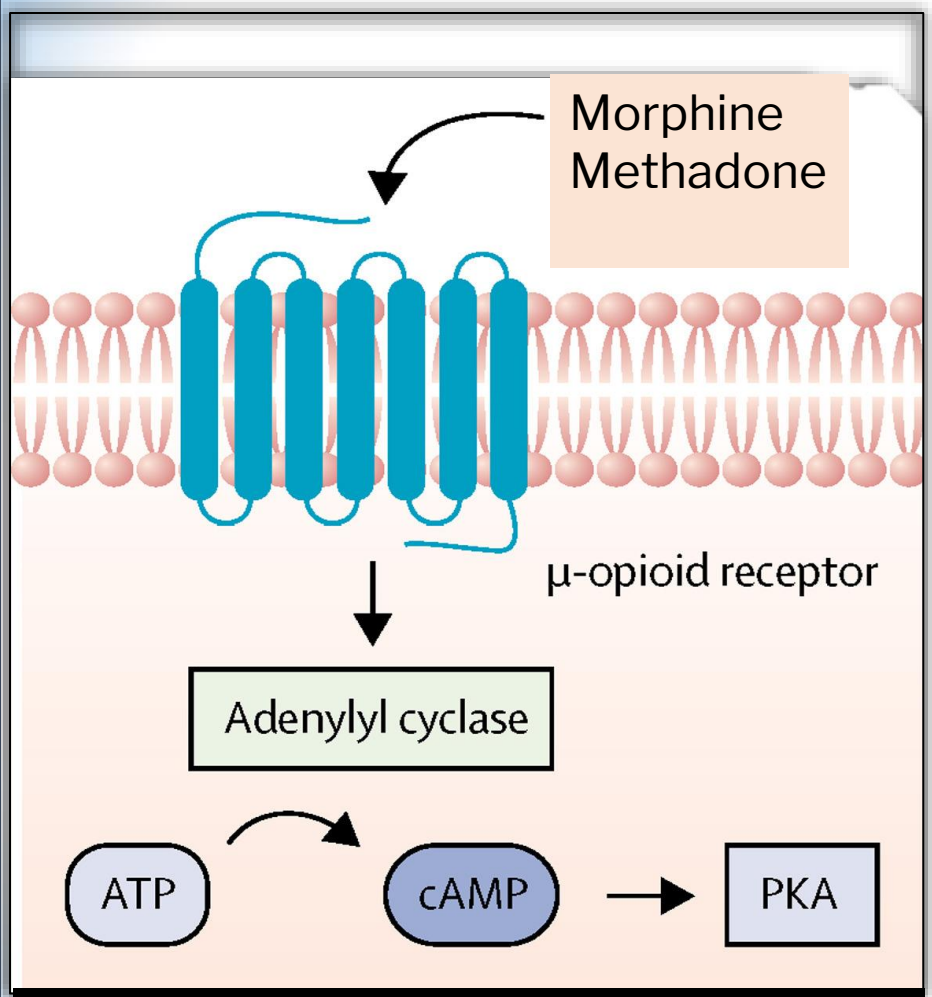
Question 1

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

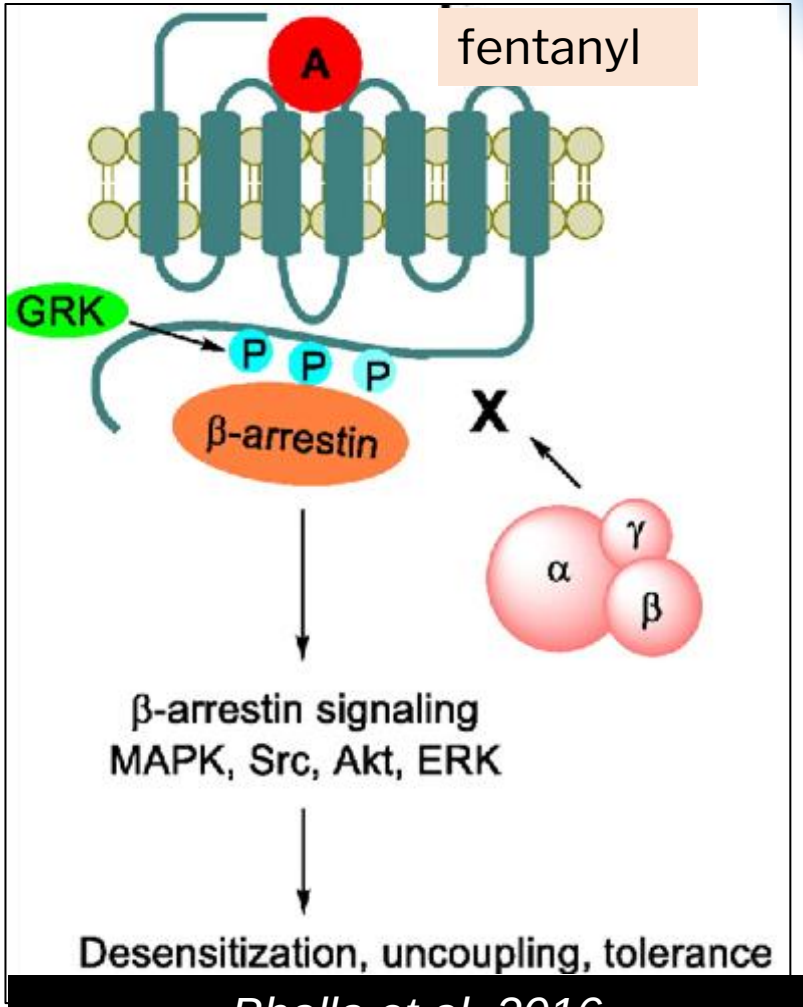
A. enkephalin
B. oxytocin
C. peptidoglycan
D. thebain

Answer: **A. enkephalin**

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	SNC80; most mu-agonists but with lower **δ** binding affinity **Enkaphalins, β-endorphins**	Naltrexone, naloxone
K	Analgesia, nociception, **dysphoria,** anticonvulsant, dissociative/hallucinogen (aversive actions of opioids)	Salvia, ibogaine **Dynorphins**	Naltrexone, naloxone, buprenorphine



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

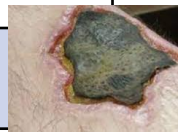
B. Mitragynine—Mu-opioid receptor partial or full agonist

C. Salvinorin—Kappa-opioid antagonist

D. Tramadol—Serotonin reuptake inhibitor

ANSWER: **C. Salvinorin—Kappa-opioid antagonist**

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 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 responsible for the most drug overdose deaths in the US?

A. Fentanyl & related analogues

B. Heroin

C. Methamphetamine

D. Prescription opioids such as oxycodone and hydrocodone

Answer: **A. Fentanyl & related analogues**

Key Points on Fentanyl

- Therapeutic properties; abuse secondary to *illicit opioids*
- 10-50x greater potency > morphine
- Numerous fentanyl analogues: carfentanil 10,000x as potent
- Overdose reversal requires 5x greater doses of naloxone than morphine-related drugs
- Receptor actions through β-arrestin second messenger system rather than cAMP system
- Can be absorbed accidentally, *unlikely to be toxic in first responders*

Herron & Brennan, 2019

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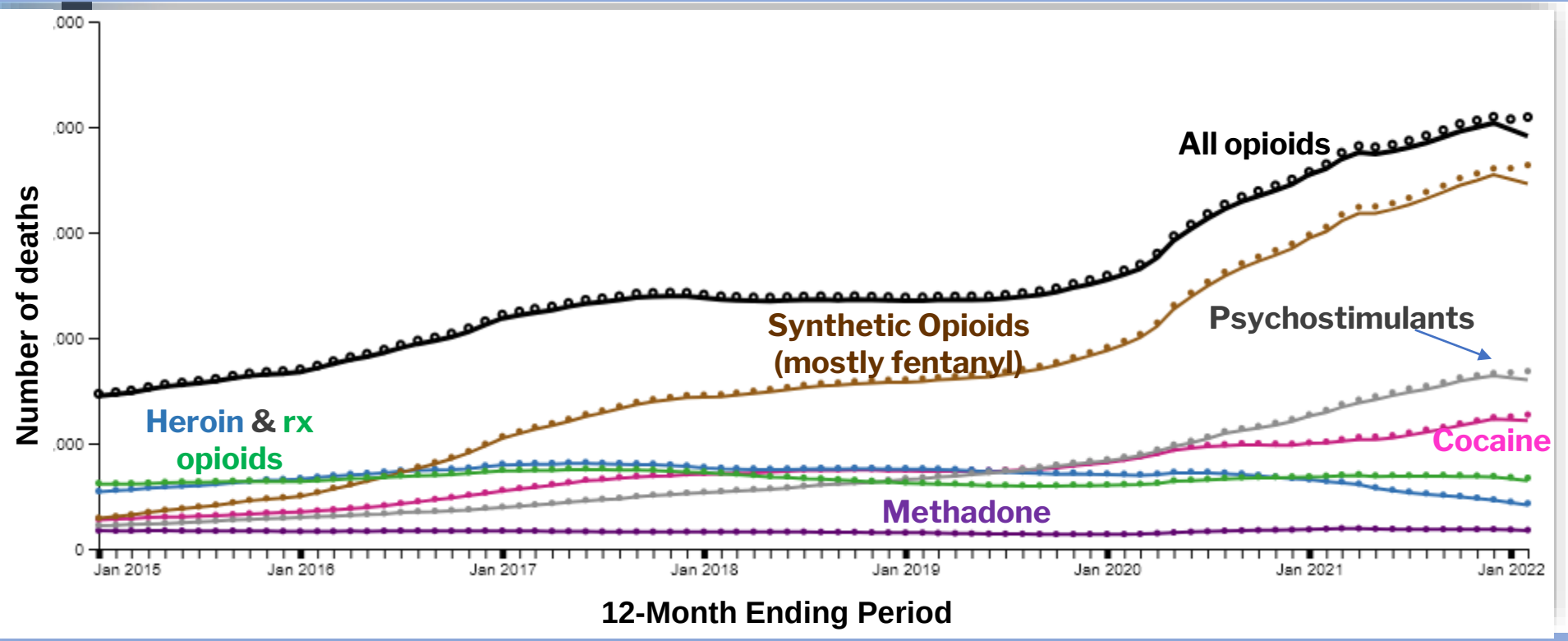
12 Month-ending Provisional Number of Drug Overdose Deaths by Drug or Drug Class: United States



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

QUESTION 4

In clinical trials comparing intramuscular naltrexone to sublingual buprenorphine for the treatment of opioid use disorder, intent-to-treat outcomes favored buprenorphine primarily because…

A. Adherence to buprenorphine was better than adherence to naltrexone in the latter stages of the trials.

B. Buprenorphine reduced cravings more than naltrexone did.

C. Buprenorphine reduced opioid use more than naltrexone did.

D. Naltrexone was more difficult to successfully initiate than buprenorphine.

ANSWER: D. **Naltrexone was more difficult to successfully initiate than buprenorphine.**

THE LANCET
Volume 391, Issue 10118, 27 January–2 February 2018, Pages 309-318

Articles

Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial

Dr Joshua D Lee MD [a], Edward V Nunes Jr MD [c], Patricia Novo MPH [b], Ken Bachrach PhD [d], Genie L Bailey MD [e, f], Snehal Bhatt MD [g], Sarah Farkas MA [b], Marc Fishman MD [h, i], Phoebe Gauthier MPH [b], Candace C Hodgkins PhD [j], Jacquie King MS [k], Robert Lindblad MD [k], David Liu MD [l], Abigail G Matthews PhD [k], Jeanine May PhD [k], K Michelle Peavy PhD [m], Stephen Ross MD [b], Dagmar Salazar MS [k] ... John Rotrosen MD [b]

Intent to Treat Analysis

	Bup	XR-NTX
Inducted onto medication*	94%	72%
Time to relapse*	14.4 weeks	8.4 wks
Relapse by week 24 (%)*	57%	65%
Weeks neg UDS*	10	4

ANSWER: D. **Naltrexone was more difficult to successfully initiate than buprenorphine.**

Per Protocol Analysis

	Bup	XR-NTX
Inducted onto medication	100%	100%
Time to relapse	15.2 weeks	20.4 weeks
Relapse by week 24 (%)	56%	52%
Weeks neg UDS	10.5	13

ANSWER: D. **Naltrexone was more difficult to successfully initiate than buprenorphine.**

QUESTION 5

Which of the following statements about opioid maintenance treatment during pregnancy is true?

A. Methadone is associated with fewer congenital anomalies compared to buprenorphine.

B. Buprenorphine is associated with a shorter duration of treatment for neonatal abstinence syndrome.

C. Rates of congenital anomalies are equal among mothers on buprenorphine and methadone, but retention in treatment is superior on buprenorphine.

D. Methadone doses in the third trimester are usually lower than they are during the first and second trimesters.

Answer: **B-Buprenorphine is associated with a shorter duration of treatment neonatal abstinence syndrome.**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neonatal Abstinence Syndrome after Methadone or Buprenorphine Exposure

Hendrée E. Jones, Ph.D., Karol Kaltenbach, Ph.D., Sarah H. Heil, Ph.D., Susan M. Stine, M.D., Ph.D., Mara G. Coyle, M.D., Amelia M. Arria, Ph.D., Kevin E. O'Grady, Ph.D., Peter Selby, M.B., B.S., Peter R. Martin, M.D., and Gabriele Fischer, M.D.

Answer B-Buprenorphine is associated with a shorter duration of treatment for neonatal abstinence syndrome.

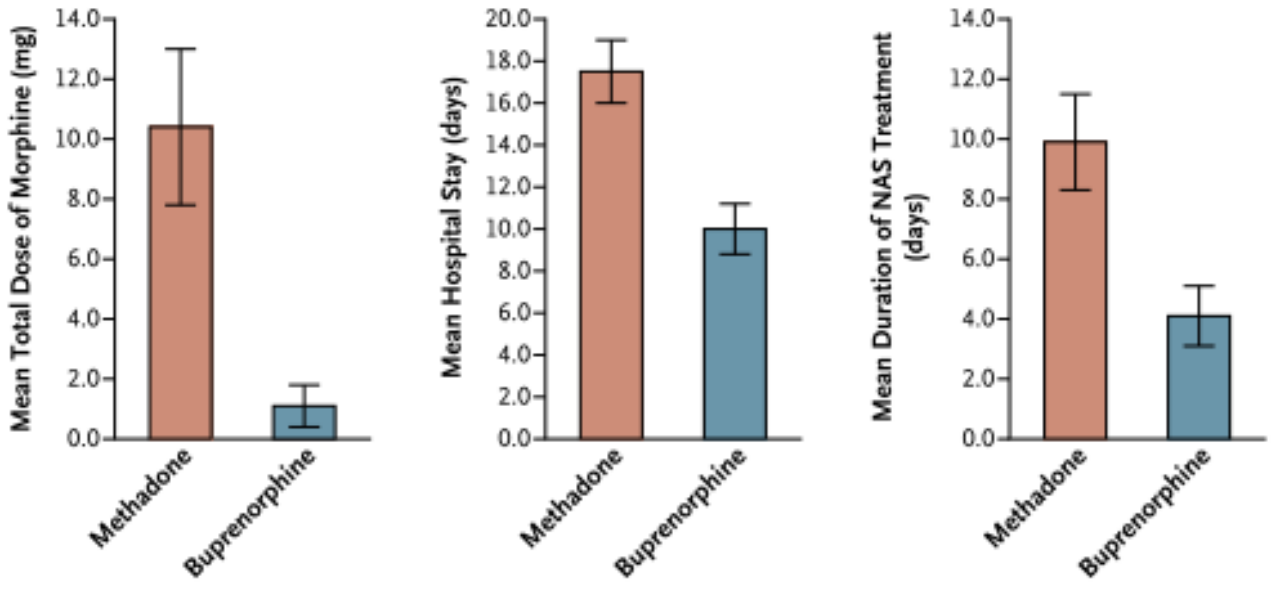


Figure 2. Mean Neonatal Morphine Dose, Length of Neonatal Hospital Stay, and Duration of Treatment for Neonatal Abstinence Syndrome.

Answer: **B. Buprenorphine is associated with a shorter duration of neonatal abstinence syndrome.**

- Retention in methadone treatment arm was superior to buprenorphine treatment arm
- Maternal outcomes were similar in buprenorphine and methadone treatment arms
- Differences in % NAS were insignificant between bup and methadone
- Treatment of NAS was shorter and required lower doses of opiates in the buprenorphine treatment arm
- Relapse rates over entire duration of study, UDS+ at L&D admission both lower in buprenorphine treatment arm

QUESTION 6

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

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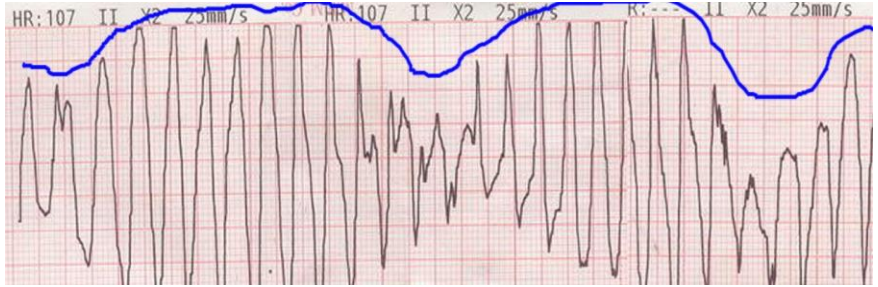
ANSWER: **C. verapamil-methadone interaction at cytochrome P450 3A4 enzyme**

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

QUESTION 7

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

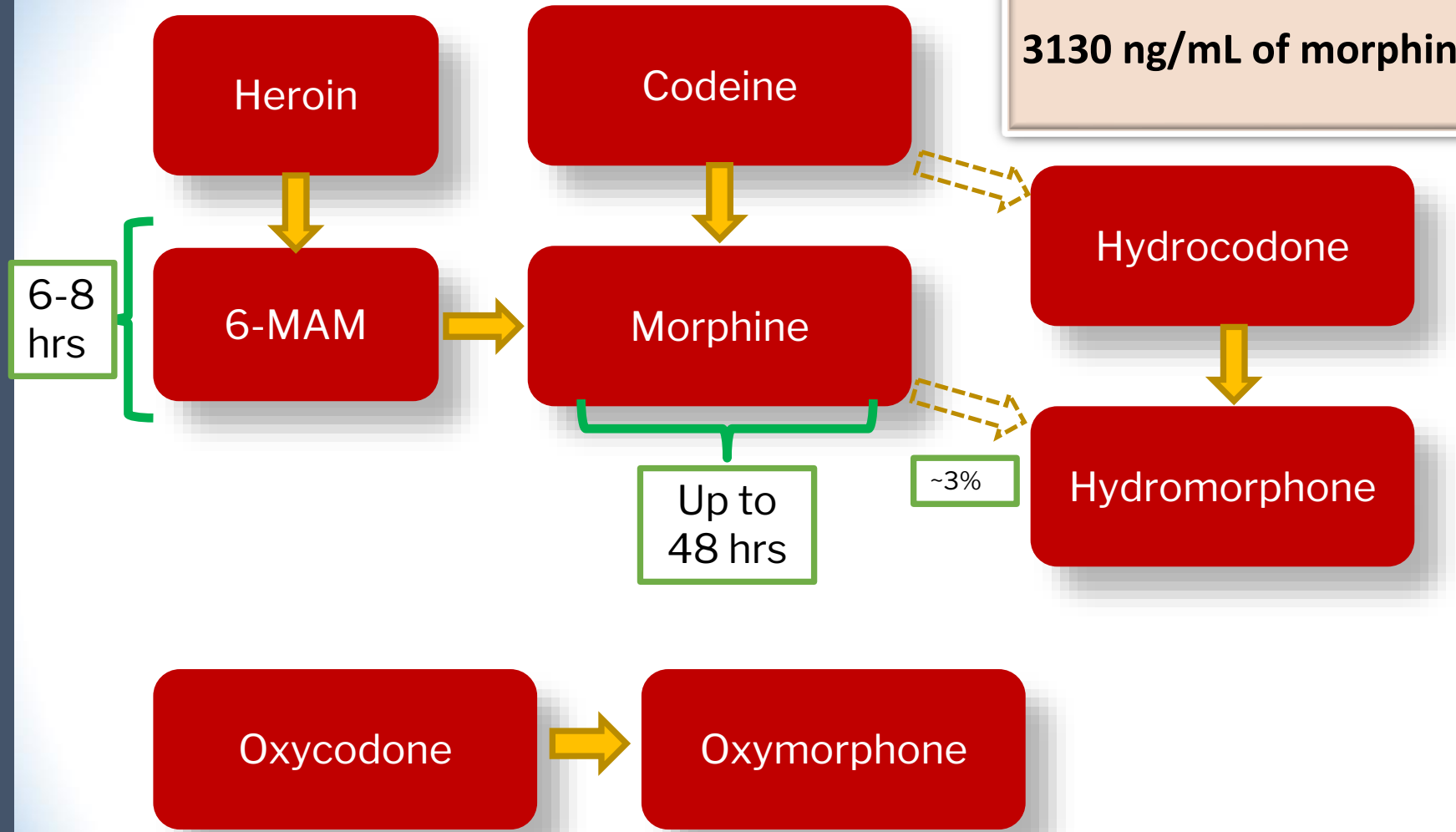
B. 5430 ng/mL of 6-monoacetyl-morphine

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

D. 3130 ng/mL of morphine

ANSWER: D.

3130 ng/mL of morphine

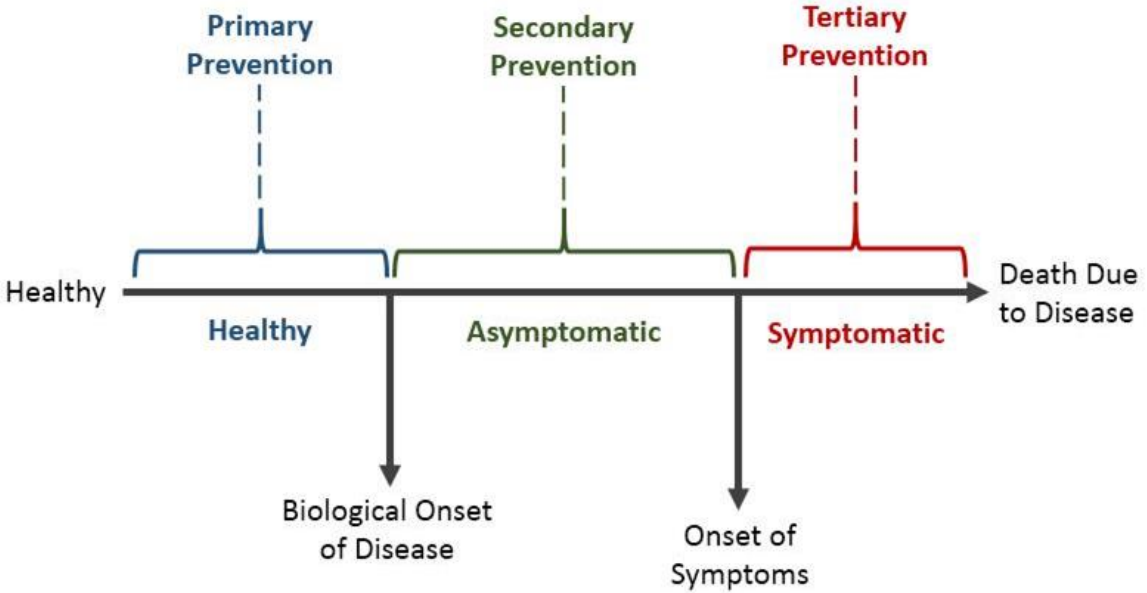


QUESTION 8

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

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

Answer: **D. Universal**



ANSWER: **D. Universal**

	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 9

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

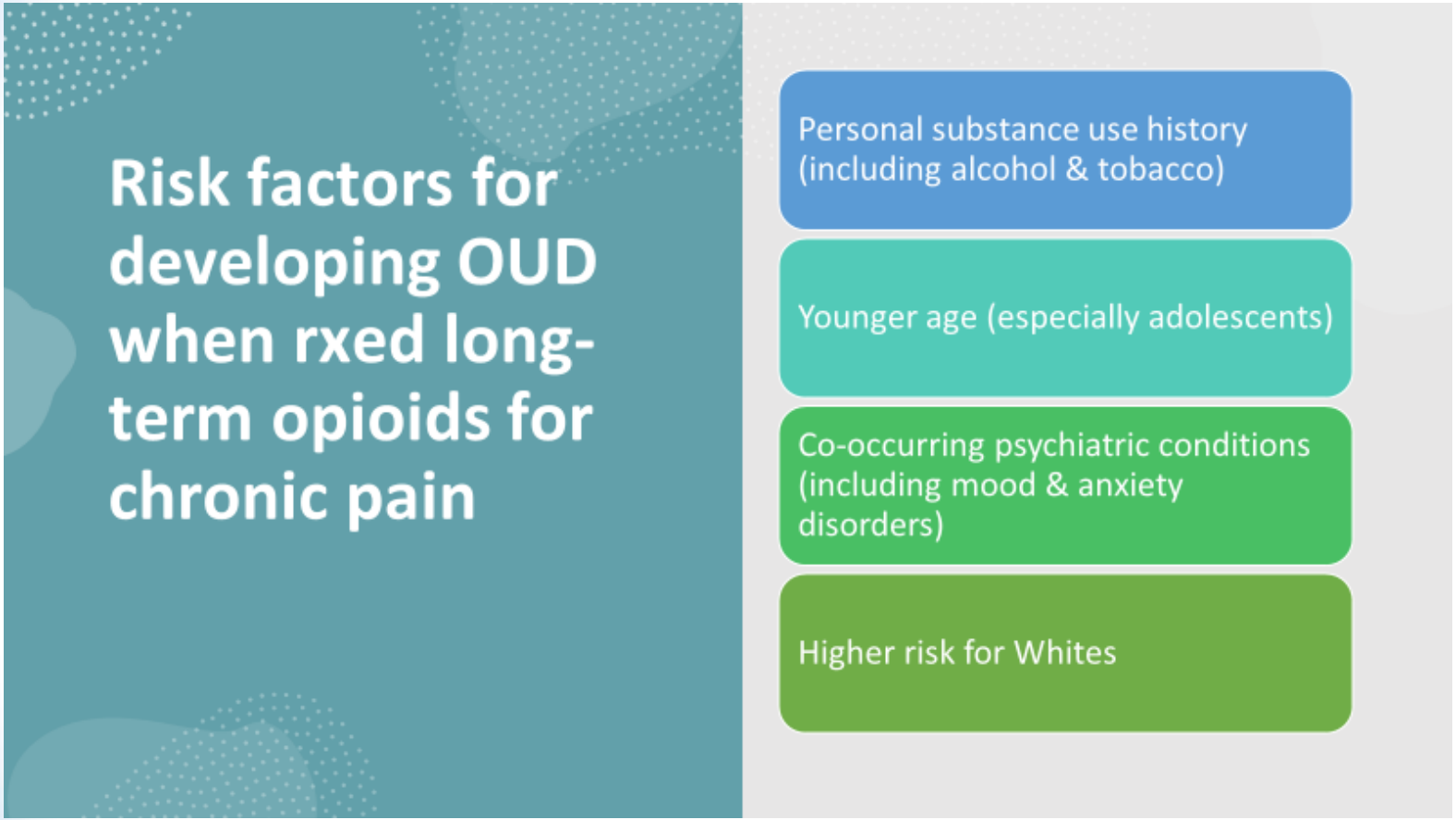
A. Adolescence

B. African-American race

C. Major depressive disorder

D. Tobacco use

Answer: B- African- American race

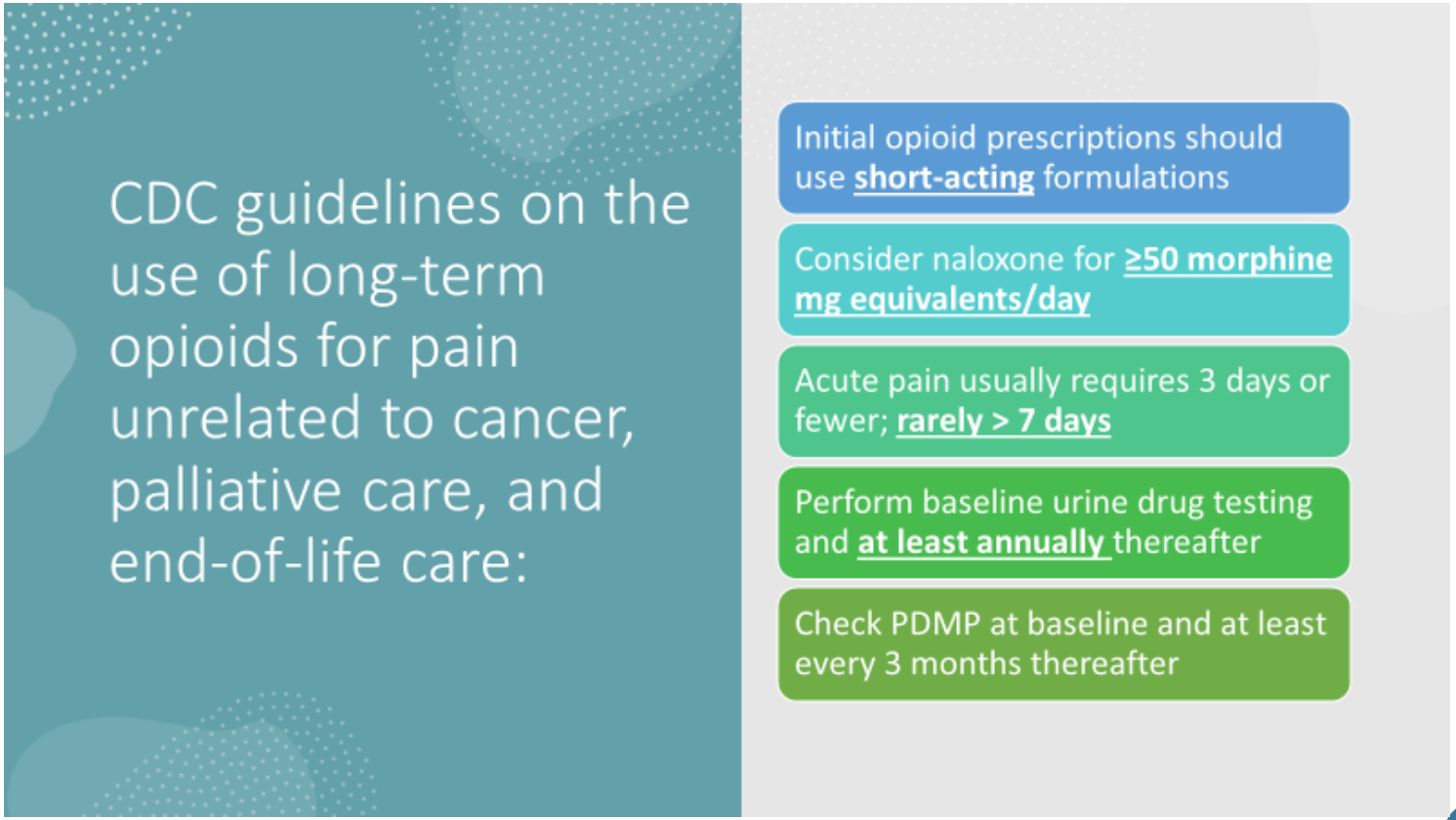


QUESTION 10

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

ANSWER: **B. Consider prescribing naloxone when opioid doses reach 50 morphine milligram equivalents or more**



QUESTION 11

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 of how to manage his perioperative pain?

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

ANSWER:
B. Continue buprenorphine and treat postoperative pain with multimodal analgesia

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
- Complete lack of analgesia has been reported in first 2 weeks on XR-NTX; better on 4th week

ANSWER: **B. Continue buprenorphine and treat postoperative pain with multimodal analgesia**

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

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

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