PCSS Medications for Opioid Use Disorders

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Methadone and Buprenorphine-Associated Drug-Drug Interactions

Theddeus Iheanacho, MD

Associate Professor of Psychiatry, Yale University

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- PCSS-MOUD aims to increase the knowledge and skills of healthcare and counseling professionals about available evidence-based treatment approaches for substance use disorder (SUD) with a particular focus on opioid use disorder (OUD). PCSS-MOUD provides free training and mentoring to practitioners on the use of medications for OUD (MOUD) and the integration of these services into mainstream health care.

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Presenter(s)

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Dr. Iheanacho is Associate Professor of Psychiatry at Yale University, and board certified in general adult psychiatry and addiction psychiatry. His research, academic, and clinical work focus on increasing access to evidence-based addiction and mental health interventions for underserved populations and in resource limited settings.

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All speakers have been advised that any recommendations involving clinical medicine must be based on evidence that is accepted within the profession of medicine as adequate justification for their indications and contraindications in patient care. All scientific research referred to, reported, or used in the presentation must conform to the generally accepted standards of experimental design, data collection, and analysis.

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Educational Objectives

At the conclusion of this activity participants should be able to:

1	Identify major clinically relevant drug-drug interactions between opioids and other medications
2	Review possible explanations for drug-drug interactions
3	Explain the physiological and pharmacokinetic mechanisms underlying adverse drug interactions
4	Develop strategies for reducing risk of drug-drug interactions within the clinical setting

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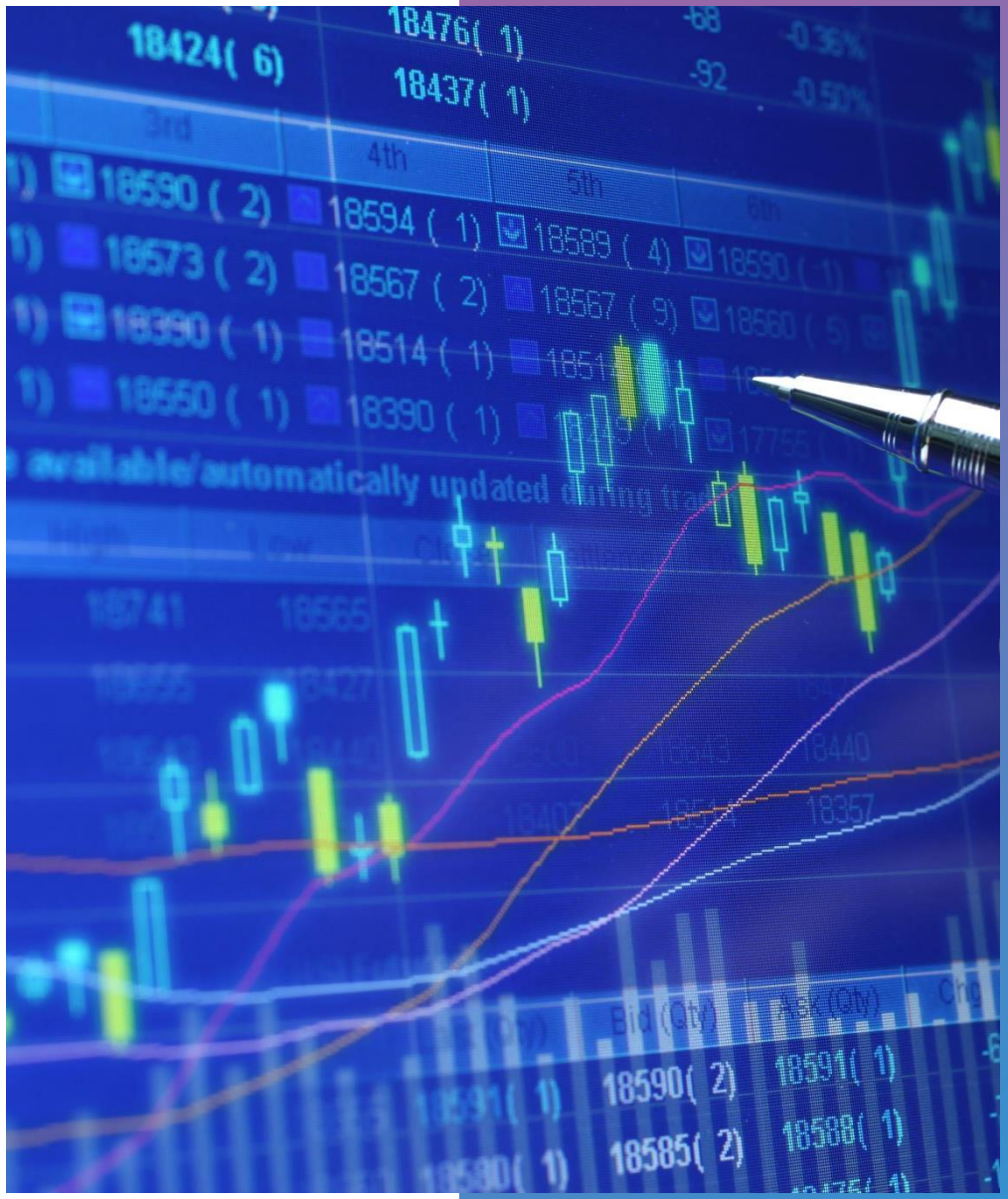
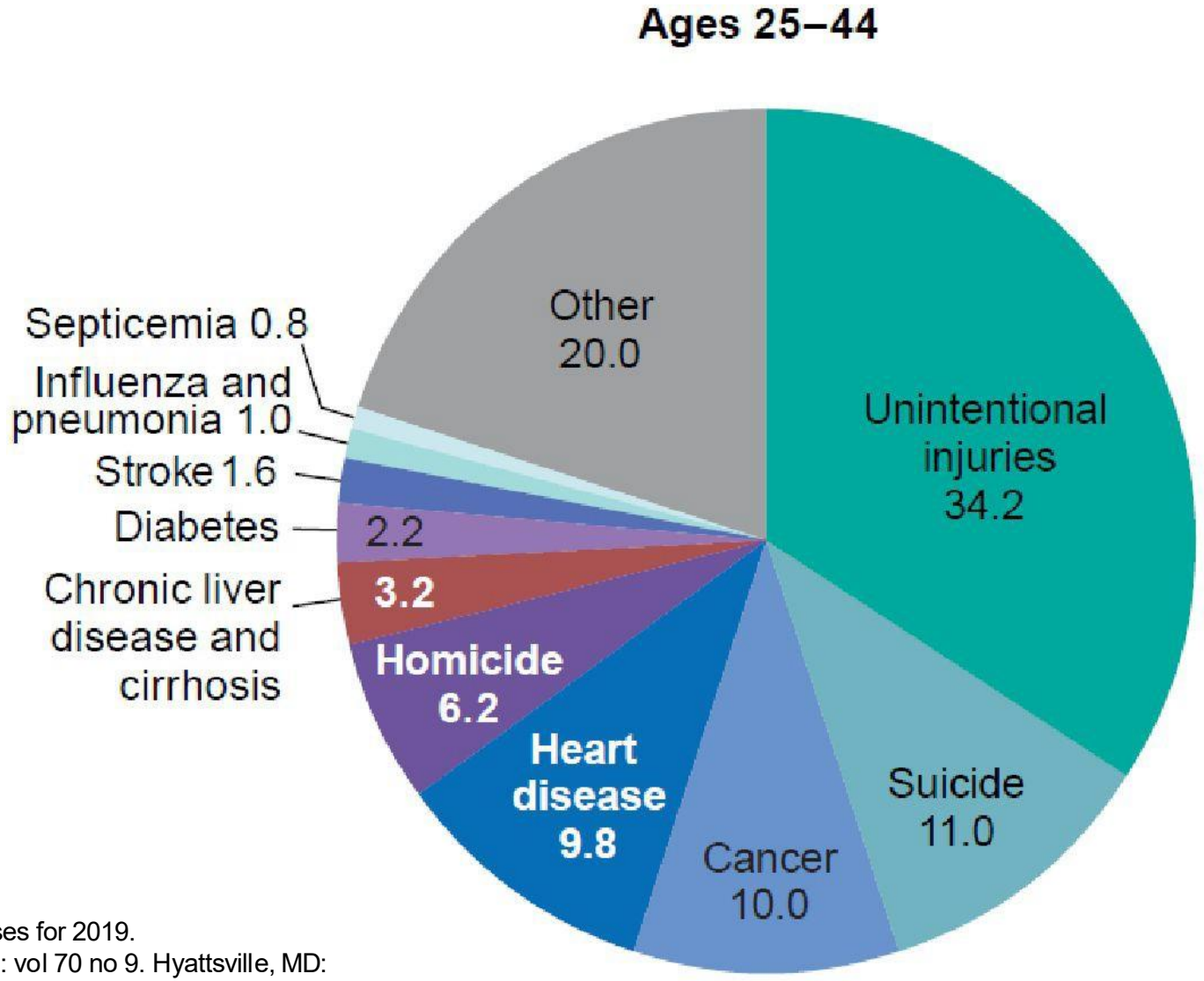
1

Opioid Overdose Trends

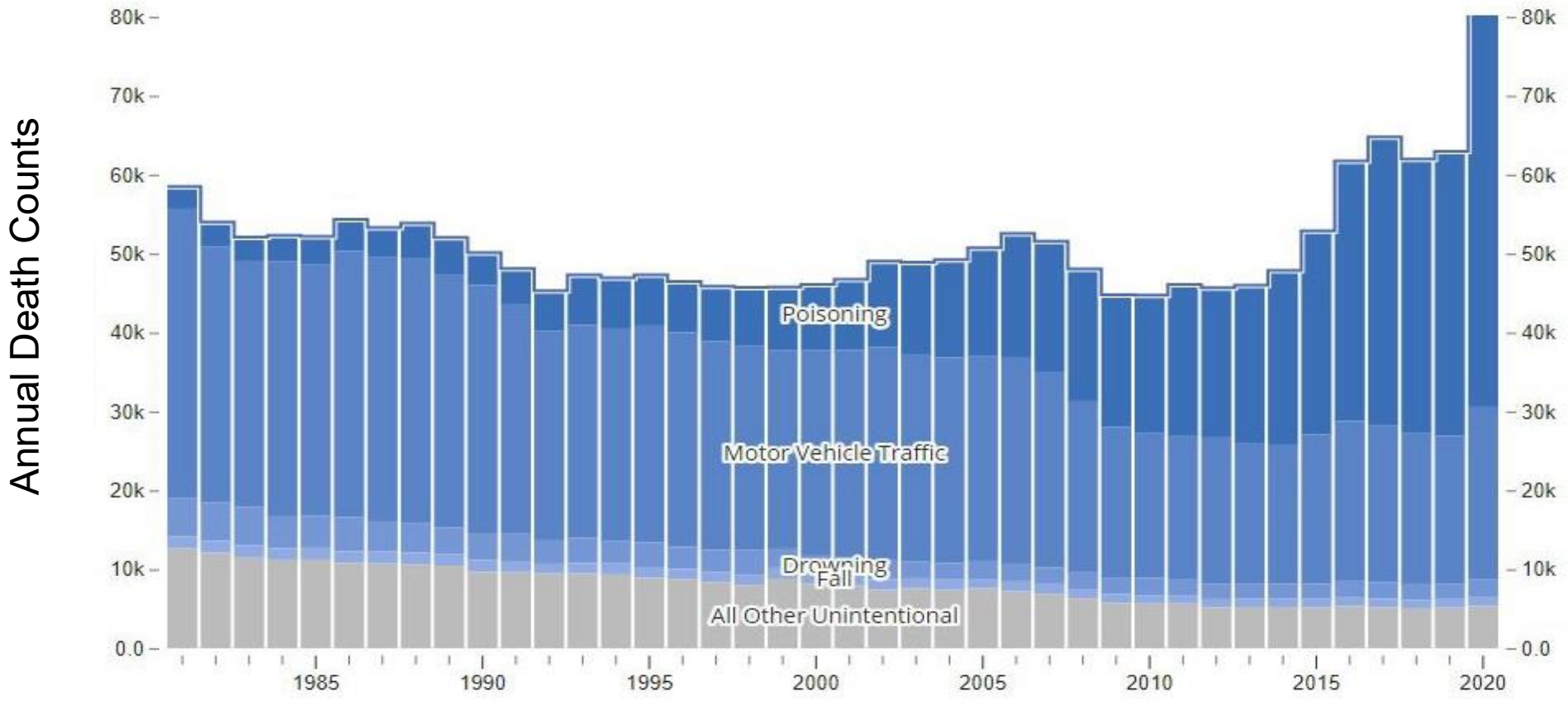


Leading Causes of Death



Heron M. Deaths: Leading causes for 2019.
National Vital Statistics Reports: vol 70 no 9. Hyattsville, MD:
National Center for Health Statistics, 2021

Subtypes of Unintentional Injuries



Overdose (poisoning) has overtaken motor vehicle accidents as cause of mortality

WISQARS Fatal Injury Data come from the National Vital Statistics System multiple-cause-of-death database 2023

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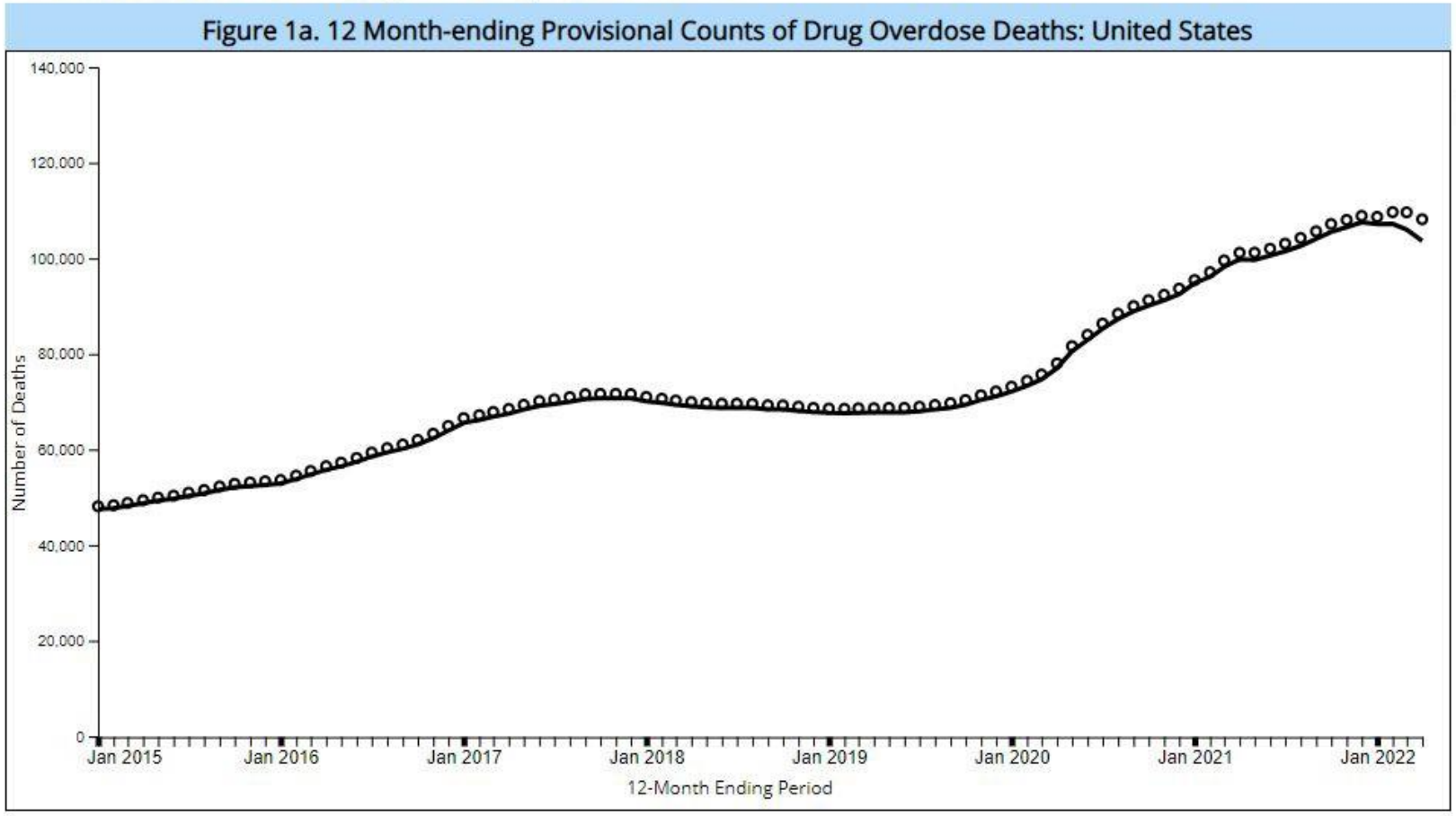
Drug Poisoning Deaths - U.S.

Based on data available for analysis on: September 04, 2022



Ahmad FB, Cisewski JA, Rossen LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. 2022.

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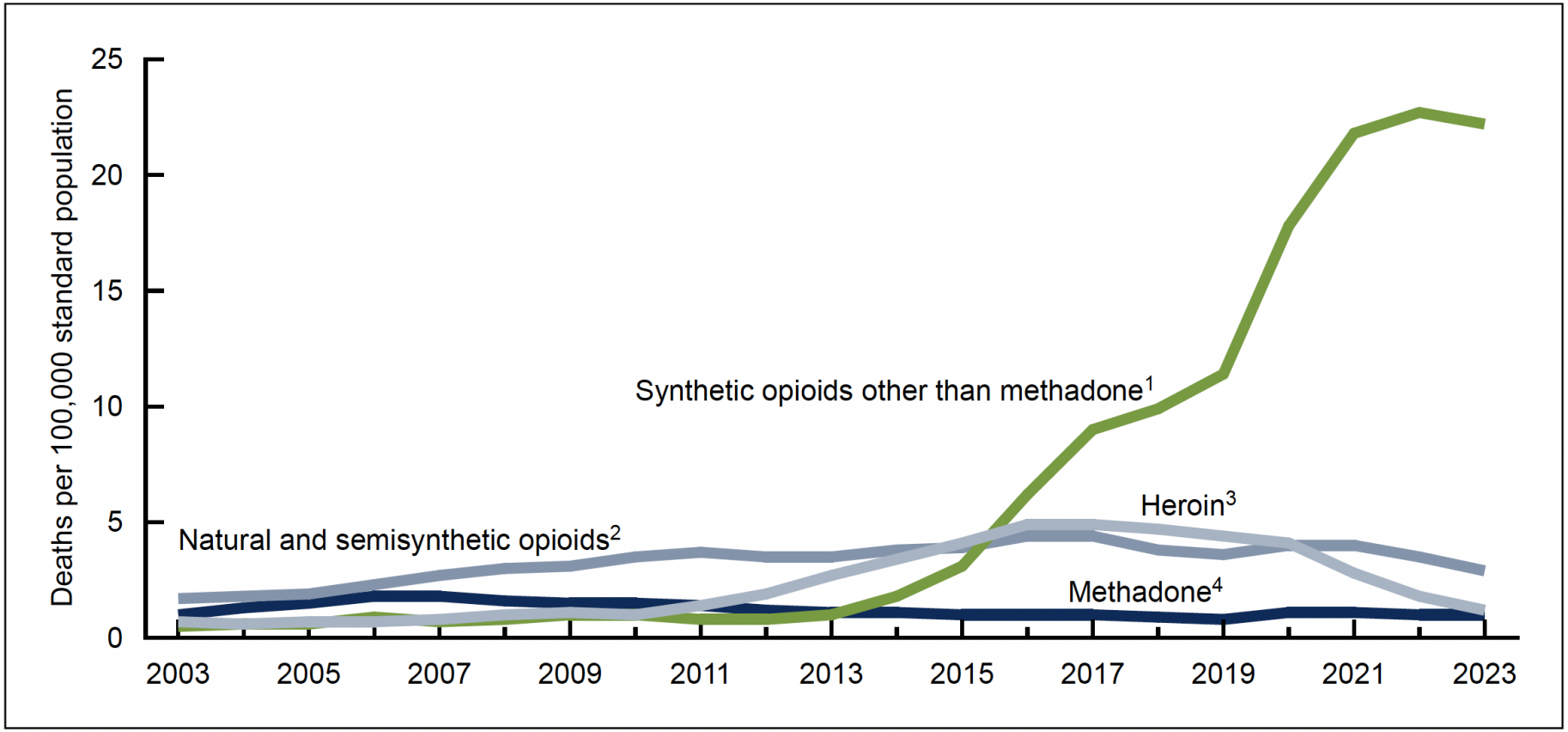
Subtypes of Opioid Overdose Deaths

Figure 4. Age-adjusted rate of drug overdose deaths involving opioids, by type of opioid: United States, 2003–2023



Synthetic opioids are the leading cause of opioid-related deaths

Spencer, M. R., Garnett, M. F., & Miniño, A. M. (2024). Drug overdose deaths in the United States, 2003-2023.

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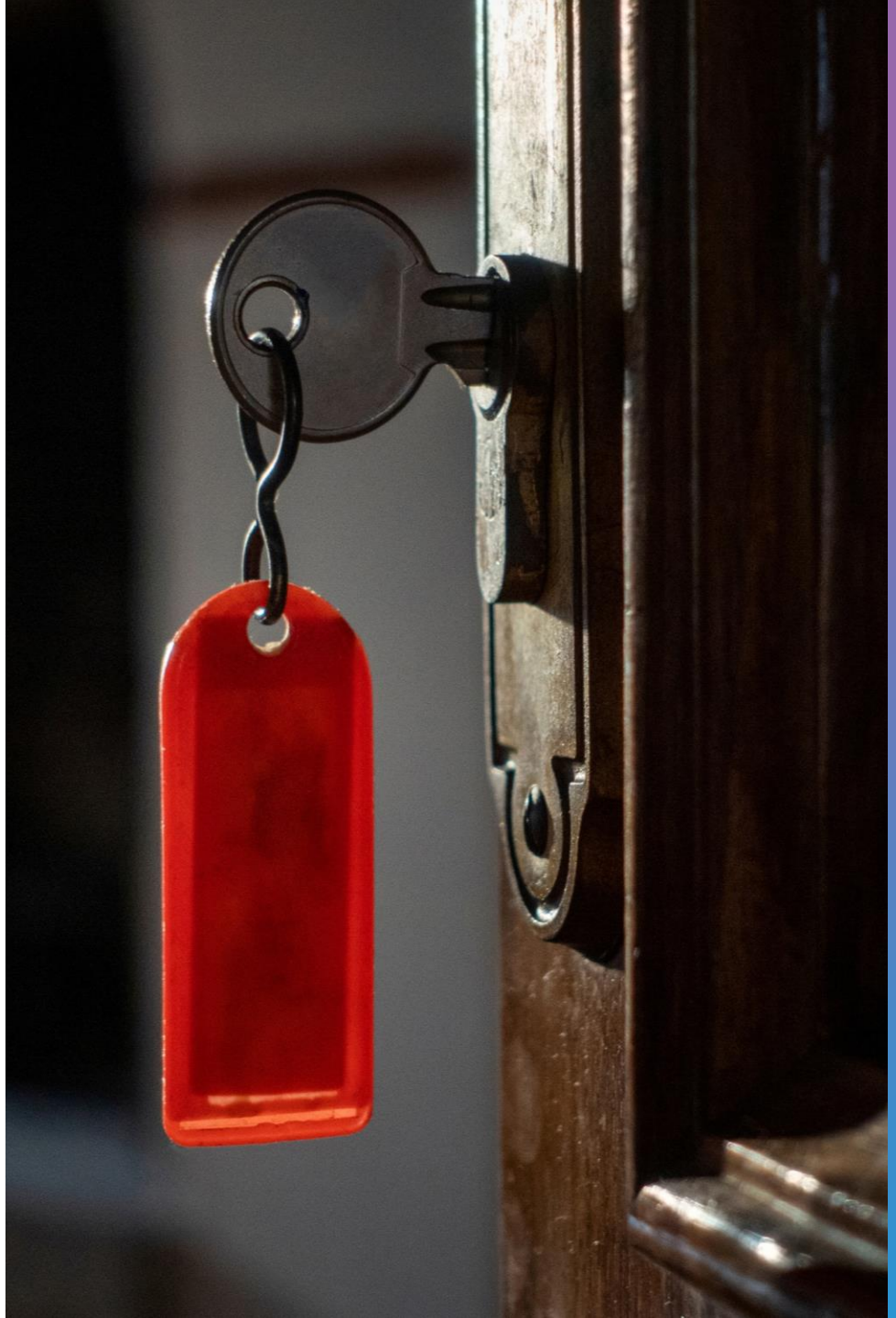
Knowledge Check

Which of the following is a key objective of this training?

A. Increase opioid prescribing rates
B. Identify clinically relevant drug–drug interactions
C. Reduce use of medications for OUD
D. Avoid patient education



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Correct Answer: B

Identify clinically relevant drug–drug interactions

Our focus in this course is understanding and managing potential drug-drug interactions that impact patients.

There is need to increase appropriate utilization of MOUDs and to minimize excess short term opioid prescription.

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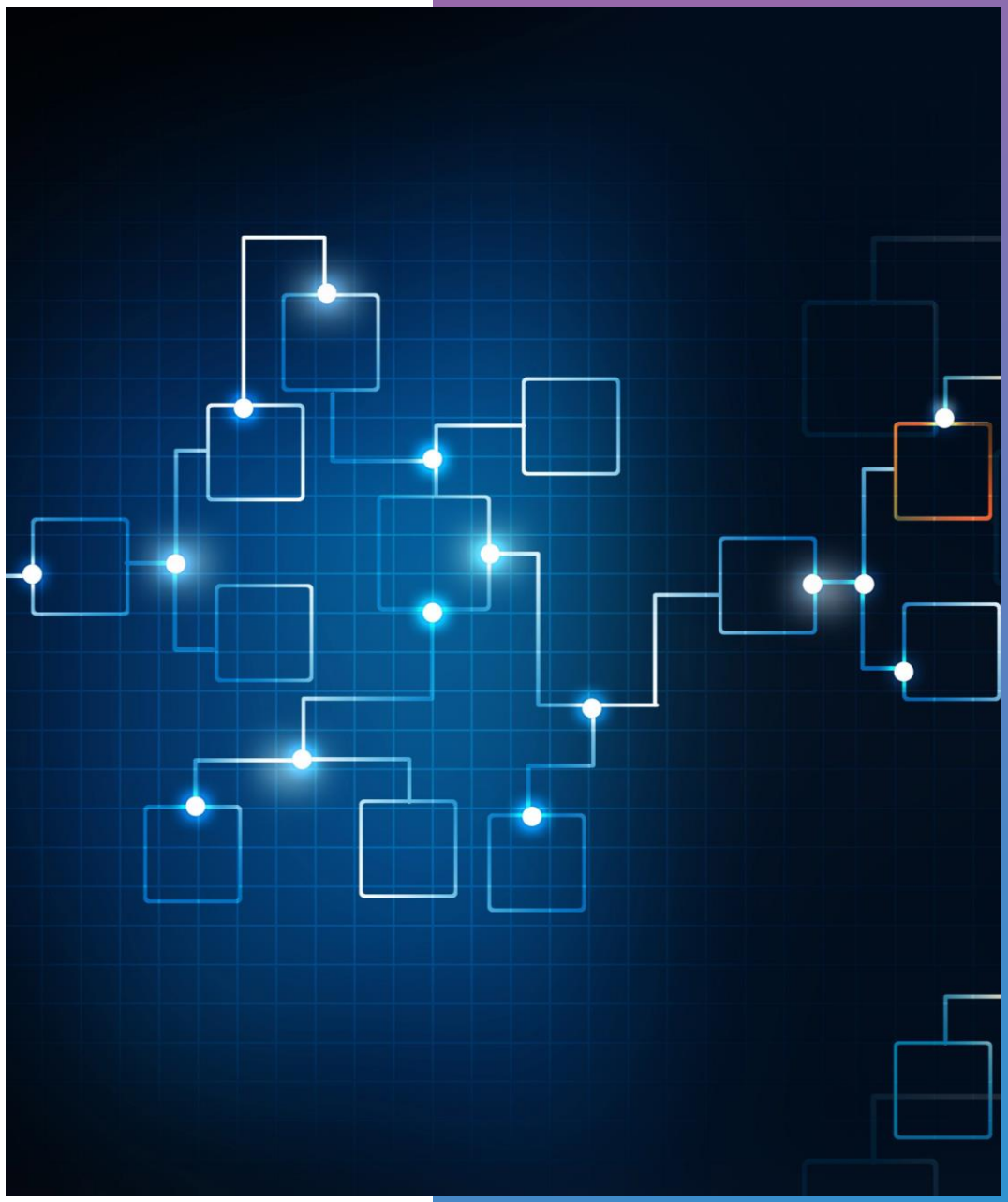
Clinically Relevant

Drug-Drug Interactions

Between opioids and other medications



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Adverse Drug Interactions

Severe (often fatal) adverse drug interactions involving opioids include:

- Overdose (accidental/intentional)
- Combining with other drugs (e.g., fentanyl, heroin, methamphetamines)
- Combining with other prescribed medications (e.g., Methadone, opioid analgesics, benzodiazepines)
- Combining with alcohol

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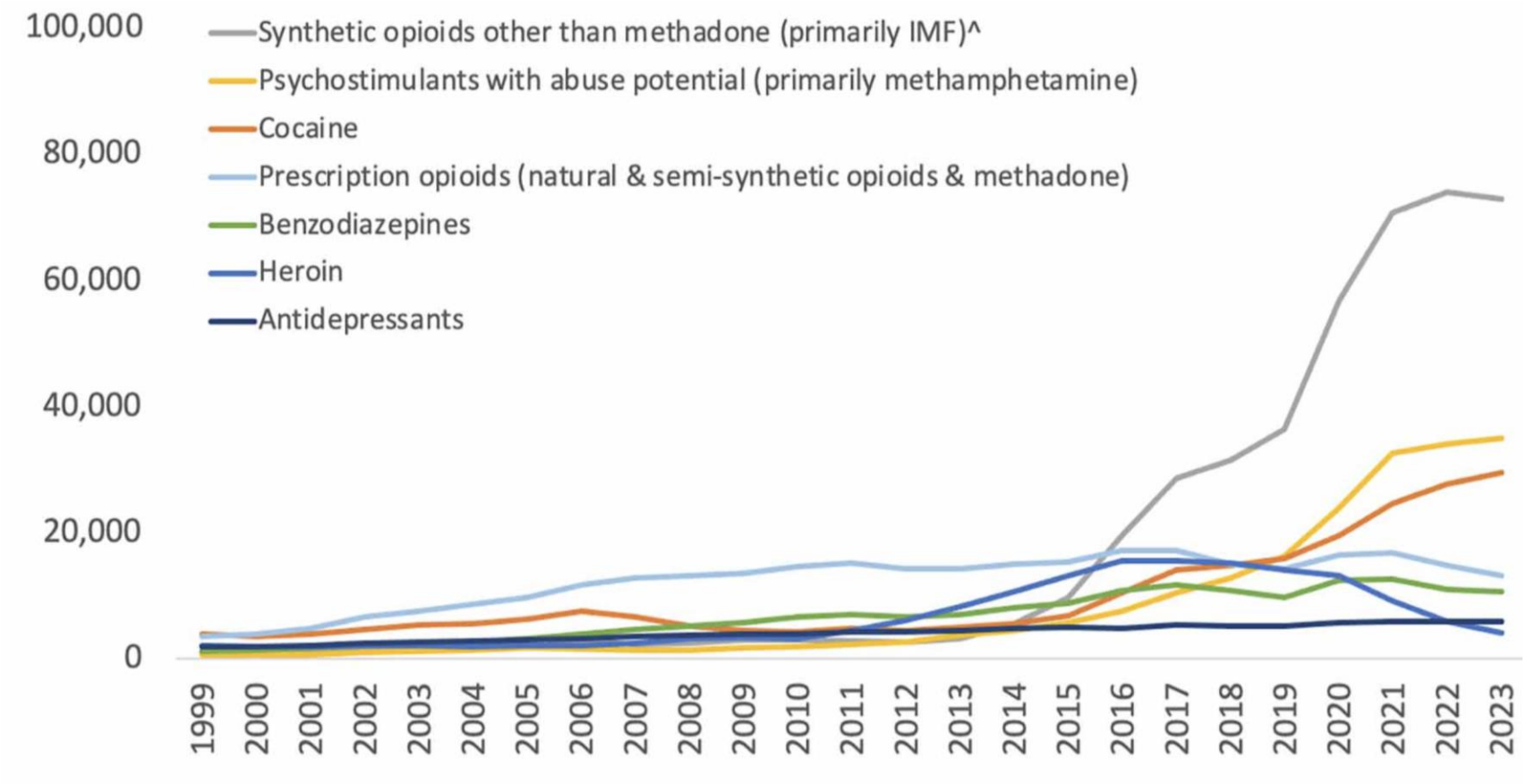
Select Drugs or Drug Categories, 1999-2023



Synthetic opioids are the leading cause of opioid-related deaths

Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2023 on CDC WONDER Online Database, released 1/2025.

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Methadone-Associated Adverse Effects

Semi-Bayes shrunk adjusted rate ratio of adverse effects with methadone	
Precipitant	**Methadone**
Overdose	
Gabapentin	1.41 (1.01–1.95)
Pregabalin	1.87 (1.13–3.10)
Baclofen	2.42 (1.46–3.99)
Diazepam	2.15 (1.27–3.65)
Alprazolam	1.70 (1.07–2.71)
Ondansetron	1.91 (1.12–3.25)
Simvastatin	1.96 (1.07, 3.59)
Temazepam	2.12 (1.06, 4.23)
Quetiapine	1.94 (1.07, 3.50)
Non-overdose adverse drug events	
Lorazepam	2.27 (1.05, 4.91)
Cardiac arrest	
Carvedilol	2.43 (1.11–5.32)

Miano, T. A., Wang, L., Leonard, C. E., Brensinger, C. M., Acton, E. K., Dawwas, G. K., ... & Hennessy, S. (2022).

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Buprenorphine-Associated Adverse Effects

Semi-Bayes shrunk adjusted rate ratio	
Precipitant	**Buprenorphine**
Overdose	
Gabapentin	2.17 (1.09–4.31)
Clonidine	2.32 (1.06–5.07)
Acetaminophen	1.96 (1.06, 3.60)
Oxycodone	1.94 (1.02–3.67)
Morphine	3.18 (1.03, 9.77)
Non-overdose adverse drug events	
None	–
Cardiac arrest	
None	–

Miano, T. A., Wang, L., Leonard, C. E., Brensinger, C. M., Acton, E. K., Dawwas, G. K., ... & Hennessy, S. (2022).

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Reasons for Multiple Medications


Legacy patients continue to receive opioid analgesics for pain


Many with pain have co-occurring medical and/or mental disorders


Patients believe prescribed drugs are ‘safe’


Lack of awareness about adverse events that can occur with multiple medications


May not understand need to take as prescribed (time of day, frequency, quantity)


Sharing medications with other patients or selling/buying to/from other patients

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Knowledge Check

Which combination increases overdose risk?

A. Opioids + Benzodiazepines
B. Opioids + Antihistamines (non-sedating)
C. Buprenorphine alone
D. Methadone with monitoring

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Correct Answer: A

Opioids + Benzodiazepines

Opioids and Benzodiazepines can both depress the respiratory system, so using them in combination can pose higher risk of overdose death.

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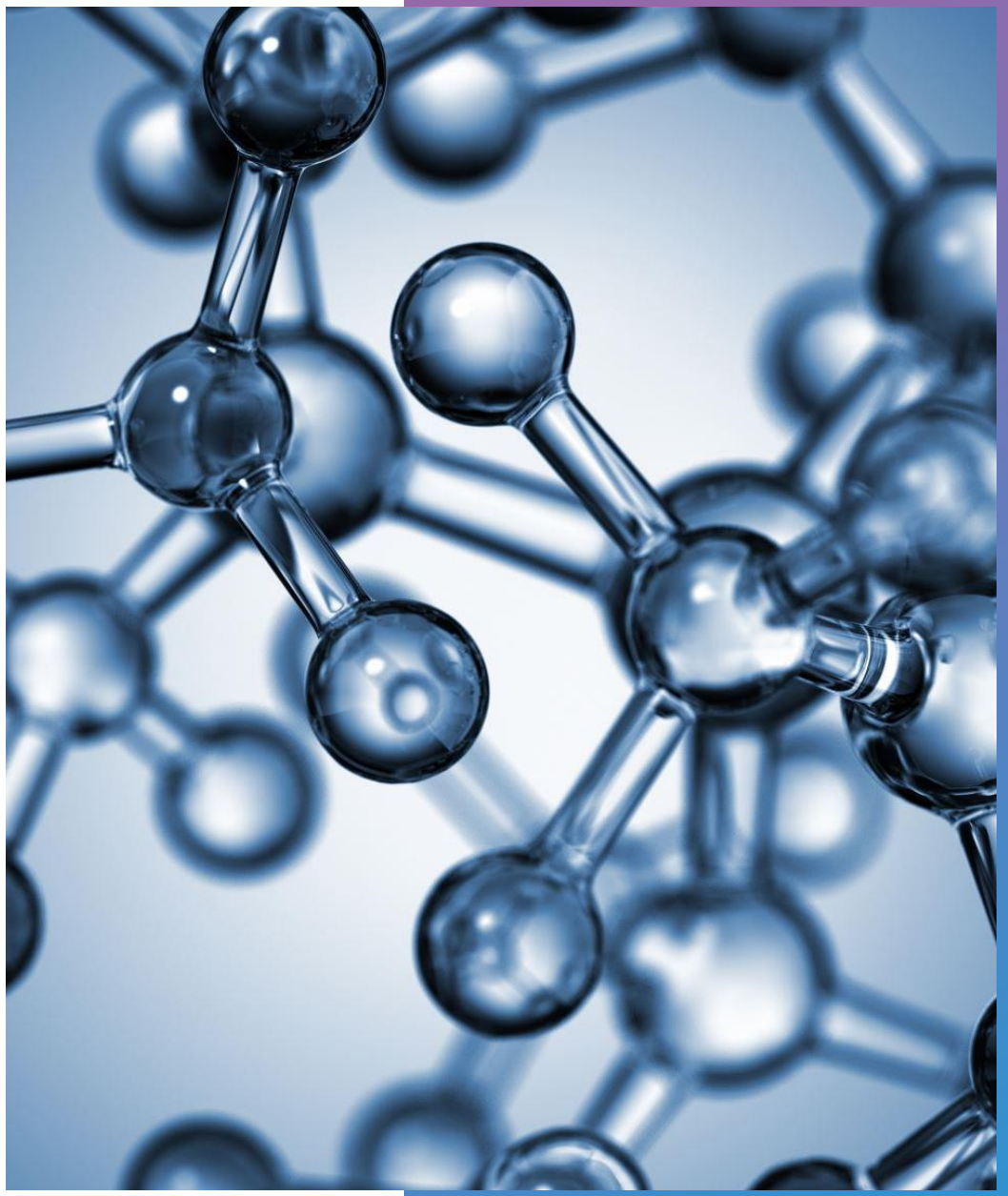
3

The Basis

for Adverse Drug Interactions

Physiological and pharmacokinetic



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Pathophysiology of Drug-Drug Interactions

Pharmacokinetic

What the body does to the drug (or not)

Pharmacodynamic

What the drug or drugs do to the body

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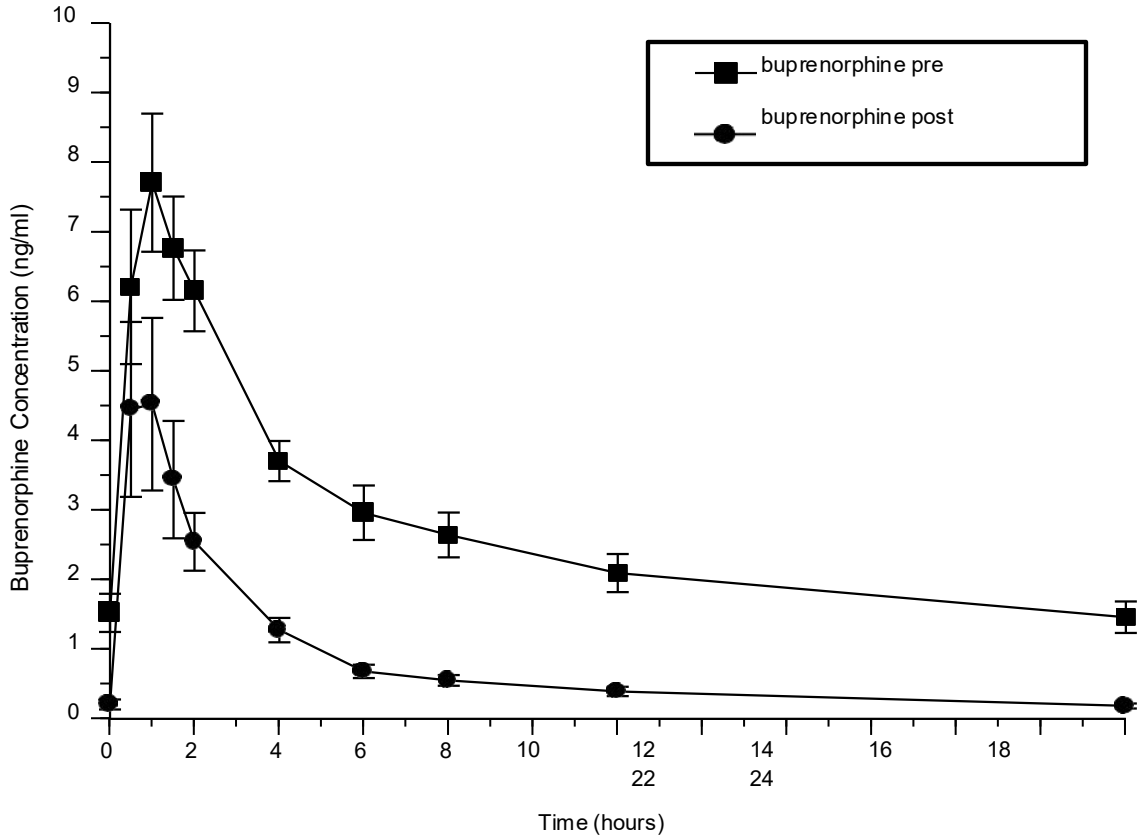
Pharmacokinetic Interactions

- Drug (in presence of other drugs)
  - May be better absorbed (e.g., slowed GI motility)
  - Altered efflux (P-glycoprotein effects)
- Inhibition or induction of metabolism; CYP enzymes or glucuronidation effects
- Net increase in exposure to drug(s) or reduction to the point of inducing physical withdrawal, including:
  - Ciprofloxacin inhibition of methadone metabolism
  - Rifampin induction of buprenorphine metabolism



Hagelberg, Nora M., et al. "Rifampicin decreases exposure to sublingual buprenorphine in healthy subjects." *Pharmacology Research & Perspectives* 4.6 (2016)

Alinejad, S., Kazemi, T., Zamani, N., Hoffman, R. S., & Mehrpour, O. (2015). A systematic review of the cardiotoxicity of methadone

Pharmacodynamic Interactions

- PK interactions may have associated pharmacodynamic consequences
- Pharmacodynamic interactions can occur in the absence of a PK interaction
- Two drugs with similar pharmacological characteristics interact synergistically
- Increases potential toxicity of drug
- Opioids and benzodiazepines (e.g., alprazolam with methadone)
- Opioids and alcohol

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Knowledge Check

Pharmacokinetic interactions refer to:

A. What drugs do to receptors
B. What the body does to a drug
C. Patient beliefs about medications
D. Only behavioral effects

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Correct Answer: B

What the body does to the drug

Pharmacokinetics is what the body does to the drugs.

Drug effects on the body is **pharmacodynamics**

Opioids and Other Drugs: Basis of Adverse Events

- Methadone metabolized by CYP 3A4, 2D6, 2B6, 2C9/10 buprenorphine metabolized by mainly 3A4
- Some SSRIs and some antipsychotics can inhibit metabolic enzymes
- May lead to increased plasma concentrations of drugs and associated toxicities
  - Fluoxetine and fluvoxamine inhibit both 3A4 and 2D6
  - Paroxetine, sertraline, citalopram, and escitalopram only inhibit CYP2D6

Opioids and Other Drugs: Basis of Adverse Events

- Methadone linked to blockade of hERG potassium channels that has been reported to increase risk for arrhythmia (Torsade de Pointes)
- As methadone concentrations rise, risk of adverse events increases
- High dose (> 100 mg/d methadone)
- Drug interactions that increase methadone exposure through inhibition of methadone metabolism
- Drug interactions that occur when an inducing drug is given; methadone dose increased to maintain efficacy; then the drug is withdrawn and methadone was not concomitantly reduced

Avoiding Adverse Interactions

- Think about **metabolic interactions**
- Provide clear **psychoeducation to patients/families** about potential toxicities: cognitive impairment, increased sedation, slowed, loud breathing
- If concomitant medications are needed, **try to use medications less likely to impair opioid metabolism**
  - Methadone: venlafaxine, SSRIs excluding fluoxetine/fluvoxamine
  - Buprenorphine: mainly 3A4 substrate; avoid fluoxetine/fluvoxamine
- **Buprenorphine may be preferable to methadone** in those needing other medications because there are fewer expected interactions, adverse events, or overdoses

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Potential Methadone Drug-Drug Interactions

Class or Specific Drug	Interaction	Putative Mechanism	Notes
Antiretrovirals			
Efavirenz, Lopinavir, Nevirapine **Elvitegravir**	Reduction in serum methadone levels	Induction of CYP 450 3A4 Induction of CYP 450 2C9/10 (Elvitegravir)	Clinically significant opioid withdrawal symptoms likely
Abacavir, Etravirine, Nelfinavir **Squinavir** **Tipranavir**	May reduce serum methadone levels	Induction of CYP 450 3A4	Clinically pertinent opioid withdrawal symptoms usually not seen with these agents
Didanosine, Stavudine	Reduction in didanosine, stavudine plasma concentration	Decreased bioavailability	Possible decreased efficacy of didanosine, stavudine
Zidovudine	Increase in zidovudine plasma concentration	Unknown	Risk of zidovudine toxicity
Delavirdine	Increased methadone serum concentration	Inhibition of CYP 450 3A4	No clinically meaningful adverse events

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Potential Methadone Drug-Drug Interactions

Class or Specific Drug	Interaction	Putative Mechanism	Notes
Antiretrovirals			
Darunavir	Increased methadone serum concentration	Inhibition of CYP 450 3A4	Clinical impact uncertain. Monitor closely.
Rilpiravine, Maraviroc	Potential risk of Torsade de Pointes (cardiac arrhythmia)	QT Prolongation	Could be additive with methadone; monitor closely
Antivirals			
Nirmatrelvir/ Ritonovir (Paxlovid)	Possible decreased methadone serum concentration	Ritonovir inhibits CYP 450 3A4 but induces CYP 450 2B6. Nirmatrelivir substrate of 3A4, uncertain if inducer or inhibitor	Clinically significant opioid withdrawal symptoms possible

Potential Methadone Drug-Drug Interactions

Class or Specific Drug	Interaction	Putative Mechanism	Notes
Antidepressants			
Tricyclics: **amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine**	Increases risk for constipation and sedation. Increases risk for QT prolongation and arrhythmia	Anticholinergic effects. Blockade of hERG channel.	Clinical experience with combination indicates it is generally safe with careful clinical monitoring.
Serotonin reuptake inhibitors: **citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline**	May increase serum methadone levels. Increased risk for serotonin syndrome	Inhibition of CYP 450 3A4, 2D6. Blockade of serotonin transporter.	Clinical experience with combination indicates it is generally safe with careful clinical monitoring.

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Potential Methadone Drug-Drug Interactions

Class or Specific Drug	Interaction	Putative Mechanism	Notes
Antidepressants			
Monoamine oxidase inhibitors: Isocarboxazid, phenelzine, selegiline, tranylcypromine	Increased risk for serotonin syndrome.	Inhibition of serotonin metabolism.	Use with extreme caution and careful clinical monitoring.
Serotonin/ norepinephrine reuptake inhibitors: Duloxetine, desvenlafaxine, venlafaxine	Increased risk for serotonin syndrome. Increases risk for QT prolongation and arrhythmia (venlafaxine)	Blockade of serotonin transporter. Blockade of hERG channel (venlafaxine).	Clinical experience with combination indicates it is generally safe with careful clinical monitoring.

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Potential Methadone Drug-Drug Interactions

Class or Specific Drug	Interaction	Putative Mechanism	Notes
Antibiotics			
Ciprofloxacin, clarithromycin, erythromycin, azithromycin	May increase methadone serum levels. Increases risk for QT prolongation and arrhythmia	Inhibition of CYP 450 3A4. Blockade of hERG channel	One case report of sedation (ciprofloxacin). Clinical monitoring required.
Rifampin	Reduction serum methadone levels	Induction of CYP 450 3A4	Severe opioid withdrawal can occur. Will need increased methadone dose. Or switch antibiotics (e.g. rifabutine)
Antifungals			
Ketoconazole, fluconazole voriconizole	May increase methadone serum levels.	Inhibition of CYP 450 3A4	Little evidence for important clinical effects

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Potential Methadone Drug-Drug Interactions

Class or Specific Drug	Interaction	Putative Mechanism	Notes
Anticonvulsants			
Carbamazepine, phenytoin	Reduction in serum methadone levels	Induction of CYP 450 3A4	Severe opioid withdrawal can occur. Will need increased methadone dose.
Antiarrthymics			
Procainamide, quinidine	Increases risk for QT prolongation and arrhythmia	Blockade of hERG channel	Careful clinical monitoring required
Amiodarone	May increase methadone serum levels. Increases risk for QT prolongation and arrhythmia	Inhibition of CYP 450 3A4. Blockade of hERG channel	Careful clinical monitoring required

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Potential Methadone Drug-Drug Interactions

Class or Specific Drug	Interaction	Putative Mechanism	Notes
Benzodiazepines	Additive CNS and respiratory depressant effects	Increased GABA activity	Careful clinical monitoring required
Barbiturates	Additive CNS and respiratory depressant effects	Increased GABA activity	Careful clinical monitoring required
Quetiapine	May increase methadone serum levels	Inhibition of CYP 450 2D6	Careful clinical monitoring required
Cimetidine	May increase methadone serum levels.	Inhibition of CYP 450 3A4	No evidence major clinical effect
Naltrexone	Precipitated opioid withdrawal	Displaces methadone from μ-opioid receptors	contraindicated

Potential Methadone Drug-Drug Interactions

Class or Specific Drug	Interaction	Putative Mechanism	Notes
Cannabidiol	May increase serum methadone levels	Cannabidiol inhibits CYP3A4 and CYP2C19	Observe for possible methadone toxicity

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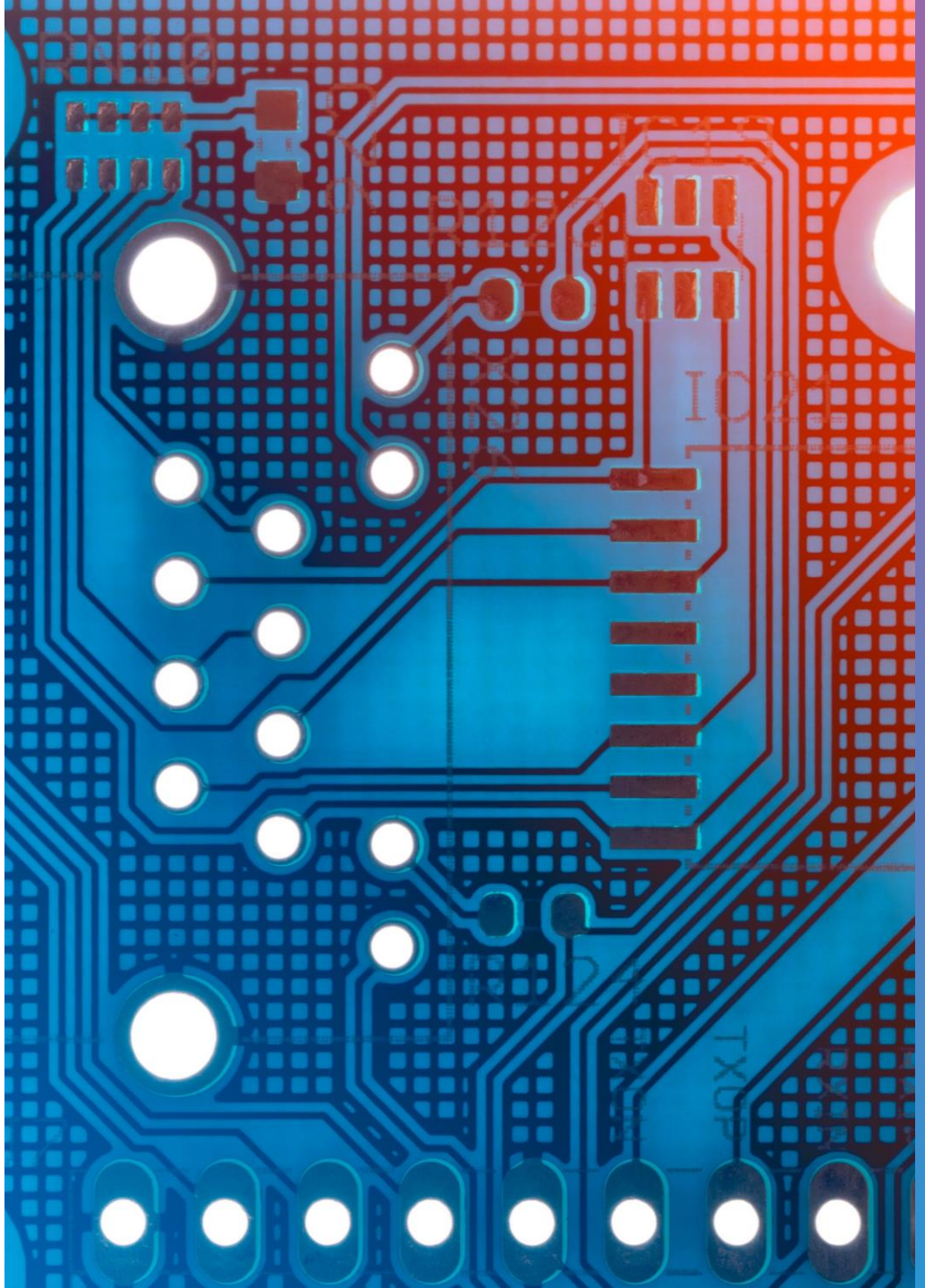
Knowledge Check

Methadone metabolism primarily involves which enzyme system?

A. CYP3A4 and related CYP enzymes
B. Renal filtration only
C. Monoamine oxidase
D. None of the above



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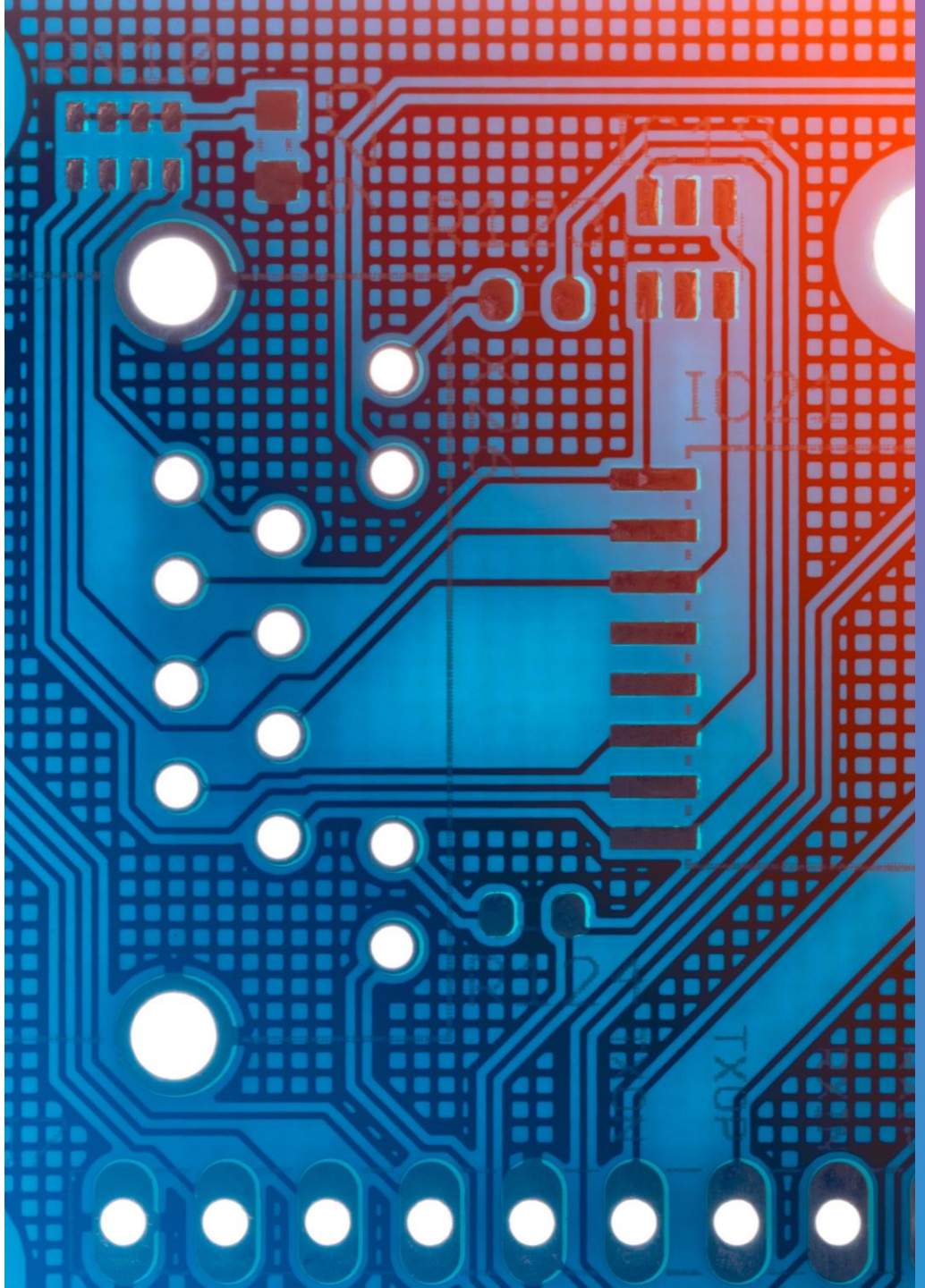
Correct Answer: A

CYP3A4 and related CYP enzymes

The CYP liver enzymes metabolize methadone and many other medications, leading to clinically relevant interactions especially in the present of liver enzymes inducers or inhibitors.



Potential Buprenorphine Drug-Drug Interactions

- Buprenorphine not as susceptible as methadone to drug-drug interactions
  - Tighter binding to receptor may make blood levels less important
  - Has an active metabolite, nor-buprenorphine
  - Partial agonist effect may mitigate some pharmacodynamic interactions, reduce risk from elevated blood levels and thus reduce overdose risk
  - Does not prolong QT interval on ECG

Potential Buprenorphine Drug-Drug Interactions

However, the following interactions are notable (mechanisms similar to those for methadone):

- Delavirdine, Darunavir, Atazanavir
  - Atazanavir does not appear to increase methadone levels
- Rifampin
- Benzodiazepines
- Voriconazole (may increase buprenorphine plasma levels through CYP 450 3A4 inhibition)
- Cannabis (may increase buprenorphine plasma levels through CYP 450 3A4 inhibition)

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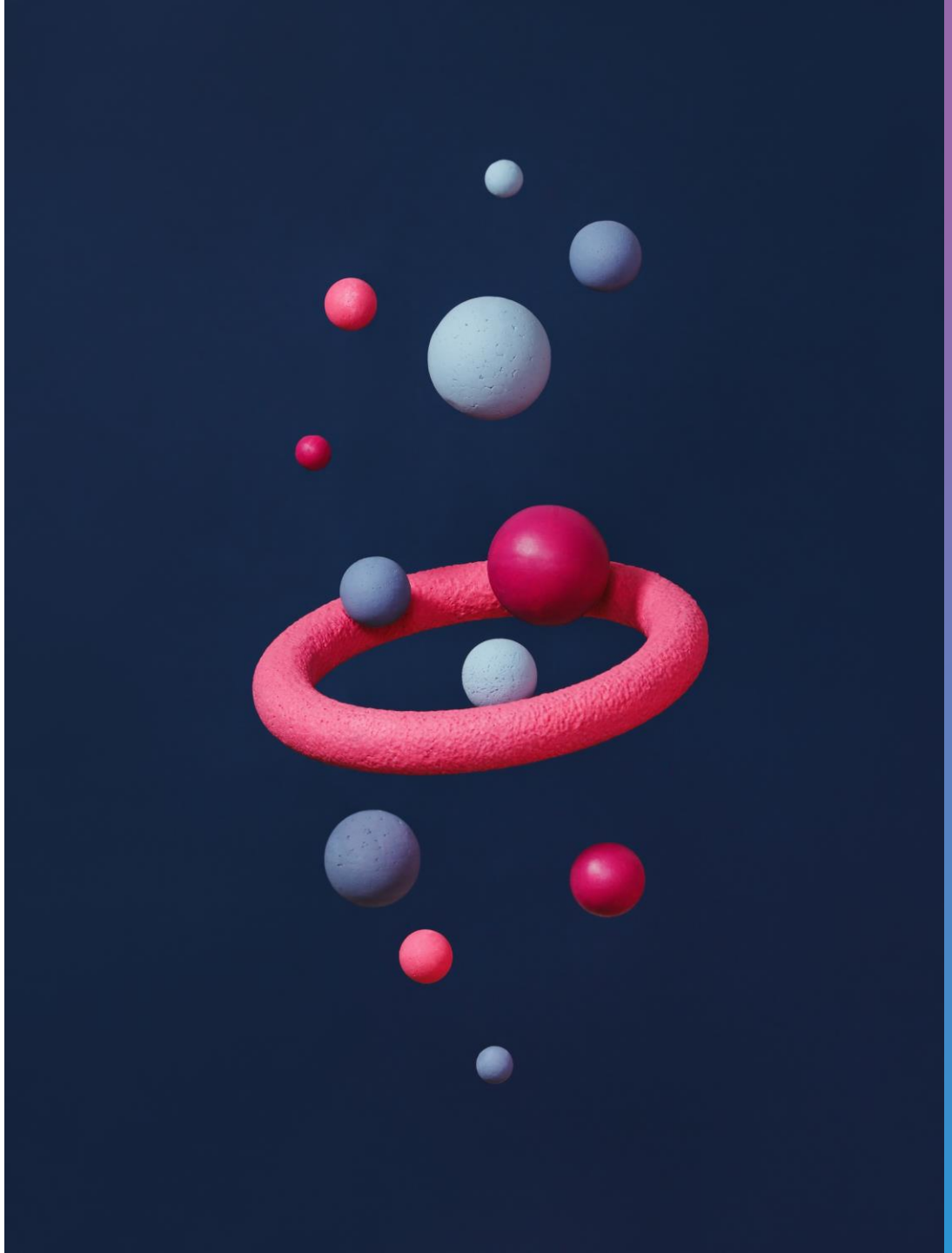
Knowledge Check

Why may buprenorphine have fewer drug–drug interactions?

A. Partial agonist effect
B. Strong receptor binding
C. Less QT prolongation risk
D. All of the above



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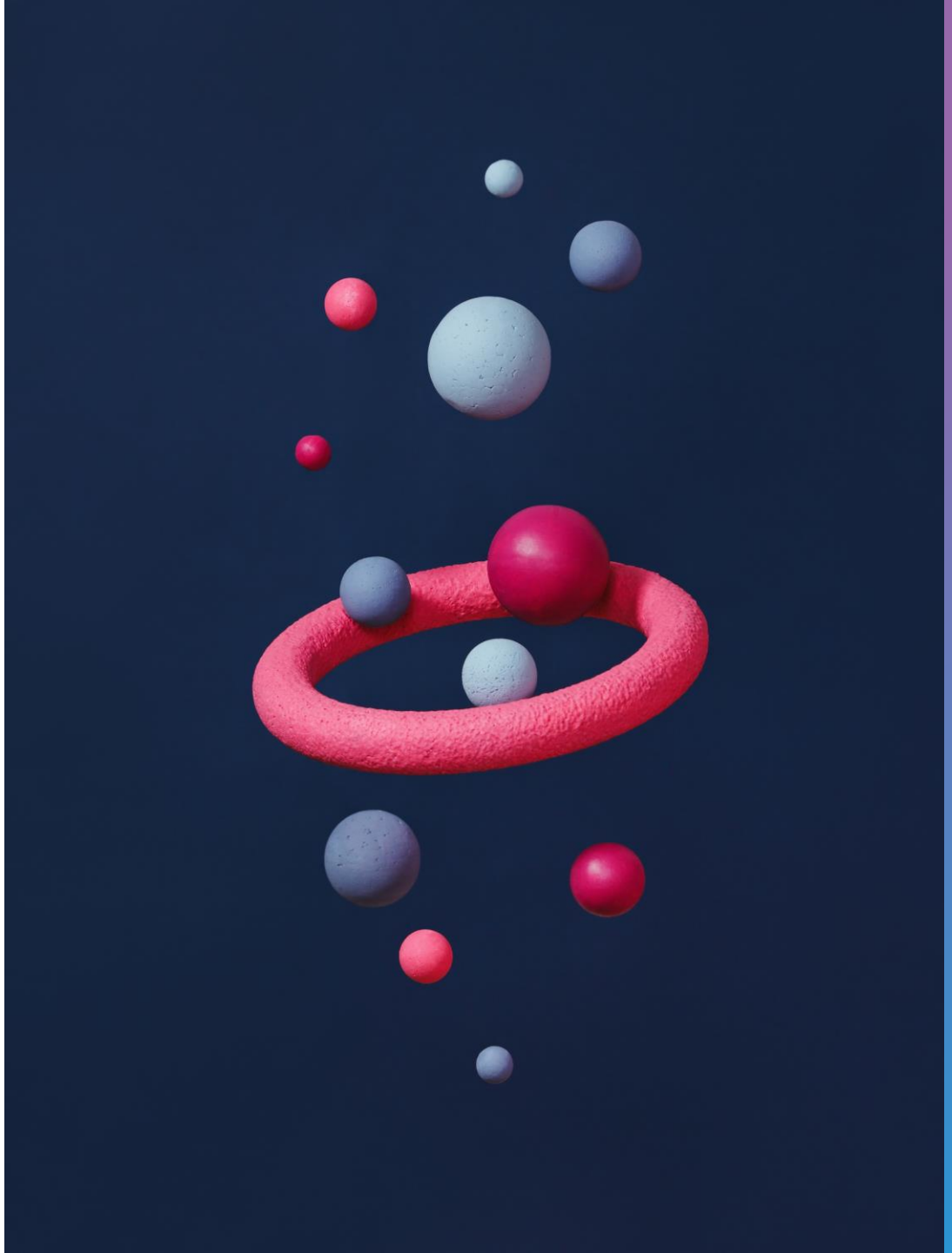
Correct Answer: D

All of the above

All of the listed explanations are characteristics of buprenorphine that reduce the extent of its drug-drug interactions



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Hep C Direct Acting Antivirals

show no clinically meaningful interaction with methadone or buprenorphine

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4

Strategies for Reducing Risk

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Strategies for Reducing Risk of Drug-Drug Interactions

Training Physicians, APRNs, PAs, and Pharmacists

- Non-opioid strategies to effectively control pain
- Safe prescribing practices
- Avoid polypharmacy whenever possible
- Clear communication/ psychoeducation to patients

Public outreach and education

Sharing important information:

- how medications interact, including basic pharmacology of opioids
- not medication sharing
- safely disposing of medications (should be available at no charge to patients!)

Leveraging PCSS-MOUD

- Use of Providers Clinical Support System-Medications for Opioid Use Disorders resources

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Team-Based Strategies to Address Risks Associated with Poly-Pharmacy

Challenges Patients May Experience	Strategies for Nurses and Other Clinicians
Legacy patients continue to receive opioid analgesics for pain	*Complete medication reconciliation at each visit, including over the counter medications*
Many with pain have co-occurring medical and/or mental disorders	*Complete care coordination, obtain collateral info from primary care team/other specialists*
Patients believe prescribed drugs are 'safe'	*Provide brief psychoeducation at each visit, reviewing drug safety profiles*
Lack of awareness about adverse events that can occur with multiple medications	*Provide brief psychoeducation at each visit including common/serious side effects*
Patients may not understand need to take as prescribed	*Review dosing frequency, timing, quantity at each visit*
Sharing medications with other patients or selling to other patients	*Review patient responsibility regarding medication safety, DEA rules/policy and legal implications*

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Knowledge Check

Which strategy helps prevent adverse drug interactions?

A. Polypharmacy when possible
B. Avoid medication reconciliation
C. Provide patient psychoeducation
D. Ignore metabolic pathways

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Correct Answer: C

Provide patient psychoeducation

The other answer options all increase risk of drug adverse effects and interactions.

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Knowledge Check

A patient on methadone starts fluoxetine. What is the concern?

A. Reduced methadone levels
B. Increased methadone levels and toxicity risk
C. No interaction
D. Immediate withdrawal

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Correct Answer: B

Increased methadone levels and toxicity risk

Fluoxetine inhibits CYP3A4 and 2D6, which can lead to increased plasma concentration of methadone and a risk of toxicity.

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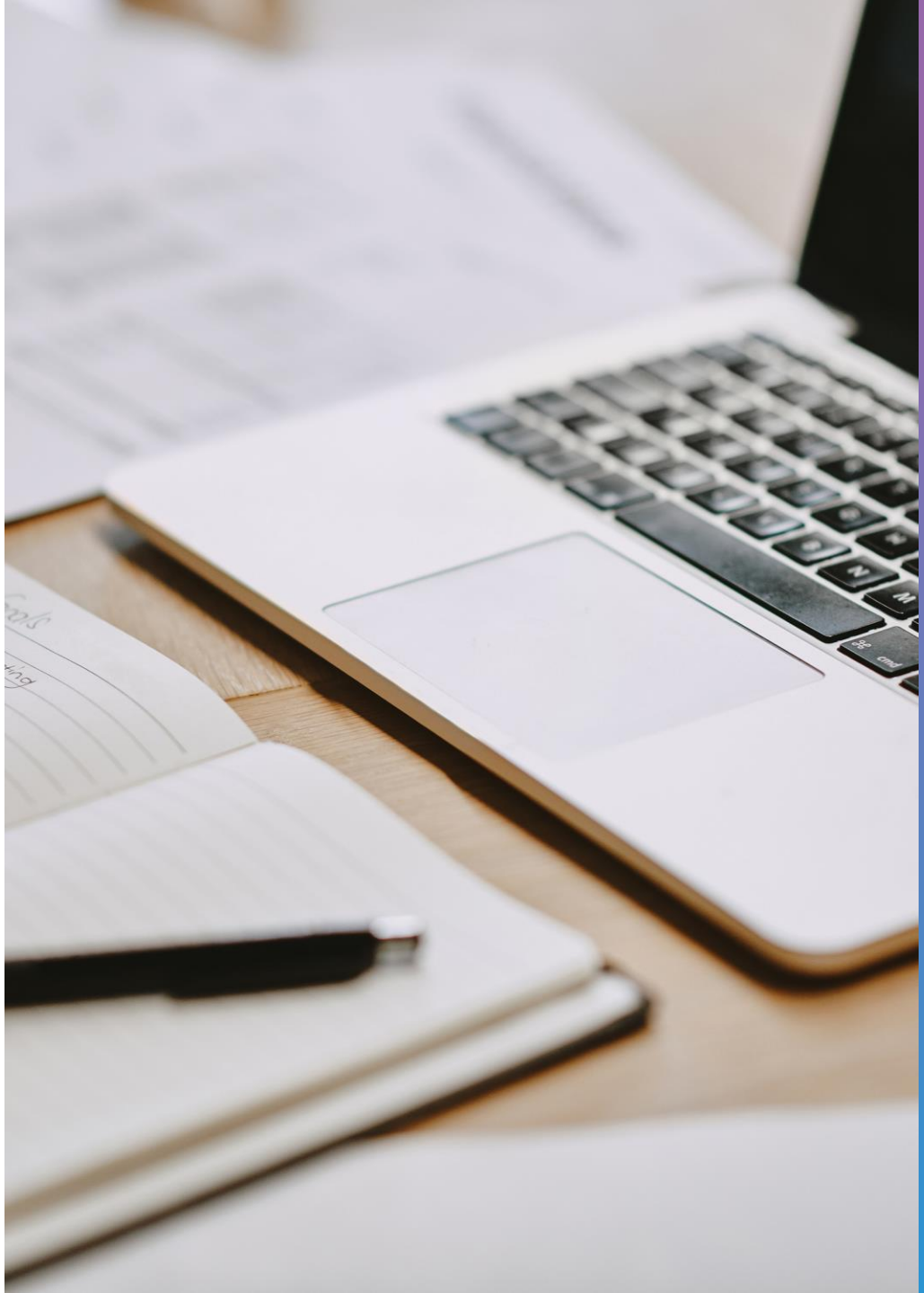
Knowledge Check

Best clinical approach when prescribing MOUD with other drugs:

A. Ignore interactions
B. Monitor, educate, and coordinate care
C. Stop all medications
D. Avoid follow-up visits



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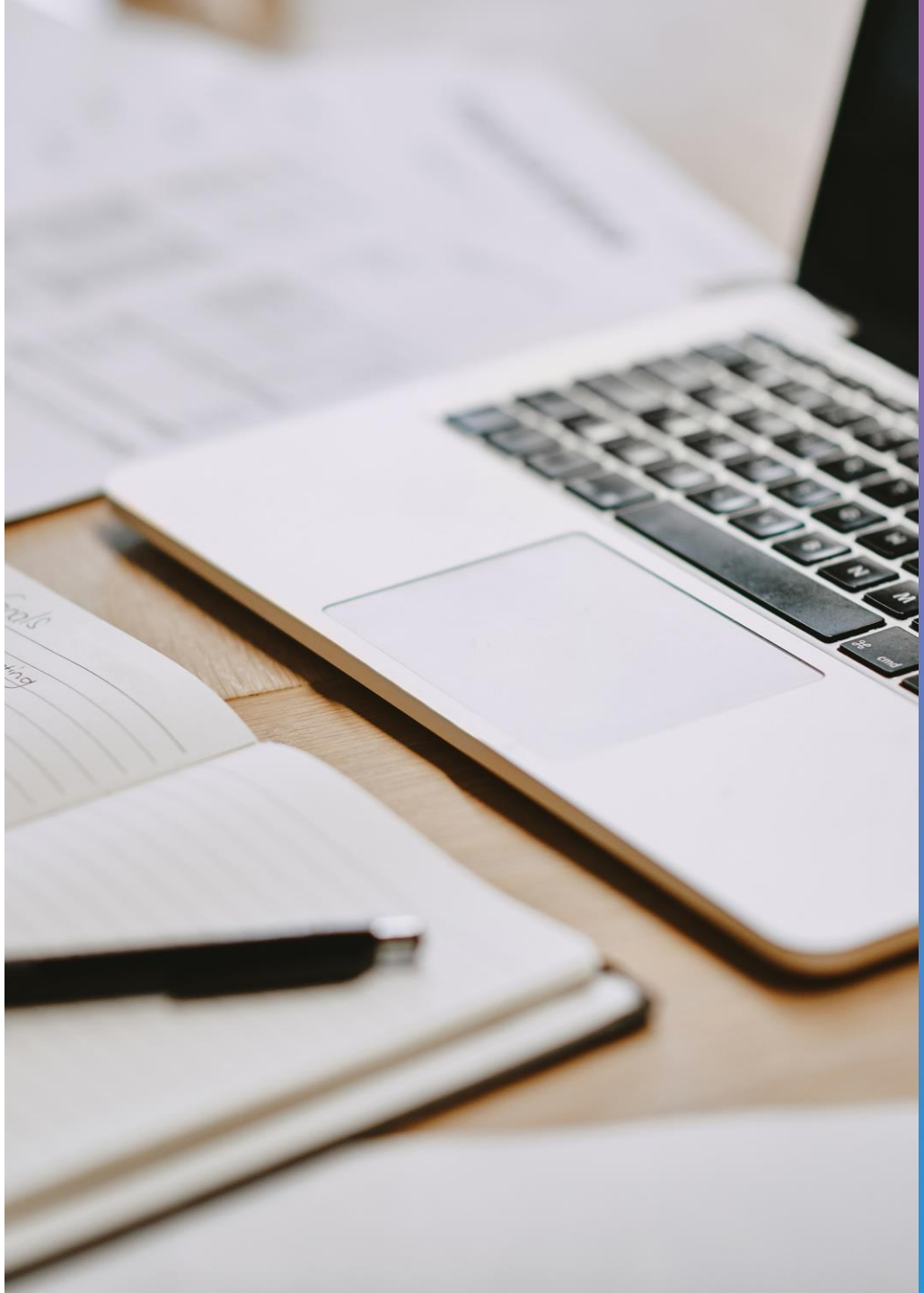
Correct Answer: B

Monitor, educate, and coordinate care

Monitoring and educating the patient and coordinating care with other providers helps manage potential drug-drug interactions. Ignoring the interactions, stopping all medications, or avoiding follow up visits all put the patients at higher risk.



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- PCSS-MOUD is led by the American Academy of Addiction Psychiatry (AAAP), in collaboration with a coalition of national professional and healthcare organizations.

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PCSS-MOUD Mentoring Program

- Designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid use disorder (MOUD).
- Supported by a national network of providers with expertise in addictions, pain, and evidence-based treatment, including MOUD.
- Three mentoring options are available to meet your needs.
- No cost to participate.

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Register here at no cost!

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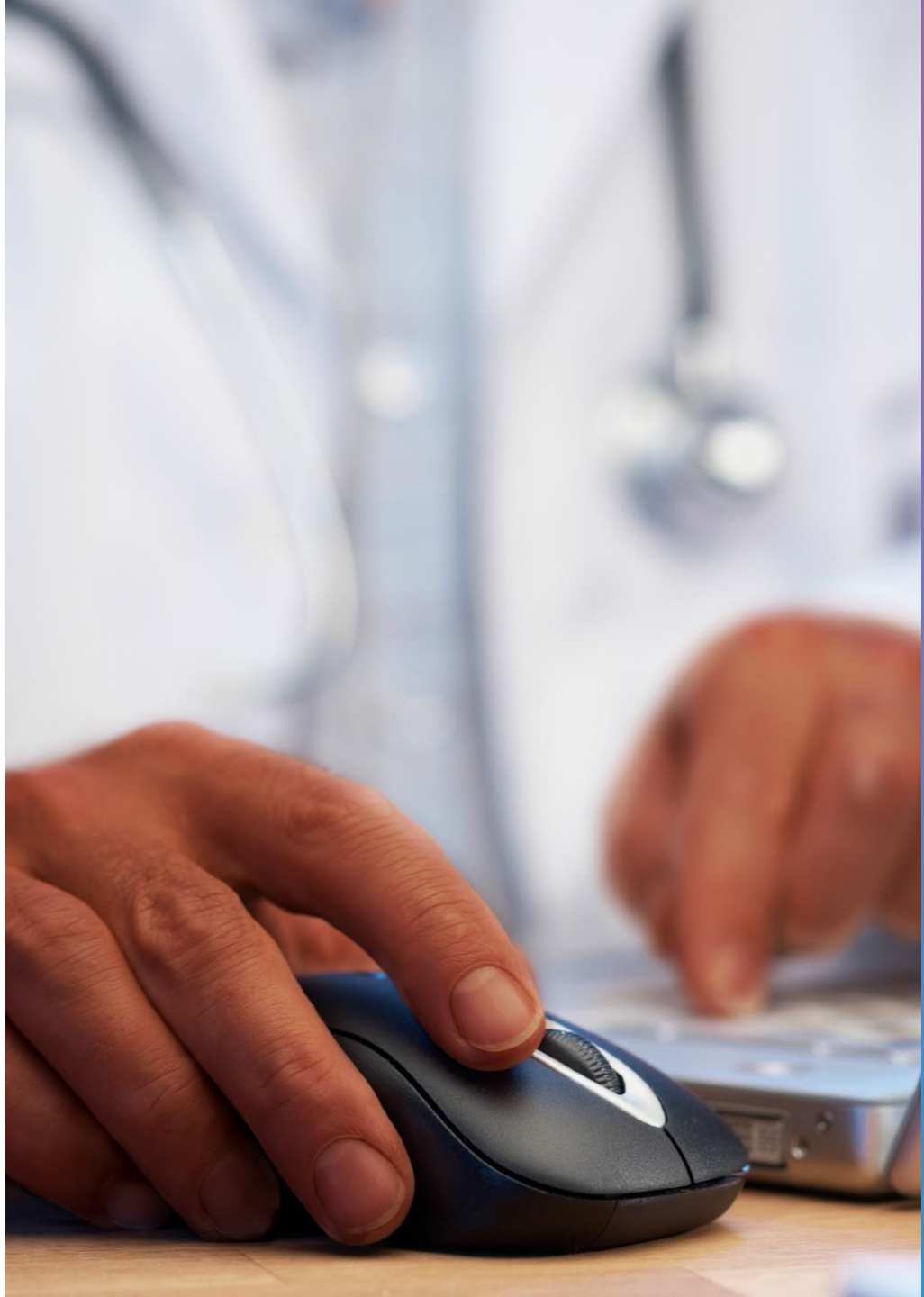

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