Emerging Drugs and Their Impact on the Opioid Crisis

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Learning Objectives

- Describe the dynamic nature of the illicit opioid supply, including common adulterants
- Identify common hospital testing modalities for detecting opioids and adulterants and understand their limitations
- Outline appropriate treatment strategies for managing opioid overdose
- Discuss how adulterants can complicate opioid overdose management

Polling Question

In 2023 and 2024, the least common opioid identified in Kentucky opioid decedent testing was:

A. Fentanyl

B. Heroin

C. Morphine

D. Buprenorphine

Counts of Substances Identified through Toxicology Testing of Drug Overdose Deaths Occurring in Kentucky, 2024

Total overdose deaths: 1,410

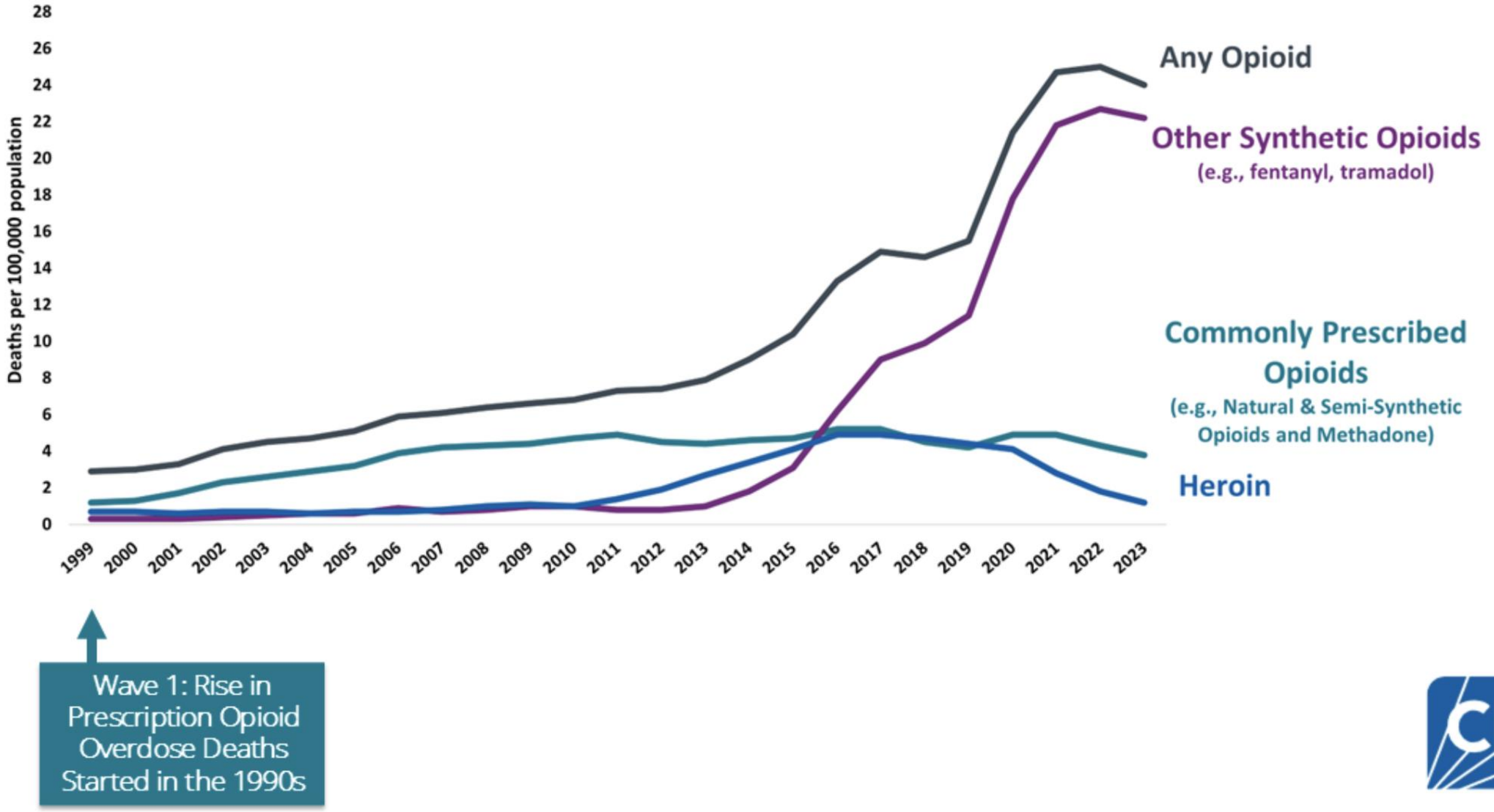
- **Fentanyl** 962
- **4-ANPP** 864
- **Methamphetamine** 781
- **Amphetamine** 650
- **Acetylfentanyl** 424
- **Caffeine** 372
- **Nicotine** 328
- **Cocaine** 314
- **Gabapentin** 248
- **THC** 239
- **Ethanol** 209
- **Morphine** 165
- **Para-Fluorofentanyl** 163
- **Naloxone** 146
- **Clonazepam** 135
- **Oxycodone** 118
- **Hydrocodone** 117
- **Alprazolam** 107
- **Buprenorphine** 90

Heroin 38

Kentucky 2024 Drug Overdose Fatality Report (https://odcp.ky.gov/Reports/2024%20Drug%20Overdose%20Fatality%20Report.pdf)

The Dynamic Nature of the Illicit Opioid Supply

Three Waves of Opioid Overdose Deaths



https://www.cdc.gov/overdose-prevention/about/understanding-the-opioid-overdose-epidemic.html
Emergency Medicine News47(4):14-15, May 2025.
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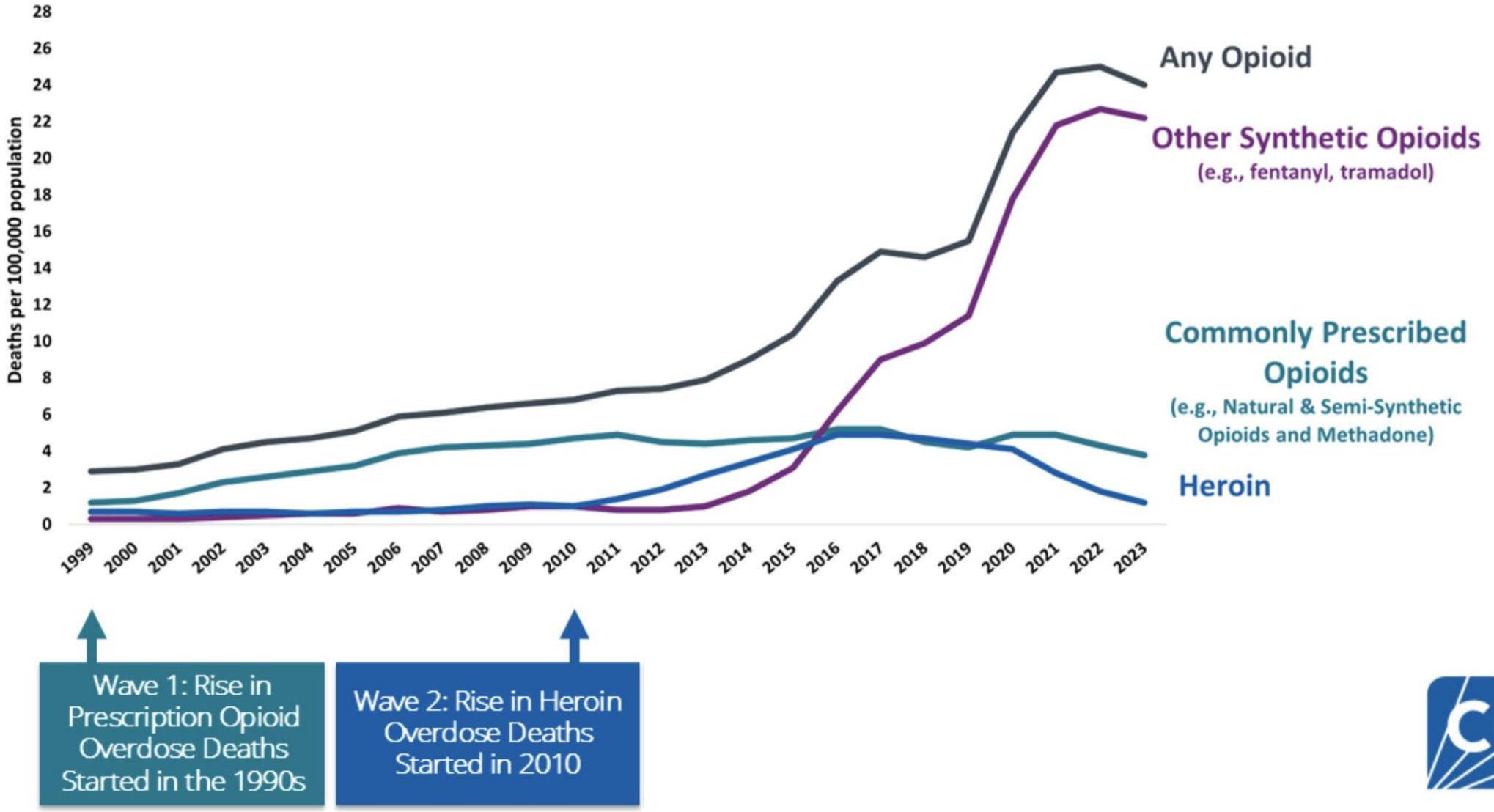

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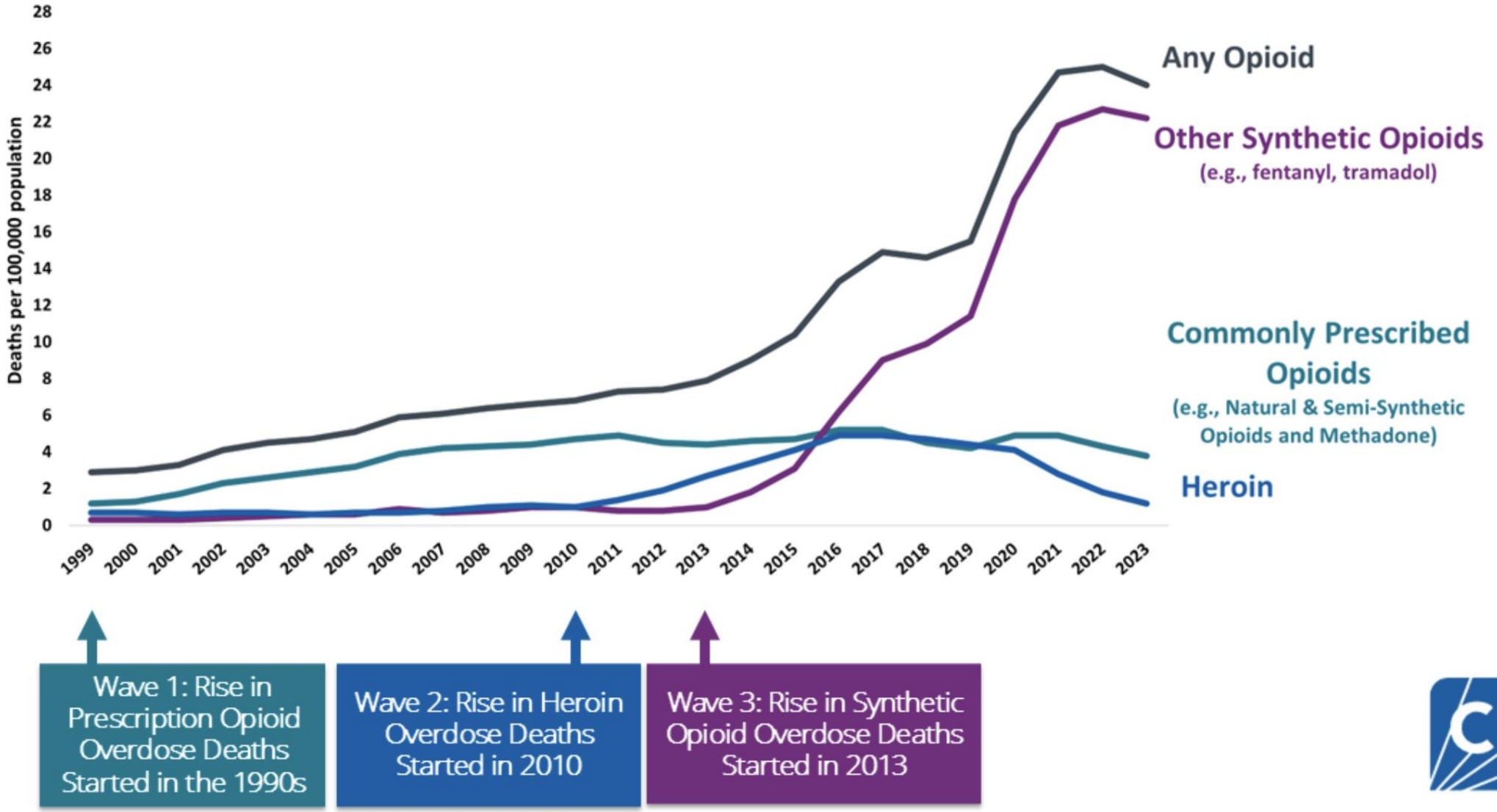

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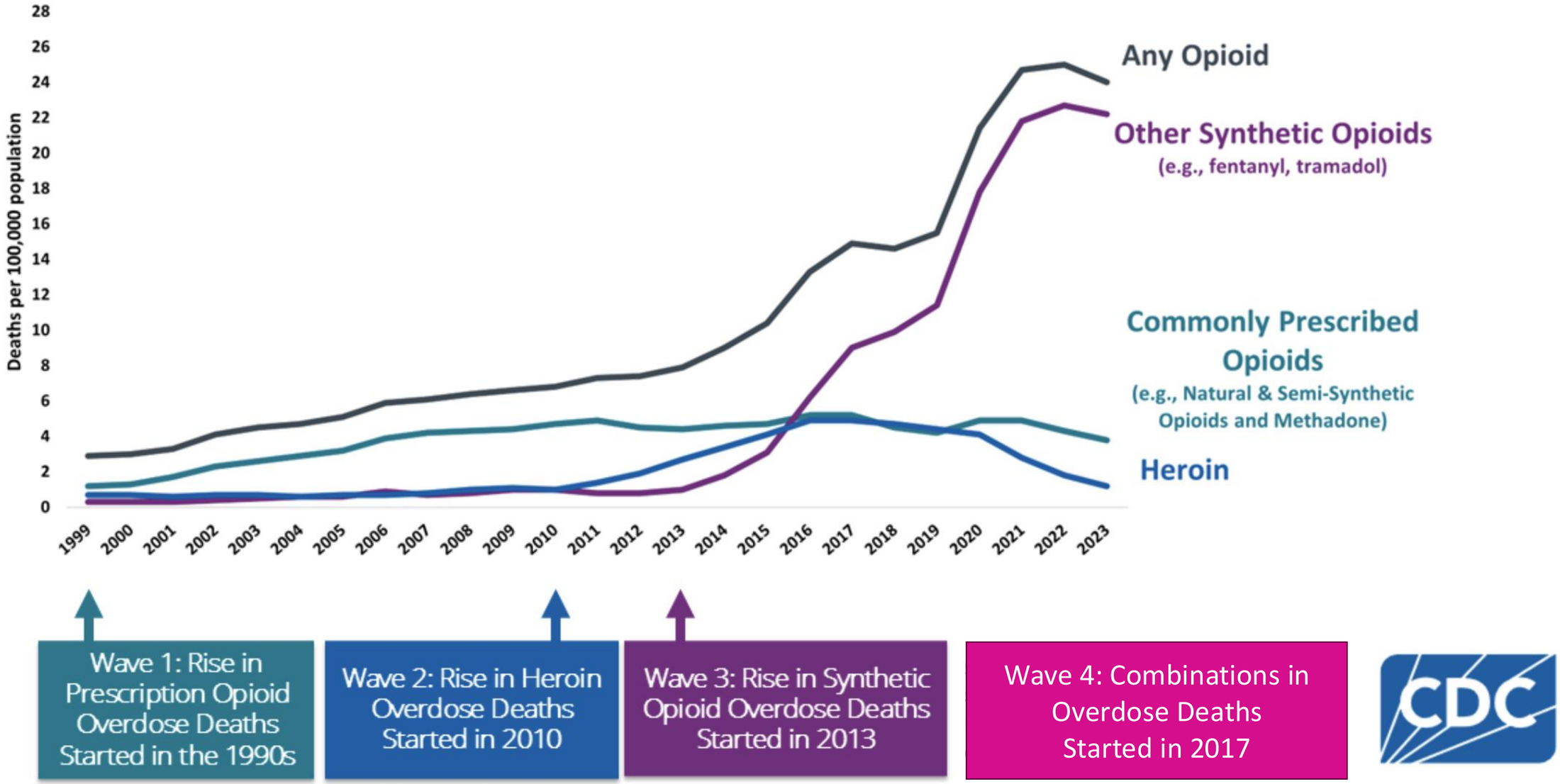
Three Waves of Opioid Overdose Deaths



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Most Common Two-Drug Combinations Identified through Toxicology for all Drug Overdose Deaths, Kentucky, 2024

Drug Combination	Total Count of Deaths	Black Decedents*	White Decedents*
4-ANPP, Fentanyl	864	129 (70.9%)	716 (55.3%)
Amphetamine, Methamphetamine	622	41 (22.5%)	575 (44.4%)
Fentanyl, Methamphetamine	509	48 (26.4%)	451 (34.8%)
4-ANPP, Methamphetamine	462	45 (24.7%)	409 (31.6%)
Amphetamine,	425	38 (20.9%)	381 (29.4%)
Acetylfentanyl, Fentanyl	424	64 (35.2%)	347 (26.8%)
4-ANPP, Acetylfentanyl	408	62 (34.1%)	334 (25.8%)
4-ANPP, Amphetamine	376	33 (18.1%)	337 (26%)
Cocaine, Fentanyl	250	78 (42.9%)	165 (12.7%)
Caffeine, Fentanyl	241	28 (15.4%)	207 (16%)
Fentanyl, Nicotine	238	38 (20.9%)	196 (15.1%)
Caffeine, Nicotine	235	23 (12.6%)	209 (16.1%)
4-ANPP, Cocaine	222	67 (36.8%)	148 (11.4%)

Kentucky 2024 Drug Overdose Fatality Report (https://odcp.ky.gov/Reports/2024%20Drug%20Overdose%20Fatality%20Report.pdf)

Limitations to what is known from postmortem data

- Impossible to know which drugs caused death or how they contributed
- Results are not available in a timely manner
- Testing varies greatly across the country
- Not all substances may be characterized
- Results from nonfatal overdoses are not captured

Where is the nonfatal overdose data?

- Traditionally, drug testing has limited value for the initial clinical treatment of overdoses
- Lack of confirmatory testing data leads to the underutilization of ICD-10-CM coding
- Many synthetic or novel substances are not detectable utilizing common laboratory testing
- Poison control is not always contacted

Kentucky Overdose Data to Action (KY OD2A)

Research supported by the Kentucky Injury Prevention and Research Center and funded by the Centers for Disease Control and Prevention (CDC)

Characterize substances involved in nonfatal drug overdoses treated in the emergency department

Identify novel substances of abuse

Kentucky Overdose Data to Action (KY OD2A)

Suspected Overdose	Remnant Samples Sequestered	Targeted Analysis	Nontarget Analysis

• Identified by emergency department clinical team
• Illicit opioids
• Other synthetics
	• Blood: serum, plasma, whole blood
	• Urine
	• Drug paraphernalia
		• Local hospital lab
		  • GC/MS
		  • LC/MS/MS
			1. Synthetic drug, where remainder of drug screen has produced little or no viable options to explain the symptoms
			2. Opioid, where remainder of drug screen has produced little or no viable options to explain the symptoms
			3. Exposure where story or UDS does not match clinical symptoms

N = ~3,030 patient encounters

~460 nontarget analysis
~32% contain opioids

Example Patient Case

- Male presenting from scene after being found down unresponsive
- Given 4mg intranasal naloxone with partial response
- Endorsed “Ren” use

Is there a synthetic marijuana present?

Drug abuse screen

Status: **Final result**

Test Result Released: **No**

0 Result Notes

Component Ref Range & Units	4 yr ago
Amphetamine Screen Urine Negative	Negative
Benzodiazepines Screen Urine Negative	Presumptive positive. Confirmation by LC-MS/MS to follow.
Cannabinoid Screen Urine Negative	Presumptive positive. Confirmation by LC-MS/MS to follow.
Cocaine Screen Urine Negative	Negative
Barbiturate Screen Urine Negative	Negative
Opiate Screen Urine Negative	Negative
Methadone Screen Urine Negative	Negative
Buprenorphine Screen Urine Negative	Presumptive positive. Confirmation by LC-MS/MS to follow.
Fentanyl Screen Urine Negative	Presumptive positive. Confirmation by LC-MS/MS to follow.
Oxycodone Screen Urine Negative	Negative
Resulting Agency	UK LAB

Example of Results from DEA Testing

Findings:

Sample ID	Sample	Date, Time	Confirmed Drug (ng/mL)
	Urine		1. Gabapentin (99300) 2. Xylazine (207) 3. Fentanyl (178) 4. Quinine (59.8) 5. Bromazolam (49.0) 6. 4-ANPP (11.0) 7. Norfentanyl* (9.0) 8. 7-Amino Clonazepam* 9. Baclofen 10. Buprenorphine 11. Diphenhydramine 12. Naloxone 13. Norbuprenorphine* 14. Nordiazepam* 15. Oxazepam* 16. Quetiapine 17. Temazepam*

KYOD2A Data

Early lessons Learned

Exposures are polysubstance

Patients do not seem to know what they are taking

Limitations to hospital testing libraries

Polysubstance complexities in illicit opioid supply

Novel Opioid Receptor Agonists

Stimulants

Designer Benzodiazepines

Xylazine & Medetomidine

Other Adulterants / Cutting Agents

Novel Opioid Receptor Agonists

>120 opioid receptor agonists

Categorized as:

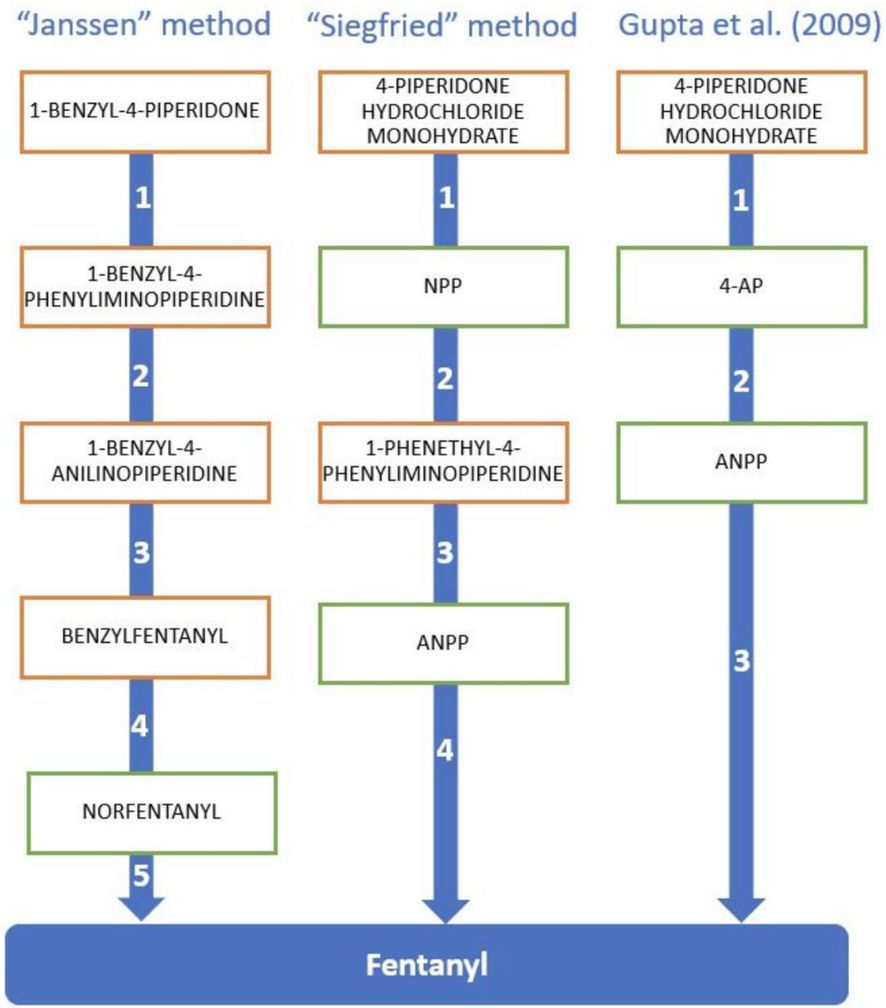
Fentanyl analogs	U series (U-47700)	Nitazenes	Piperazines	Miscellaneous

- Rationale for Addition:
  - Cheap
  - Potent
  - Byproduct of Synthesis
  - Metabolite

- Reported Effects:
  - Respiratory Depression
  - Pupillary Constriction
  - Decreased Consciousness

https://www.unodc.org/documents/scientific/The_Challenge_of_NPS_A_technical_update_2024.pdf

Fentanyl Synthesis



https://www.unodc.org/LSS/Announcement/Details/b152bda5-5d71-4f7e-9d68-1bdd9af04a83

Fentanyl and Fentanyl Analogs

Findings:

Sample ID	Sample	Date, Time	Confirmed Drug (ng/mL)	
	Whole Blood		1. Gabapentin (137)	
			2. 11-nor-9-carboxy-delta-9-THC* (118)	
			3. Methamphetamine (21.9)	Stimulant
			4. Fentanyl (17.9)	Opioids
			5. Norfentanyl* (5.5)	
			6. 4-ANPP (0.8)	
			7. 7-Amino Clonazepam*	
			8. Clonazepam	Benzodiazepines
			9. Diazepam	
			10. Diphenhydramine	Adulterants / Cutting Agents
			11. Lidocaine	
			12. Naloxone	
			13. Nordiazepam*	
			14. Norpseudoephedrine	
			15. Oxazepam*	
			16. Temazepam*	

Found unresponsive after snorting an unknown substance.

Given 4mg IN naloxone, with response.

Required repeat naloxone 0.4mg IV x2 while in the ED and was started on a naloxone drip.

KYOD2A Data

Fentanyl and Fentanyl Analogs

Findings:

Sample ID	Sample	Date	Time	Confirmed Drug (ng/mL)
	Plasma			1. Benzoylecgonine* (109) 2. Ecgonine Methyl Ester* 3. Codeine (1.9) 4. Morphine (11.4) 5. *para*-Fluorofentanyl (3.3) 6. Despropionyl-*para*-Fluorofentanyl* (0.3) 7. Norfentanyl* (1.4) 8. Methadone

Presented after ingesting an “8-ball” of heroin. Reported being "spooked" by police.

Became somnolent, RR 15, HR 44 SBP 130s. Pt was given 0.4mg of naloxone when respirations became shallow.

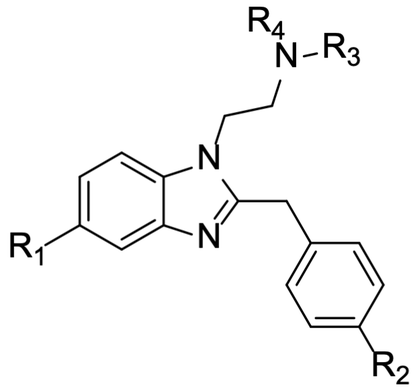
Post naloxone, became agitated and left AMA.

KYOD2A Data

Nitazenes

Table 1: Nitazene Potency Relative to Fentanyl

Type of Nitazene	Potency Relative to Fentanyl[xiii] [xiv]
butonitazenes and etodesnitazenes	25% to 50% as strong
ISO— the most common nitazene	5X to 9X times stronger
N-pyrrolidino protonitazenes	Up to 25X times stronger
N-pyrrolidino etonitazenes	Up to 43X times stronger



	R_1	R_2	R_3	R_4
metonitazene	NO_2	OCH_3	CH_2CH_3	CH_2CH_3
metodesnitazene	H	OCH_3	CH_2CH_3	CH_2CH_3
etonitazene	NO_2	OCH_2CH_3	CH_2CH_3	CH_2CH_3
etodesnitazene	H	OCH_2CH_3	CH_2CH_3	CH_2CH_3
protonitazene	NO_2	$OCH_2CH_2CH_3$	CH_2CH_3	CH_2CH_3
butonitazene	NO_2	$OCH_2CH_2CH_2CH_3$	CH_2CH_3	CH_2CH_3
isotonitazene	NO_2	$OCH(CH_3)_2$	CH_2CH_3	CH_2CH_3
clonitazene	NO_2	Cl	CH_2CH_3	CH_2CH_3
flunitazene	NO_2	F	CH_2CH_3	CH_2CH_3
etonitazepyne	NO_2	OCH_2CH_3	$-CH_2CH_2CH_2CH_2-$	
etonitazepipne	NO_2	OCH_2CH_3	$-CH_2CH_2CH_2CH_2CH_2-$	

https://www.oas.org/ext/DesktopModules/MVC/OASDnnModules/Views/Item/Download.aspx?type=1&id=1045&lang=1

KYOD2A Data

Nitazenes

Findings:

Sample ID	Sample	Date	Time	Confirmed Drug (ng/mL)
	Plasma			1. Butonitazene (7.3) 2. Fentanyl (0.2*) 3. Norfentanyl**(0.6) 4. MDEA (0.9) 5. Methamphetamine (13.4) 6. Acetaminophen

Opioids

Stimulant

Brought in by EMS, became combative and altered post naloxone administration. Required ketamine IM for sedation prior to arrival.

https://www.deadiversion.usdoj.gov/drug_chem_info/benzimidazole-opioids.pdf

KYOD2A Data

Kentucky Office of Homeland Security
2d ·

Public Safety Advisory: Cychlorphine Dete... more

2.7K 619 15.4K

Stimulants

The largest category of novel psychoactive substances (NPSs) ~400 individual substances having been reported

Common Examples:

Amphetamine	Methamphetamine	Cocaine	MDMA	Synthetic cathinones

- Rationale for Addition:
  - Counterbalance sedative effects
  - Synergistic effects
  - Prevent withdrawal
- Reported Effects:
  - Stimulatory effect on the CNS
  - Modulate the levels and activity of neurotransmitters (dopamine, norepinephrine, and serotonin).

https://www.unodc.org/documents/scientific/The_Challenge_of_NPS_A_technical_update_2024.pdf

Stimulants

Findings:

Sample ID	Sample	Date	Time	Confirmed Drug (ng/mL)
	Plasma			1. Benzoylecgonine* (109) 2. Ecgonine Methyl Ester* 3. Codeine (1.9) 4. Morphine (11.4) 5. *para*-Fluorofentanyl (3.3) 6. Despropionyl-*para*-Fluorofentanyl* (0.3) 7. Norfentanyl* (1.4) 8. Methadone

Presented after ingesting an “8-ball” of heroin. Reported being "spooked" by police.

Became somnolent, RR 15, HR 44 SBP 130s. Pt was given 0.4mg of naloxone when respirations became shallow.

Post naloxone, became agitated and left AMA.

KYOD2A Data

Stimulants

Found unresponsive by boyfriend. Was awake on EMS arrival but passed out.

Given 4mg IN naloxone, with response.

Required Ketamine IV, and Midazolam IM Prior to ED arrival for combativeness.

Drug abuse screen

Status: **Final result**

Test Result Released: **Yes (seen)**

0 Result Notes

Component Ref Range & Units	3 yr ago
Amphetamine Screen Urine Cutoff: 500 ng/mL	Presumptive positive. Confirmation by LC-MS/MS to follow.
Benzodiazepines Screen Urine Cutoff: 200 ng/mL	Presumptive positive. Confirmation by LC-MS/MS to follow.
Cannabinoid Screen Urine Cutoff: 50 ng/mL	Negative
Cocaine Screen Urine Cutoff: 300 ng/mL	Negative
Barbiturate Screen Urine Cutoff: 200 ng/mL	Negative
Opiate Screen Urine Cutoff: 300 ng/mL	Negative
Methadone Screen Urine Cutoff: 300 ng/mL	Negative
Buprenorphine Screen Urine Cutoff: 10 ng/mL	Negative
Fentanyl Screen Urine Cutoff: 1 ng/mL	Presumptive positive. Confirmation by LC-MS/MS to follow.
Oxycodone Screen Urine Cutoff: 100 ng/mL	Negative
Resulting Agency	UK LAB

KYOD2A Data

Stimulants

Findings:

Sample ID	Sample	Date, Time	Confirmed Drug (ng/mL)
	Whole Blood		1. Methamphetamine (126000) 2. Amphetamine (15400) 3. Norfentanyl* (13600) 4. N,N-Dimethylamphetamine (9570) 5. 4-OH Methamphetamine* (8075) 6. Fentanyl (2250) 7. Beta-Hydroxy Fentanyl (410) 8. Benzoylecgonine* (23.6) 9. Xylazine (23.5) 10. 4-ANPP (14.4) 11. Ketamine 12. Naloxone 13. Nordiazepam 14. Oxazepam 15. Promethazine

Found unresponsive by boyfriend. Was awake on EMS arrival but passed out.

Given 4mg IN naloxone, with response.

Required Ketamine IV, and Midazolam IM Prior to ED arrival for combativeness.

KYOD2A Data

Designer Benzodiazepines

Similar chemical structures and clinical effects to traditional benzodiazepines

Have never been licensed for medical use

Common Novel Examples:

Etizolam	Phenazepam	Bromazolam

- Rationale for Addition:
  - Intensify and/or prolong the euphoric effects
- Reported Effects:
  - Sedation
  - Amnesia
  - Euphoria

https://www.unodc.org/documents/scientific/The_Challenge_of_NPS_A_technical_update_2024.pdf

Van Amsterdam. Drug and Alcohol Dependence. 272 (2025) 112708

Designer Benzodiazepines

Findings:

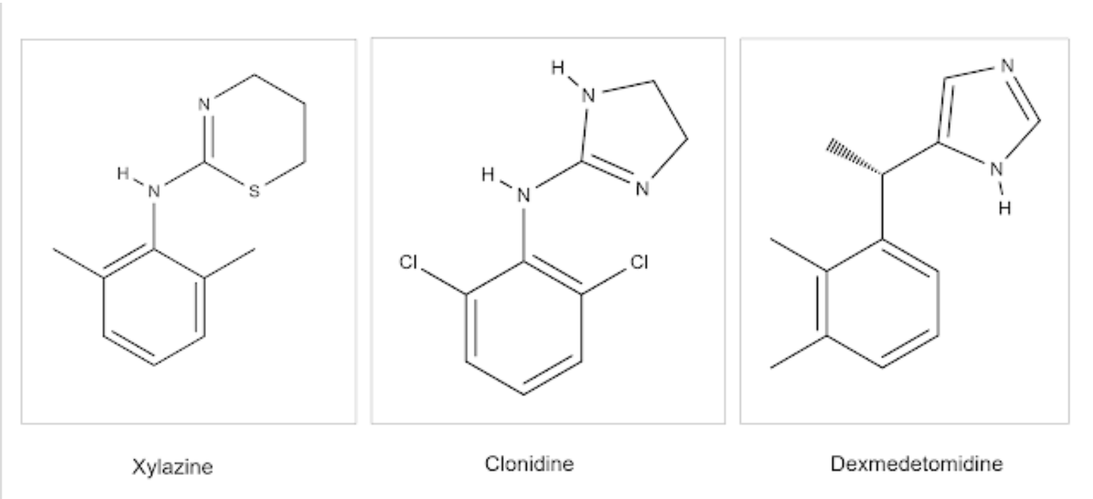
Sample ID	Sample	Date, Time	Confirmed Drug (ng/mL)
	Urine		1. Gabapentin (99300) 2. Xylazine (207) 3. Fentanyl (178) 4. Quinine (59.8) 5. Bromazolam (49.0) 6. 4-ANPP (11.0) 7. Norfentanyl* (9.0) 8. 7-Amino Clonazepam* 9. Baclofen 10. Buprenorphine 11. Diphenhydramine 12. Naloxone 13. Norbuprenorphine* 14. Nordiazepam* 15. Oxazepam* 16. Quetiapine 17. Temazepam*

KYOD2A Data

Xylazine / Medetomidine

Alpha-2 adenoreceptor agonists

Non-opioid sedative, analgesic and muscle relaxant



- Rationale for Addition:
  - Enhance the euphoric and analgesic effects
  - Reduce frequency of injections
- Reported Effects:
  - Sedation
  - Respiratory depression
  - Hypotension
  - Bradycardia
  - Wounds
  - Severe withdrawal

https://www.unodc.org/documents/scientific/The_Challenge_of_NPS_A_technical_update_2024.pdf

Van Amsterdam. Drug and Alcohol Dependence. 272 (2025) 112708

Xylazine / Medetomidine

Findings:

Sample ID	Sample	Date, Time	Confirmed Drug (ng/mL)
	Urine		1. ~~Norfentanyl* (98.0)~~ 2. Xylazine (60.9) 3. ~~Fentanyl (52.1)~~ 4. 4-ANPP (26.6) 5. Tramadol (16.4) 6. Desmethyl-*cis*-Tramadol* (5.2) 7. Benzoylecgonine* (4.7**) 8. 7-Amino Clonazepam 9. Acetaminophen 10. Atorvastatin 11. Diazepam 12. Diphenhydramine 13. Furosemide 14. Lidocaine 15. Naloxone 16. Nordiazepam* 17. Nordoxepin* 18. Oxazepam* 19. Temazepam*

Presented after injecting fentanyl.

Drowsy, required stimulation for questioning. Delayed onset respiratory depression.

BP: 76/54 (61)
HR: 41
SpO2: 90%

Naloxone 2mg IV given with no response

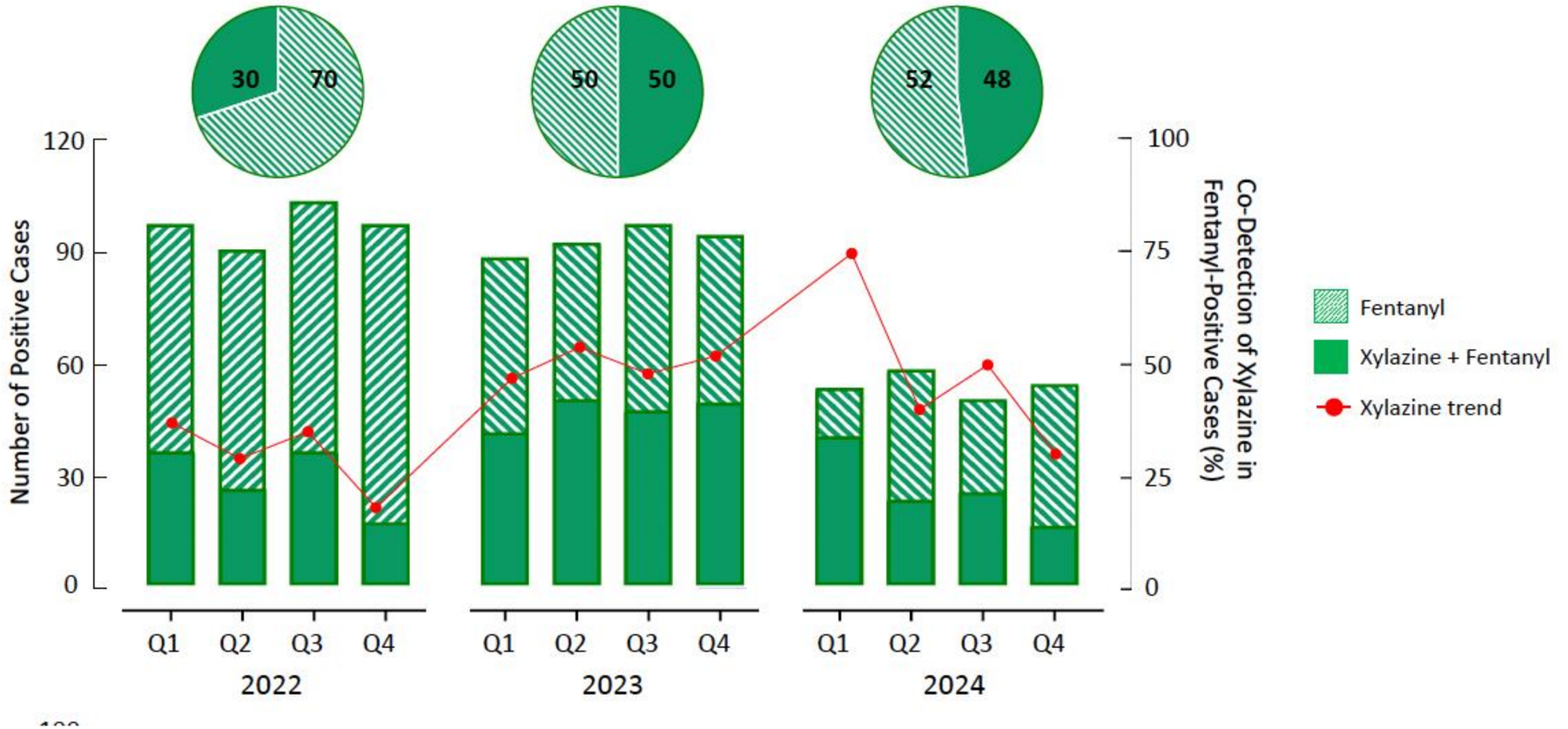
KYOD2A Data

As Xylazine Use Declines, Is Mitragynine Becoming the New Trend in Illicit Drug Use?

Hind Malaeb, PhD, William Feeney, PhD, Ibrahim Choucair, PhD, NRCC, DABCC

Department of Pathology and Laboratory Medicine, University of Kentucky Medical Center, Lexington, KY

Poster # B-325



Adulterants Versus Cutting Agents

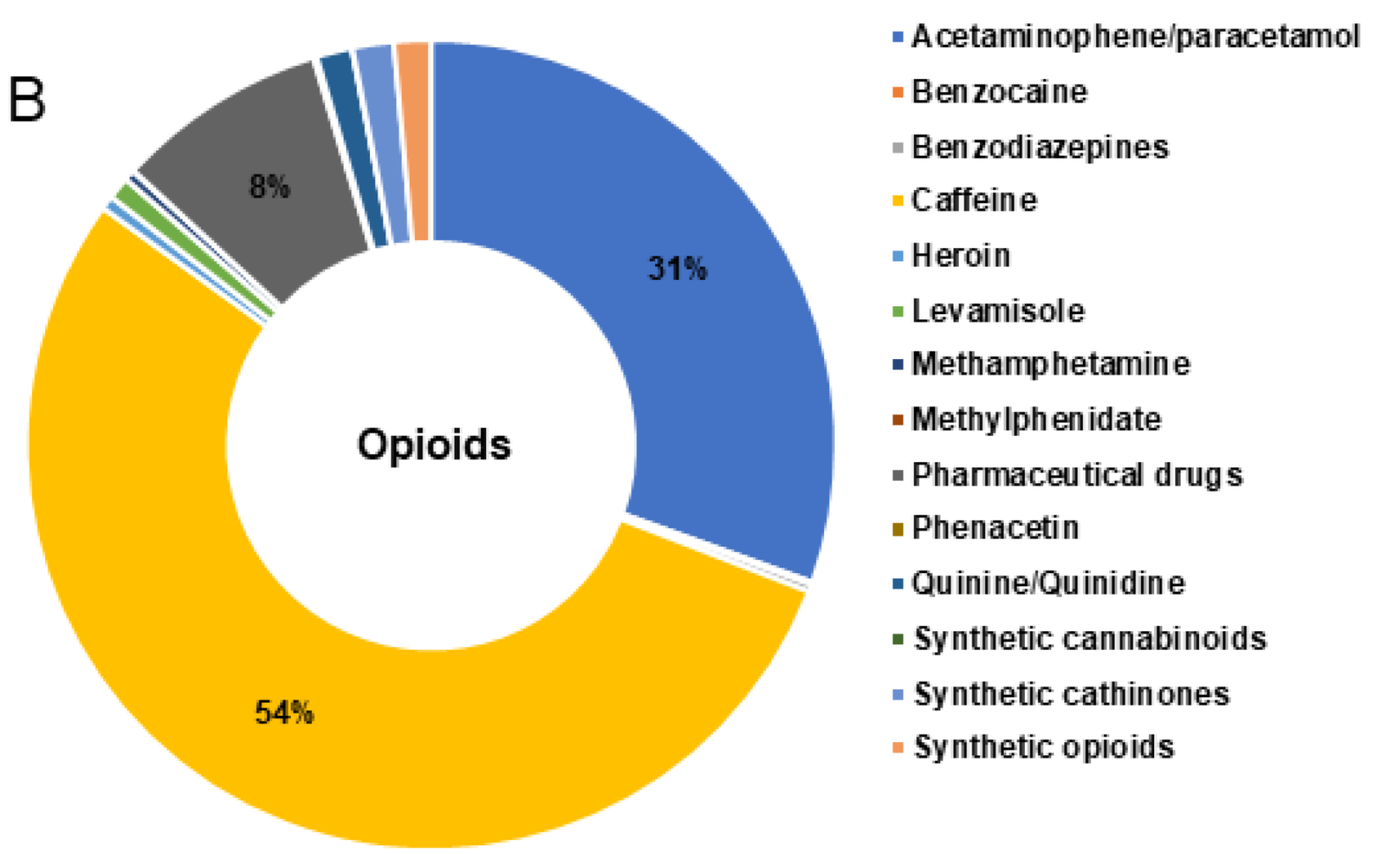
Adulterants

- Pharmacologically active
- Generally added for a contributory effect, but can also be added for bulking
- Potential for adverse effects or drug-drug interactions

Cutting Agents

- Inert fillers
- Make the substance easier to measure, distribute, and use

Adulterants Present in Illicit Opioids



Common in Kentucky

Acetaminophen
Caffeine
Dextromethorphan
Diphenhydramine
Guaifenesin
Hydroxyzine
Quetiapine
Quinine
Metamizole
Phenacetin
Theophylline
Tramadol

Benzocaine
Lidocaine
Procaine

Levamisole
Phenylbutazone
Acepromazine
Xylazine

Int. J. Mol. Sci. **2022**, 23, 14619

Polysubstance complicates care

- Variability in potency
- Erratic responses to naloxone
- Limitations in detection
- Alterations in work-up during treatment
- Withdrawal challenges

Polling Question

All of the following statements regarding common hospital drug testing are true except:

A. Substance must be known

B. Testing varies greatly between facilities

C. Has major impacts on patient care

D. Is labor- and time-intensive

E. Has many false positives and negatives

Common Hospital Testing Modalities

Illicit Drugs

Types of Toxicology Testing

Presumptive testing by immunoassay (“drug screen”)

- Presence of drug classes and/or their metabolites in a urine sample
  - If the concentration of a drug is high enough
- Typically, the first test used to identify drug classes in the urine
- Available in most hospitals

Confirmatory testing by gas or liquid chromatography

- Used to confirm a positive drug screen result or definitively identify a detected substance
- Detects the presence of specific drugs and/or metabolites in a urine sample
- Available at larger institutions

Every laboratory has different testing capabilities.

https://legislativeanalysis.org/wp-content/uploads/2024/01/Fentanyl-Screening-in-Hospitals.pdf

Immunoassay	Gas chromatography/mass spectrometry (GC-MS)	Liquid chromatography tandem mass spectrometry (LC-MS/MS)
• Antibodies to detect the presence of selected drugs and/or metabolites	• Chromatography • Confirmatory or definitive testing	• Chromatography • Requires small volumes of substrate
• Fast	• Slower (6-24 hours)	• Slower (12-24 hours)
• Cheap	• Expensive	• Expensive
• Qualitative	• Qualitative	• Quantitative
• Limited library • Known detection thresholds	• Lower detection thresholds	• Lower detection thresholds
• Lacks specificity • Followed by a confirmatory test	• Low likelihood of false results	• Analysis has a second analytical separation step • Lower susceptibility to false results caused by concomitant usage
• NIDA 5: marijuana, cocaine, opiates, amphetamines, and phencyclidine • 10-panel • Drugs of Abuse Screens	• Comprehensive urine drug screen	• Pain management drug screens • Drugs of abuse screen (reflex)

Immunoassay	Gas chromatography/mass spectrometry (GC-MS)	Liquid chromatography tandem mass spectrometry (LC-MS/MS)

• Amphetamines
• Benzodiazepines
• Cannabinoids
• Cocaine
• Barbiturate
• Opiate
• Methadone
• Buprenorphine
• Fentanyl
• Oxycodone
	• >450 substances
	• Many prescription and OTC medications
	• Common opioids
	• Common stimulants
	• Common benzodiazepines
	• MDMA
	• Ketamine
	• PCP
	• Xylazine
	• Naloxone
	• Medications for Opioid Use Disorder (MOUD)
		• Detects both prescription and illicit
		  • Opioids
		  • Benzodiazepines
		  • Stimulants
		  • Associated metabolites
		• Barbiturates
		• THC
		• PCP
		• MOUD

Toxicology Testing Example

- Urine sample for a patient who recently used heroin

Presumptive Testing

Presumptive Positive:

Opiates

Immunoassay

Drug abuse screen

Status: **Final result**

Test Result Released: **No**

0 Result Notes

Component Ref Range & Units	4 yr ago
Amphetamine Screen Urine Negative	Negative
Benzodiazepines Screen Urine Negative	Negative
Cannabinoid Screen Urine Negative	Negative
Cocaine Screen Urine Negative	Negative
Barbiturate Screen Urine Negative	Negative
Opiate Screen Urine Negative	Presumptive positive. Confirmation by LC-MS/MS to follow.
Methadone Screen Urine Negative	Negative
Buprenorphine Screen Urine Negative	Negative
Fentanyl Screen Urine Negative	Negative
Oxycodone Screen Urine Negative	Negative
Resulting Agency	UK LAB

https://legislativeanalysis.org/wp-content/uploads/2024/01/Fentanyl-Screenin

Toxicology Testing Example

- Urine sample for a patient who recently used heroin

Presumptive Testing

Presumptive Positive:
Opiates

Immunoassay

Confirmatory Testing

Positive:
Heroin
6-MAM
Morphine

GC/MS

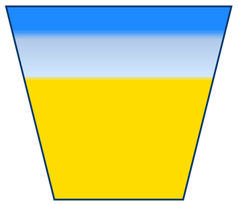
Positive w/concentrations:
Heroin
6-MAM
Morphine

LC/MS/MS

https://legislativeanalysis.org/wp-content/uploads/2024/01/Fentanyl-Screening-in-Hospitals.pdf

Toxicology Testing Example

- Urine sample for a patient who recently used fentanyl adulterated with synthetic fentanyl



Presumptive Testing

Presumptive Positive: Fentanyl

Immunoassay

Synthetic fentanyl may cross react

Drug abuse screen

Status: **Final result**

Test Result Released: **No**

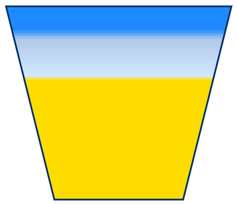
0 Result Notes

Component Ref Range & Units	4 yr ago
Amphetamine Screen Urine Negative	Negative
Benzodiazepines Screen Urine Negative	Presumptive positive. Confirmation by LC-MS/MS to follow.
Cannabinoid Screen Urine Negative	Negative
Cocaine Screen Urine Negative	Negative
Barbiturate Screen Urine Negative	Negative
Opiate Screen Urine Negative	Negative
Methadone Screen Urine Negative	Negative
Buprenorphine Screen Urine Negative	Presumptive positive. Confirmation by LC-MS/MS to follow.
Fentanyl Screen Urine Negative	Presumptive positive. Confirmation by LC-MS/MS to follow.
Oxycodone Screen Urine Negative	Negative
Resulting Agency	UK LAB

https://legislativeanalysis.org/wp-content/uploads/2024/01/Fentanyl-Screenin

Toxicology Testing Example

- Urine sample for a patient who recently used fentanyl adulterated with synthetic fentanyl



Presumptive Testing

Presumptive Positive:

Fentanyl

Immunoassay

Synthetic fentanyl may be detected

Confirmatory Testing

Positive:

Fentanyl

Norfentanyl

GC/MS

Positive w/ concentrations:

Fentanyl

Norfentanyl

LC/MS/MS

Synthetic fentanyl likely not detected

https://legislativeanalysis.org/wp-content/uploads/2024/01/Fentanyl-Screening-in-Hospitals.pdf

Limitations of Hospital Drug Testing

- Substance must be known and in the testing library
- Testing varies greatly between facilities
- Takes time
- Testing has minimal impact on initial patient care
- Depending on the structural similarity, some cross-reactivity may exist

Testing complexities in illicit opioid supply

Novel Opioid Receptor Agonists

- Unpredictable cross-reactivity with immunoassays
- Require confirmatory testing but limitations in laboratory libraries
- Concomitant with fentanyl

Stimulants

- Detection and cross-reactivity varies by stimulant

Designer Benzodiazepines

- Developed to evade standard testing
- Require confirmatory testing but limitations in laboratory libraries

Xylazine & Medetomidine

- Require confirmatory testing but limitations in laboratory libraries
- Concomitant with fentanyl

Other Adulterants / Cutting Agents

- Detection and cross-reactivity varies by agent

Every laboratory has different testing capabilities

Test Strips

- Immunoassay
- High cut-off concentrations of >1000 ng/mL
- More effective for the detection of drugs or paraphernalia

Findings:

Sample ID	Sample	Date, Time	Confirmed Drug (ng/mL)
	Urine		1. Norfentanyl* (98.0) 2. Xylazine (60.9) 3. Fentanyl (52.1) 4. 4-ANPP (26.6) 5. Tramadol (16.4) 6. Desmethyl-*cis*-Tramadol* (5.2) 7. Benzoylecgonine* (4.7**) 8. 7-Amino Clonazepam 9. Acetaminophen 10. Atorvastatin 11. Diazepam 12. Diphenhydramine 13. Furosemide 14. Lidocaine 15. Naloxone 16. Nordiazepam* 17. Nordoxepin* 18. Oxazepam* 19. Temazepam*

Polling Question

Which intervention should be performed first for a person dropped off in the ambulance bay who is non-responsive to sternal rub and has shallow respirations? The driver reported they used heroin and passed out.

A. Assisted ventilations

B. Chest compressions

C. Naloxone

D. Intubation

Opioid Overdose Management

Symptomatic and Supportive Care

- Airway
- Breathing
- Circulation
- Naloxone should be administered for respiratory depression

Naloxone is not a substitute for emergency medical care.

Naloxone Administration

Adult (Nonopioid-Dependent)

- IV, IM, SC: initial dose of 0.4-2 mg; repeat doses every 2-3 minutes; up to 10 mg
- IM, SC (Evzio): 0.4 mg or 2 mg (1 autoinjector); repeat doses every 2-3 minutes
- Intranasal: 2 mg (1 mg per nostril); may be repeated every 3-5 minutes
- Nebulized: 2 mg placed in atomizer with ~3 ml of SWFI or NS, titrated to effect; *some respiratory drive needs to be present*

Adult (Opioid-Dependent)

- IV, IM, SC: Initial dose of 0.1-0.2 mg; repeat doses may be required every 2-3 minutes
- *Administer slowly to prevent withdrawal*

Child

- Age <5 years or ≤20 kg: 0.1 mg/kg/dose; repeat doses every 2-3 minutes
- Age ≥5 years or >20 kg: 2 mg/dose; repeat doses every 2-3 minutes

Naloxone infusion

- Two-thirds of the total initial dose required to restore breathing every hour should be delivered

Am J Ther. 2017 Sept 13 [

Naloxone Administration

Can precipitate acute withdrawal

- Anxiety, aggression, nausea, vomiting, diarrhea, abdominal pain, and rhinorrhea

Pulmonary edema, cardiovascular instability, and seizures

- Occur infrequently at dosages in line with those recommended for opioid overdose management

Am J Ther. 2017 Sept 13 [

Naloxone Dosing Changes Over Time

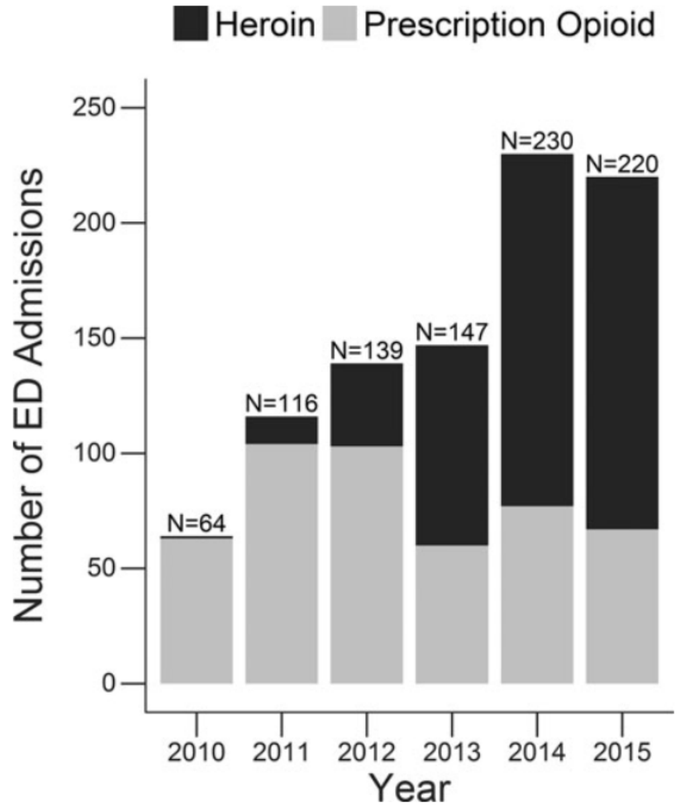


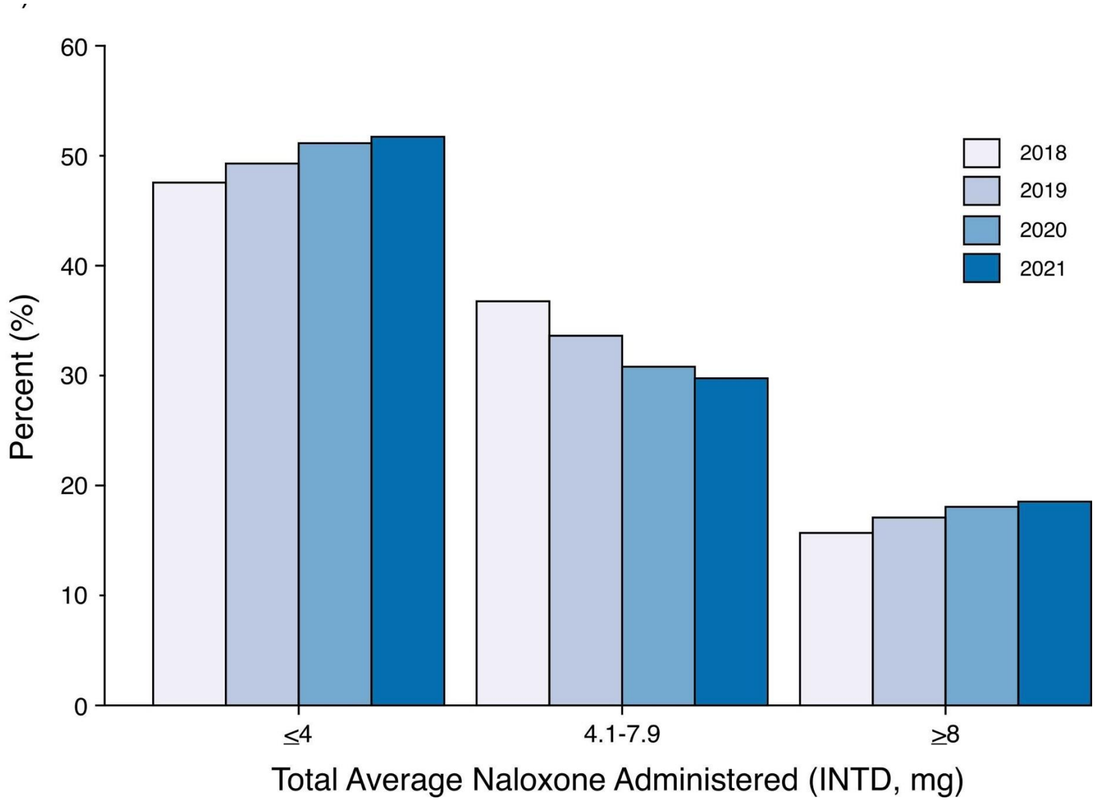
Figure 2. Numbers of patients with heroin and nonheroin (prescription) opioid overdoses by year of presentation to the emergency department (ED).

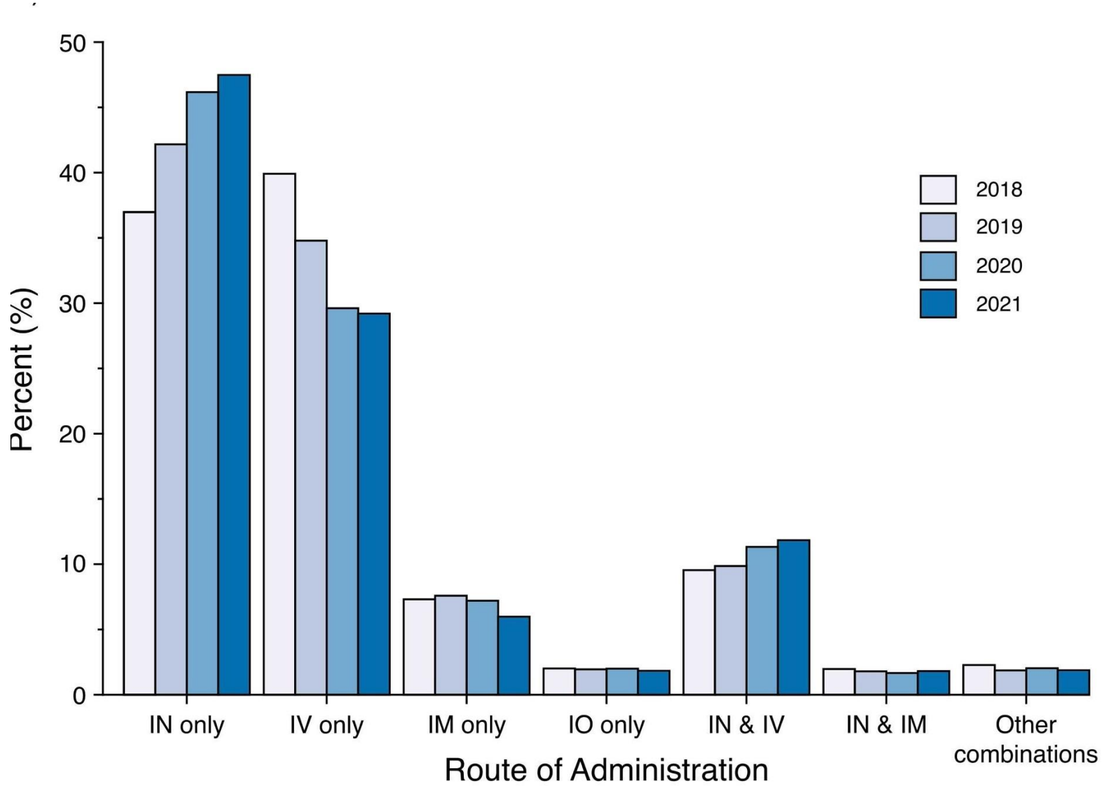
- Those presenting with heroin overdose, more likely to receive naloxone prehospital but less likely to require naloxone in the hospital

- Patients with nonheroin opioid overdoses required more continuous infusions of naloxone and admission to the intensive care unit

Pharmacotherapy.Vol. 37 Issue 7, pp. 781–790, 2017

Naloxone administration in emergency medical services (EMS) encounters for suspected opioid overdose, Kentucky, 2018–2021





Drug and Alcohol Dependence. Volume 255, 1 February 2024, 111062

Polling Question

Despite the widespread presence of adulterants in the opioid supply, should naloxone still be used in every suspected opioid overdose?

A. Yes, naloxone is minimal risk

B. No, it does not work on adulterants

C. Maybe, I need more information

Adulterants Complicating Opioid Overdose Management

Traditional Thinking

- Naloxone is FDA-approved specifically to reverse respiratory depression from opioid use
- Component of the “coma cocktail” for 50 years
- Both diagnostic and therapeutic

StatPearls Publishing; 2025 Jan-. https://www.ncbi.nlm.nih.gov/books/NBK441910/

Complication: Unmasking of Stimulants

Findings:

Sample ID	Sample	Date, Time	Confirmed Drug (ng/mL)
	Whole Blood		1. Methamphetamine (126000) 2. Amphetamine (15400) 3. Norfentanyl* (13600) 4. N,N-Dimethylamphetamine (9570) 5. 4-OH Methamphetamine* (8075) 6. Fentanyl (2250) 7. Beta-Hydroxy Fentanyl (410) 8. Benzoylecgonine* (23.6) 9. Xylazine (23.5) 10. 4-ANPP (14.4) 11. Ketamine 12. Naloxone 13. Nordiazepam 14. Oxazepam 15. Promethazine

Found unresponsive by boyfriend. Was awake on EMS arrival but passed out.

Given 4mg IN naloxone, with response.

Required Ketamine IV, and Midazolam IM Prior to ED arrival for combativeness.

KYOD2A Data

Complication: Unmasking of Stimulants

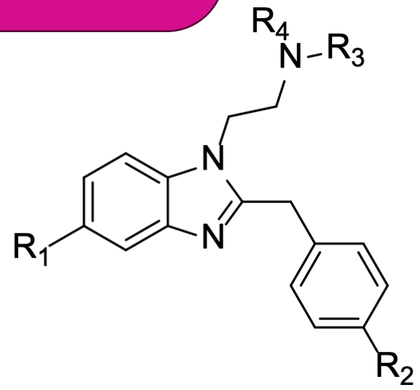
Findings:

Sample ID	Sample	Date	Time	Confirmed Drug (ng/mL)
	Plasma			1. Butonitazene (7.3) 2. Fentanyl (0.2*) 3. Norfentanyl**(0.6) 4. MDEA (0.9) 5. Methamphetamine (13.4) 6. Acetaminophen

Opioids

Stimulant

Brought in by EMS, became combative and altered post-naloxone administration. Required ketamine IM for sedation prior to arrival.



	R_1	R_2	R_3	R_4
metonitazene	NO_2	OCH_3	CH_2CH_3	CH_2CH_3
metodesnitazene	H	OCH_3	CH_2CH_3	CH_2CH_3
etonitazene	NO_2	OCH_2CH_3	CH_2CH_3	CH_2CH_3
etodesnitazene	H	OCH_2CH_3	CH_2CH_3	CH_2CH_3
protonitazene	NO_2	$OCH_2CH_2CH_3$	CH_2CH_3	CH_2CH_3
butonitazene	NO_2	$OCH_2CH_2CH_2CH_3$	CH_2CH_3	CH_2CH_3
isotonitazene	NO_2	$OCH(CH_3)_2$	CH_2CH_3	CH_2CH_3
clonitazene	NO_2	Cl	CH_2CH_3	CH_2CH_3
flunitazene	NO_2	F	CH_2CH_3	CH_2CH_3
etonitazepyne	NO_2	OCH_2CH_3	$-CH_2CH_2CH_2CH_2-$	
etonitazepipne	NO_2	OCH_2CH_3	$-CH_2CH_2CH_2CH_2CH_2-$	

https://www.deadiversion.usdoj.gov/drug_chem_info/benzimidazole-opioids.pdf

KYOD2A Data

Complication: Alterations in Naloxone Response

Findings:

Sample ID	Sample	Date, Time	Confirmed Drug (ng/mL)
	Whole Blood		1. Gabapentin (137) 2. 11-nor-9-carboxy-delta-9-THC* (118) 3. Methamphetamine (21.9) — Stimulant 4. Fentanyl (17.9) 5. Norfentanyl* (5.5) 6. 4-ANPP (0.8) — Opioids 7. 7-Amino Clonazepam* 8. Clonazepam 9. Diazepam — Benzodiazepines 10. Diphenhydramine 11. Lidocaine 12. Naloxone 13. Nordiazepam* 14. Norpseudoephedrine 15. Oxazepam* 16. Temazepam*

Found unresponsive after snorting an unknown substance.

Given 4mg IN naloxone, with response.

Required repeat naloxone 0.4mg IV x2 while in the ED and was started on a naloxone drip.

KYOD2A Data

Complications: Of Clinical Care

- Xylazine-associated wounds
  - Complicate disposition
  - Satellite wounds
  - Frequency is unknown
- Xylazine-associated withdrawal
- Cardiovascular and neurologic complications associated with stimulants
- Adulterant-opioid or adulterant-adulterant interactions

N Engl J Med 2023; 388:2209-2212

Polysubstance Presence is Complicating

Key Takeaways

1) The illicit opioid supply is ever-changing and heavily adulterated
2) Hospital testing for adulterants and novel substances is limited and highly variable across facilities
3) The mainstays of treatment have not changed
   - Symptomatic and supportive care
   - Naloxone

QUESTIONS?

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