Understanding Fatal Overdoses

to Inform Product Development & Public Health Interventions to Manage Overdose

The public meeting will begin shortly

REAGAN-UDALL FOUNDATION FOR THE FDA

Housekeeping

REAGAN-UDALL FOUNDATION FOR THE FDA

Due to the meeting size, your microphone and video will remain off during the meeting.

This public meeting is being recorded. The slides, transcript, and video recording will be available on the FDA Foundation website after the meeting.

While we won't have time to directly address audience questions during today's meeting, you may use the Zoom chat function for comments.

Today's Agenda

REAGAN-UDALL FOUNDATION FOR THE FDA

1 p.m.	Welcome & Introduction – Susan C. Winckler, RPh, Esq.
1:05 p.m.	Opening Remarks – Robert M. Califf, MD, MACC
1:15 p.m.	Session 1: Current Landscape of Drug Use & Overdose in the U.S.
2:15 p.m.	Session 2: Pharmacology of Opioids & Overdose Management Products
3:20 p.m.	Break
3:30 p.m.	Session 3: Real-World Experiences Managing Opioid Overdose
4:45 p.m.	Adjourn

Day 2 continues tomorrow at 1pm (Eastern)

REAGAN-UDALL FOUNDATION for the Food and Drug Administration

Opening Remarks

Robert M. Califf, MD, MACC
Commissioner of Food and Drugs
U.S. Food and Drug Administration

Session 1: Current Landscape of Drug Use & Overdose in the U.S.

REAGAN-UDALL FOUNDATION FOR THE FDA

Presenters

Christopher M. Jones, PharmD, DrPH, MPH
Centers for Disease Control and Prevention

Angela Huskey, PharmD
Millennium Health

Eric D. Wish, PhD
University of Maryland

The Drug Overdose Crisis in the U.S.: What the Latest Data Tell Us

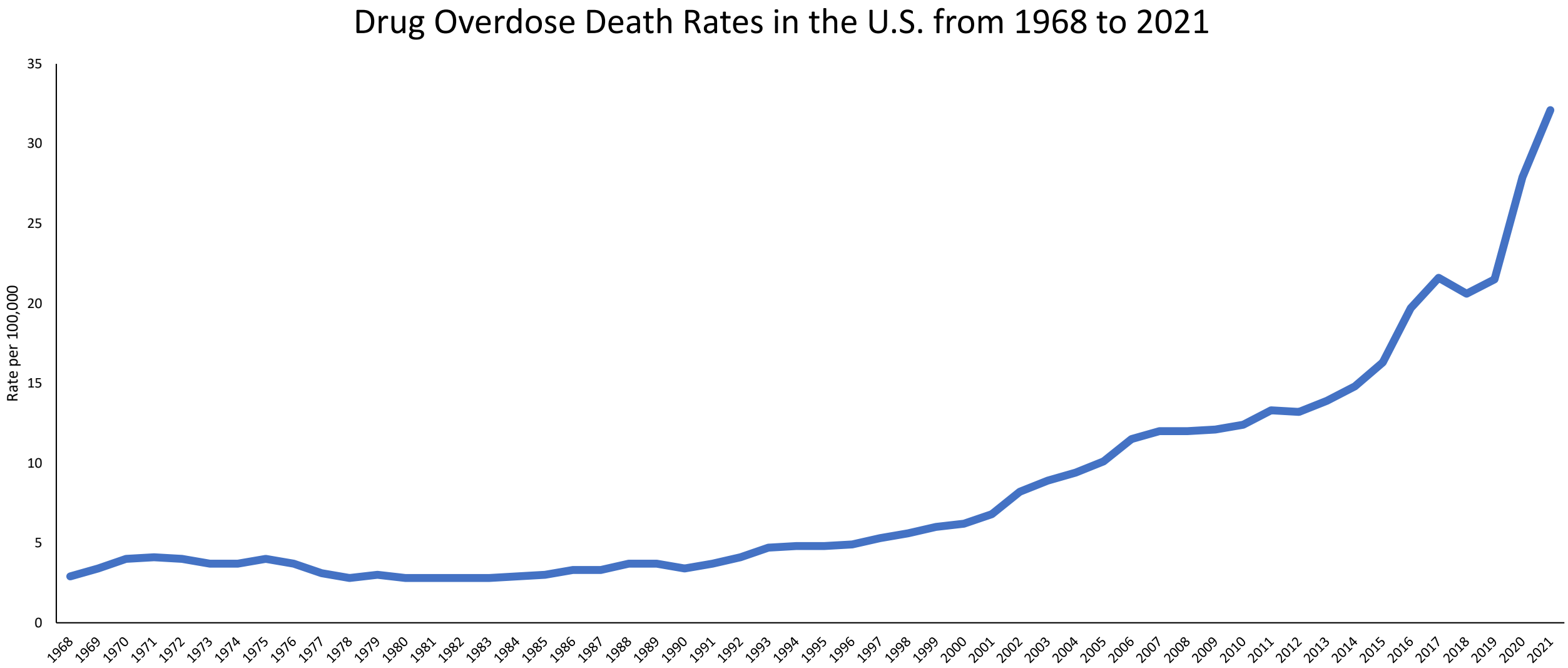
Christopher M. Jones, PharmD, DrPH, MPH

CAPT, US Public Health Service
Director
National Center for Injury Prevention and Control
Centers for Disease Control and Prevention

CDC Injury Prevention

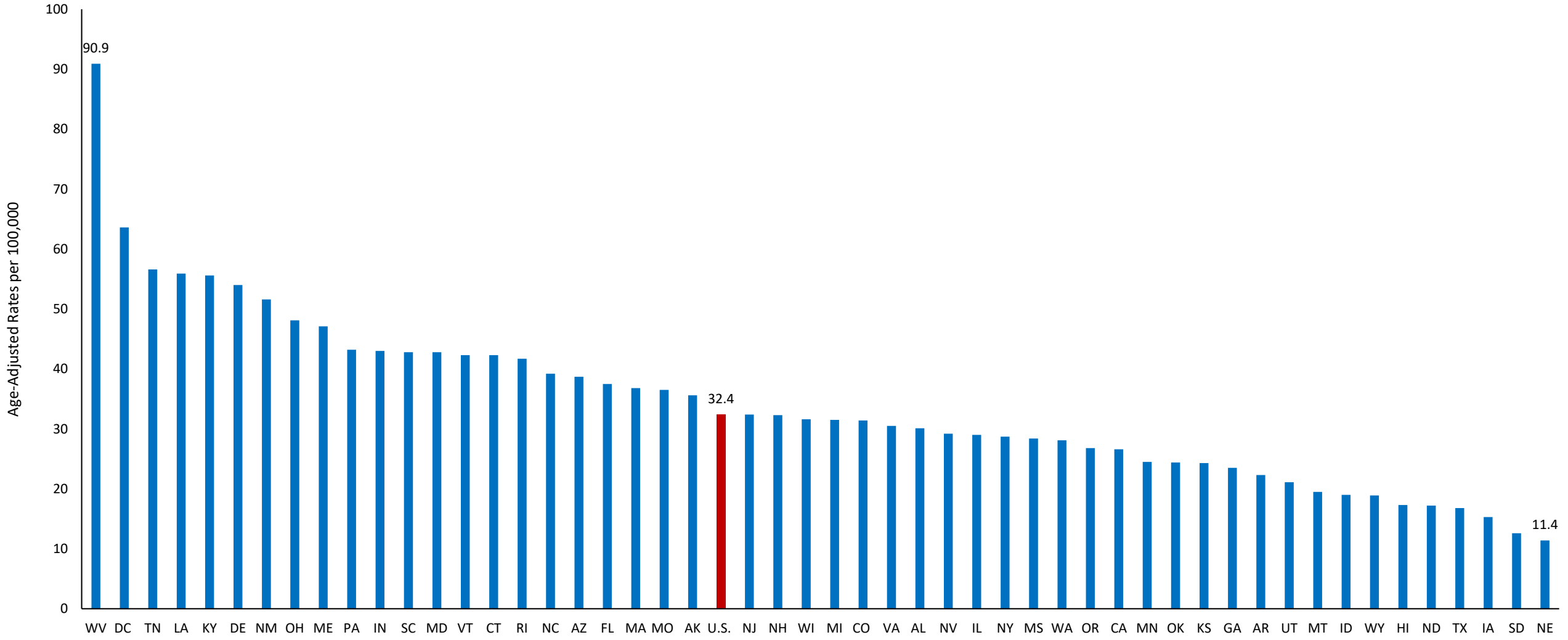
Overdose Death Trends

Current State of the Overdose Crisis – 1968 to 2021



Source: CDC WONDER National Vital Statistics Systema, 2022.

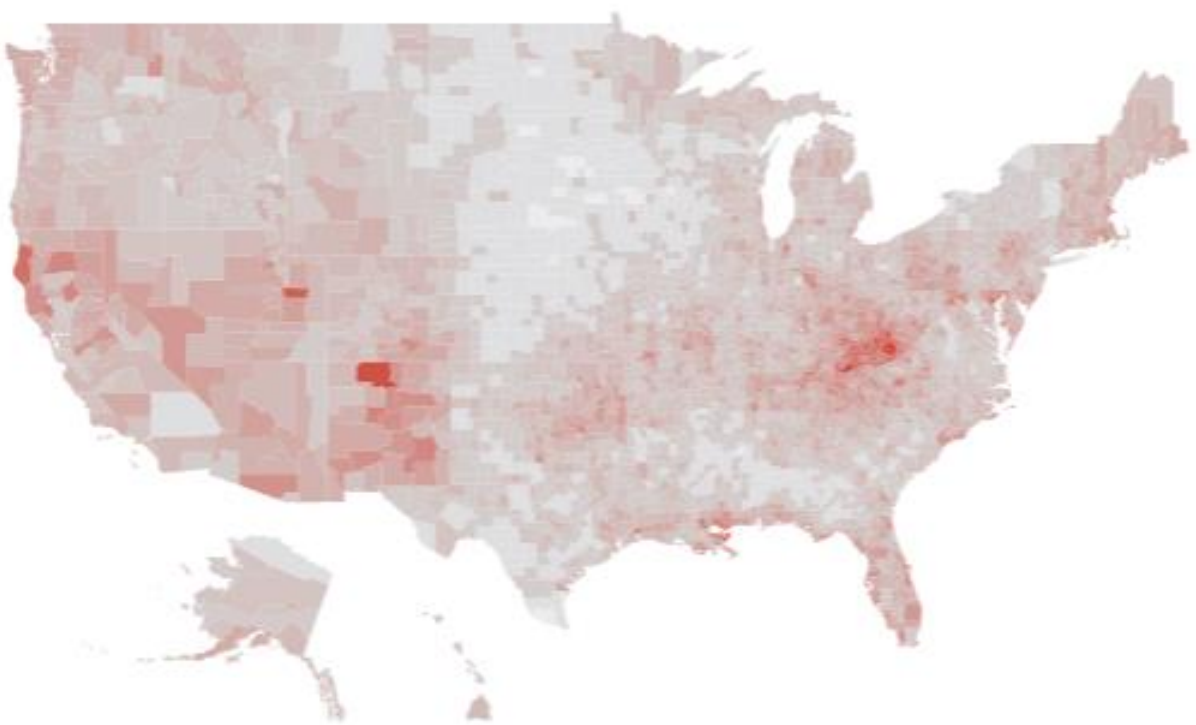
State Drug Overdose Death Rates, U.S., 2021



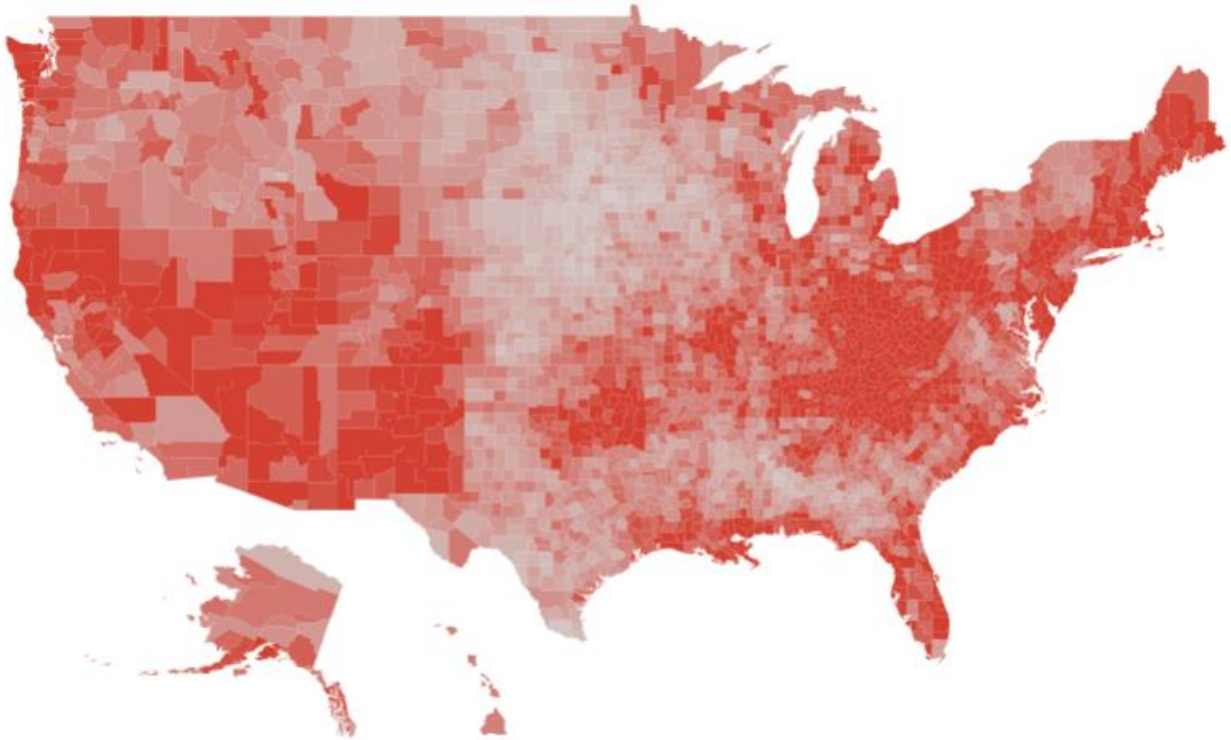
Source: CDC WONDER National Vital Statistics Systema, 2022.

Overdose Crisis Over Time at the County Level

2003



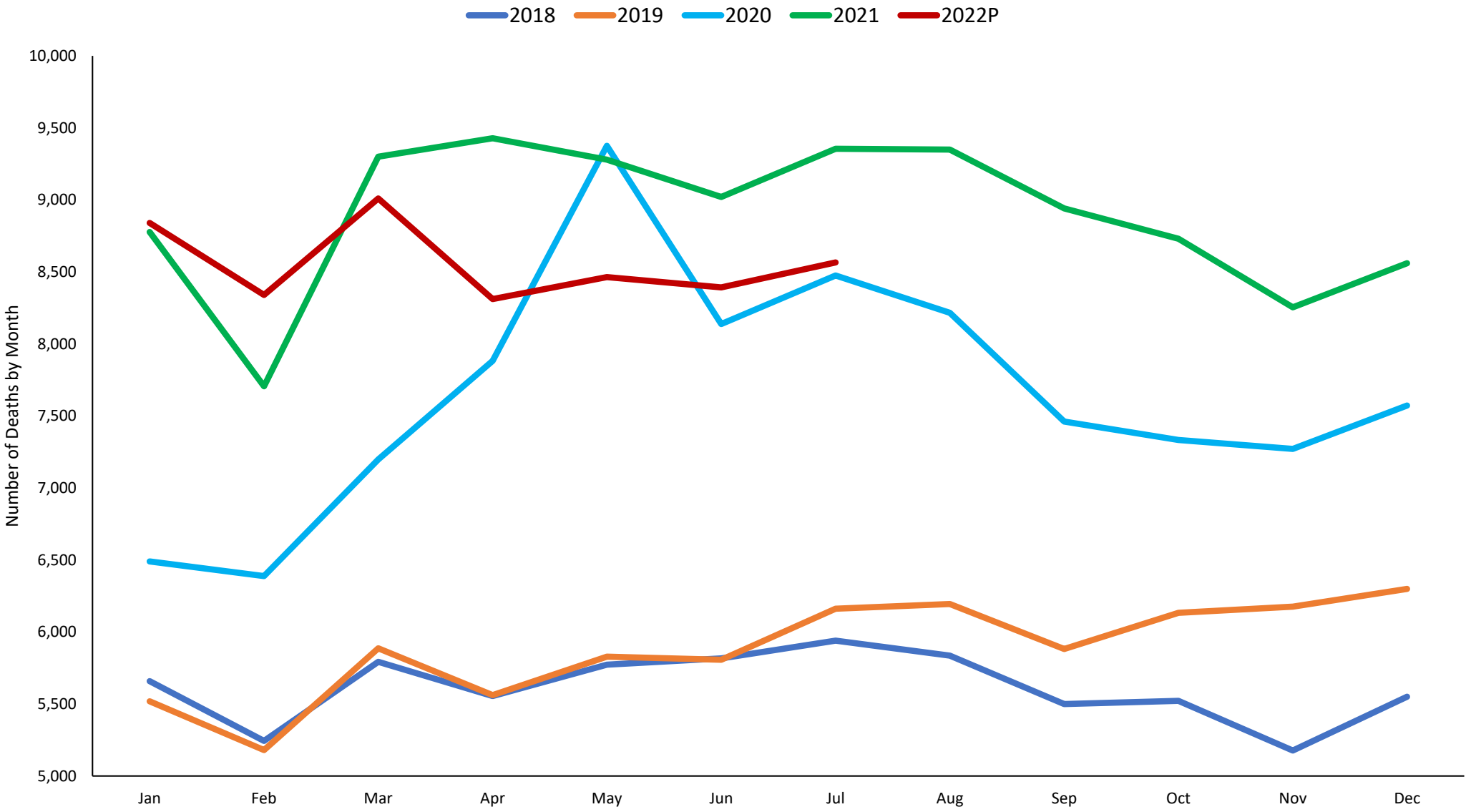
2021



Rate per 100,000 population

Source: CDC NCHS. . NCHS Data Visualization Gallery - Drug Poisoning Mortality (cdc.gov)

Latest Monthly Data on Overdose Deaths, 2018-2022P

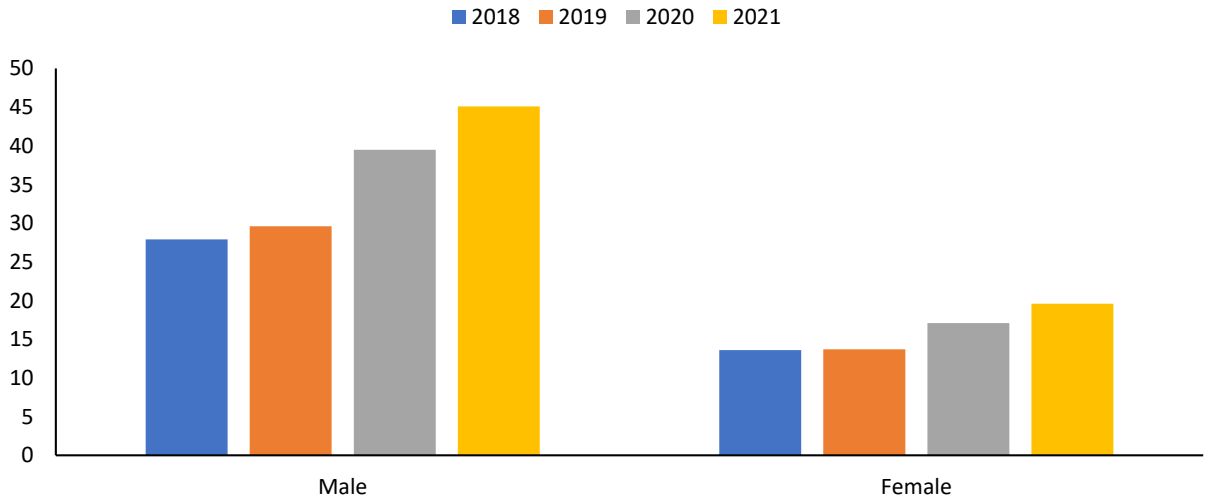


Source: CDC NCHS. NVSS/WONDER, 2022.

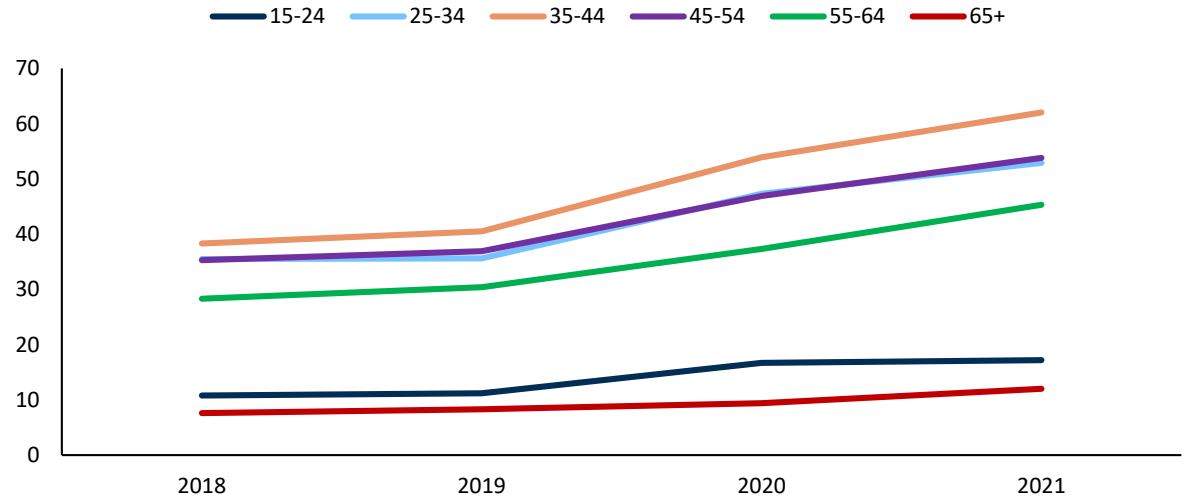
Drug Overdose Deaths 2018-2021

Drug Overdose Deaths by Demographics, 2018-2021

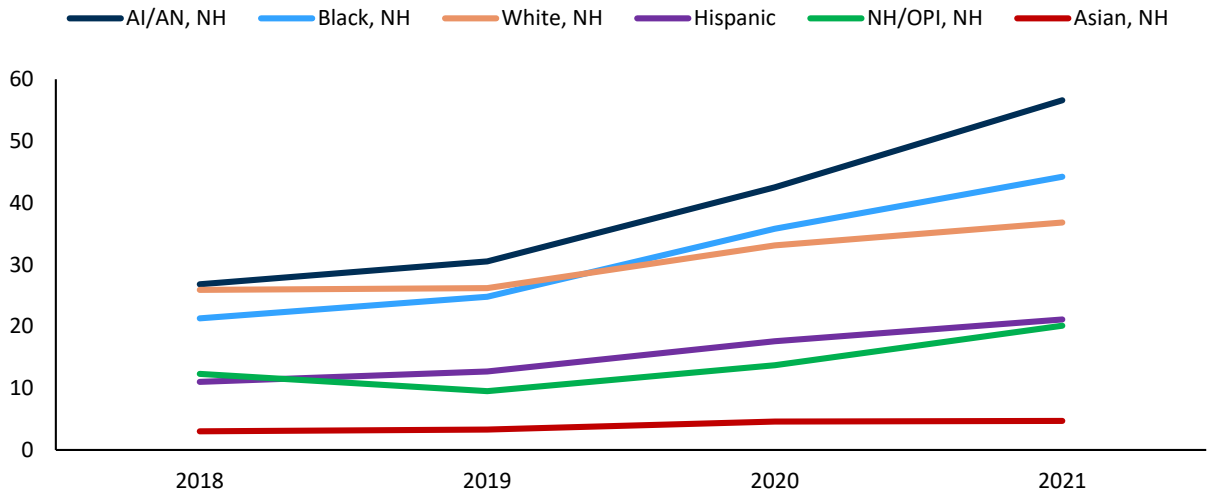
Age-Adjusted Rate per 100K by Gender



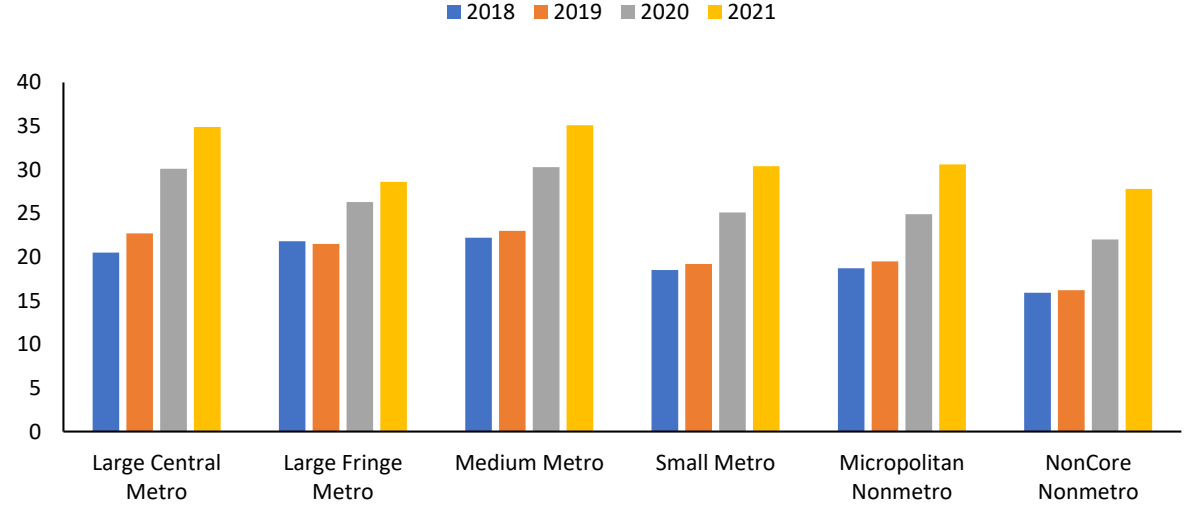
Rate per 100K by Age Group



Age-Adjusted Rate per 100K by Race/Ethnicity

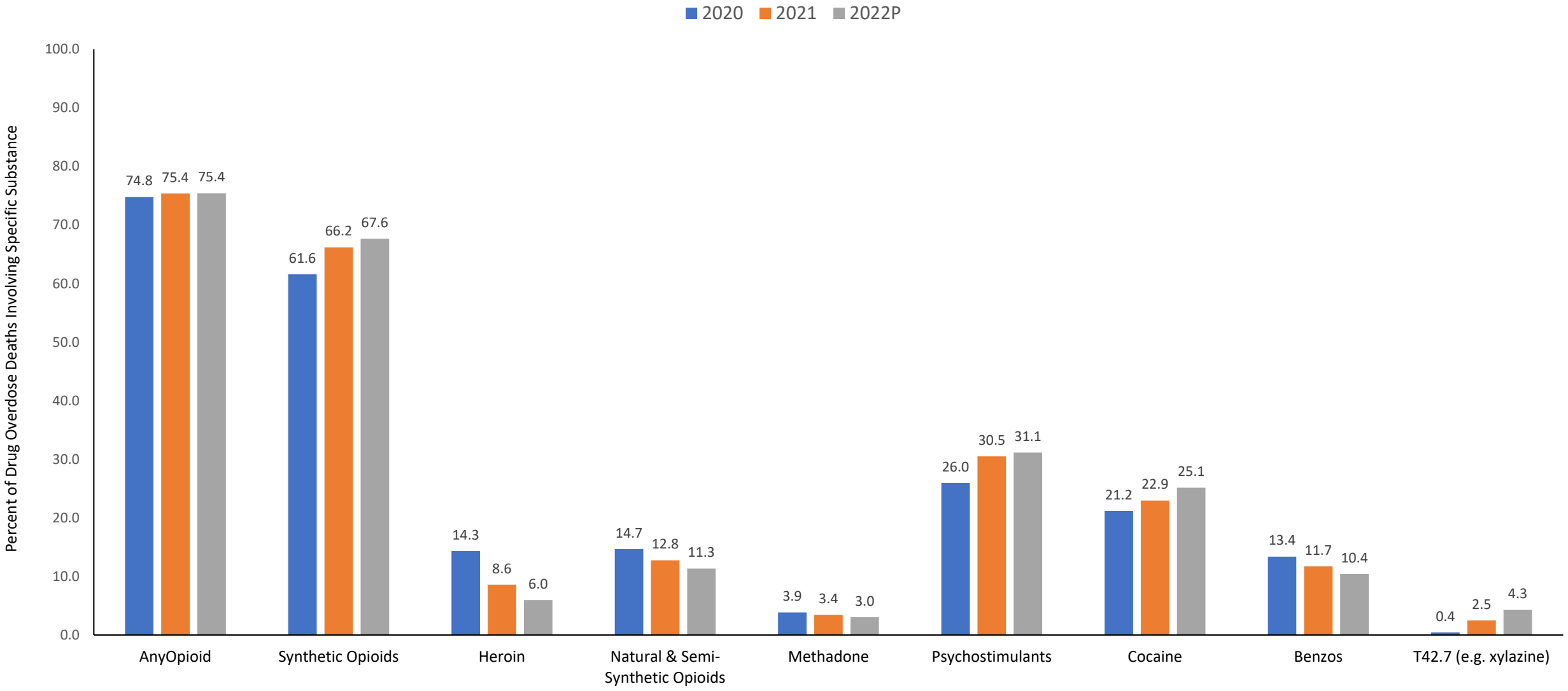


Rate per 100K by Urbanization



Source: CDC NVSS Wonder, 2022

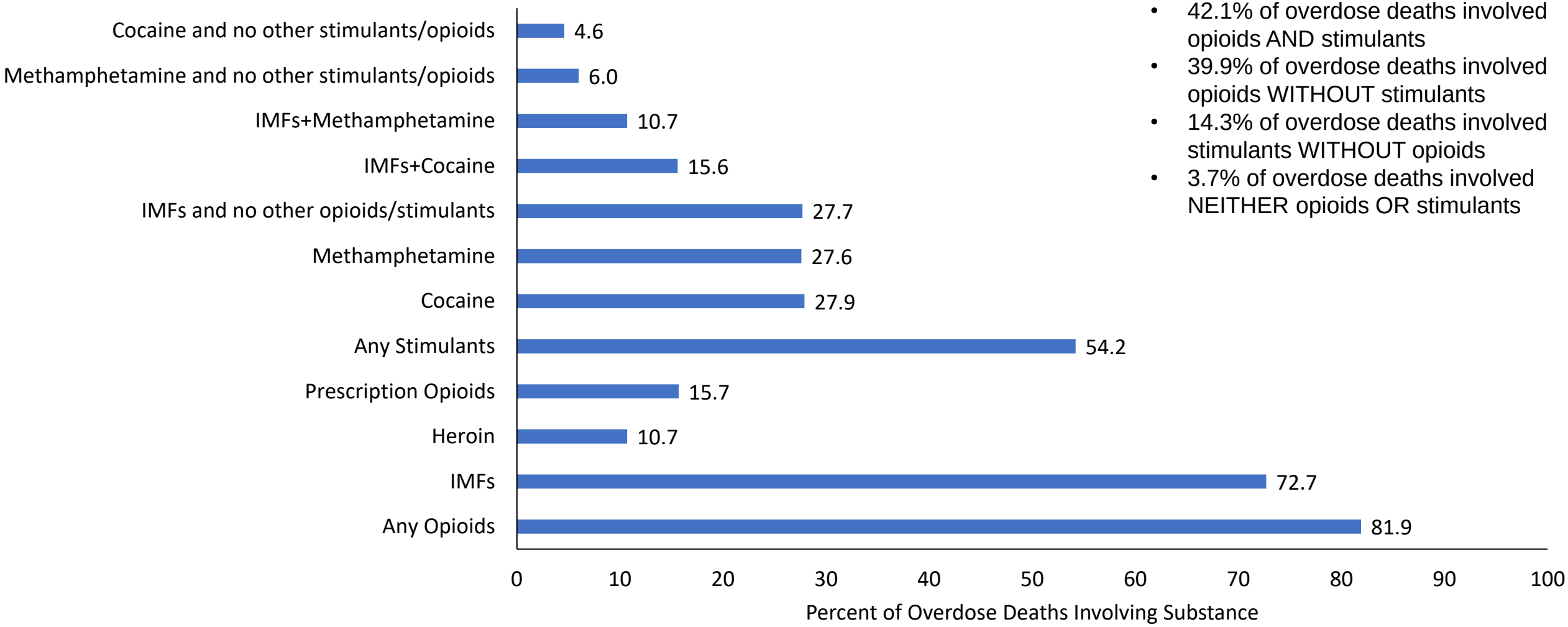
Substances Involved in Overdose Deaths, 2020-2022P



2022 data are provisional

Source: CDC NVSS Wonder, 2022

Substances Involved in Overdose Deaths from CDC SUDORS Data in 32 States in 2021

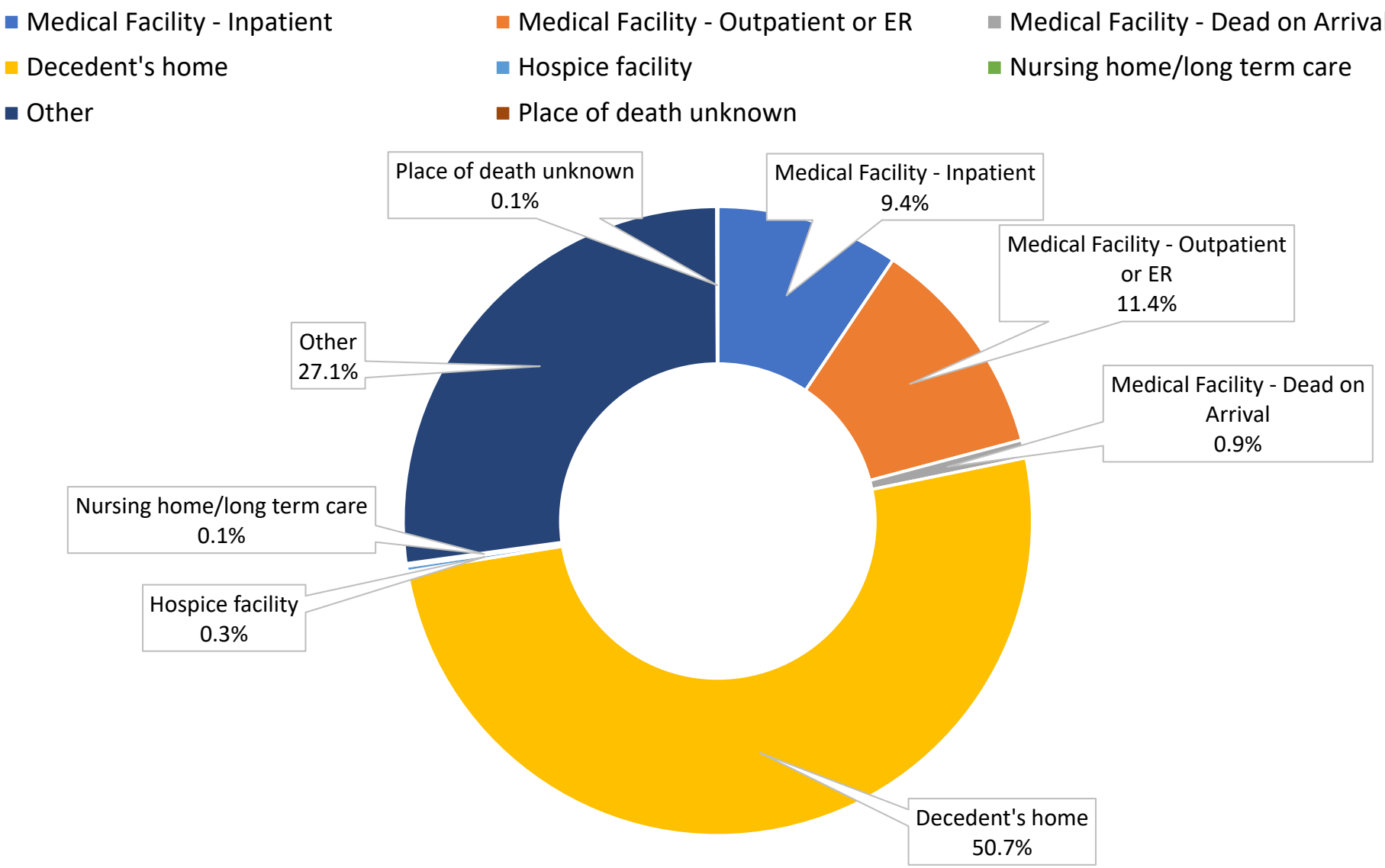


- 42.1% of overdose deaths involved opioids AND stimulants
- 39.9% of overdose deaths involved opioids WITHOUT stimulants
- 14.3% of overdose deaths involved stimulants WITHOUT opioids
- 3.7% of overdose deaths involved NEITHER opioids OR stimulants

IMFs = Illicitly manufactured fentanyls

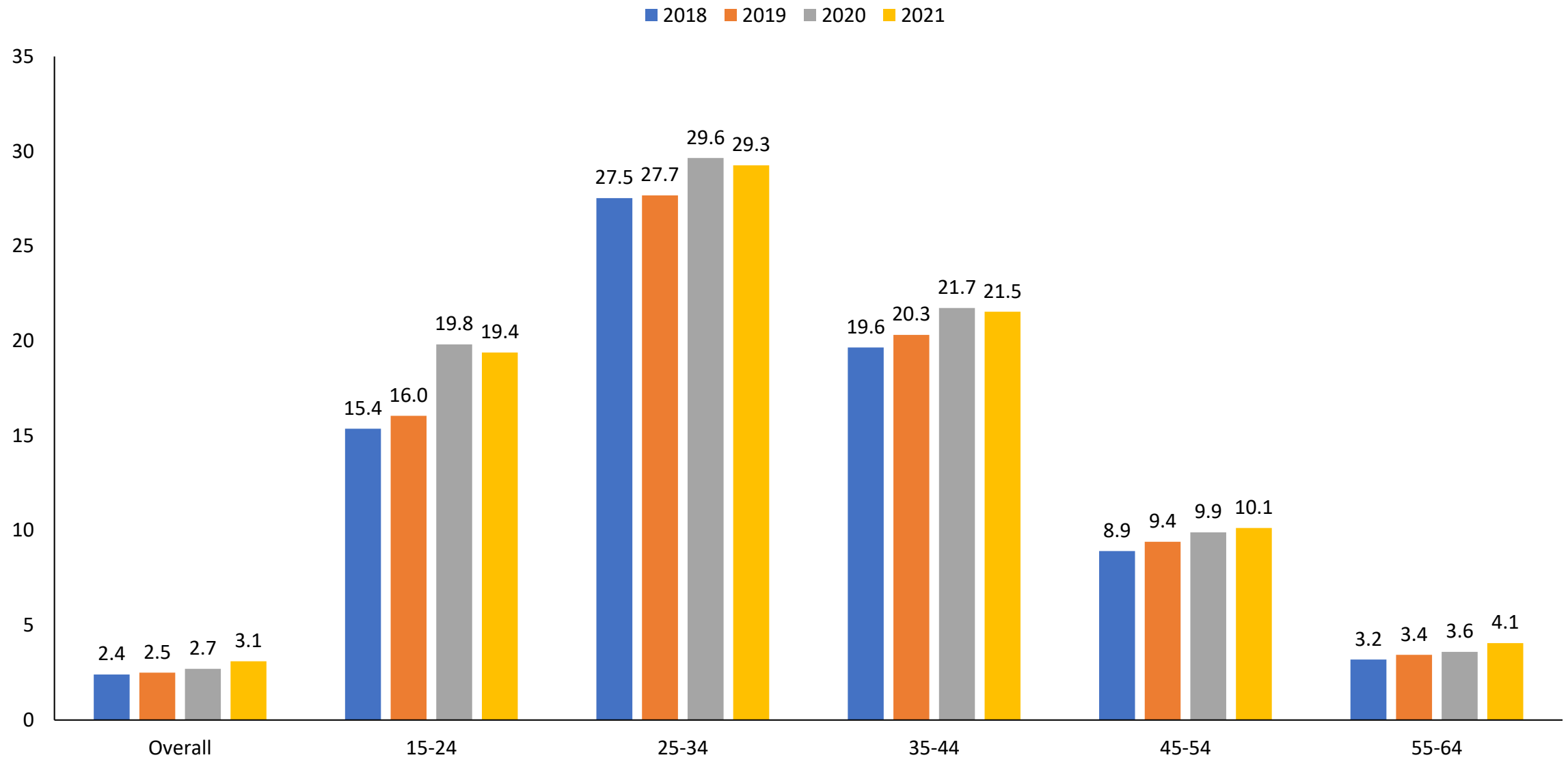
Source: SUDORS Dashboard: Fatal Overdose Data | Drug Overdose | CDC Injury Center

Place of Drug Overdose Death, 2021



Source: CDC NVSS Wonder, 2022

Percent of Deaths in the U.S. Due to Drug Overdose, Overall and by Specific Age Groups, 2018-2021

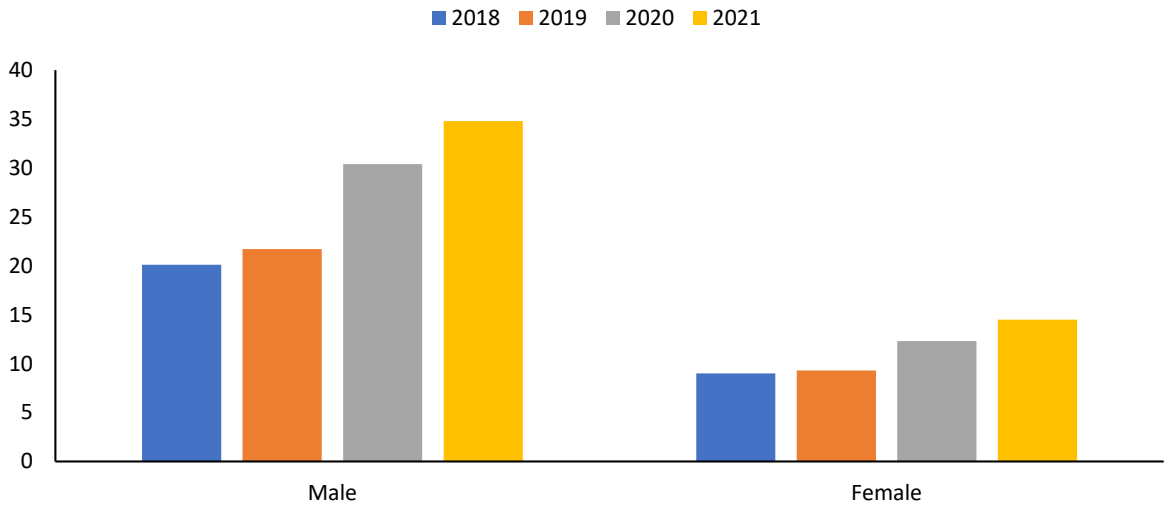


Source: CDC NVSS Wonder, 2022

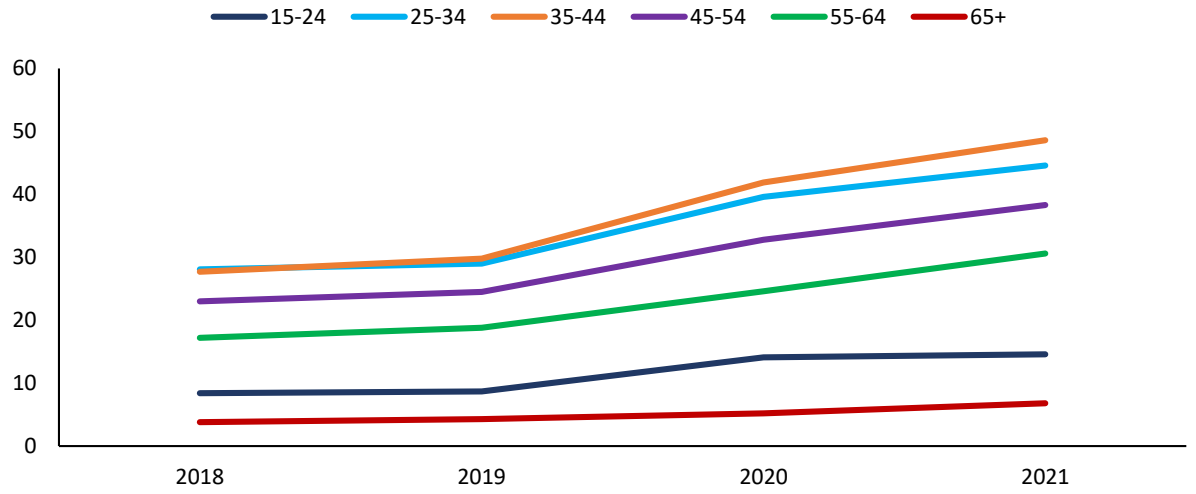
Opioid-Involved Overdose Deaths 2018-2021

Opioid-Involved Overdose Deaths by Demographics, 2018-2021

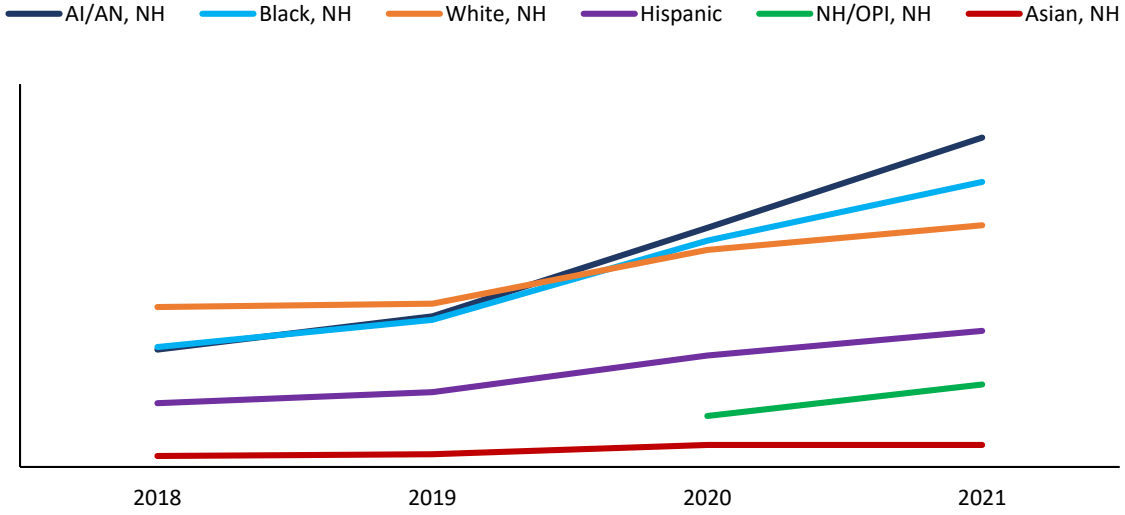
Age-Adjusted Rate per 100K by Gender



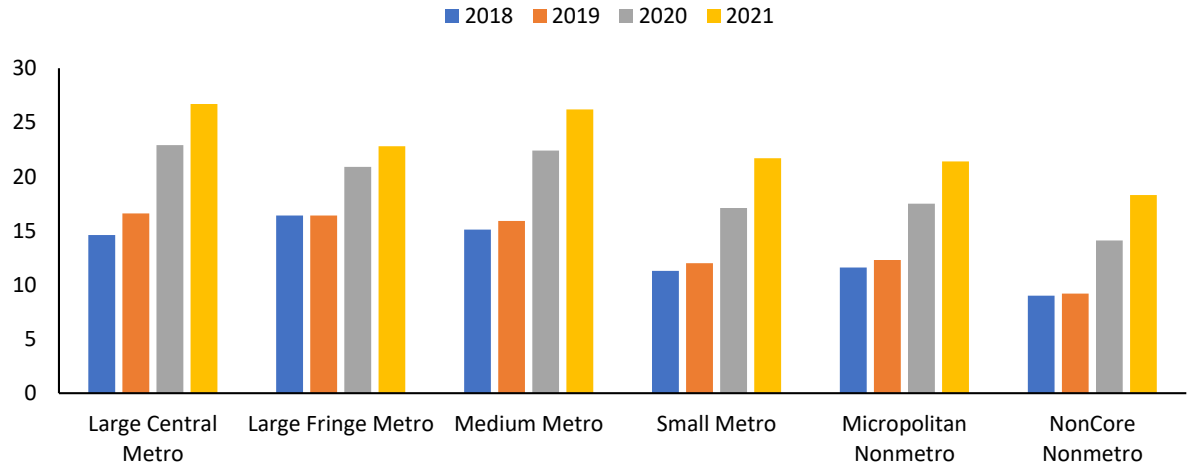
Rate per 100K by Age Group



Age-Adjusted Rate per 100K by Race/Ethnicity

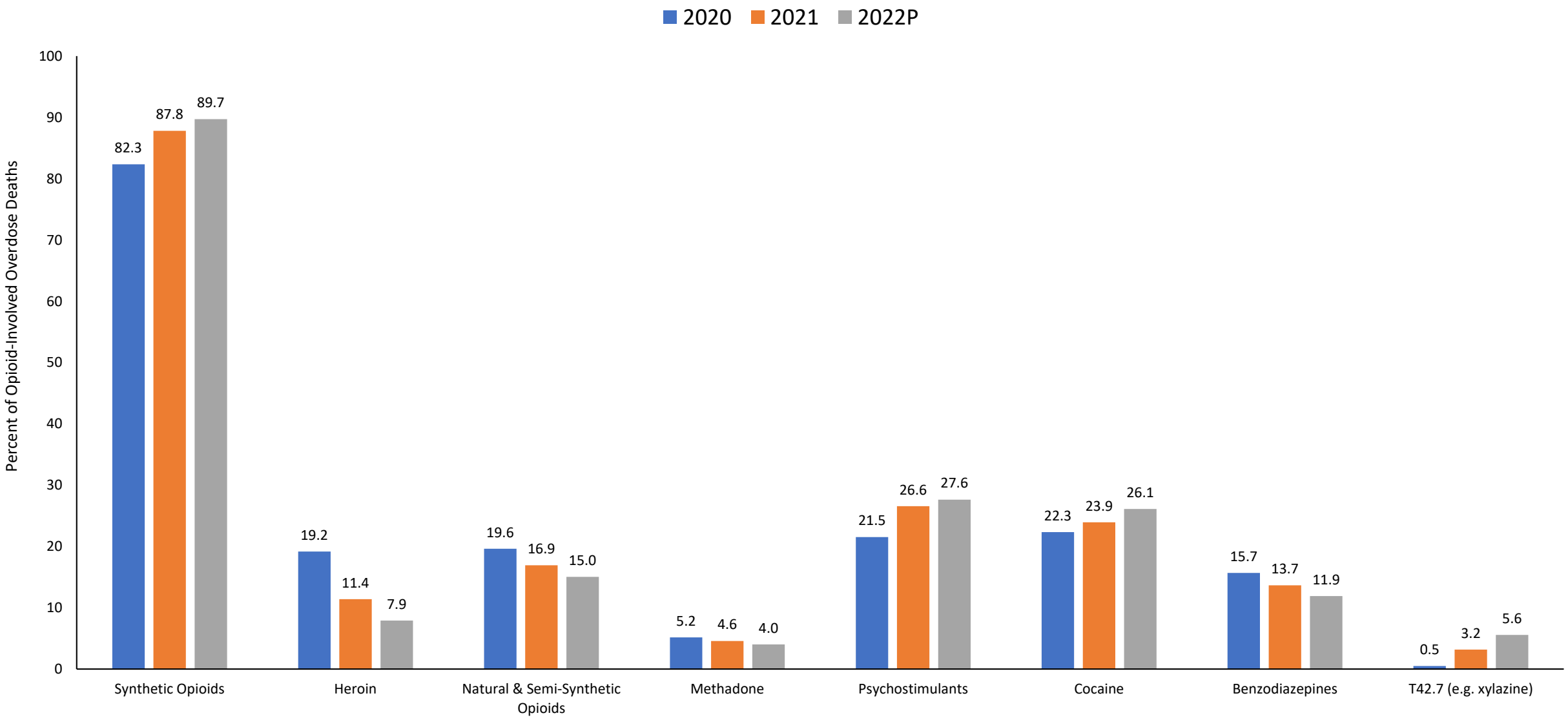


Rate per 100K by Urbanization



Source: CDC NVSS Wonder, 2022

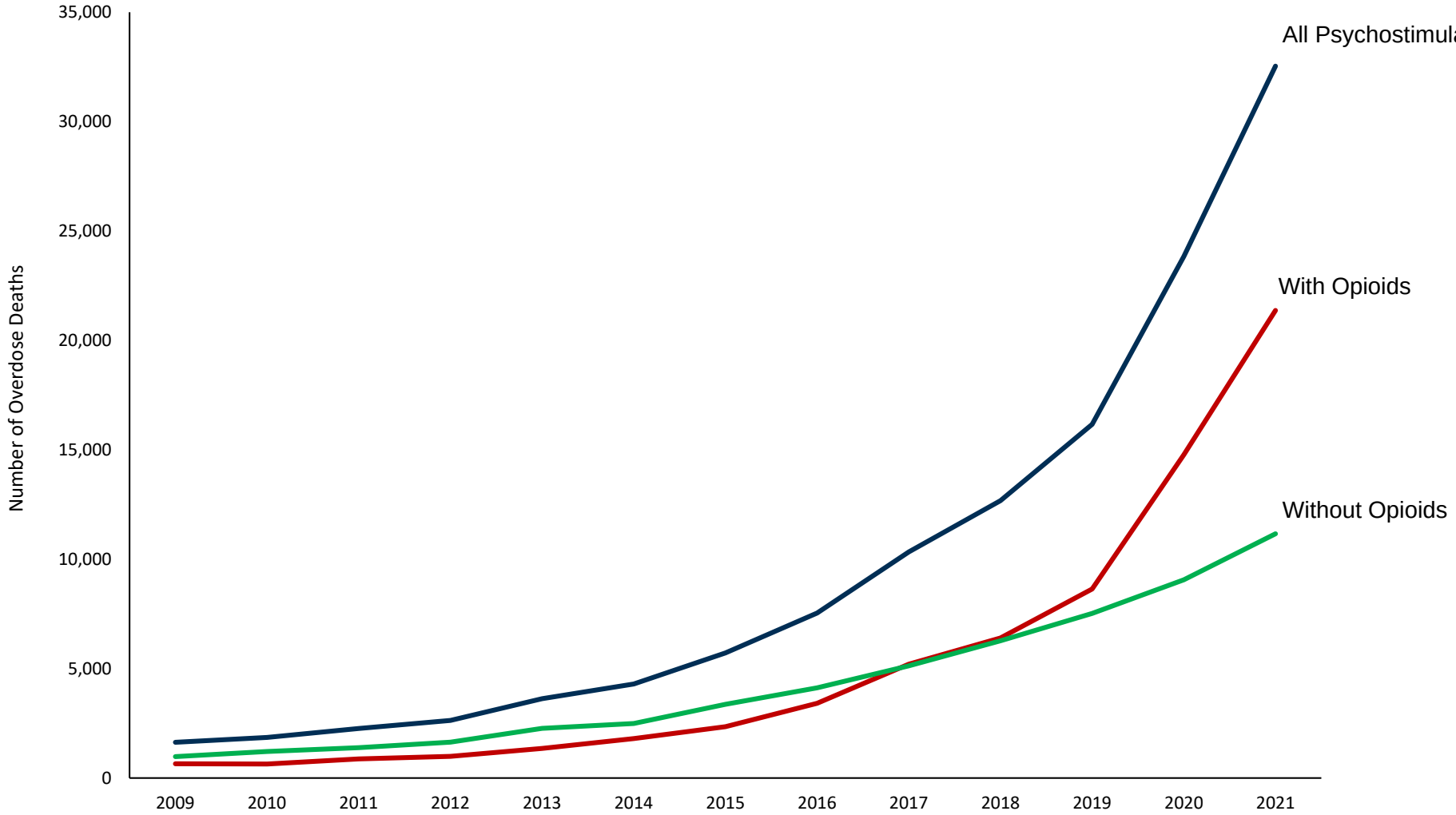
Drugs & Drug Classes Involved in Opioid-Involved Overdose Deaths



2022 data are provisional

Stimulant-Involved Overdoses

Psychostimulant-Involved Overdose Deaths, U.S., 2009-2021



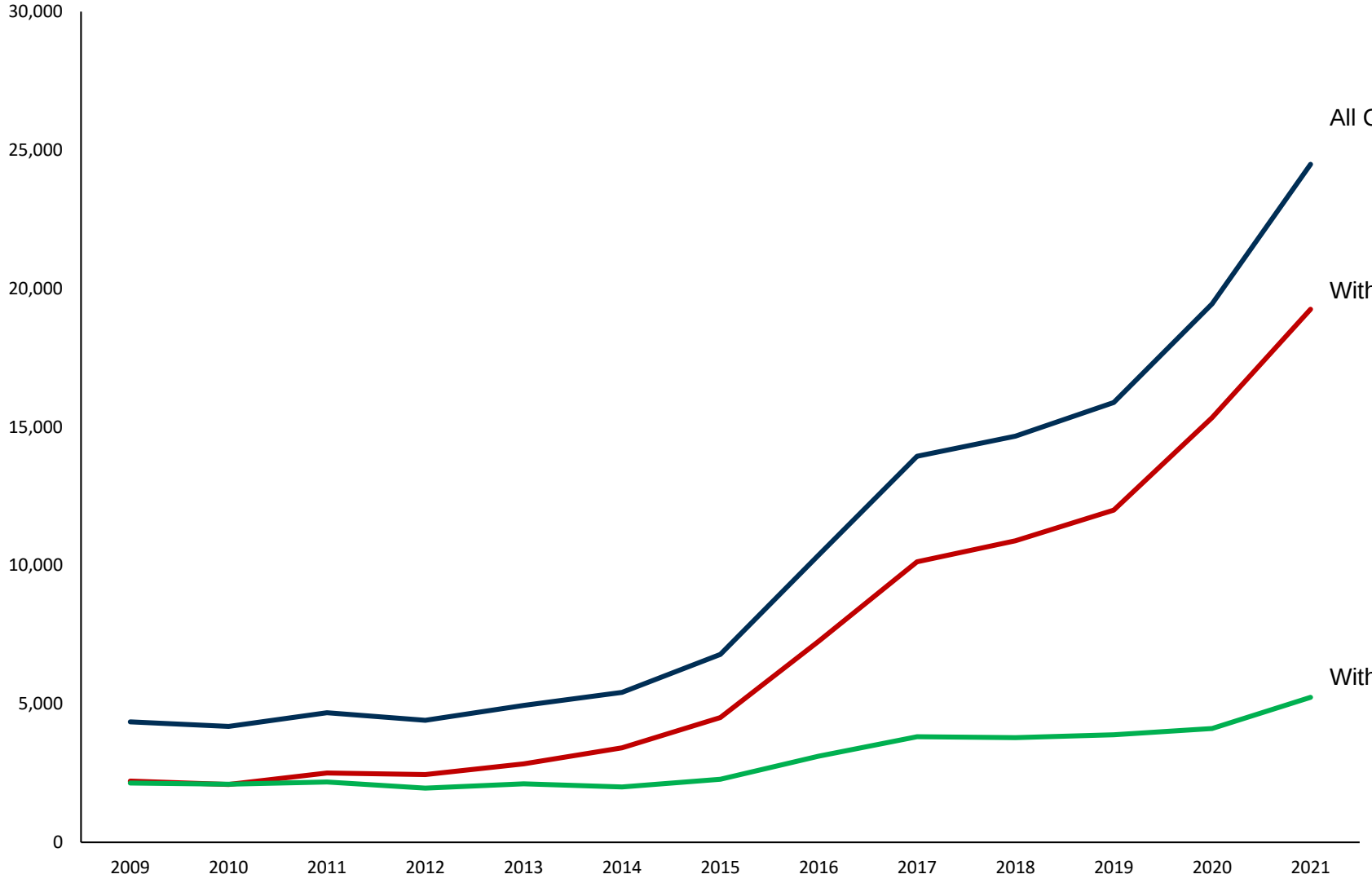
Percent involving Opioids
2018-2022P

- 2018 - 50.5%
- 2019 – 53.5%
- 2020 – 62.0%
- 2021 – 65.7%
- 2022P – 66.9%

Source: NVSS Wonder, 2022

2022 data are provisional

Cocaine-Involved Overdose Deaths, U.S., 2009-2021



Percent involving Opioids
2018-2022P

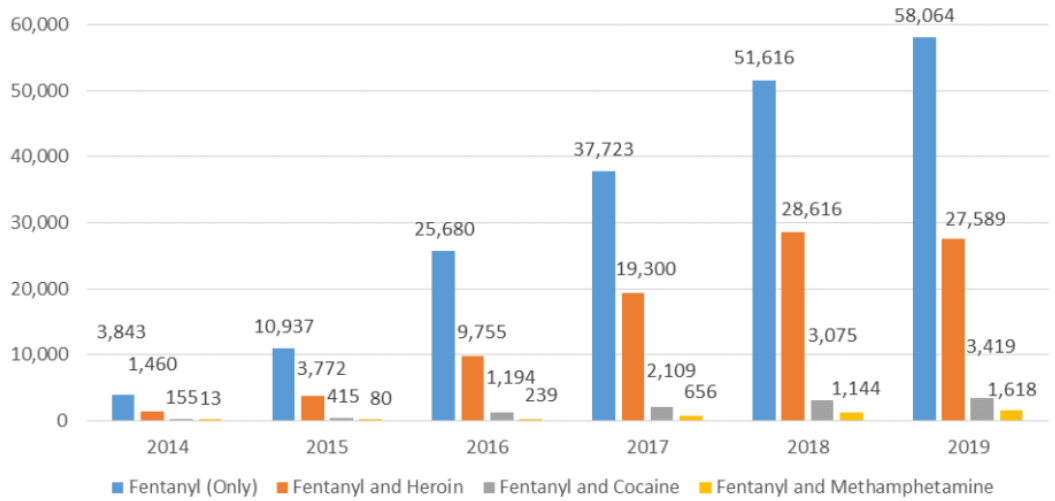
- 2018 – 74.2%
- 2019 – 75.5%
- 2020 – 78.9%
- 2021 – 78.6%
- 2022P – 78.3%

Source: NVSS Wonder, 2022

2022 data are provisional

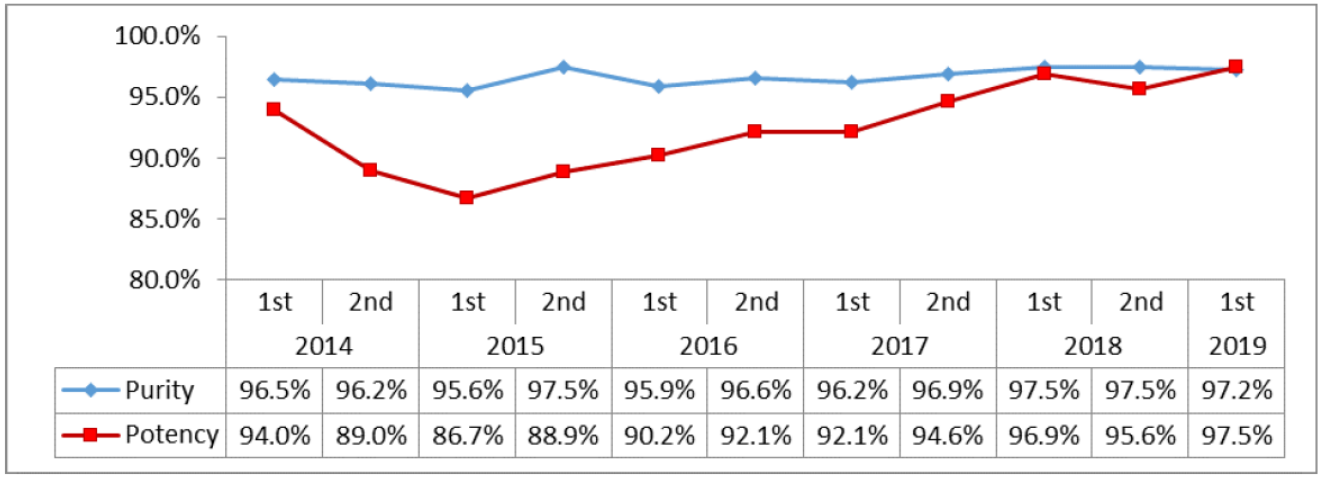
Supply Considerations

Figure 4. Fentanyl Combination Reports to NFLIS-Drug, 2014 – 2019



Source: National Forensic Laboratory Information System-Drug Retrieved July 10, 2020

Methamphetamine Purity and Potency



	1st 2014	2nd 2014	1st 2015	2nd 2015	1st 2016	2nd 2016	1st 2017	2nd 2017	1st 2018	2nd 2018	1st 2019
Purity	96.5%	96.2%	95.6%	97.5%	95.9%	96.6%	96.2%	96.9%	97.5%	97.5%	97.2%
Potency	94.0%	89.0%	86.7%	88.9%	90.2%	92.1%	92.1%	94.6%	96.9%	95.6%	97.5%

Source: DEA Methamphetamine Profiling Program

Source: DEA. 2020 National Drug Threat Assessment

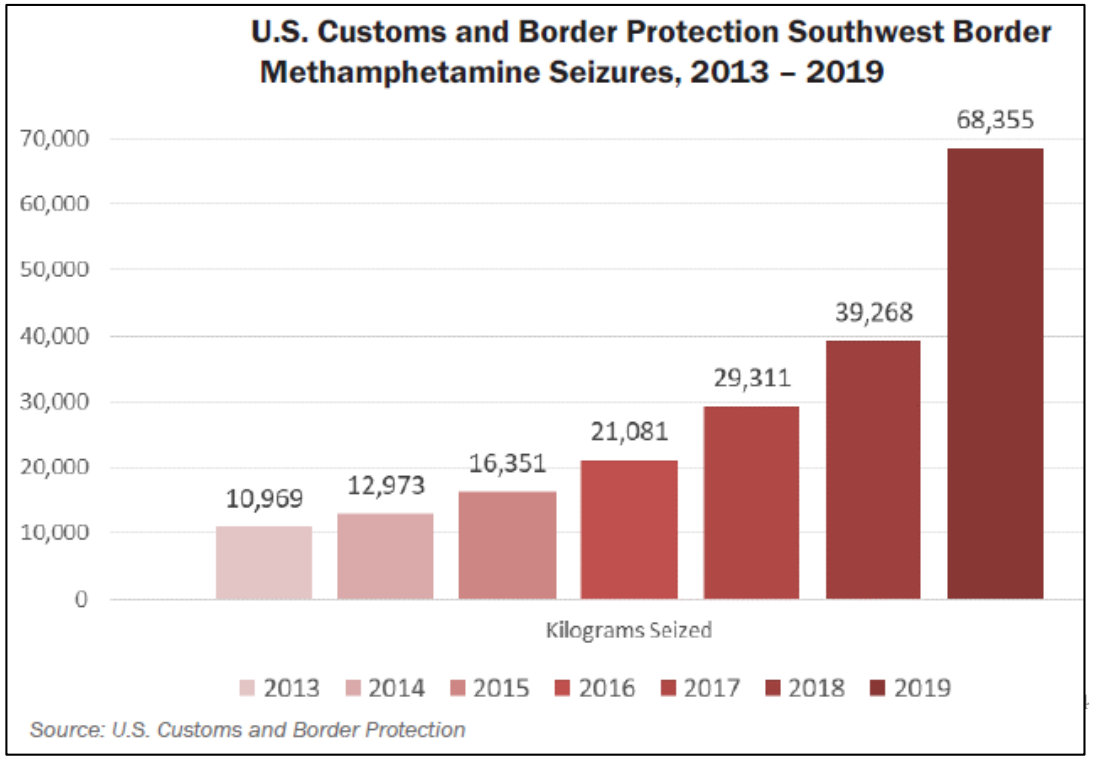
Figure 11. Counterfeit Oxycodone Tablet Containing Fentanyl

Source: Santa Clara, California Department of Health

Figure 49. Counterfeit Adderall Tablets Containing Methamphetamine seized in Michigan

Source: Michigan State Police

U.S. Customs and Border Protection Southwest Border Methamphetamine Seizures, 2013 – 2019



Source: U.S. Customs and Border Protection

Supply Considerations

Figure A.1 National trend estimates for fentanyl, alprazolam, and oxycodone, January 2001–December 2021

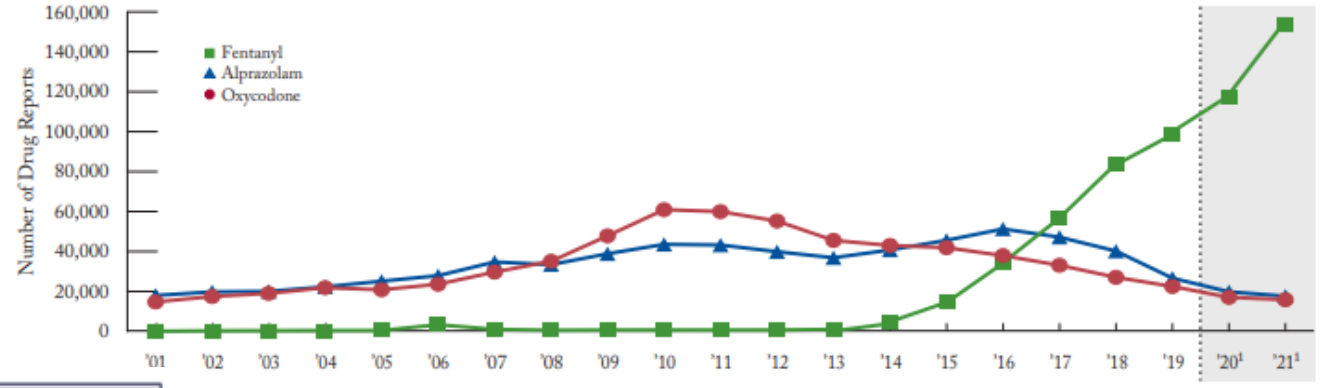


Figure A.3 National trend estimates for methamphetamine, cannabis/THC, and cocaine, January 2001–December 2021

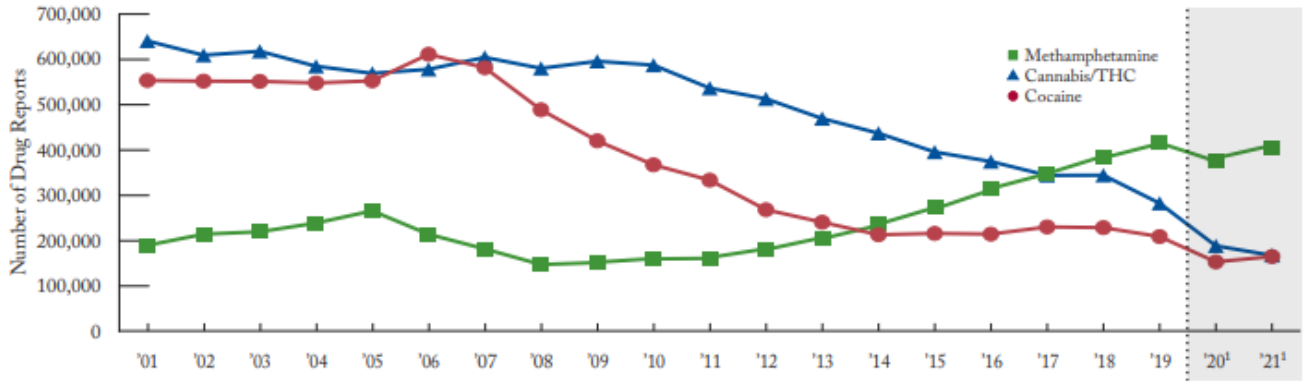
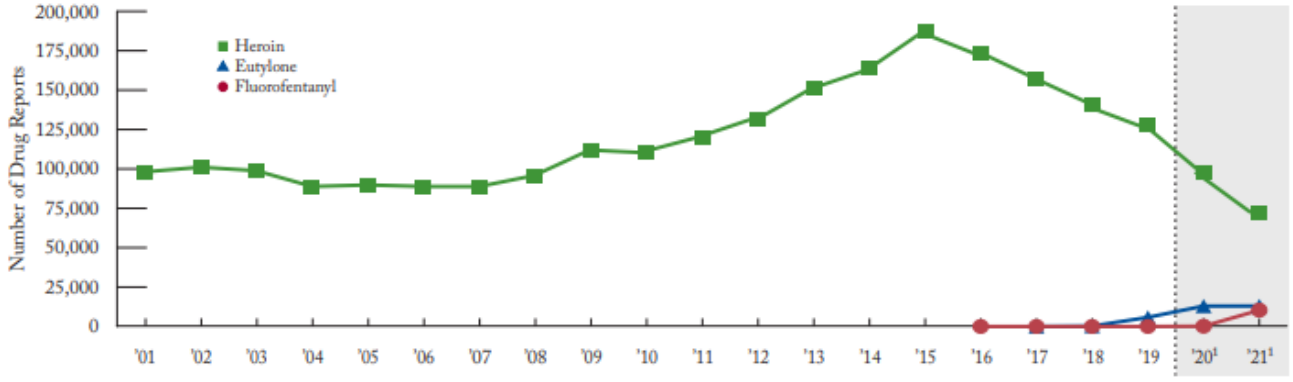


Figure A.4 National trend estimates for heroin, eutylone, and fluorofentanyl, January 2001–December 2021



Source: DEA 2021 NFLIS:

Current State of the Drug Overdose Crisis

- Overdose crisis continues to be dominated by illicit synthetic opioids such as illicitly made fentanyl (IMF) and fentanyl analogs, but most overdose deaths also involve other drugs
- The patterns of substances used and how they are being used is changing, with rising stimulant use and co-use of opioids and stimulants, especially injection use
- Substance use and overdose patterns are tied to changes in supply:
  - Westward expansion of IMF and analogs
  - Eastward expansion of methamphetamine
  - Counterfeit pills containing IMF and analogs
  - Proliferation of highly potent synthetic opioids into an unpredictable illicit drug supply increases overdose risk, especially among those using multiple substances and those unknowingly exposed
- Many missed opportunities for intervention and response
- We need to think about this holistically, not drug by drug

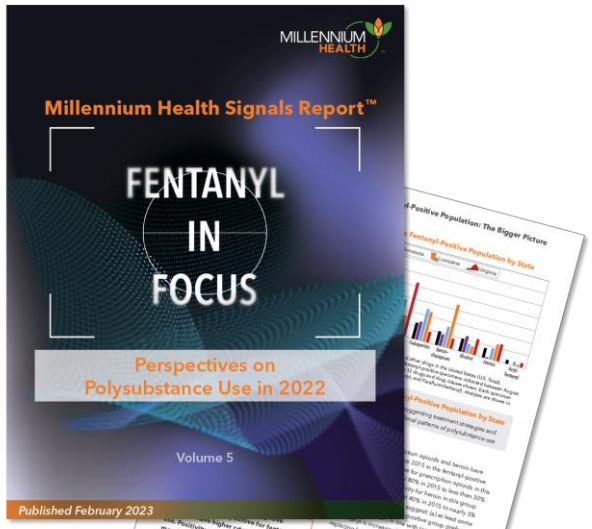
Christopher M. Jones, PharmD, DrPH, MPH
CAPT, US Public Health Service
Director, National Center for Injury Prevention and Control

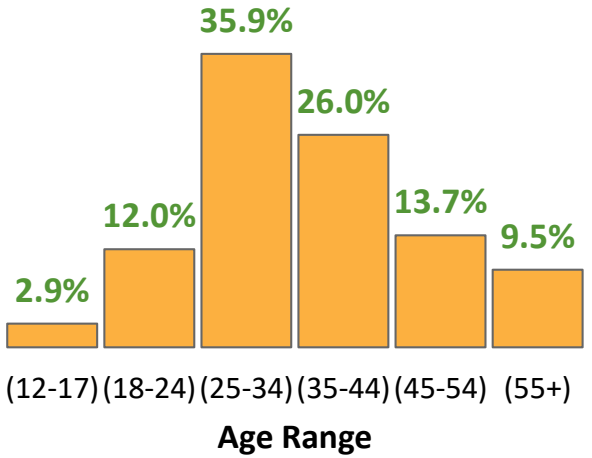
Applying Clinical Drug Testing Data for Real-Time Surveillance of Drug Use Trends

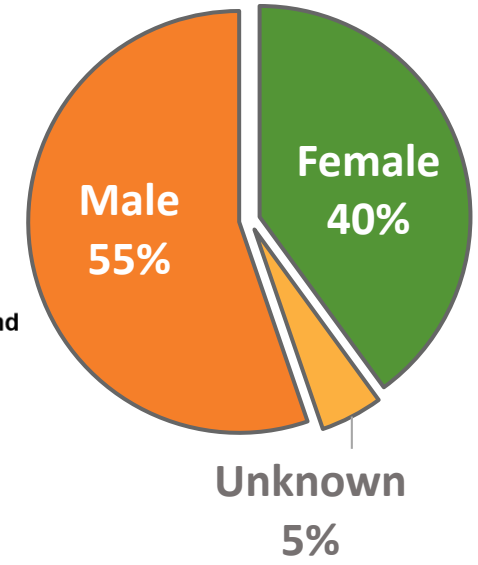
Angela Huskey, PharmD, CPE
Chief Clinical Officer, Millennium Health
angela.huskey@millenniumhealth.com

Methods

- Cross-sectional analysis of definitive urine drug testing (UDT) results from over 4.5 million specimens and more than 600,000 unique patients
- Collected in substance use disorder (SUD) treatment facilities in all 50 U.S. states between 2015 - 2022
- Positivity rates were adjusted by U.S. census division where appropriate







Millennium Health LLC. Fentanyl in Focus: Perspectives on Polysubstance Use in 2022. Millennium Health Signals Report™, Voume 5. https://www.millenniumhealth.com/signalsreport/. Published February, 2023.

Urine Drug Test Results Significantly and Strongly Correlate with Overdose Mortality

JAMA Network Open

THE OHIO STATE UNIVERSITY
COLLEGE OF MEDICINE

Original Investigation | Public Health

Analysis of Urine Drug Test Results From Substance Use Disorder Treatment Practices and Overdose Mortality Rates, 2013-2020

Penn Whitley, BA; Leah LaRue, PharmD, CMPP, PMP; Soledad A. Fernandez, PhD; Steven D. Passik, PhD; Eric Dawson, PharmD; Rebecca D. Jackson, MD

Abstract

IMPORTANCE Drug overdose deaths in the US are currently the highest ever recorded; data collected from public health surveillance sources can help to identify emerging drug use patterns associated with overdose mortality rates, but the time lag in results often limits utility. Urine drug testing (UDT) is one potentially underused source that could augment surveillance efforts through timely data collection.

OBJECTIVE To evaluate the correlation between real-time UDT results from a proprietary national database and overdose mortality data from the National Vital Statistics System.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cross-sectional study included 500 000 urine specimens submitted for UDT by substance use disorder (SUD) treatment health care practices and collected between January 1, 2013, and December 31, 2020. Real-time UDT data were obtained from the Millennium Health proprietary national database, and overdose mortality data were obtained from the National Vital Statistics System of the Centers for Disease Control and Prevention (CDC WONDER). Specimens were analyzed for specific drugs in 5 categories (cocaine, heroin, methamphetamine, synthetic opioids, and other opioids) using liquid chromatography–tandem mass spectrometry. Participants were adults aged 18 years and older who provided urine specimens at SUD treatment practices.

EXPOSURES Urine drug testing.

MAIN OUTCOMES AND MEASURES The primary outcome was the correlation between UDT positivity rates and overdose mortality rates at national, state, and county levels. Univariate and multivariate regression models were also used to evaluate the association between state- and county-level overdose mortality and standardized UDT positivity rates.

Key Points

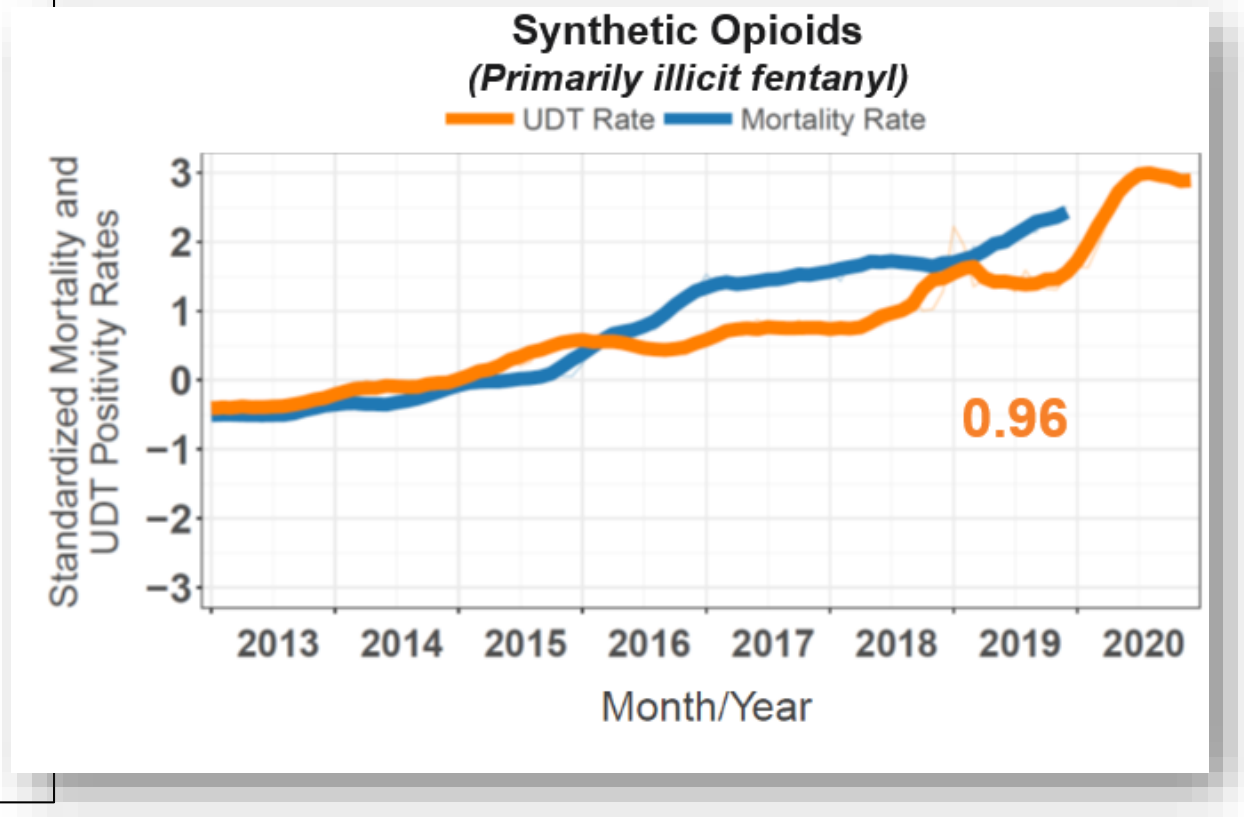
Question Do urine drug test (UDT) results correlate with overdose mortality rates?

Findings In this cross-sectional study of 500 000 unique urine specimens collected from substance use disorder treatment practices, UDT results for 5 drug categories were correlated with overdose mortality rates at national, state, and county levels. Correlation was strongest for synthetic opioids and methamphetamine, and multivariate regression analysis using state-level data revealed that synthetic opioid and methamphetamine UDT positivity rates were significantly associated with overdose deaths.

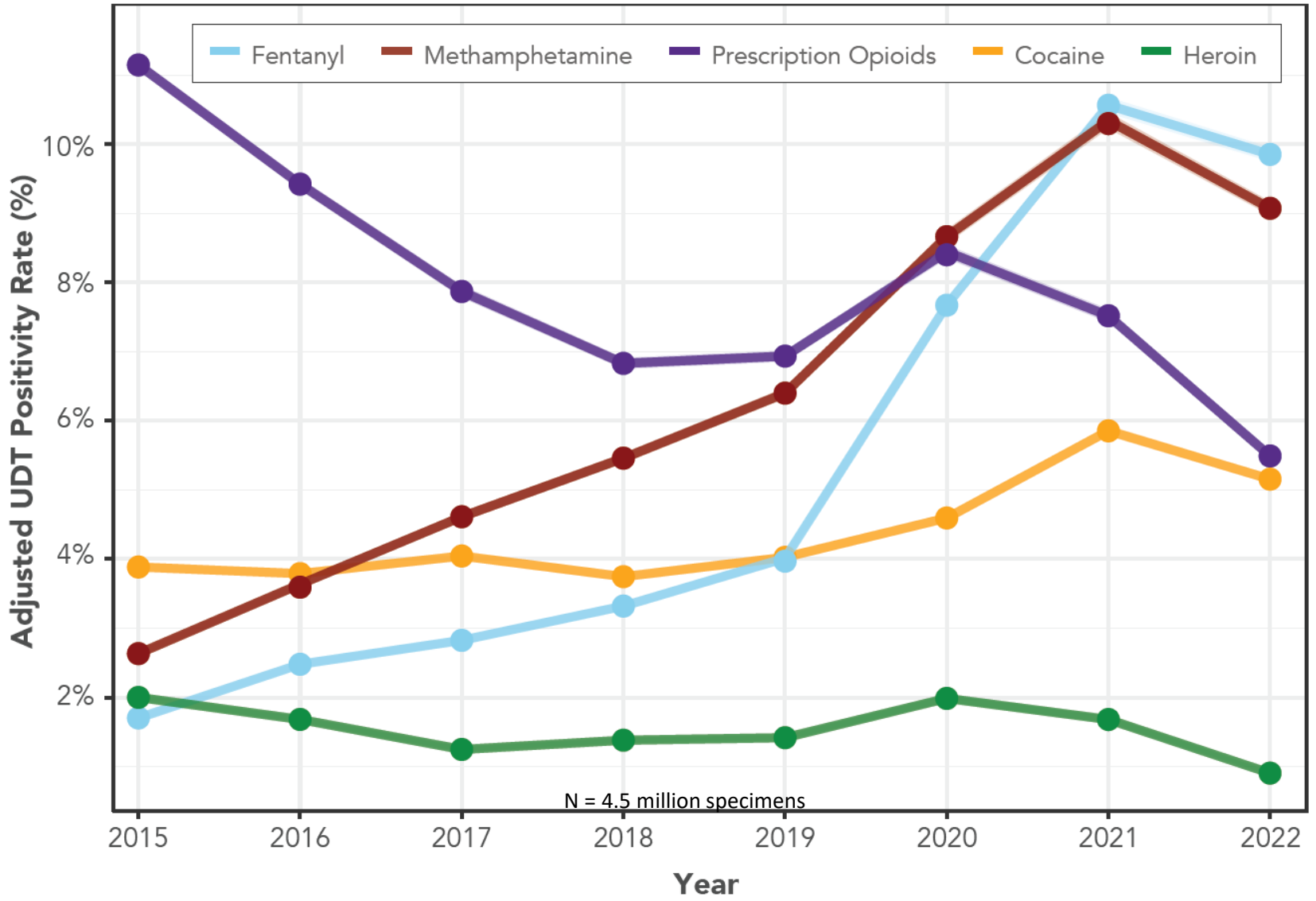
Meaning This study's findings suggest that UDT is a valuable data source that is capable of informing real-time surveillance efforts.

+ Invited Commentary

+ Supplemental content



Whitley P, LaRue L, Fernandez SA, Passik SD, Dawson E, Jackson RD. Analysis of Urine Drug Test Results From Substance Use Disorder Treatment Practices and Overdose Mortality Rates, 2013-2020. *JAMA Netw Open*. 2022;5(6):e2215425. Published 2022 Jun 1. doi:10.1001/jamanetworkopen.2022.15425.



Adjusted UDT Positivity Rates and 95% confidence interval (CI) values for fentanyl, methamphetamine, prescription opioids (hydrocodone, oxycodone, morphine, codeine, and tramadol; without a reported prescription), cocaine, and heroin in patient specimens collected in SUD treatment settings from 2015 through 2022. Positivity rates were adjusted by U.S. Census Division using GEE logistic regression

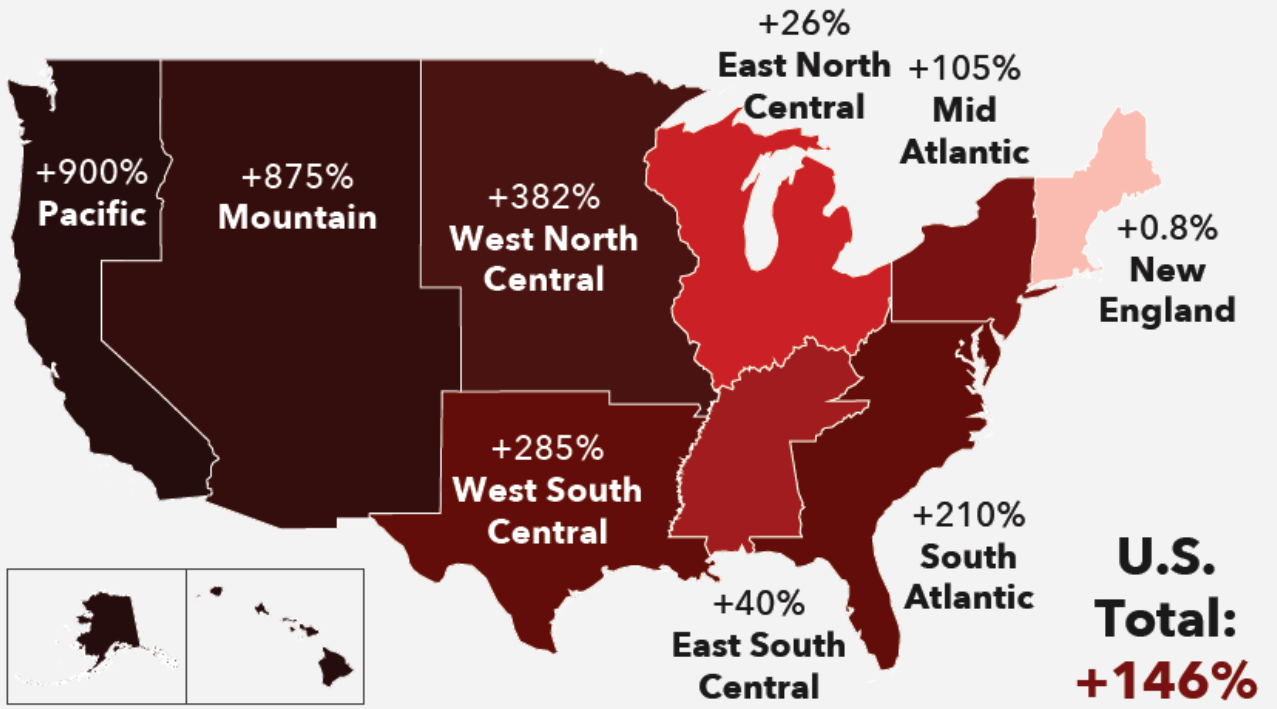
Millennium Health LLC. Fentanyl in Focus: Perspectives on Polysubstance Use in 2022. Millennium Health Signals Report™, Voume 5. https://www.millenniumhealth.com/signalsreport/. Published February, 2023.

Fentanyl use continues to rise across the country, most dramatically in Pacific and Mountain regions

Fentanyl

	UDT Positivity	
U.S. Census Division	2019	2022
Pacific	1.0%	9.8%
Mountain	1.5%	14.5%
West North Central	2.2%	10.6%
West South Central	1.6%	6.2%
East North Central	7.2%	9.1%
East South Central	7.7%	10.8%
Mid Atlantic	1.4%	3.0%
South Atlantic	5.4%	16.6%
New England	8.7%	8.8% (NS)
US Total	4.0%	9.9%

Percent Change



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Geographical Analysis of Drug Use Trends

Methamphetamine

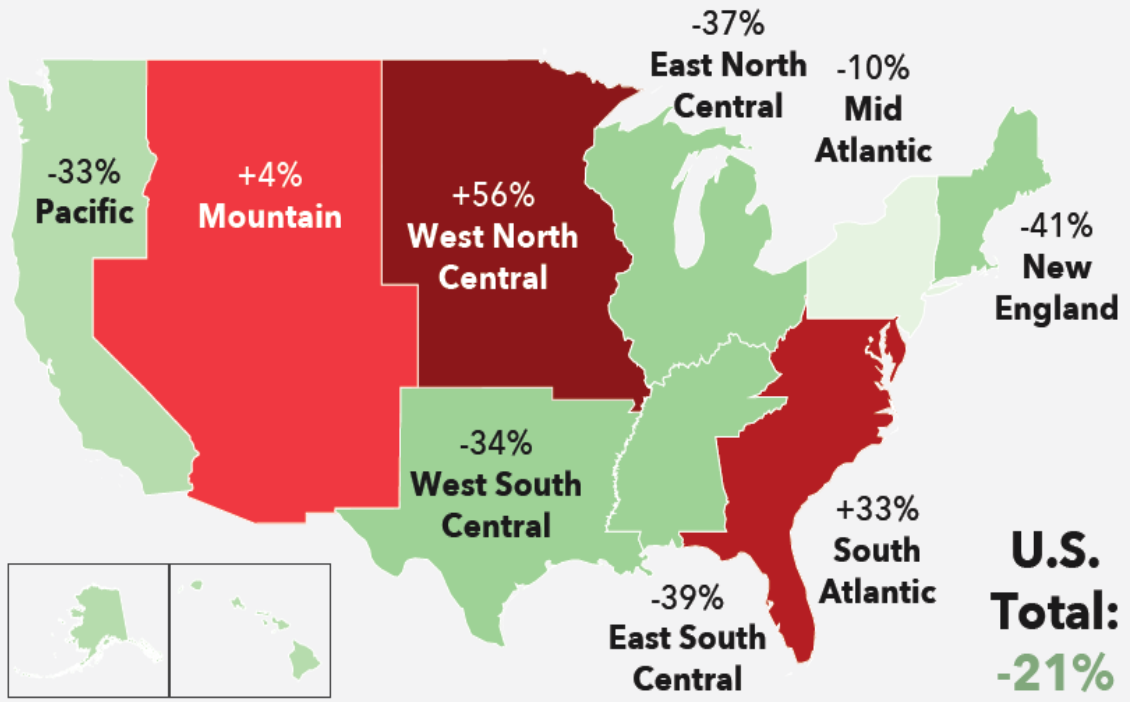
U.S. Census Division	UDT Positivity 2019	2022
Pacific	10.4%	12.1%
Mour		
West Nort		
West Sout		
East Nortl		
East Soutl		
Mid At		
South A		
New En		
US T		

Percent Change

Prescription Opioids

U.S. Census Division	UDT Positivity 2019	2022
Pacific	11.6%	7.8%
Mountain	3.6%	3.7% (NS)
West North Central	4.1%	6.4%
West South Central	6.3%	4.2%
East North Central	6.6%	4.2%
East South Central	9.0%	5.5%
Mid Atlantic	5.4%	4.8% (NS)
South Atlantic	7.2%	9.6%
New England	5.6%	3.3%
US Total	6.9%	5.5%

Percent Change



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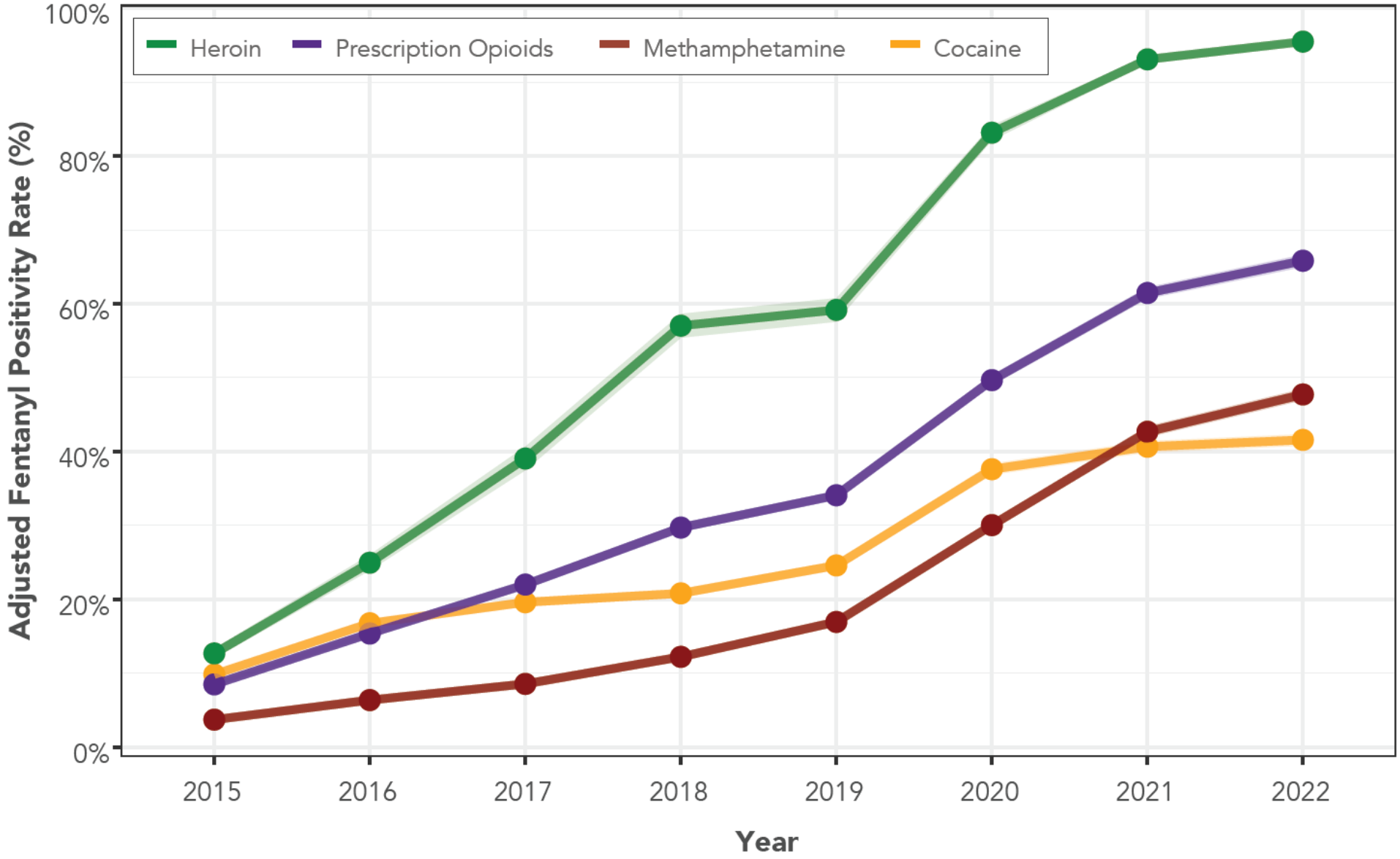


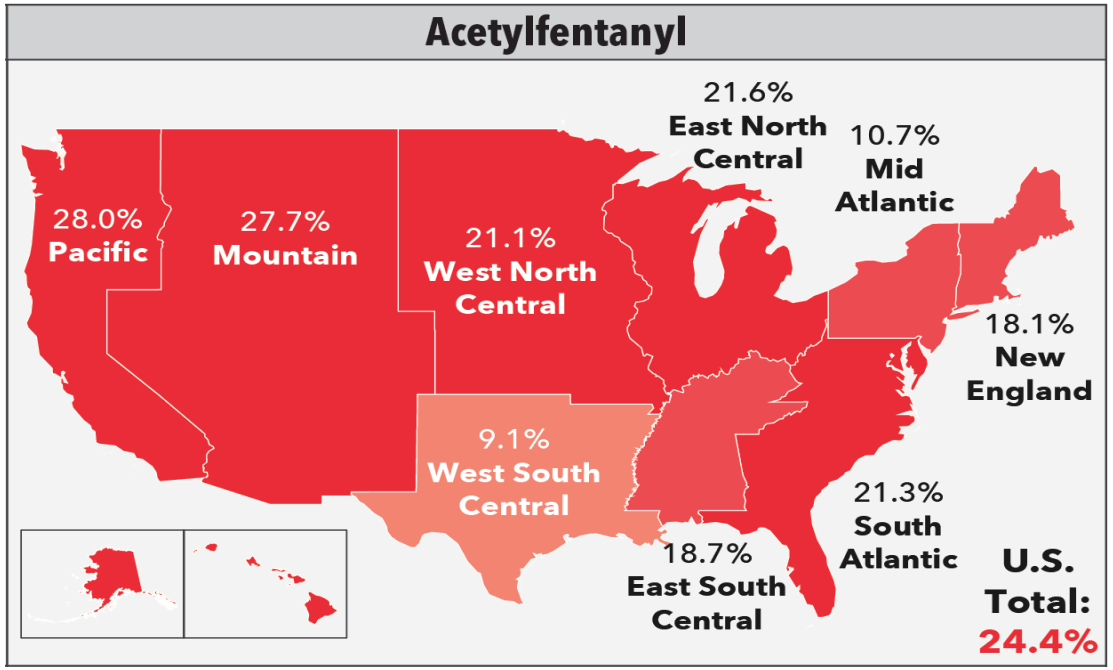
The proportion of fentanyl-positive specimens among individuals positive for heroin, prescription opioids, methamphetamine, or cocaine from 2015 through 2022. Shading represents 95% confidence interval (CI) values. UDT positivity rates were adjusted for U.S. Census Division (see Methods).

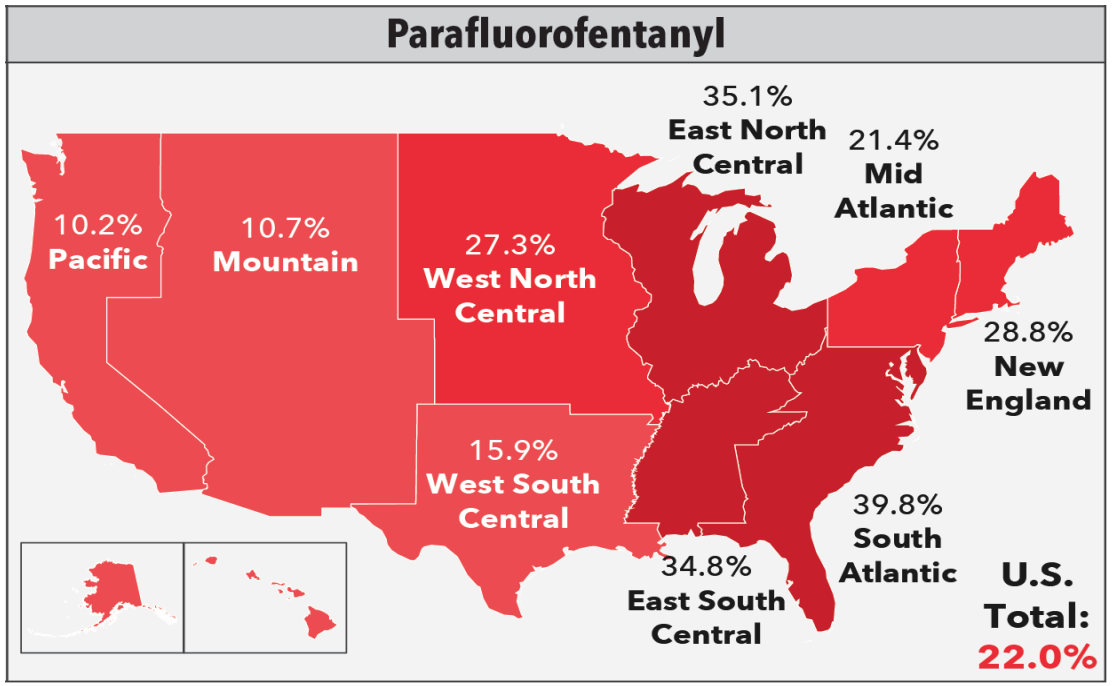
Millennium Health LLC. Fentanyl in Focus: Perspectives on Polysubstance Use in 2022. Millennium Health Signals Report™, Voume 5. https://www.millenniumhealth.com/signalsreport/. Published February, 2023.

Over 60% of specimens positive for fentanyl were also positive for one or more fentanyl analogues, with geographic differences

<u>These geographical differences may have important clinical implications</u>:

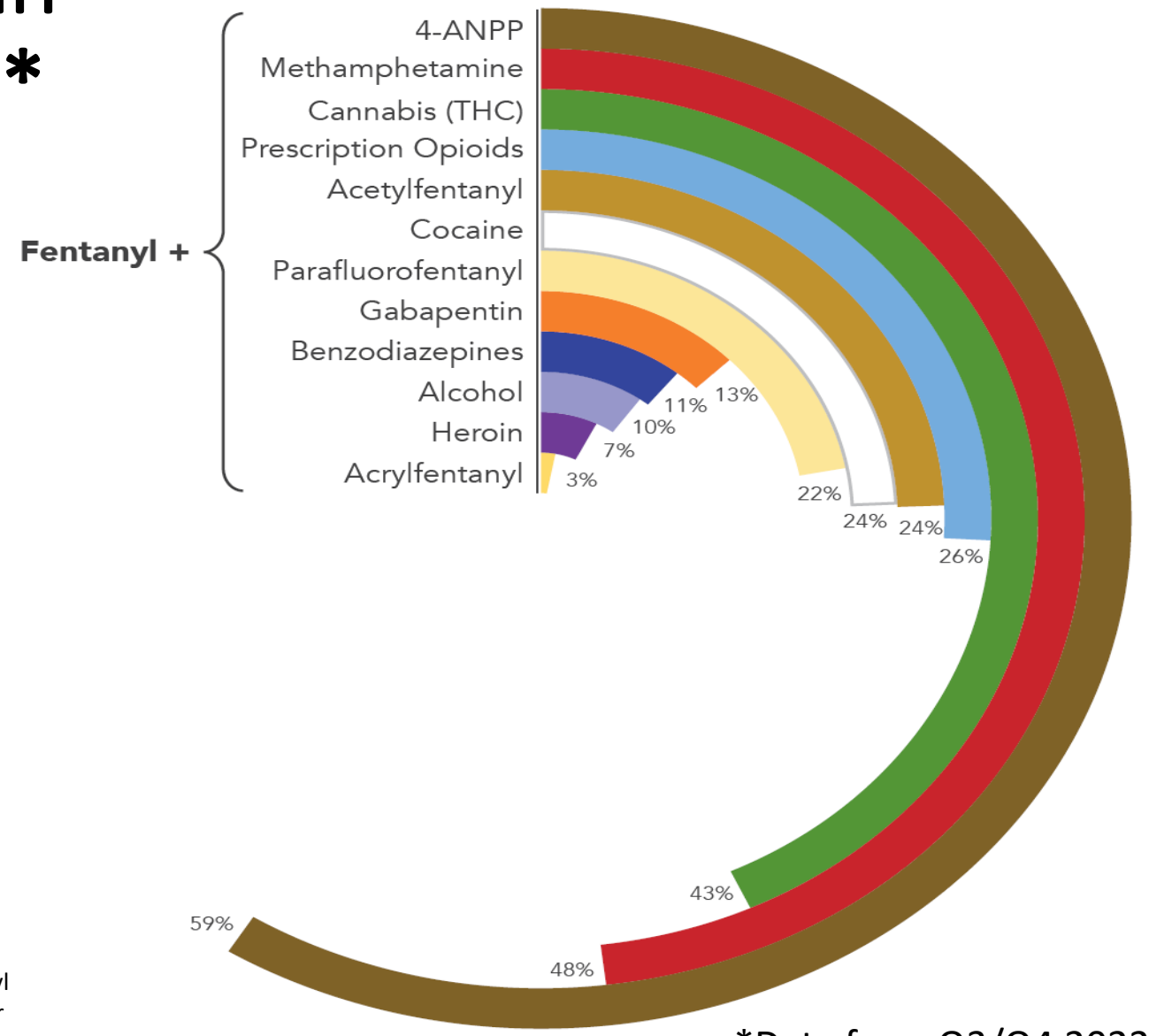
- Will naloxone be as effective in an individual in one region vs another?
- Do fentanyl test strips fully capture the presence and significance of fentanyl analogues?
- Does an individual entering treatment in Georgia require a different initiation strategy than someone in Montana?





Polysubstance Use Patterns in Fentanyl-Positive Specimens*

- Methamphetamine and cannabis (THC) were the second and third most detected
- Prescription opioids were detected in more than 1 in 4 specimens
- Cocaine was detected in more than 1 in 5 specimens
- Gabapentin was found in 13%
- Benzodiazepines and alcohol were found in ~10%

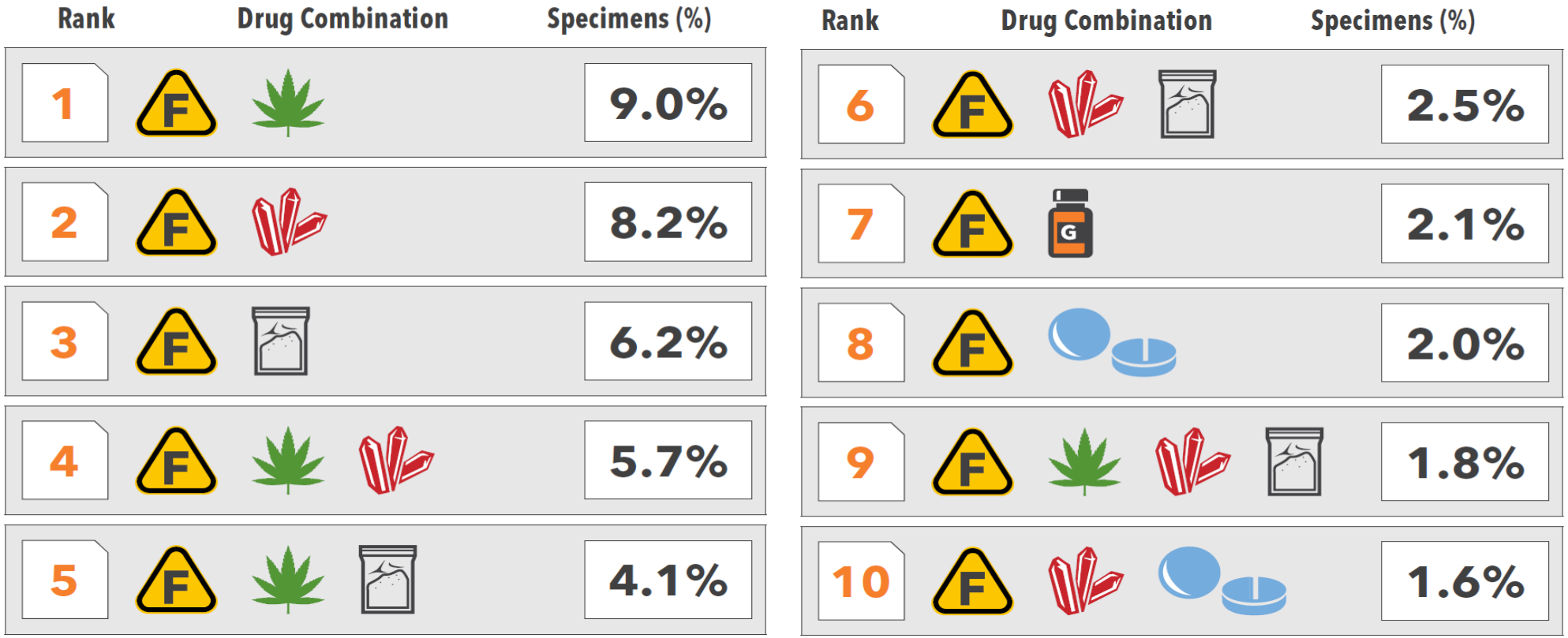


*Data from Q3/Q4 2022

The proportion of fentanyl-positive specimens in the United States that were positive for fentanyl analogues and other drugs. Crude UDT Positivity Rates were estimated for specimens positive for fentanyl that were collected between August and December 2022 and used to calculate the proportion of specimens also positive for the 12 drugs or drug classes shown.

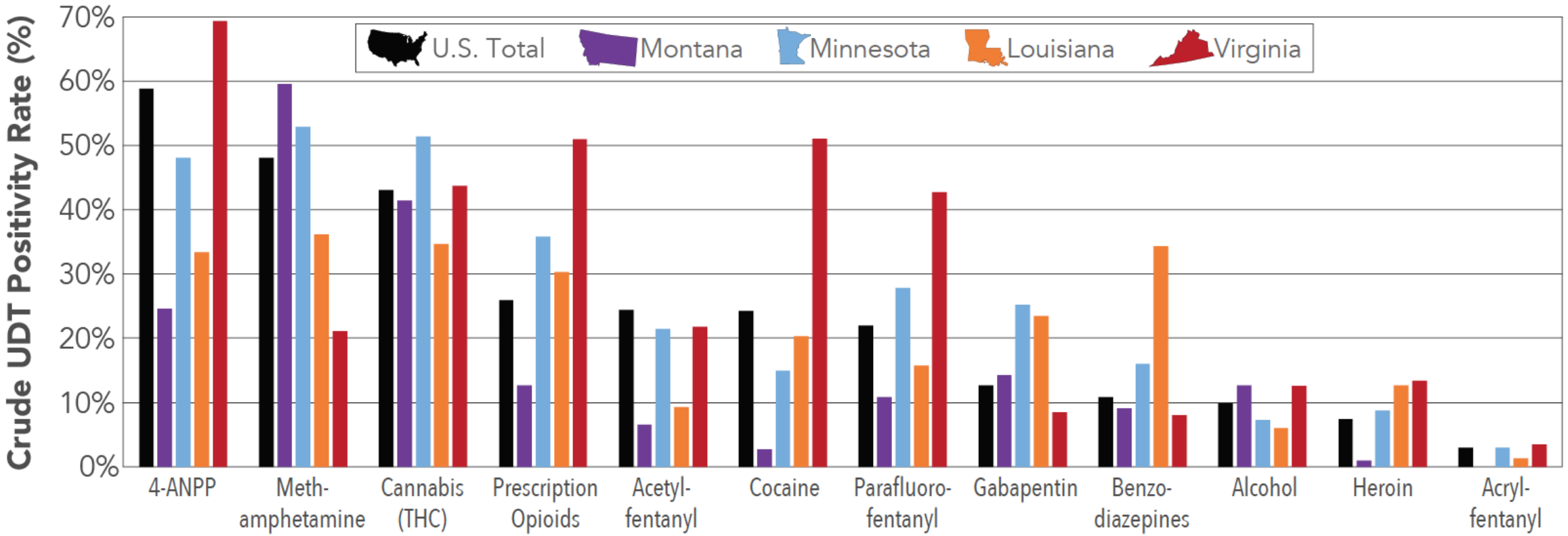
Millennium Health LLC. Fentanyl in Focus: Perspectives on Polysubstance Use in 2022. Millennium Health Signals Report™, Voume 5. https://www.millenniumhealth.com/signalsreport/. Published February, 2023.

Top 10 Drug Combinations in Fentanyl-Positive Population



Millennium Health LLC. Fentanyl in Focus: Perspectives on Polysubstance Use in 2022. Millennium Health Signals Report™, Voume 5. https://www.millenniumhealth.com/signalsreport/. Published February, 2023.

National Polysubstance Use & Geographic Variations



The proportion of fentanyl-positive specimens that were positive for fentanyl analogues and other drugs in the United States (U.S. Total), Montana, Minnesota, Louisiana, and Virginia. Crude UDT Positivity Rates were estimated in fentanyl-positive specimens collected between August and December 2022 and used to calculate the proportion of specimens also positive for the 12 drugs and drug classes shown.

Millennium Health LLC. Fentanyl in Focus: Perspectives on Polysubstance Use in 2022. Millennium Health Signals Report™, Voume 5. https://www.millenniumhealth.com/signalsreport/. Published February, 2023.

Conclusions

- Fentanyl and methamphetamine were the top drugs found among those receiving care in SUD treatment settings in 2022
  - We are cautiously optimistic that decreases in UDT positivity throughout 2022 may herald continued decreases in overdose mortality

- Focusing on a single drug neglects the fact that polysubstance use is generally the rule rather than the exception
  - Fentanyl was present in 40-95% of specimens that were positive other drugs
  - More than 60% of fentanyl-positive specimens contained one or more fentanyl analogues that may alter the risk profile of illicitly manufactured fentanyl
  - Over 80% of individuals who were positive for fentanyl were also positive for additional drugs, which may complicate treatment and impact efficacy of interventions

- Critical to maintain awareness of current drug use trends because patterns of polysubstance use vary over time and geographically

CESAR'S EMERGENCY DEPARTMENT DRUG SURVEILLANCE (EDDS) PROGRAM: **THE NEED FOR EXPANDED TESTING**

ERIC D. WISH, PH. D.; AMY S. BILLING, MSSA; EBONIE MASSEY, MA; MARGARET HSU, MHS;
AND ERIN ARTIGIANI, MA
CESAR: CENTER FOR SUBSTANCE USE AND HEALTH RESEARCH,
UNIVERSITY OF MARYLAND, COLLEGE PARK

FDA: UNDERSTANDING FATAL OVERDOSES TO INFORM DRUG DEVELOPMENT AND PUBLIC HEALTH INTERVENTIONS TO MANAGE OVERDOSE

MARCH 8, 2023

USING URINALYSIS RESULTS AS AN EPIDEMIOLOGIC TOOL

- Drug Use Forecasting/Arrestee Drug Abuse Monitoring (DUF/ADAM): 1986-2014; NIJ, ONDCP
- Maryland Offender Population Urinalysis Study (OPUS): 1999-2009; MD-GOCCP
- Community Drug Early Warning System (CDEWS): 2013-2019; ONDCP
- Drug Outbreak Testing Service (DOTS): 2017-2019; NIDA-NDEWS
- Maryland EDDS Pilot Study: 2018-2019; MPower
- National EDDS - 2020-2023; ONDCP
- Maryland EDDS (MD-EDDS) – 2022-2023; OOCC

23% OR LESS OF SUSPECTED SYNTHETIC CANNABINOID OVERDOSE PATIENTS TESTED POSITIVE FOR THE DRUG

Percentage Positive for Likely Illicit Selected Drugs, By Site
(N=175 specimens collected between January 2016 and October 2016)‡

Positive by CDEWS Lab for:	Prince George's Hospital Center (N=106) %	UMMC, Midtown Campus (N=69) %
1. Marijuana	69	61
2. Cocaine	22**	46**
3. PCP	47***	3***
4. Any New Psychoactive Substance (NPS)	22	32
5. Any Synthetic Cannabinoid (SC)	23	20
6. Any Fentanyl^	4***	28***
7. 6-Monoacetylmorphine (6-MAM)	0***	13***
8. Methamphetamine	3	3
Positive for Any (of 8)	91%	94%
Positive for Any (excluding marijuana)	74%	75%
Number of Drugs/Drug Classes in Specimen (of 8):		
0	9	6
1	28	29
2	39	32
3	14	22
4	8	10
5	<1	1
6	<1	0
Total:	100%	100%
Mean Number of Drugs Found Positive (of 8):	1.89	2.06

24%

33%

Note: LSD and Amphetamine were excluded from this data.
‡Specimens from the Prince George's Hospital Center Emergency Department were collected between January 2016 and October 2016. Specimens from the University of Maryland Medical Center, Midtown Campus, Emergency Department were collected between February 2016 and September 2016.

^It is not possible to definitively determine whether the presence of these drugs were due to illicit use or whether drugs were administered or prescribed by a physician; however, drug test results with evidence of the drug being administered to the patient by emergency department staff or evidence of patient taking the drug by prescription were counted as negative in this analysis.
**p<.01 based on Chi Square.
***p<.001 based on Fisher's Exact Test or Chi Square.

In the absence of toxicological results, hospital clinical records can only provide patients' and physicians' impressions about the drugs involved

CESAR: Center for Substance Use and Health Research, 2023

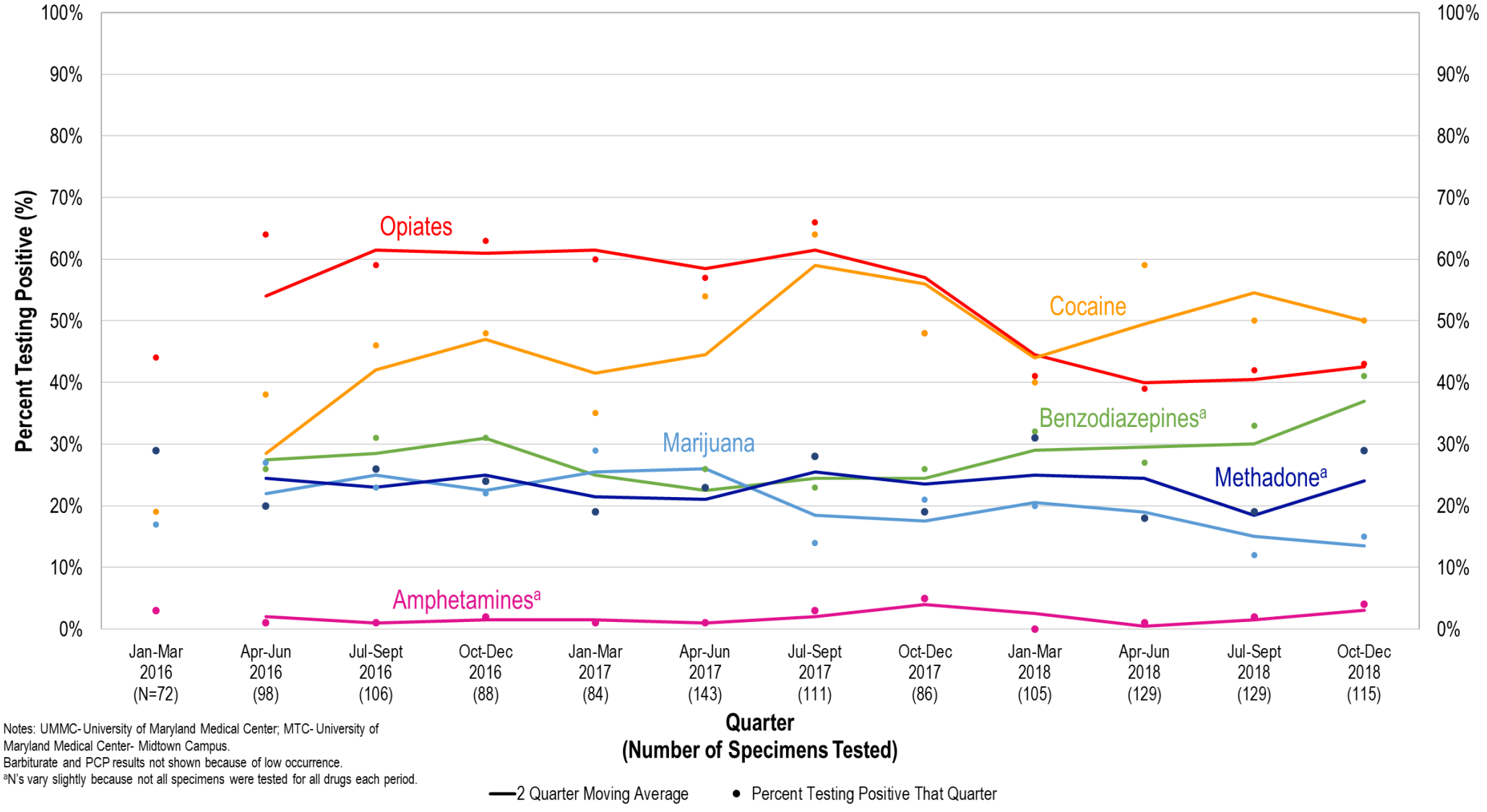
NATIONAL AND MARYLAND EDDS

- The Emergency Department Drug Surveillance (EDDS) program offers the country a new tool for tracking the drugs to which ED overdose patients have been exposed. There are two types of EDDS initiatives:
  - National EDDS collects quarterly hospital electronic health records (EHRs) containing limited data sets of patient urinalysis results and a one-time sample of 150 already tested urines that are sent to the EDDS collaborating laboratory for re-testing for 500+ substances (Initiated in 2017, N=31 participating hospitals).
  - Maryland EDDS collects quarterly EHRs but no urine specimens; We give each hospital 50 fentanyl dip sticks with which to test consecutive hospital positive specimens (goal = 20 hospitals across Maryland).

EDDS Pilot 2018-2019

Drugs Detected in Specimens from UMMC and MTC Emergency Department (ED) Drug Overdose Patients

(N=1,266 positive and negative specimens tested from January 2016 through December 2018)



Notes: UMMC- University of Maryland Medical Center; MTC- University of Maryland Medical Center- Midtown Campus.
Barbiturate and PCP results not shown because of low occurrence.
[a]N's vary slightly because not all specimens were tested for all drugs each period.

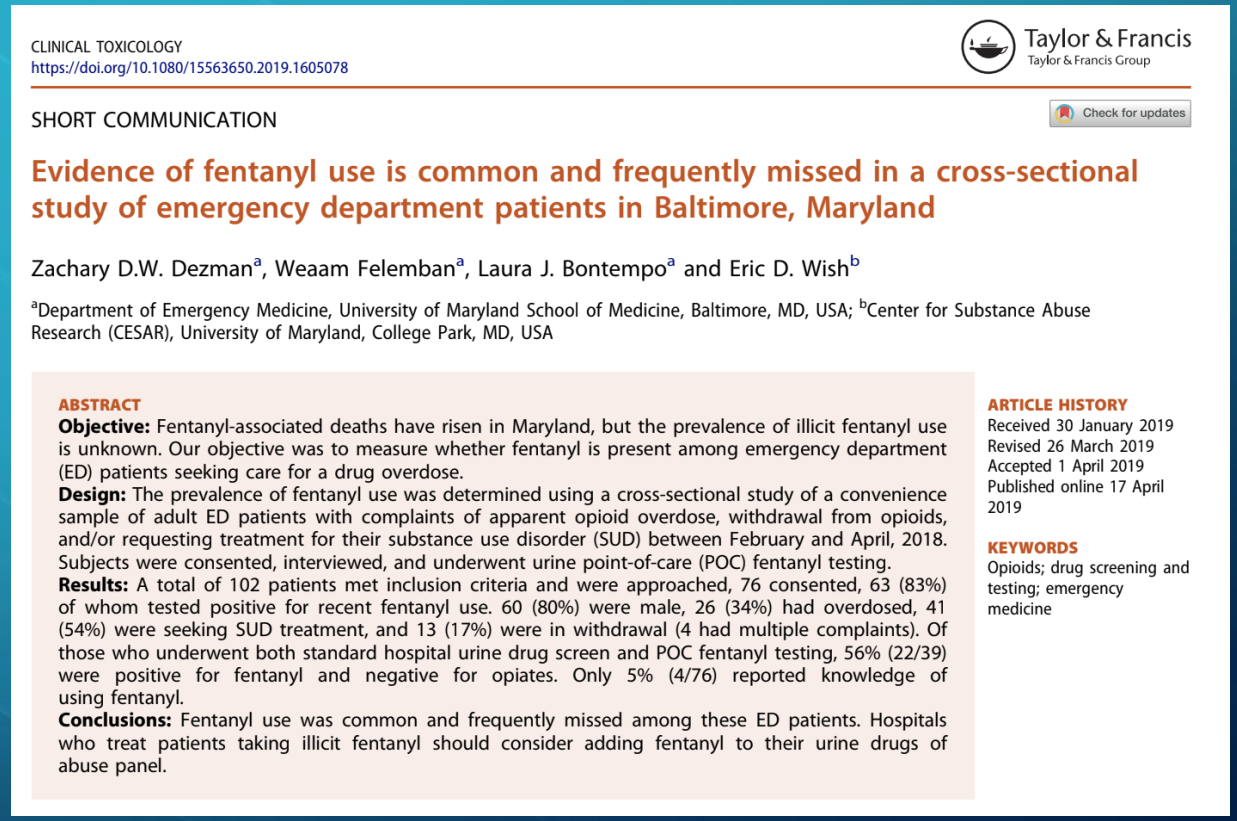
CESAR: Center for Substance Use and Health Research, 2023

Source: CESAR, University of Maryland, College Park, Baltimore, 2023

Evidence of fentanyl use is common and frequently missed in a cross-sectional study of emergency department patients in Baltimore, Maryland*

- Adult ED patients with apparent opioid overdose, withdrawal from opioids, or requesting treatment for SUD.
- 83% tested positive for recent fentanyl use
- 56% of those who had standard urine drug screen and fentanyl testing tested positive for fentanyl but negative for opiates.
- Only 5% reported knowingly taking fentanyl.

*Supported by a grant from the University of Maryland Strategic Partnership: *MPowering the State: Opioid Use Disorders Initiative*



CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2019.1605078

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SHORT COMMUNICATION

Evidence of fentanyl use is common and frequently missed in a cross-sectional study of emergency department patients in Baltimore, Maryland

Zachary D.W. Dezman[a], Weaam Felemban[a], Laura J. Bontempo[a] and Eric D. Wish[b]

[a]Department of Emergency Medicine, University of Maryland School of Medicine, Baltimore, MD, USA; [b]Center for Substance Abuse Research (CESAR), University of Maryland, College Park, MD, USA

ABSTRACT

Objective: Fentanyl-associated deaths have risen in Maryland, but the prevalence of illicit fentanyl use is unknown. Our objective was to measure whether fentanyl is present among emergency department (ED) patients seeking care for a drug overdose.

Design: The prevalence of fentanyl use was determined using a cross-sectional study of a convenience sample of adult ED patients with complaints of apparent opioid overdose, withdrawal from opioids, and/or requesting treatment for their substance use disorder (SUD) between February and April, 2018. Subjects were consented, interviewed, and underwent urine point-of-care (POC) fentanyl testing.

Results: A total of 102 patients met inclusion criteria and were approached, 76 consented, 63 (83%) of whom tested positive for recent fentanyl use. 60 (80%) were male, 26 (34%) had overdosed, 41 (54%) were seeking SUD treatment, and 13 (17%) were in withdrawal (4 had multiple complaints). Of those who underwent both standard hospital urine drug screen and POC fentanyl testing, 56% (22/39) were positive for fentanyl and negative for opiates. Only 5% (4/76) reported knowledge of using fentanyl.

Conclusions: Fentanyl use was common and frequently missed among these ED patients. Hospitals who treat patients taking illicit fentanyl should consider adding fentanyl to their urine drugs of abuse panel.

ARTICLE HISTORY
Received 30 January 2019
Revised 26 March 2019
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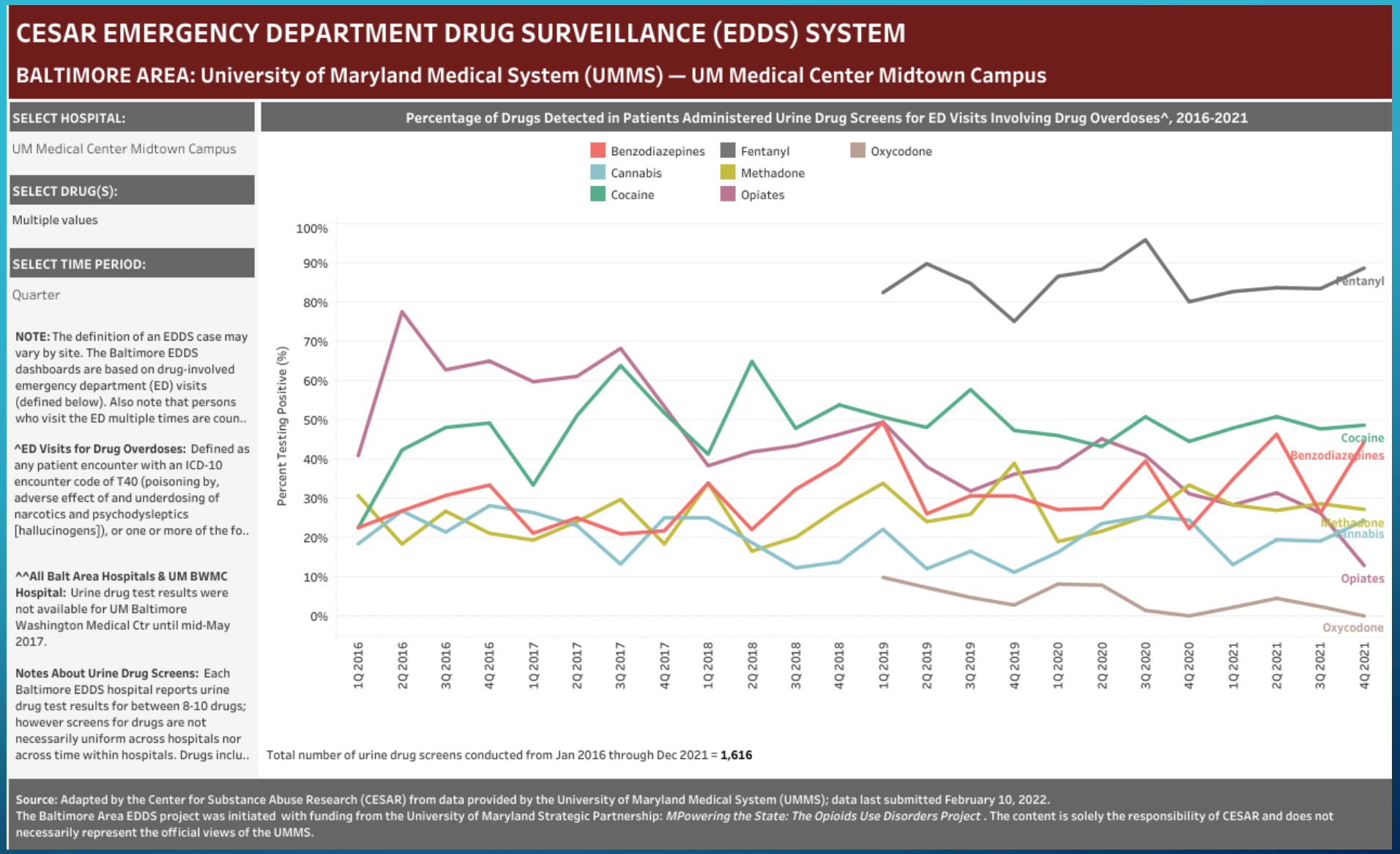
Published online 17 April 2019

KEYWORDS
Opioids; drug screening and testing; emergency medicine

Dezman, Z., Felemban, W., Bontempo, L., & Wish, E. (2020). Evidence of fentanyl use is common and frequently missed in a cross-sectional study of emergency department patients in Baltimore, Maryland. *Journal of Clinical Toxicology*, 58(1), 59-61.

CESAR: Center for Substance Use and Health Research, 2023

Source: CESAR, University of Maryland

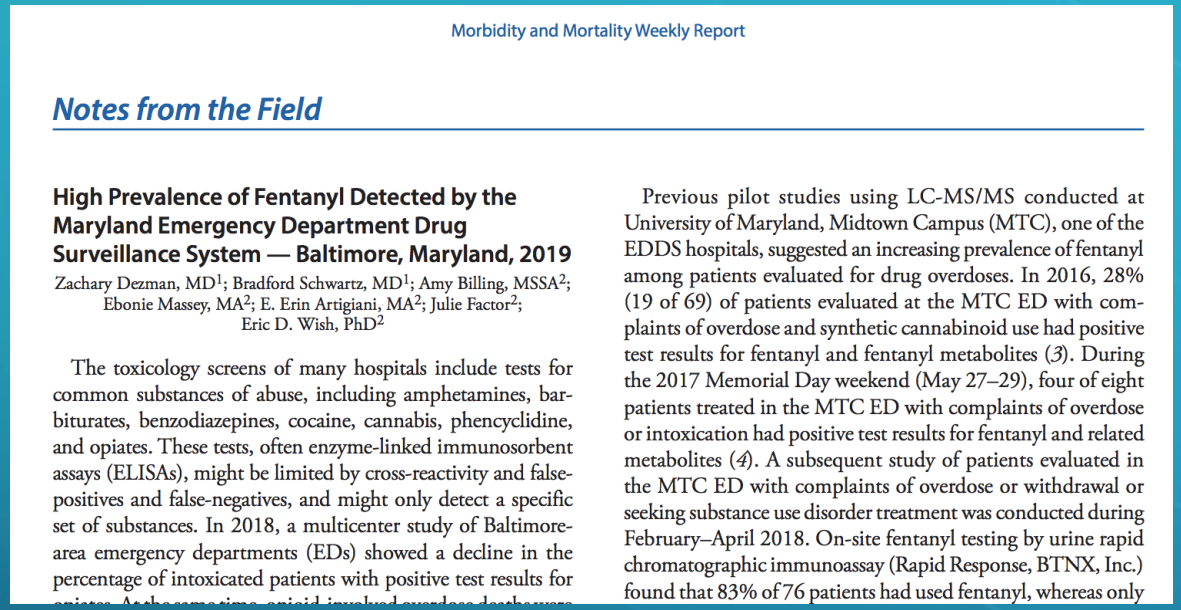


- Fentanyl (89%) was almost twice as prevalent as most other drugs detected, even as opiates (13%) reached their series low.

CESAR: Center for Substance Use and Health Research, 2023

Source: CESAR Publication # 2022-3 College Park, October 2022

MMWR High Prevalence of Fentanyl Detected by Maryland EDDS – Baltimore, Maryland 2019*



Morbidity and Mortality Weekly Report

Notes from the Field

High Prevalence of Fentanyl Detected by the Maryland Emergency Department Drug Surveillance System — Baltimore, Maryland, 2019

Zachary Dezman, MD[1]; Bradford Schwartz, MD[1]; Amy Billing, MSSA[2]; Ebonie Massey, MA[2]; E. Erin Artigiani, MA[2]; Julie Factor[2]; Eric D. Wish, PhD[2]

The toxicology screens of many hospitals include tests for common substances of abuse, including amphetamines, barbiturates, benzodiazepines, cocaine, cannabis, phencyclidine, and opiates. These tests, often enzyme-linked immunosorbent assays (ELISAs), might be limited by cross-reactivity and false-positives and false-negatives, and might only detect a specific set of substances. In 2018, a multicenter study of Baltimore-area emergency departments (EDs) showed a decline in the percentage of intoxicated patients with positive test results for

Previous pilot studies using LC-MS/MS conducted at University of Maryland, Midtown Campus (MTC), one of the EDDS hospitals, suggested an increasing prevalence of fentanyl among patients evaluated for drug overdoses. In 2016, 28% (19 of 69) of patients evaluated at the MTC ED with complaints of overdose and synthetic cannabinoid use had positive test results for fentanyl and fentanyl metabolites (*3*). During the 2017 Memorial Day weekend (May 27–29), four of eight patients treated in the MTC ED with complaints of overdose or intoxication had positive test results for fentanyl and related metabolites (*4*). A subsequent study of patients evaluated in the MTC ED with complaints of overdose or withdrawal or seeking substance use disorder treatment was conducted during February–April 2018. On-site fentanyl testing by urine rapid chromatographic immunoassay (Rapid Response, BTNX, Inc.) found that 83% of 76 patients had used fentanyl, whereas only

Dezman, Z., Schwartz, B., Billing, A., Massey, E., Artigiani, E. E., Factor, J., & Wish, E. (2020). *Notes from the Field:* High prevalence of fentanyl detected by the Maryland Emergency Department Drug Surveillance System – Baltimore, Maryland, 2019. *MMWR Morb Mortal Wkly Rep,* 69(23):724–726. http://dx.doi.org/10.15585/mmwr.mm6923a3

- After analysis of EDDS data, two hospitals introduced fentanyl testing as part of their routine urinalysis screen.
- Fentanyl was detected in 73 to 87% of patients tested in each calendar quarter of 2019.
- 61% of the fentanyl positive specimens contained two or more drugs/drug classes in addition to fentanyl.
- Hospitals and medical systems throughout the United States might consider adding fentanyl to their routine drug testing panels.

*Supported by a grant from the University of Maryland Strategic Partnership: *MPowering the State: Opioid Use Disorders Initiative*

Source: CESAR, University of Maryland

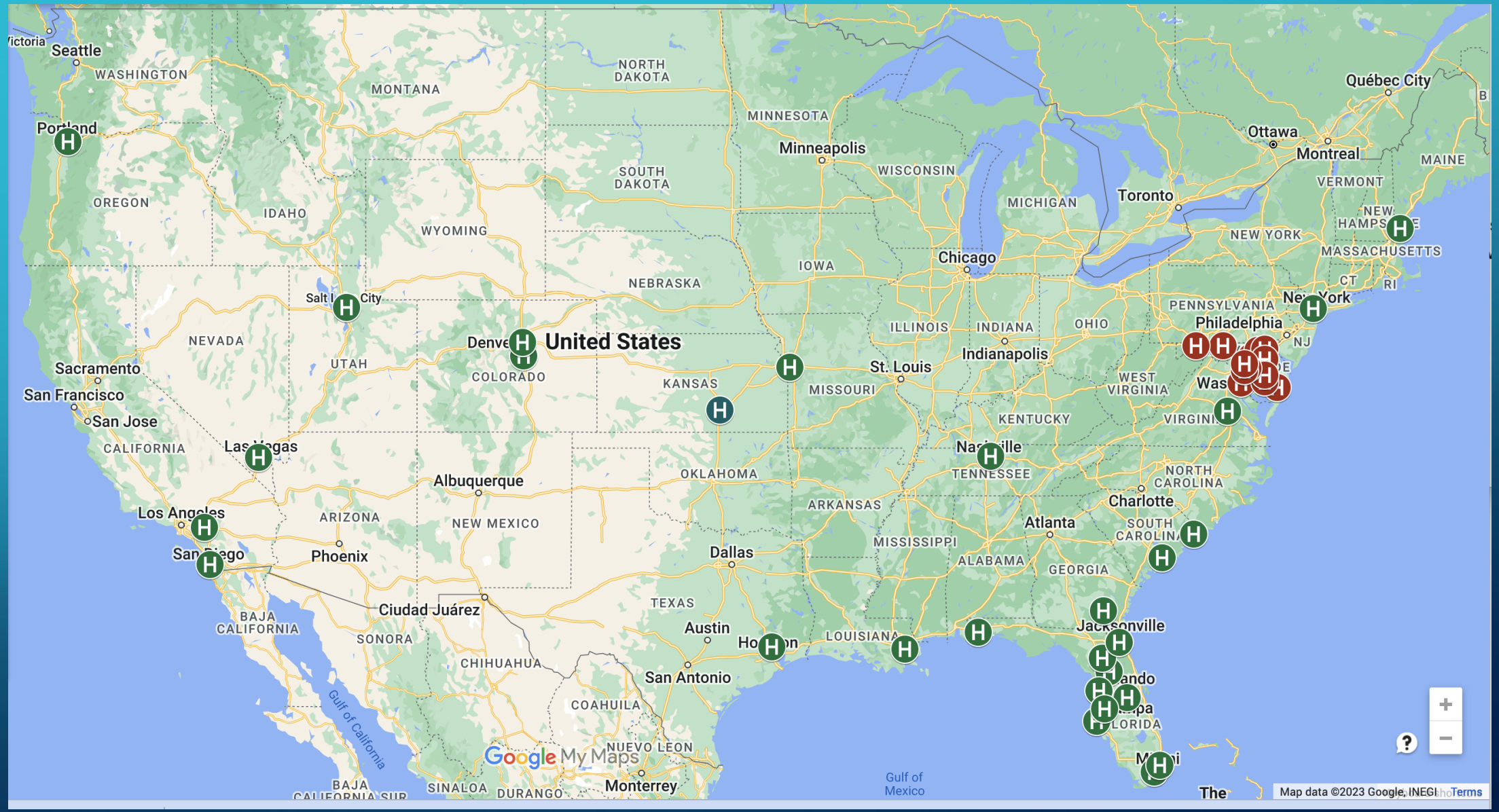
PARTICIPATION IN EDDS HAS INSPIRED OTHER HOSPITALS AND CALIFORNIA TO INITIATE ROUTINE FENTANYL TESTING

- Routine testing started in 2 Baltimore hospitals in January 2019.
- Following their participation in EDDS Phase I, University of Utah Hospital (Salt Lake City, UT) added fentanyl to their routine screen.
- CA also recently passed legislation requiring fentanyl testing as part of standard hospital drug testing (Tyler's Law, California's SB864).
- MD is currently considering legislation similar to the CA law.

CESAR: Center for Substance Use and Health Research, 2023

Source: CESAR, University of Maryland, College Park, September 2023

NATIONAL EDDS 2023



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FENTANYL/NORFENTANYL EDDS TEST RESULTS, BY HOSPITAL'S DRUG SCREEN RESULT

(N=1,663 SPECIMENS SUBMITTED BY HCA HOSPITALS

	Positive for Fentanyl/Norfentanyl	
	Hospital found Positive for any drug	**Hospital found Negative for all drugs**
Grand Strand Medical Center, SC	(n=100) 28%	(n=50) 10%
TriStar Skyline Medical Center, TN	(100) 25%	(50) 10%
Riverside Community Hospital, CA	(100) 24%	(50) 14%
Trident Medical Center, SC	(100) 16%	(50) 4%
MountainView Hospital, NV	(101) 15%	(51) 2%
HCA Florida West, FL	(100) 13%	(50) 0%
HCA Florida Orange Park, FL	(106) 9%	(50) 2%
HCA Florida Brandon Hospital, FL	(56) 7%	(23) 0%
Memorial Satilla Health, GA	(100) 6%	(50) 4%
Houston Healthcare Kingwood, TX	(100) 6%	(50) 4%
HCA Florida Aventura, FL	(103) 4%	(58) 0%
HCA Florida North Florida, FL	(45) 2%	(20) 0%

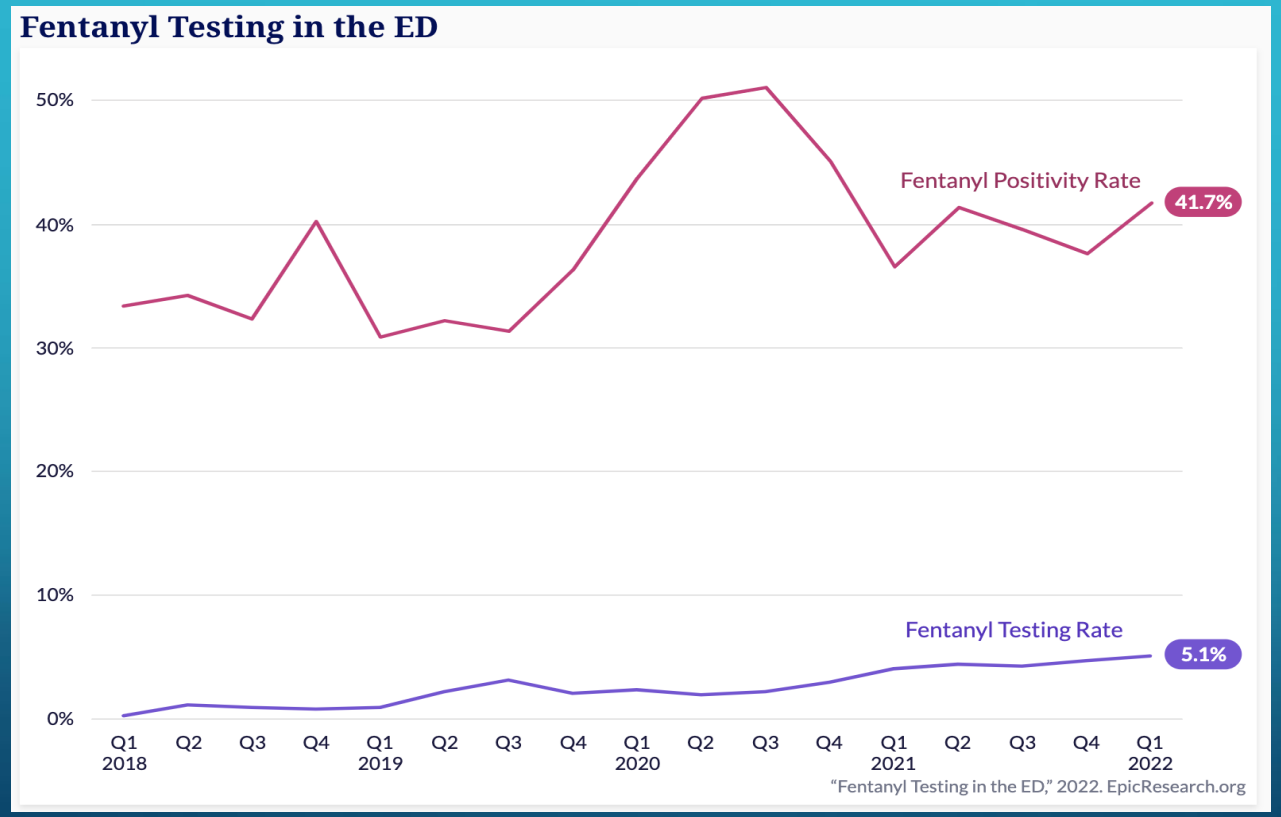
Note: None of these hospitals routinely test patients for fentanyl.

[a]Specimens were selected from consecutive emergency department patients aged 18 years or older that had undergone drug toxicology testing.

Emergency Department Drug Surveillance (EDDS), CESAR: Center for Substance Use and Health Research, University of Maryland, College Park. https://cesar.umd.edu/landing/EDDS

- The EDDS expanded retesting found that fentanyl was more likely to be detected in specimens for which the hospital's screens had detected any drug.
- But none of these hospitals routinely test patients' urine specimens for fentanyl.

Epic Research and EDDS Collaborative Study Found Only 5% Of Over 300,000 Overdose Patients Were Tested For Fentanyl

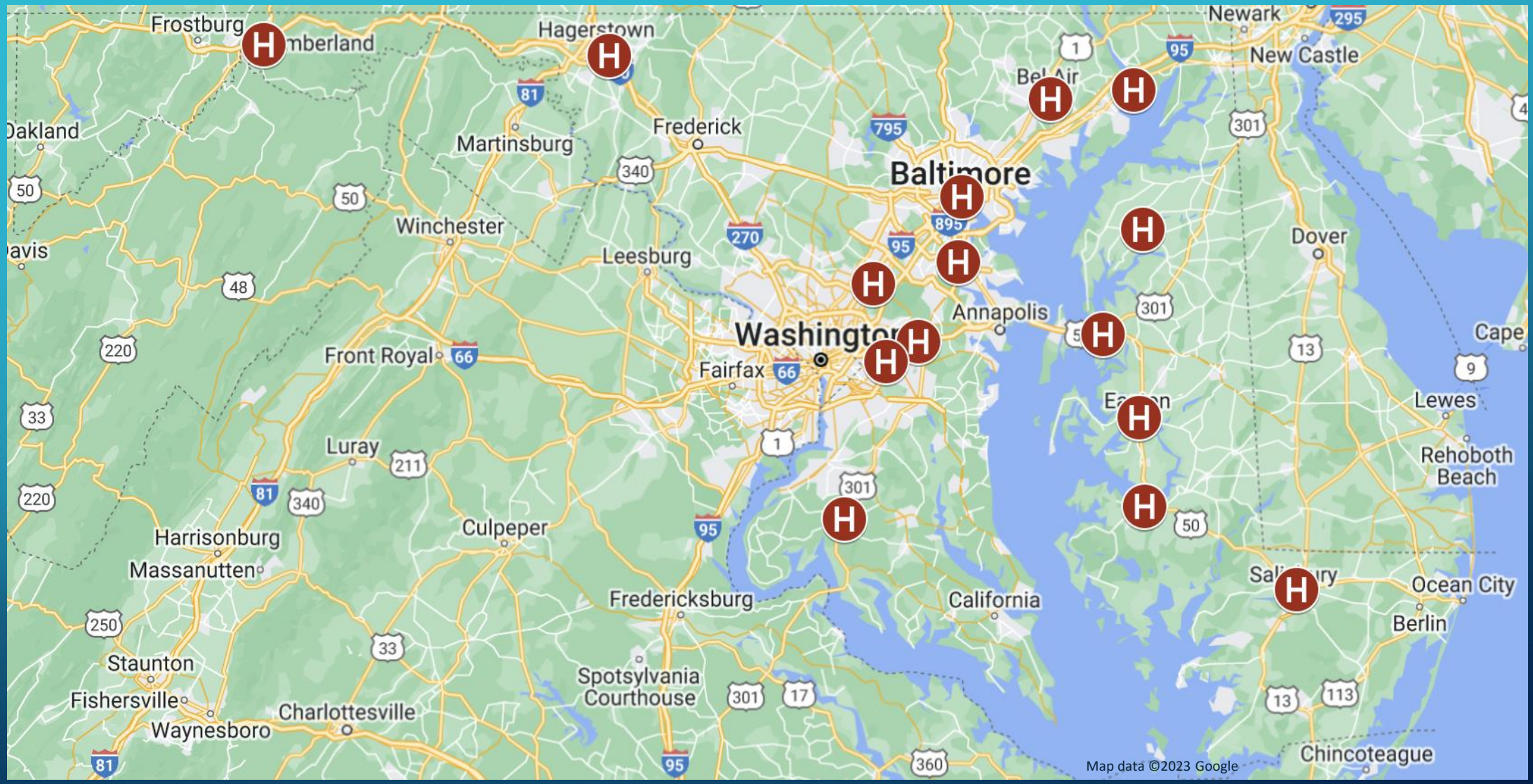


- Fentanyl is rarely tested for in ED visits.
- When it is tested, almost half (41.7%) tested positive for the drug in Q1, 2022.

Little et al., August 23, 2022

CESAR: Center for Substance Use and Health Research, 2023

MD-EDDS 2023



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MD-EDDS FENTANYL DIPSTICK STUDY RESULTS IN 8 HOSPITALS

	Positive for Fentanyl by Dipstick	Of Specimens Positive for Fentanyl, also Positive for Opiates
UM Shore Medical Center at Chestertown, Chestertown, MD	(n=50) 24%	(12) 8%
Meritus Medical Center, Hagerstown, MD	(50) 20%	(10) 30%
UM Baltimore Washington Medical Center, Glen Burnie, MD	(50) 14%	(7) **
UM Upper Chesapeake Medical Center, Bel Air, MD	(50) 14%	(7) **
UM Shore Medical Center at Cambridge, Cambridge, MD	(50) 12%	(6) **
UM Capital Region Medical Center, Largo, MD	(50) 6%	(3) **
UM Charles Regional Health Center, La Plata, MD	(50) 4%	(2) **
UM Shore Medical Center at Easton, Easton, MD	(50) 2%	(1) **
All Hospitals	(400) 12%	(48) 19%

**Too few cases to calculate meaningful statistics.

Specimens were selected from consecutive patients from any hospital unit positive for at least one drug by the hospital's testing. Patients that were administered fentanyl as part of their medical care at the hospital were excluded from the sample.

None of these hospitals routinely test for fentanyl.

CESAR: Center for Substance Use and Health Research, 2023

COMPARISON OF THE DRUGS DETECTED BY THE HOSPITAL IN SPECIMENS THAT THE DIPSTICK FOUND POSITIVE OR NEGATIVE FOR FENTANYL

(N=400 SPECIMENS SUBMITTED BY 8 HOSPITALS)[A]

Hospital Found Positive for:	Positive for Fentanyl by Dipstick (N=48) %	Negative for Fentanyl by Dipstick (N=352) %
Cocaine	63***	24***
Marijuana	(n=47) 43*	(n=350) 58*
Methadone	(n=39) 39***	(n=214) 8***
Benzodiazepines	27	21
Amphetamines	21*	9*
Opiates	19	10
Oxycodone	(n=26) 8	(n=224) 10
PCP	(n=29) 7	(n=221) 7
Barbiturates	4	5
Buprenorphine	(n=10) 0	(n=47) 9

[a]Consecutive specimens were selected from any hospital unit that the hospital's testing had found positive for at least one drug. Patients that were administered fentanyl as part of their medical care at the hospital were excluded.
Hospitals include: UM Shore Medical Center at Chestertown (Chestertown, MD), Meritus Medical Center (Hagerstown, MD), UM Baltimore Washington Medical Center (Glen Burnie, MD), UM Upper Chesapeake Medical Center (Bel Air, MD), UM Shore Medical Center at Cambridge (Cambridge, MD), UMD Capital Region Medical Center (Largo, MD), UM Charles Regional Health Center (La Plata, MD), and UM Shore Medical Center at Easton (Easton, MD).
N's vary due to hospitals not testing for each drug.
*p<.05 by Chi-Square or Fisher's Exact Test; ***p<.001 by Chi-Square or Fisher's Exact Test.

CONCLUSIONS

- ***There is a need*** for most hospitals to add fentanyl to their standard urinalysis panels so that patients may be properly treated and informed of the drugs to which they are being exposed.
- ***There is also a need*** to establish a national epidemiologic system for collecting and analyzing hospital patients' urinalysis results in order to monitor drug epidemics.

LEARN MORE

- Join the CESAResearch Network:
  - https://cesar.umd.edu/ under Items of Interest or
  - https://network.cesaresearch.org/login

- Access EDDS hospital data and reports:
  - https://cesar.umd.edu/landing/EDDS

HOSPITAL EHR DATA FROM ED VISITS PRESENTED IN INTERACTIVE DASHBOARDS TO TRACK TRENDS IN VISIT CHARACTERISTICS AND DRUG TEST RESULTS

Includes hospital visits involving a patient aged 18 years or older presenting to the emergency department and administered a urine drug screen that returned an interpreted drug test result

CESAR: Center for Substance Use and Health Research, 2023

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www.cesar.umd.edu/landing/edds

@CESAResearch

Session 2: Pharmacology of Opioids & Overdose Management Products

REAGAN-UDALL FOUNDATION FOR THE FDA

Presenters

Albert Dahan, MD, PhD
Leiden University Medical Center

David Strauss, MD, PhD
U.S. Food and Drug Administration

Reactor Panel

Bruce Goldberger, PhD
University of Florida College of Medicine

Alexander A. Vinks, PharmD, PhD
Cincinnati Children's Hospital Medical Center

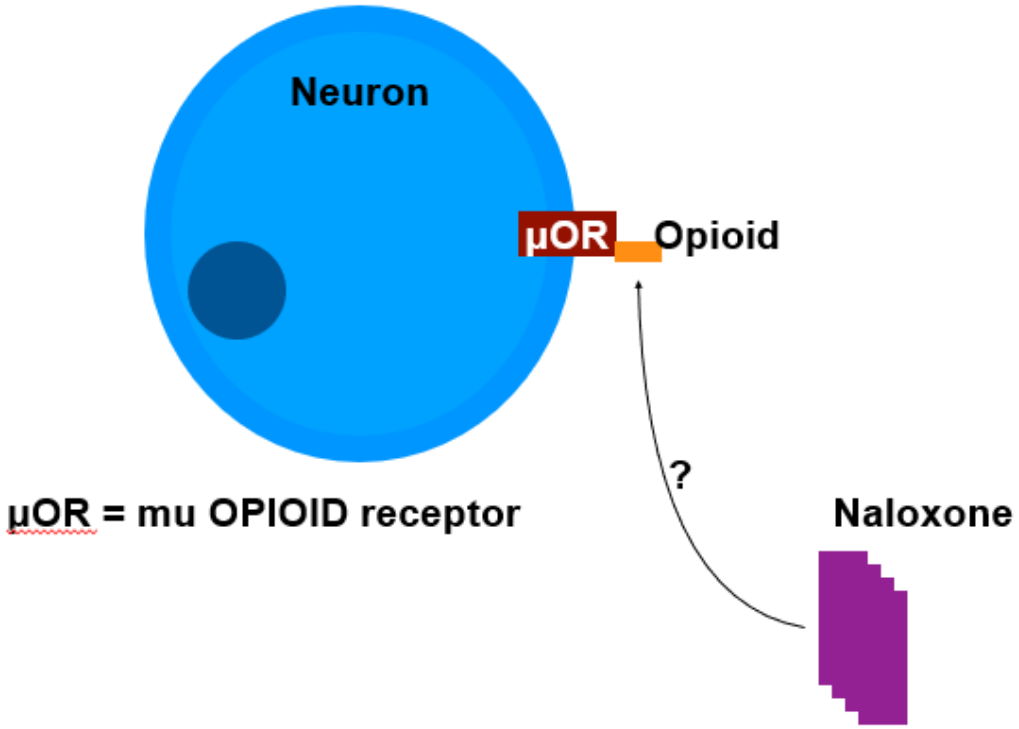
Leiden University Medical Center

Reversal of opioid-induced respiratory depression

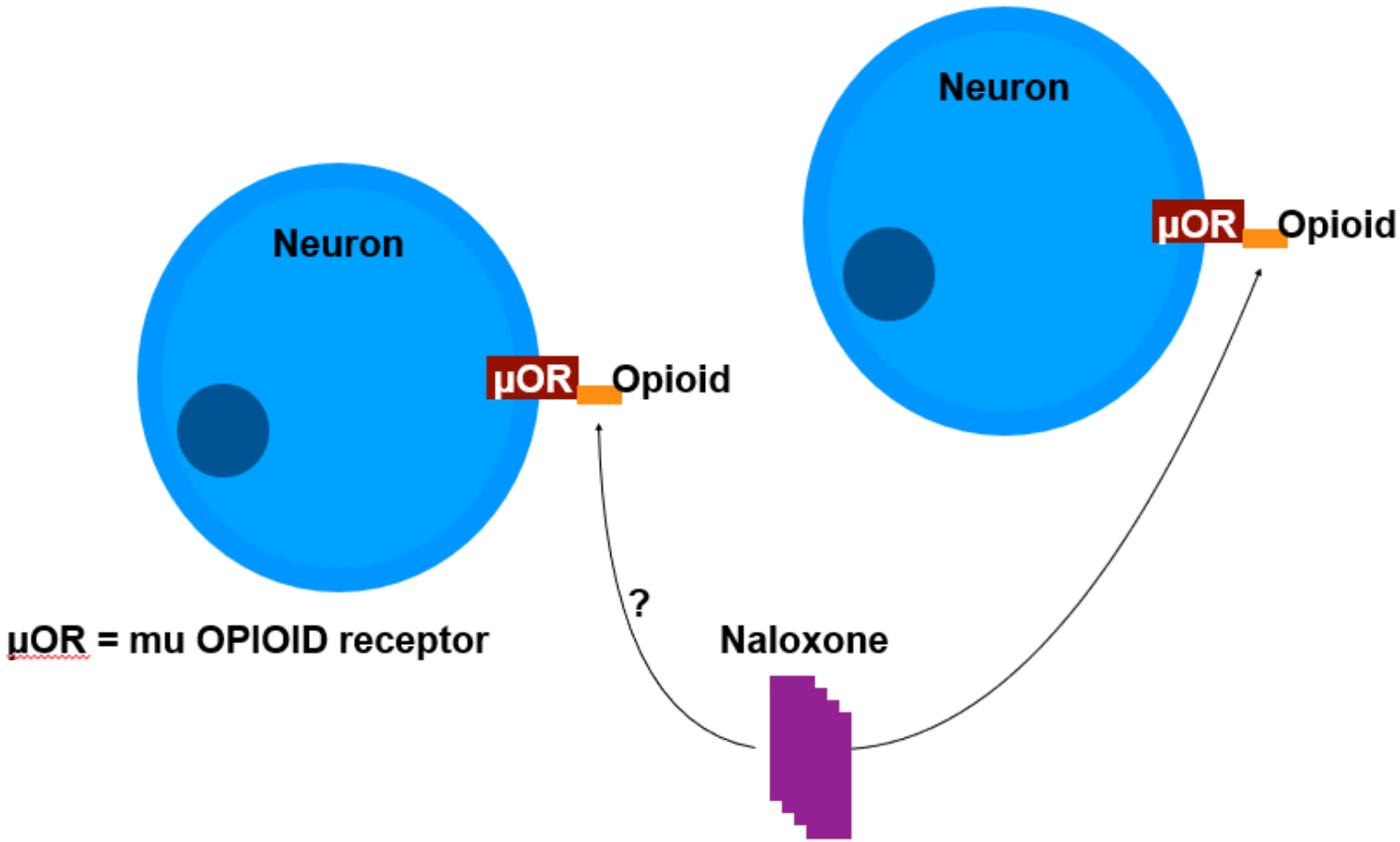
- Fentanyl and congeners

Albert Dahan MD PhD, professor of Anesthesiology

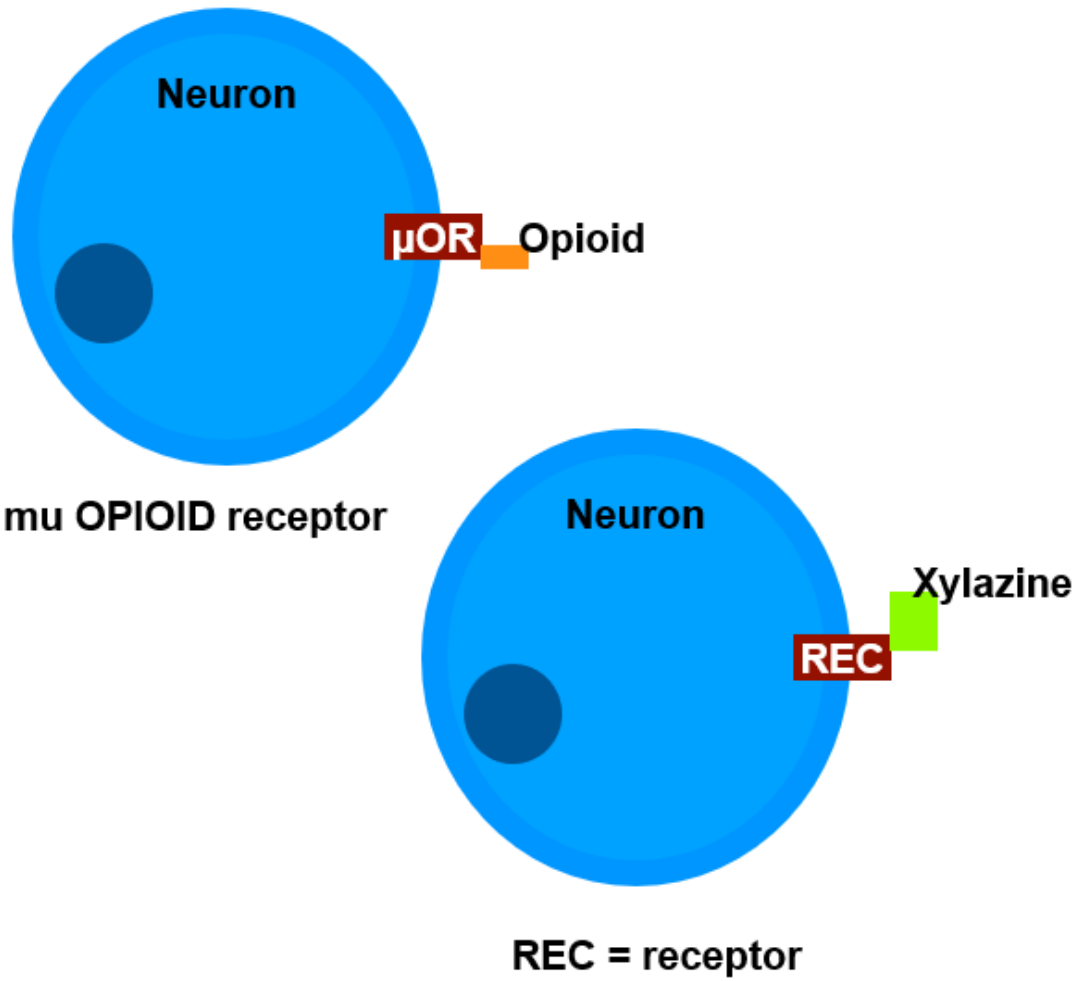
How difficult is it for naloxone to replace an opioid from a respiratory neuron?

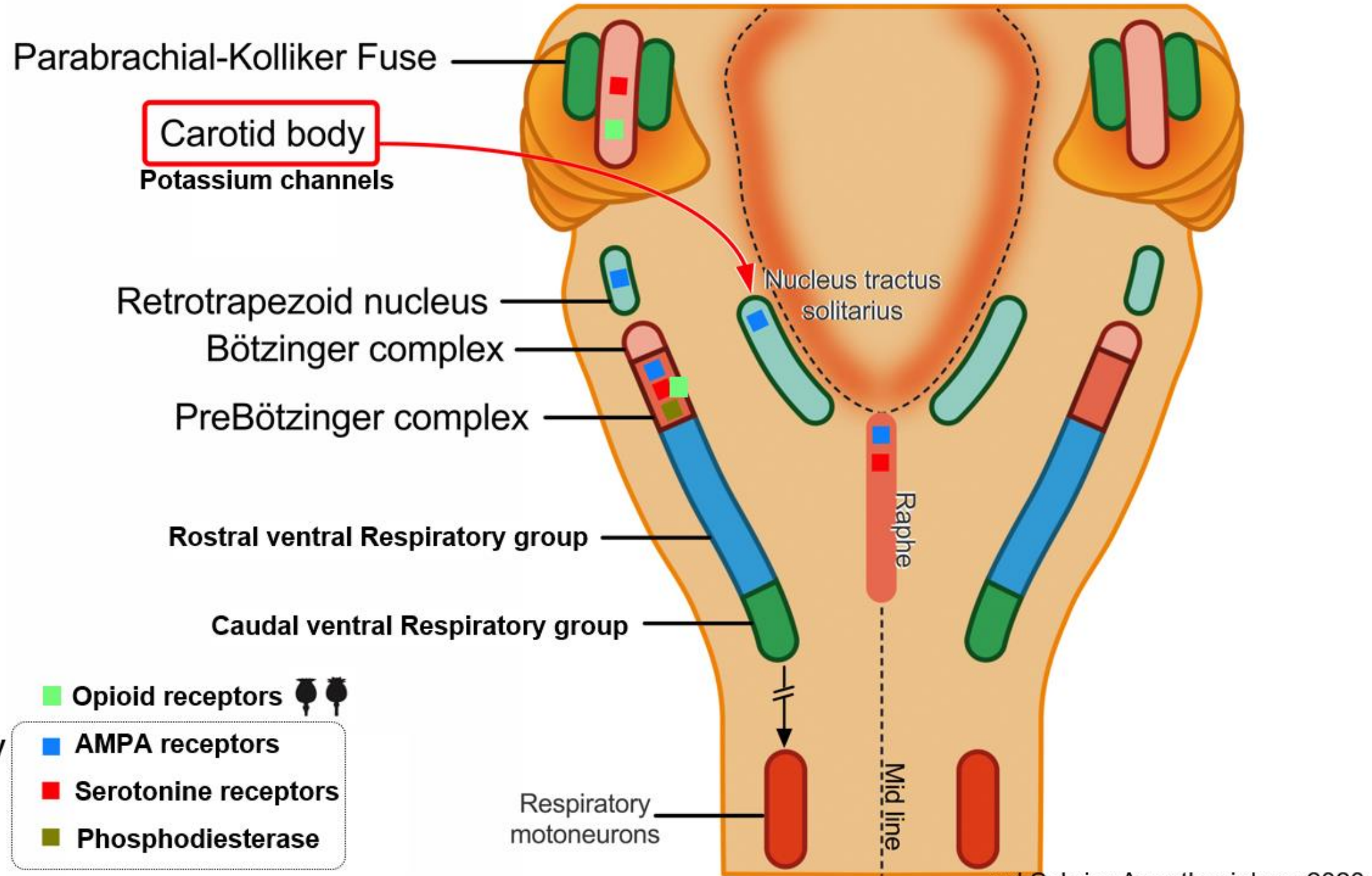


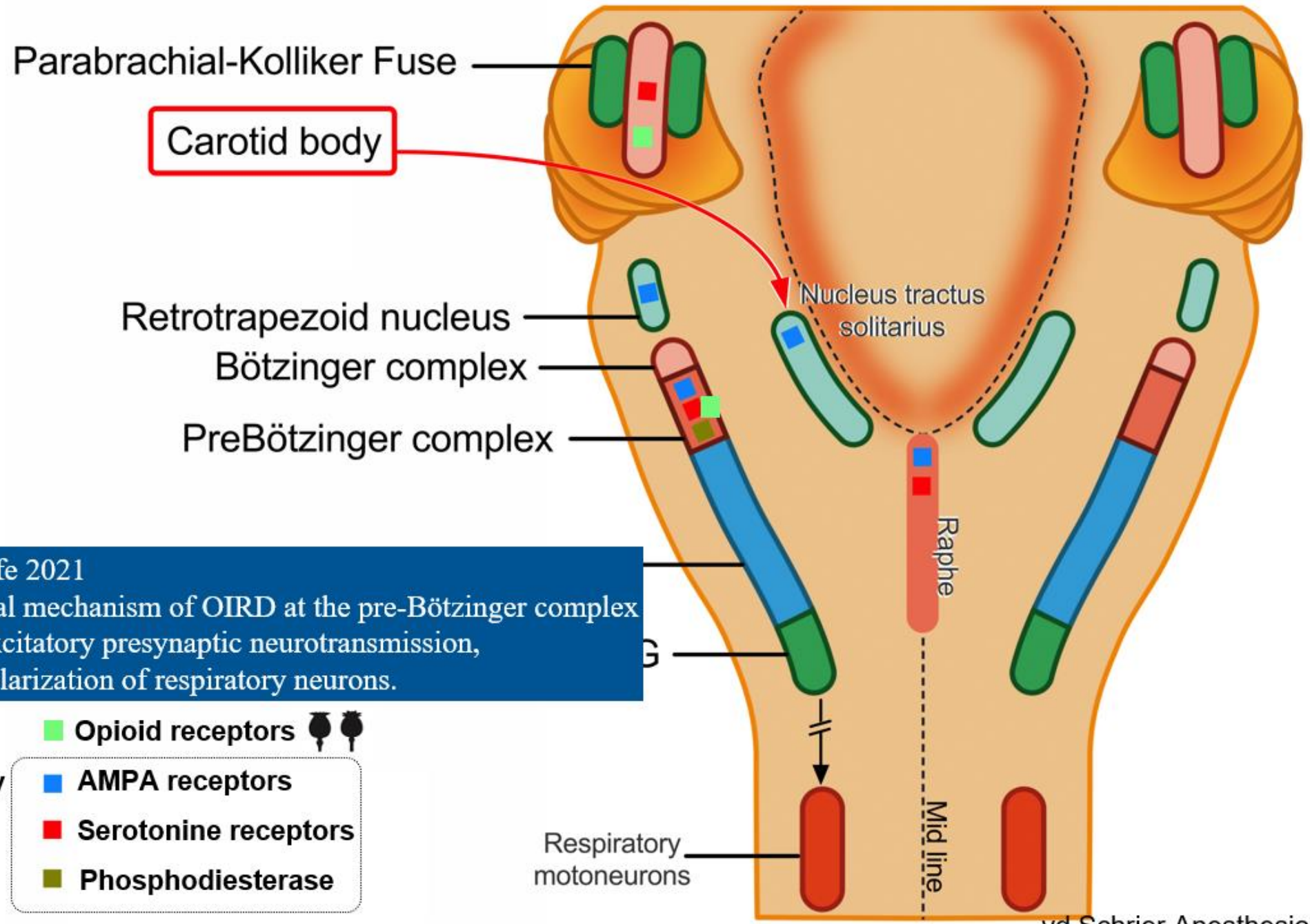
How effective is naloxone in restoring respiratory activity?



How effective is naloxone in restoring respiratory activity? If not effective what to do next?

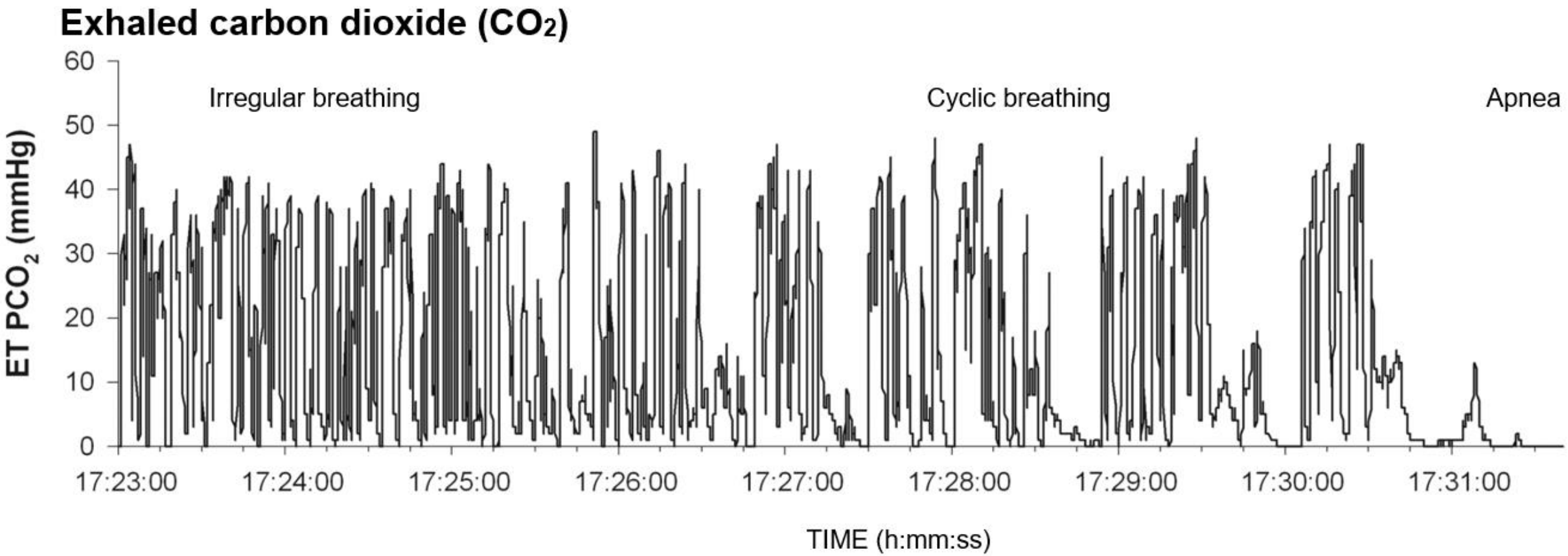



Parabrachial-Kolliker Fuse
Carotid body
Potassium channels
Retrotrapezoid nucleus
Bötzinger complex
PreBötzinger complex
Rostral ventral Respiratory group
Caudal ventral Respiratory group
Nucleus tractus solitarius
Raphe
Mid line
Respiratory motoneurons
Respiratory excitatory receptor systems
Opioid receptors
AMPA receptors
Serotonine receptors
Phosphodiesterase



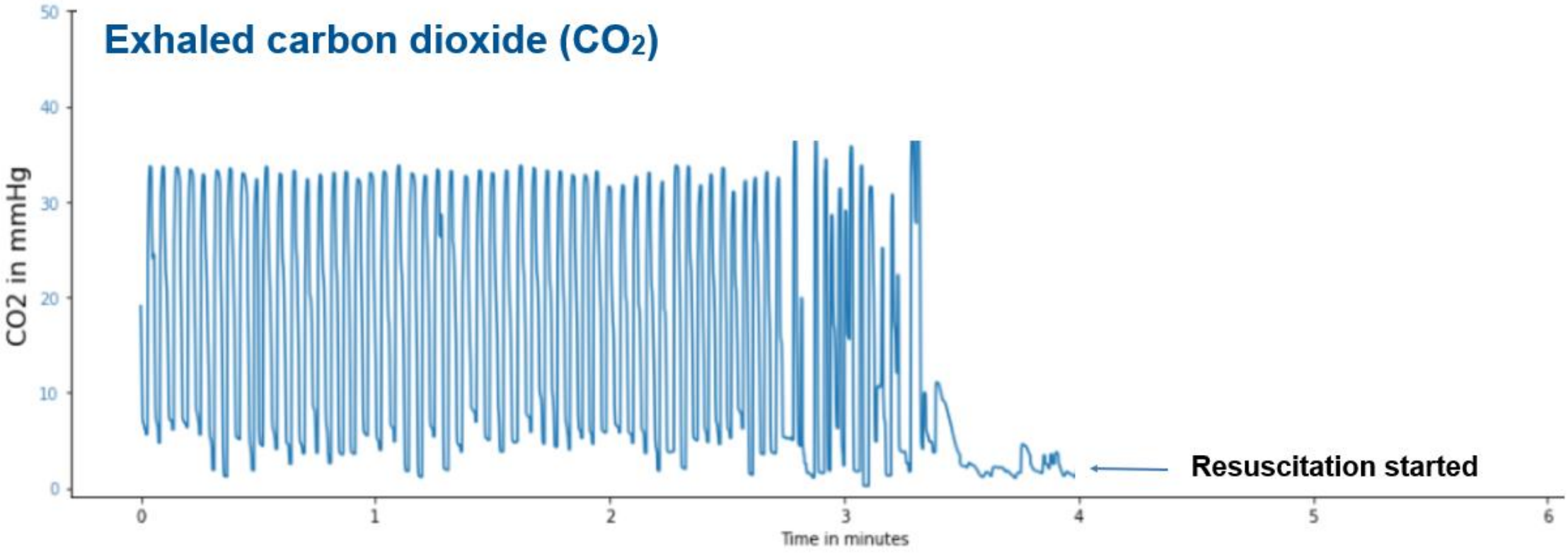
vd Schrier Anesthesiology 2020

Opioid overdose - Respiratory phenotype 1



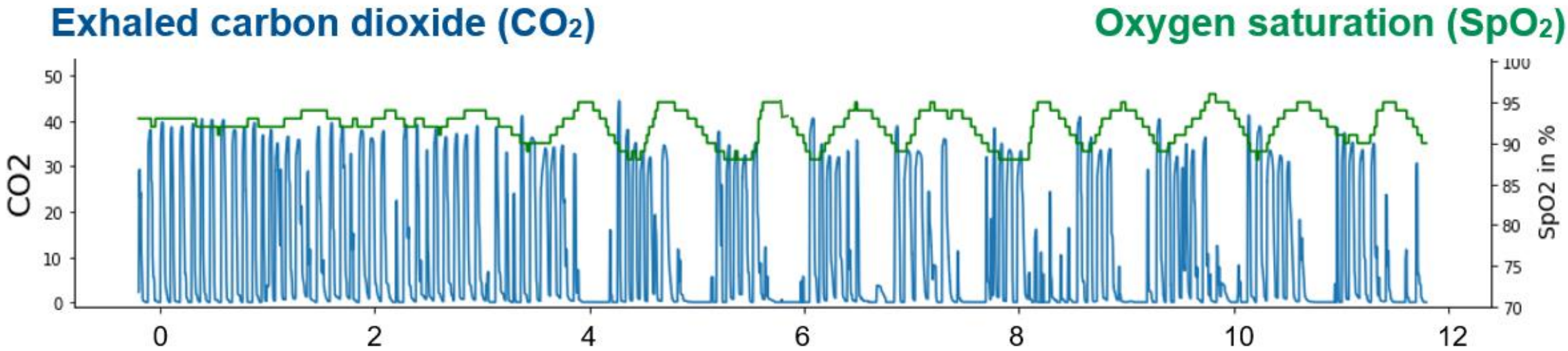
vd Schrier 2023

Opioid overdose - Respiratory phenotype 2

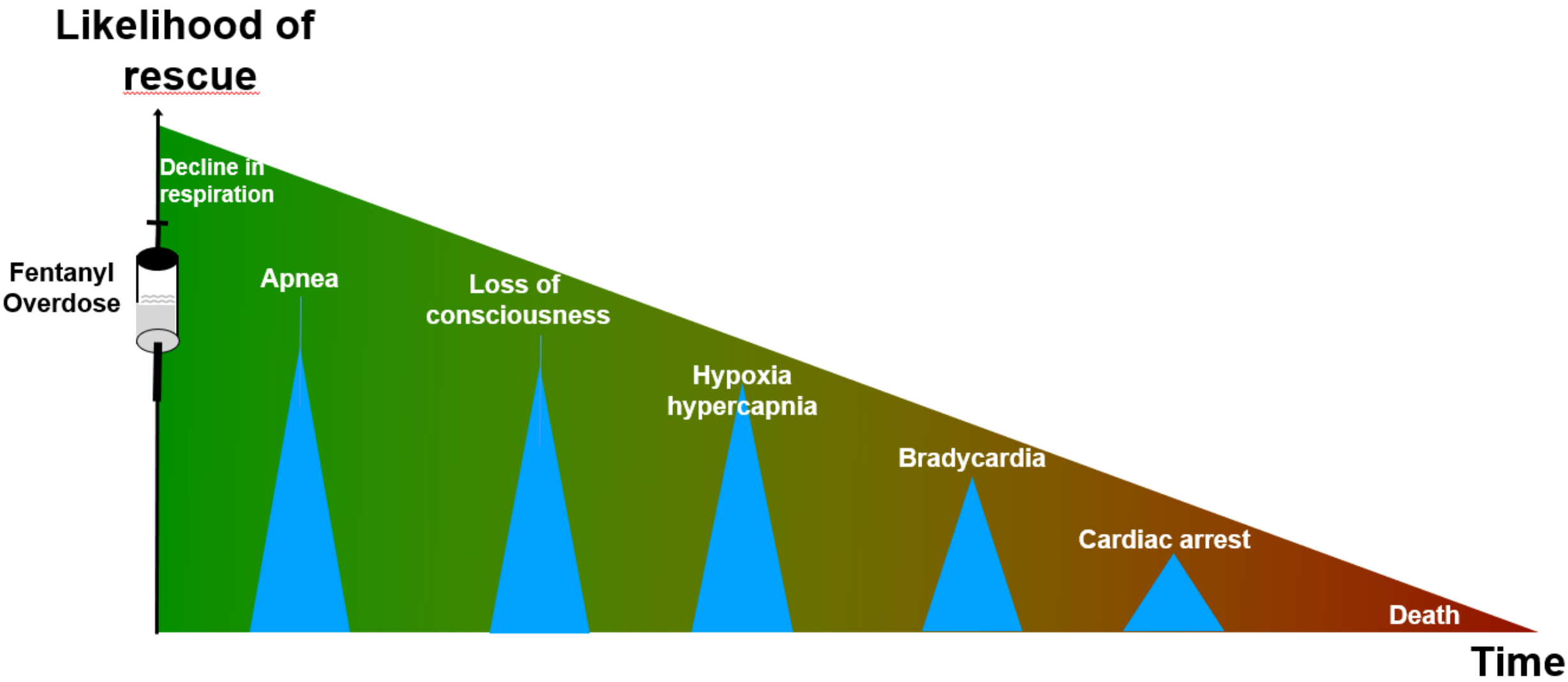


Dahan 2023

Opioid overdose - Respiratory phenotype 3



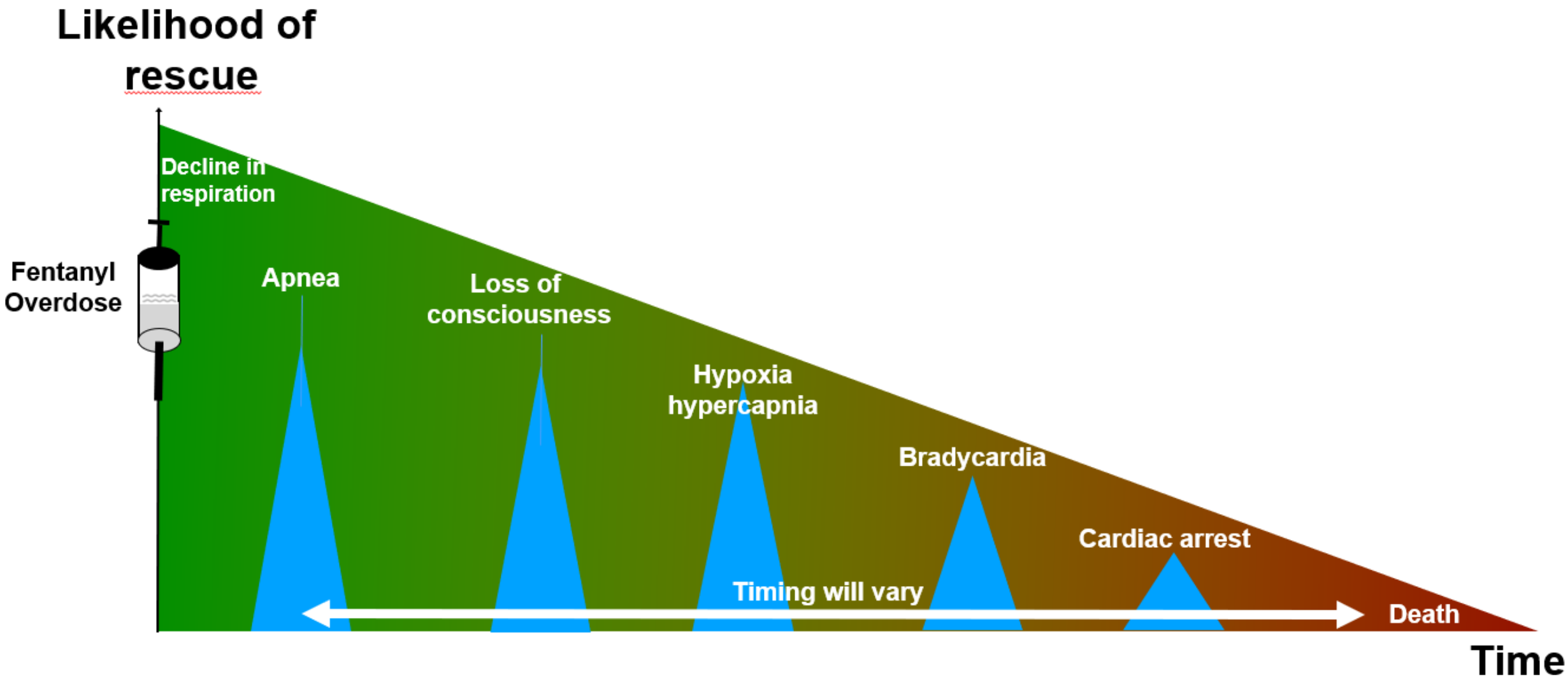
Dahan 2023



Questions to ask

Is the individual still breathing?

More important: does the individual still have a pulse?

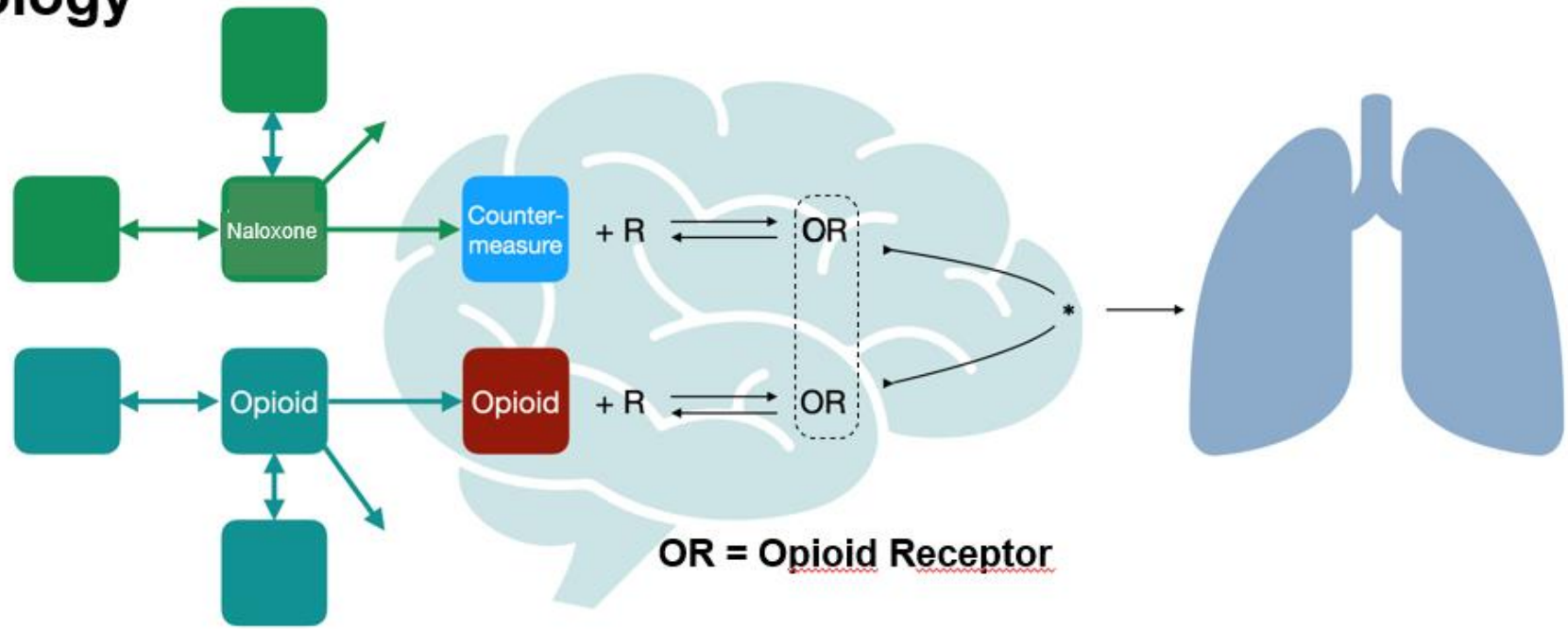


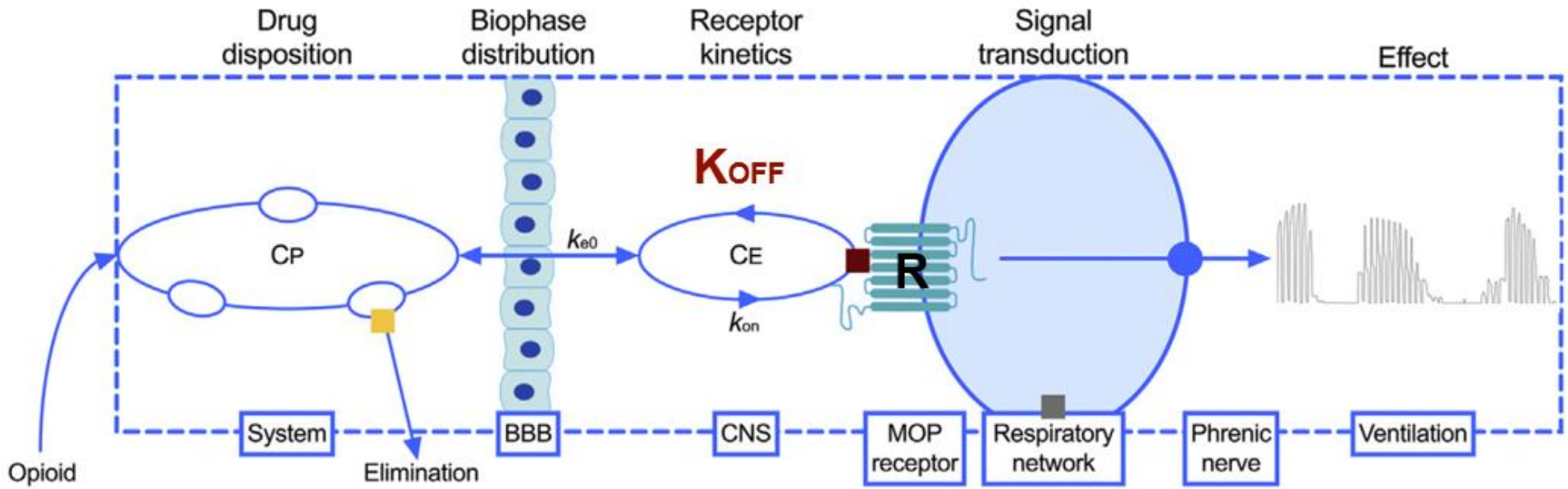
Questions to ask

Is the individual still breathing?

More important: does the individual still have a pulse?

Fentanyl Pharmacology





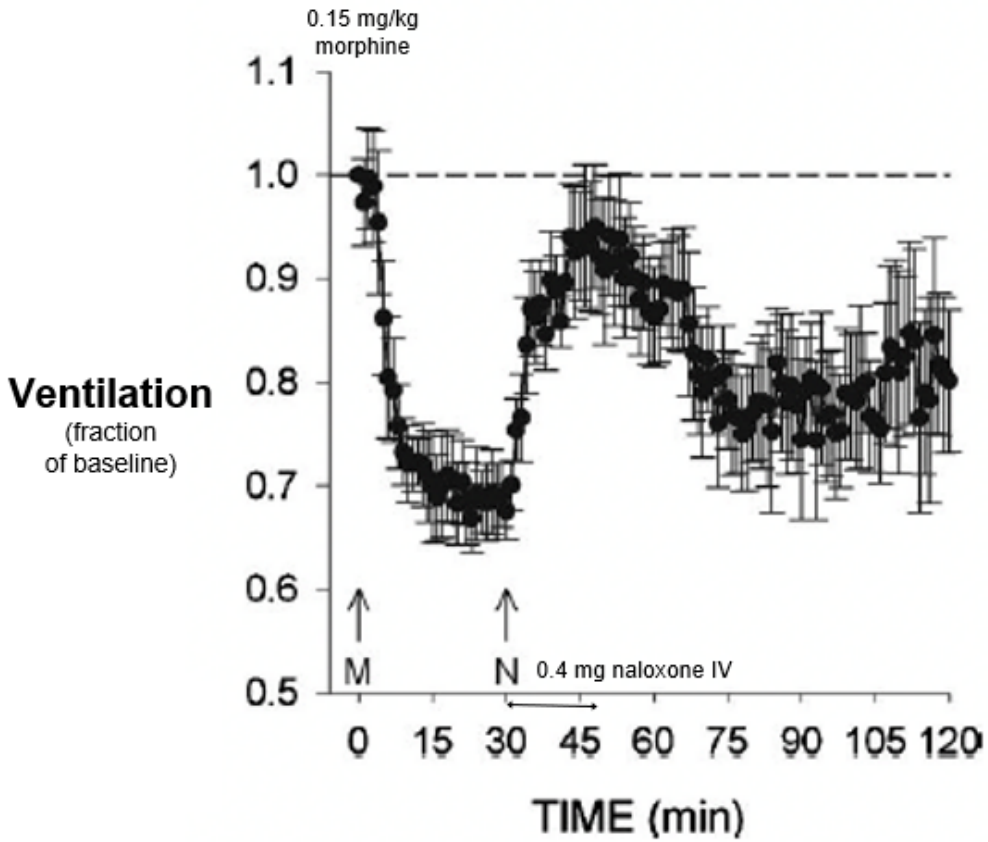
Algera 2023

The opioid's receptor kinetics determines the efficacy of naloxone

The shorter K_{OFF} the more difficult it is for naloxone to disperse the opioid from its receptor

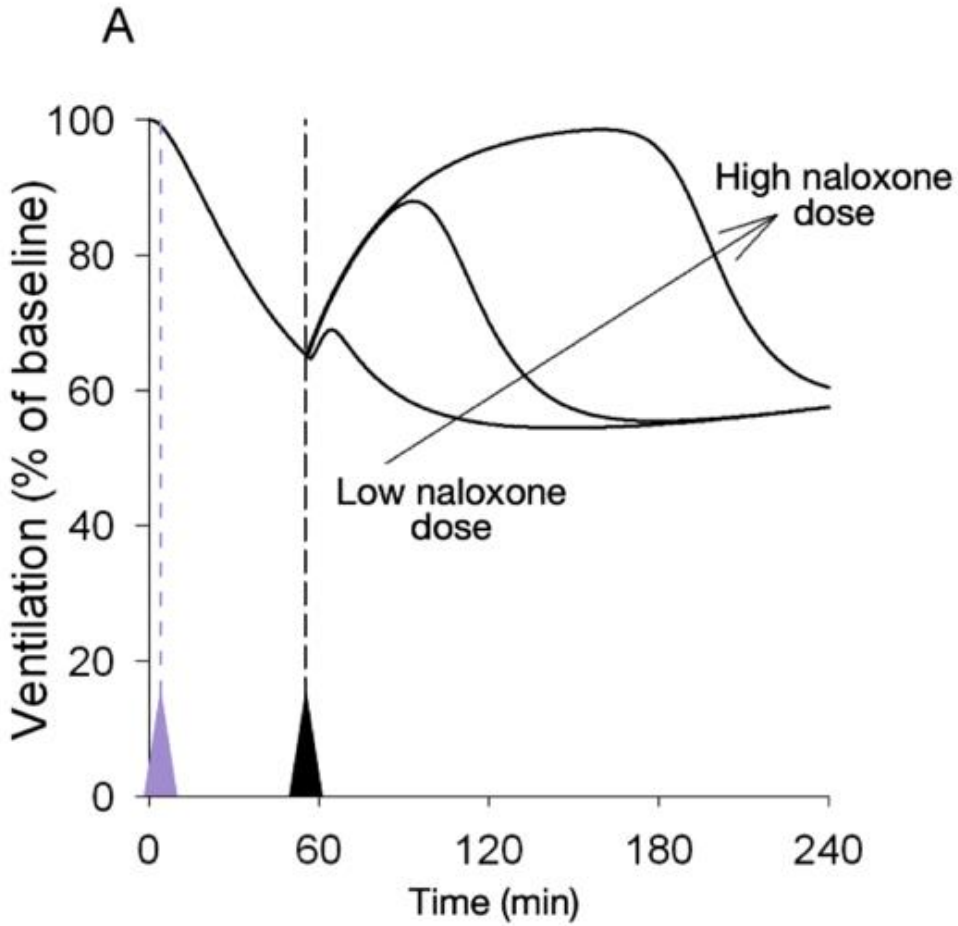
	K_i	Receptor Kinetics K_{OFF} min^{-1}	Blood → Brain kinetics $t½k_{e0}$
Oxycodone	**26**		**40 min**
Fentanyl	**1.35**	**0.004**	**5 min**
Morphine	**1.1**	**0.002**	**60 min**
Hydromorphone	**0.37**		
Buprenorphine	**0.22**	**0.0002**	**75 min**
Sufentanil	**0.14**	**0.001**	**5 min**
Carfentanil	**0.05**	**0.00025**	**5 min**
Naloxone	**1.1**	**0.04**	**< 1 min**

v Lemmen 2023

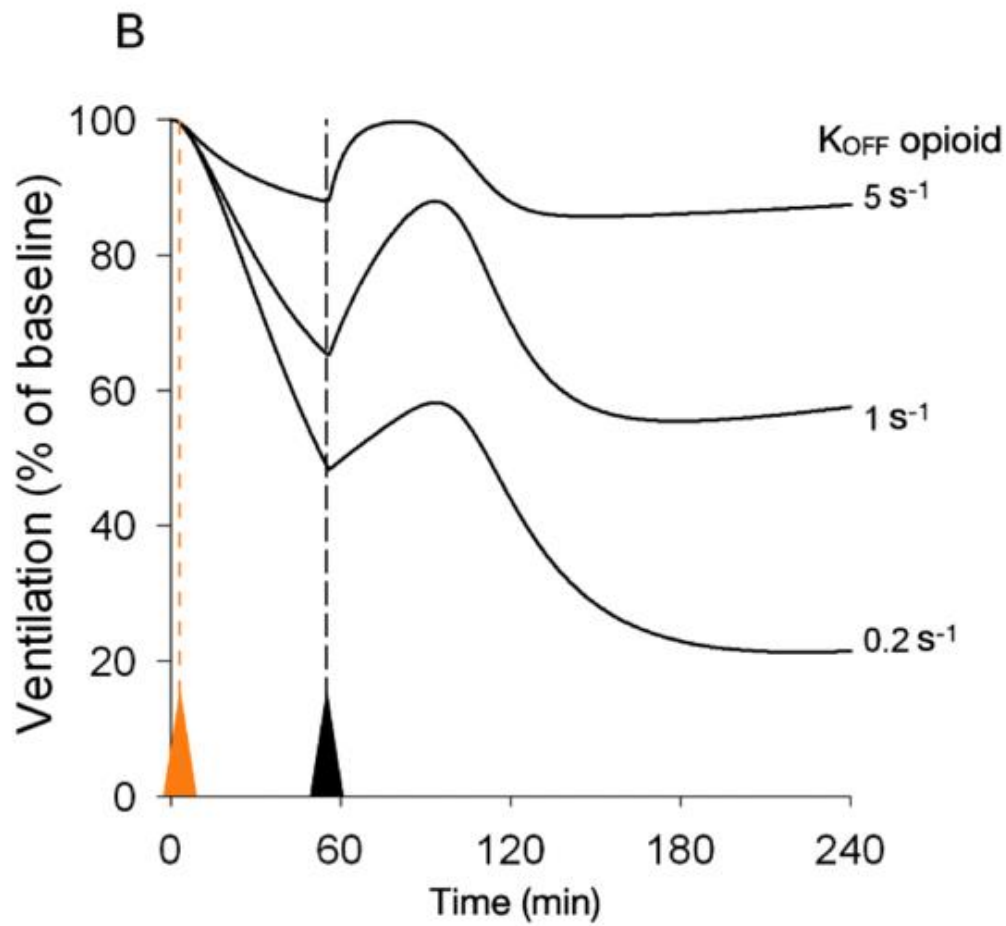


Olofsen 2010

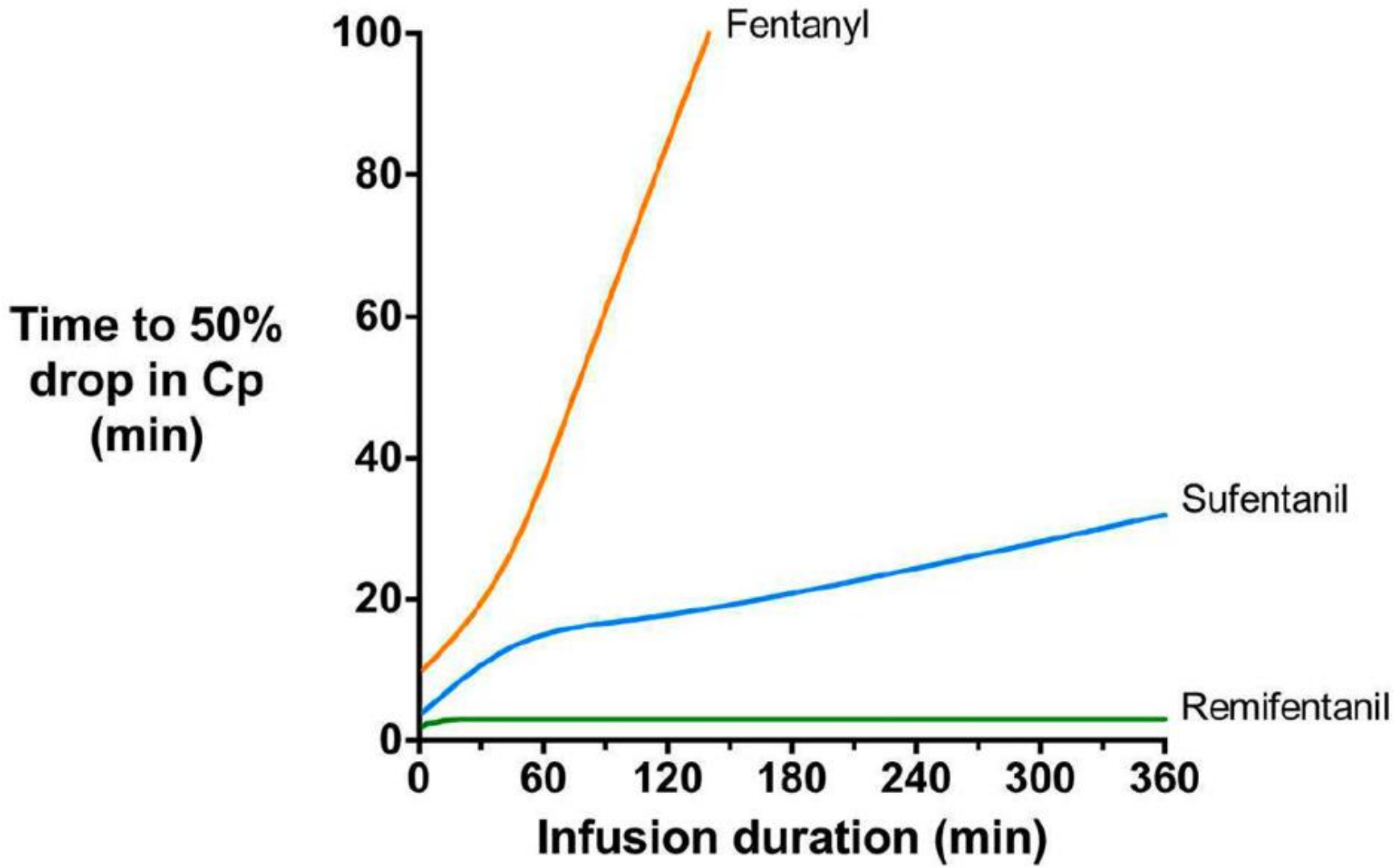
Fixed K_{OFF}: increasing naloxone dose effect



Variable K_{OFF}: fixed naloxone dose effect



Martini 2011


Time to 50% drop in Cp (min)
100
80
60
40
20
0
0
60
120
180
240
300
360
Infusion duration (min)
Fentanyl
Sufentanil
Remifentanil

Dahan 2023

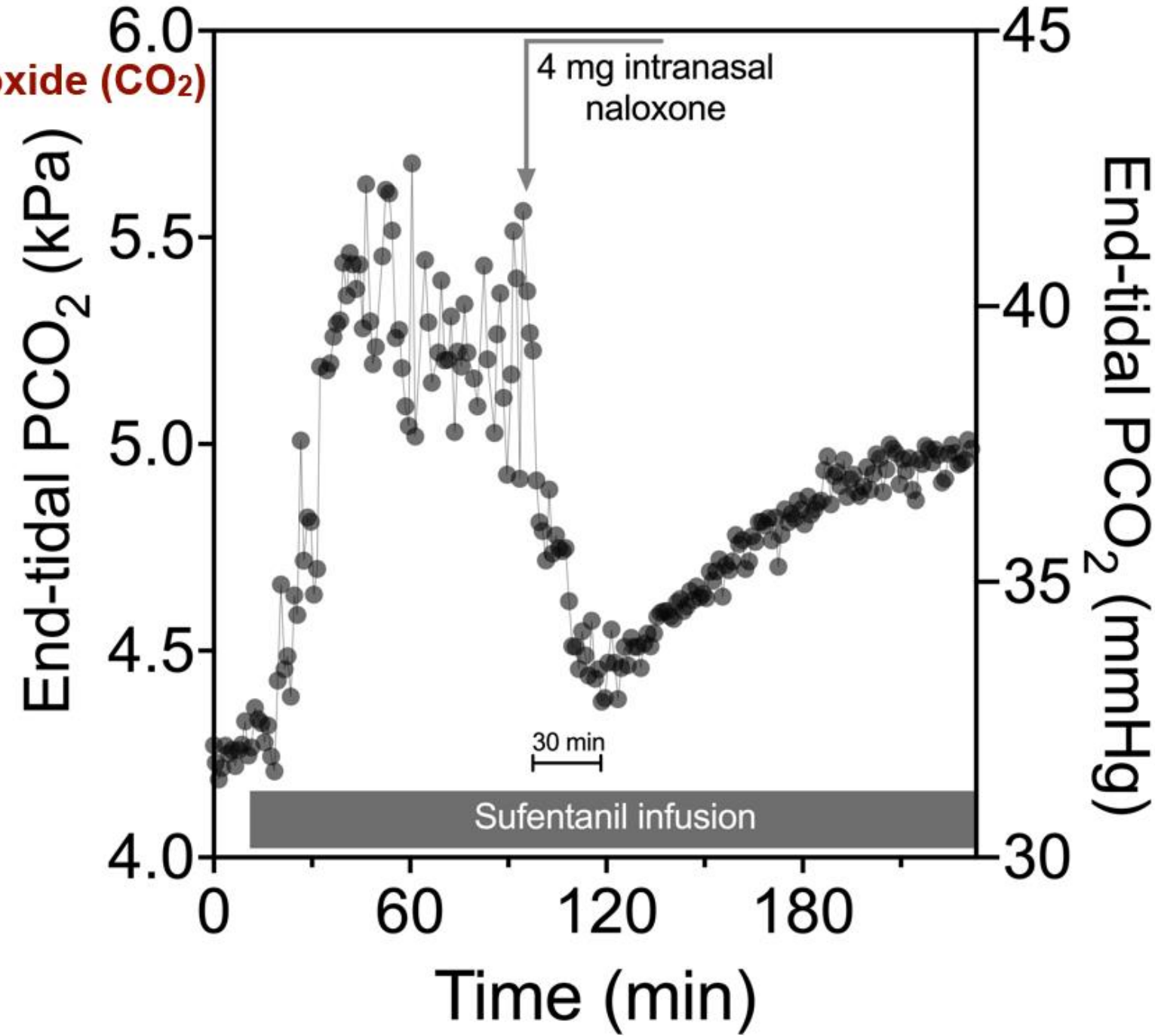
Fentanyl overdose is difficult to reverse because of

1. Slow receptor kinetics (sufentanil and carfentanil are more difficult to reverse)
2. Fentanyl accumulates in the system

Solution

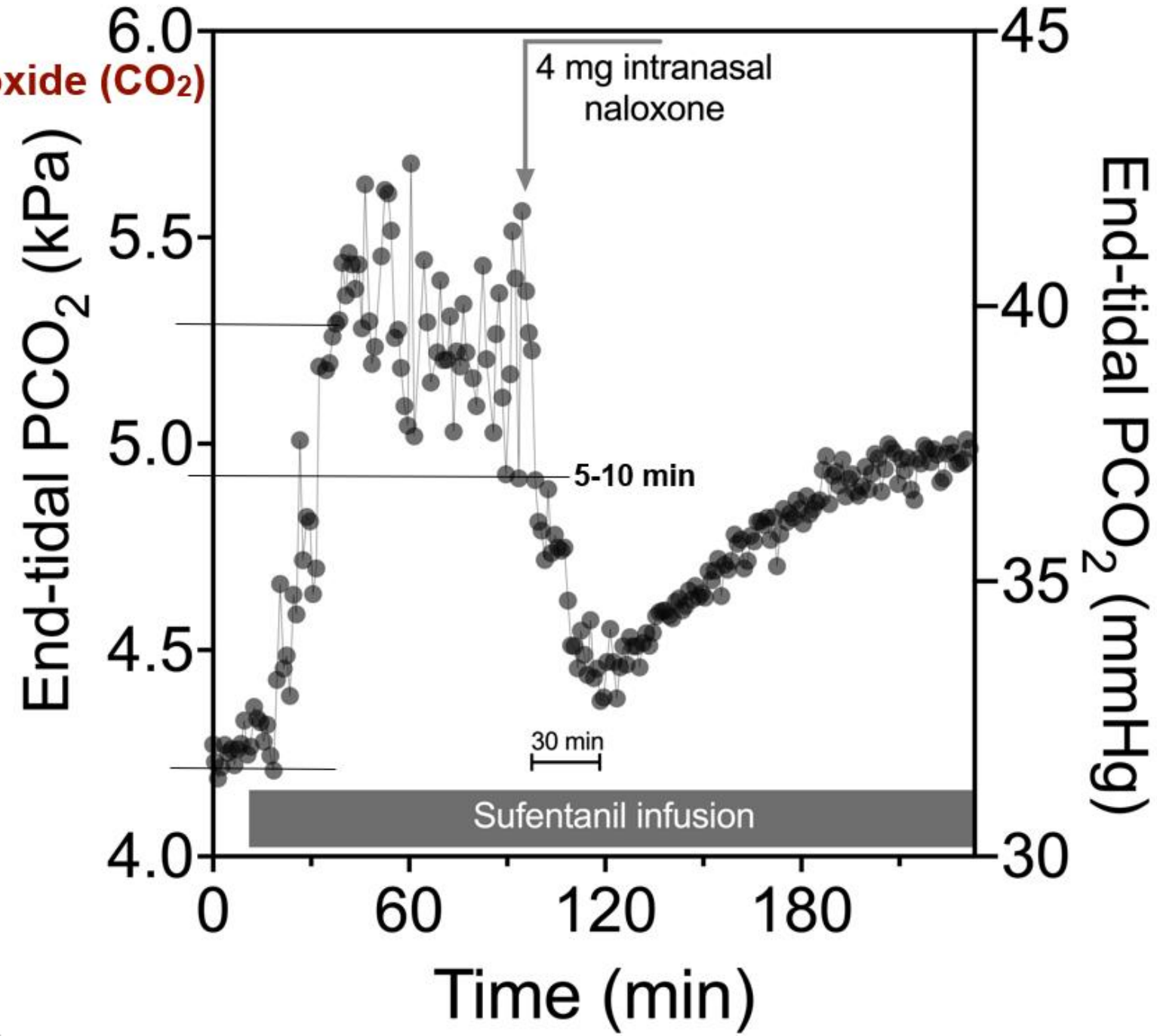
1. Initiate early on chest compressions and artificial ventilation
2. High dose naloxone (in the community setting) **intramuscular or intranasal**
3. High dose ± continuous naloxone infusion (in hospital setting)

Exhaled carbon dioxide (CO_2)



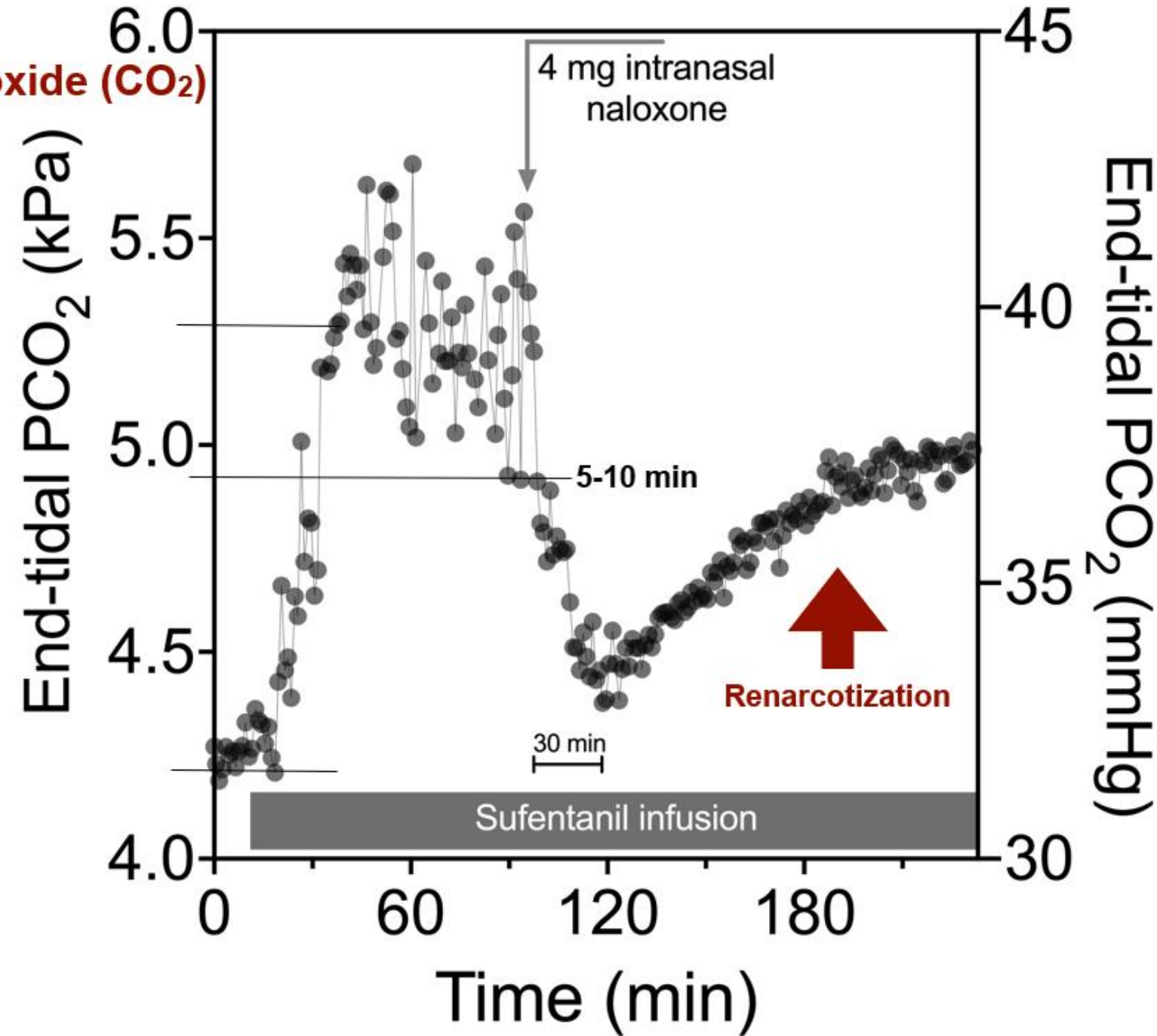
v Lemmen 2023

Exhaled carbon dioxide (CO_2)



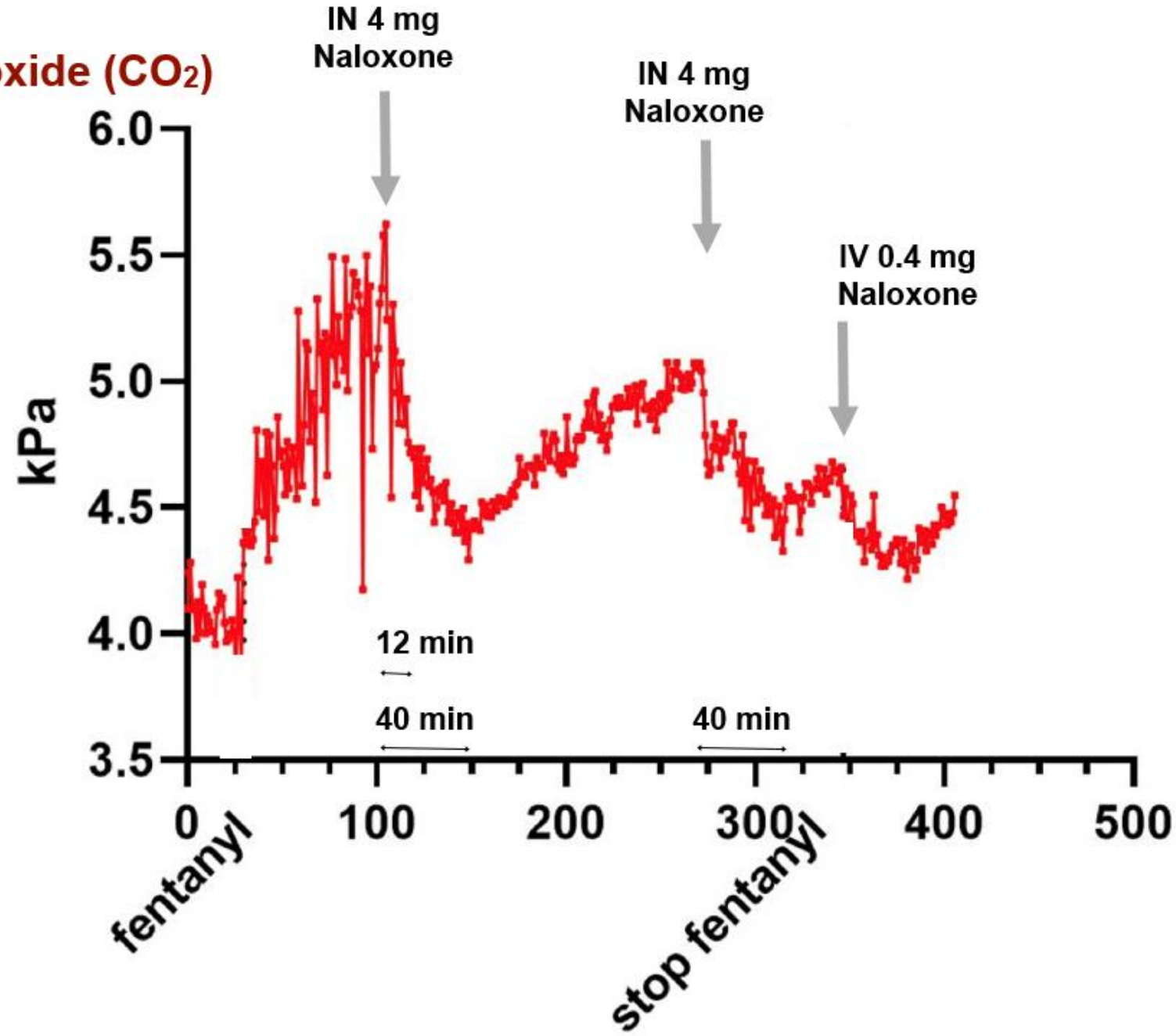
v Lemmen 2023

Exhaled carbon dioxide (CO_2)



v Lemmen 2023

Exhaled carbon dioxide (CO_2)



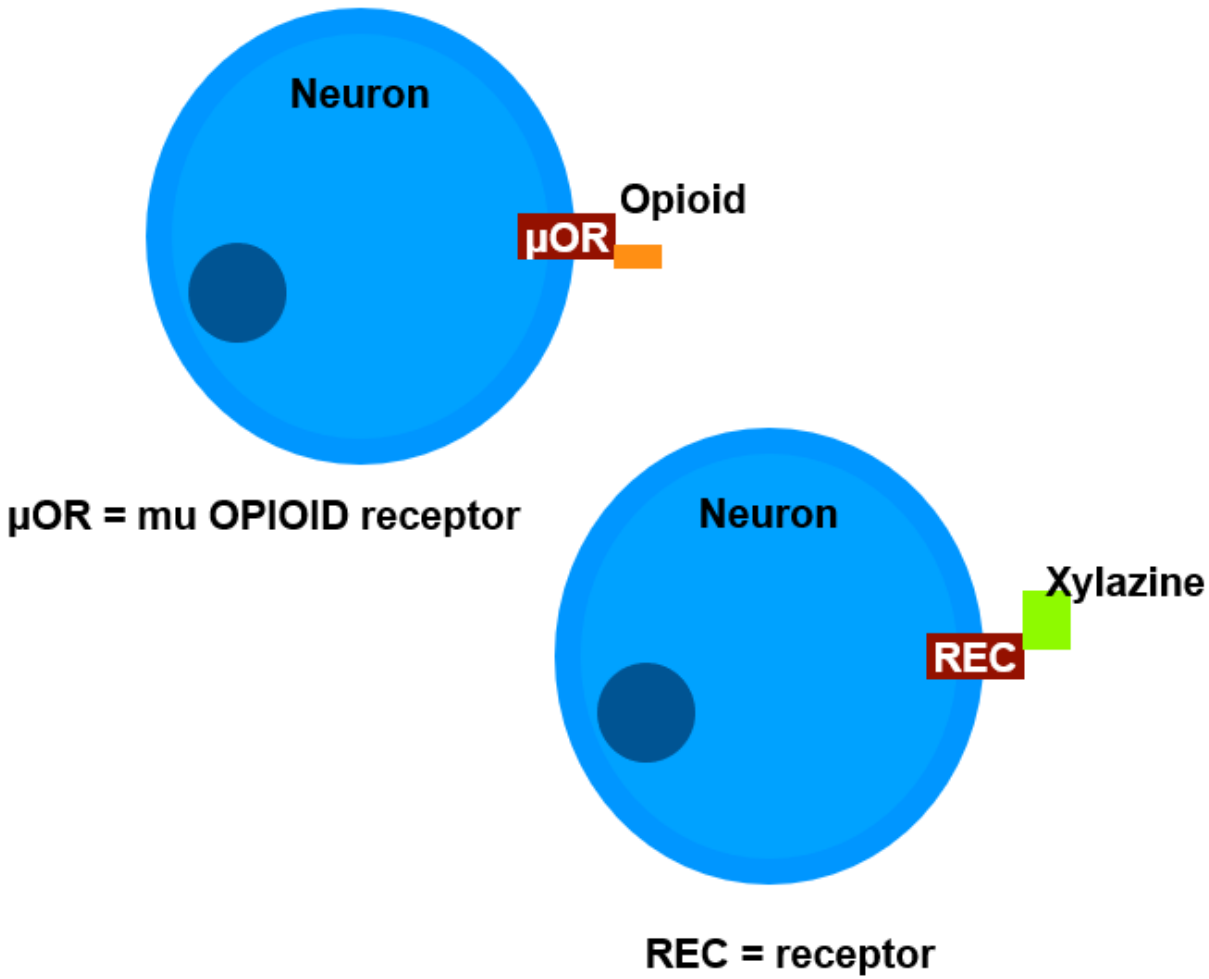
Fentanyl overdose is difficult to reverse because of

1. Slow receptor kinetics (sufentanil and carfentanil are more difficult to reverse)
2. Fentanyl accumulates in the system

Solution

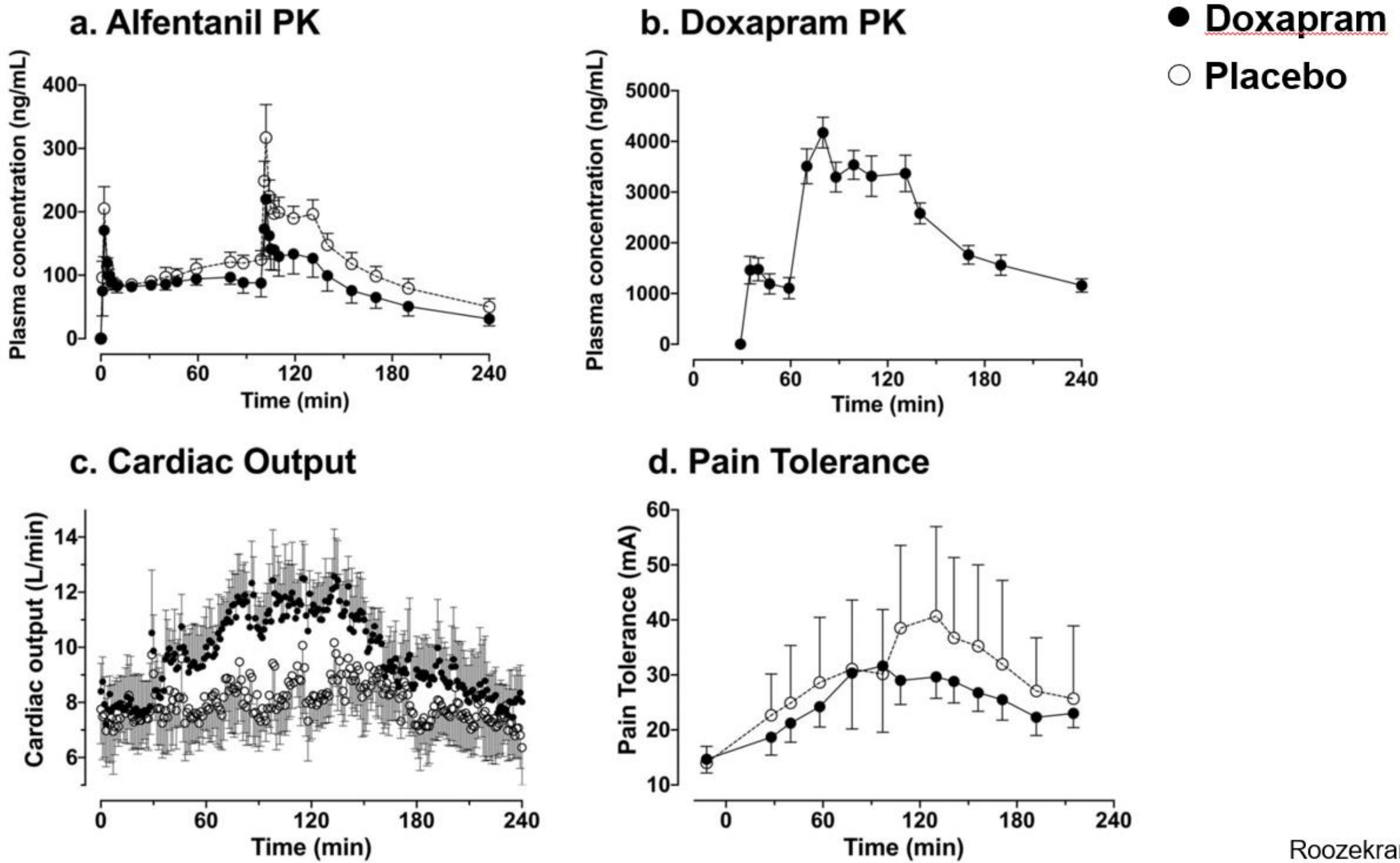
1. Initiate early on chest compressions and artificial ventilation
2. High dose naloxone (in the community setting) **4 or even better 8 mg IN naloxone**
3. High dose ± continuous naloxone infusion (in hospital setting)
4. Be prepared for extreme withdrawal and excited delirium

How effective is naloxone in restoring respiratory activity? If not effective what to do next?



Fentanyl overdose combined with another high dose and potent respiratory depressant

1. Naloxone alone won't work
2. Initiate chest compression
3. Give IN naloxone and an agnostic respiratory stimulant
4. None of the respiratory stimulators are currently well scrutinized and more research is needed
5. Possible agents include ENA001 - doxapram - CX717



Roozekrans 2017

U.S. FOOD & DRUG ADMINISTRATION

Assessment of Intranasal Naloxone Repeat Dosing Strategies

March 8, 2023

David Strauss, MD, PhD
Director, Division of Applied Regulatory Science
Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research

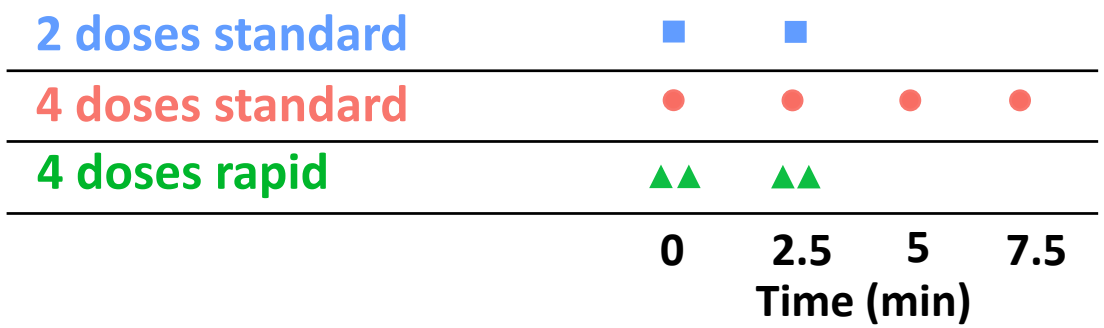
This presentation reflects the views of the author and should not be construed to represent FDA's view or policies

Background

- Community use intranasal naloxone products are sold in packages with 2 single-use nasal sprays
- Approved for administration as a single dose with repeat doses every 2 to 3 minutes if the patient does not respond
- Fentanyl(s) can cause rapid respiratory depression and death and may require higher naloxone doses
- Questions have emerged as to whether current naloxone dosing is adequate in the era of illicitly manufactured fentanyl(s)
  - Should more than 2 doses be included in packaging?
  - Are higher doses needed?

Study Design

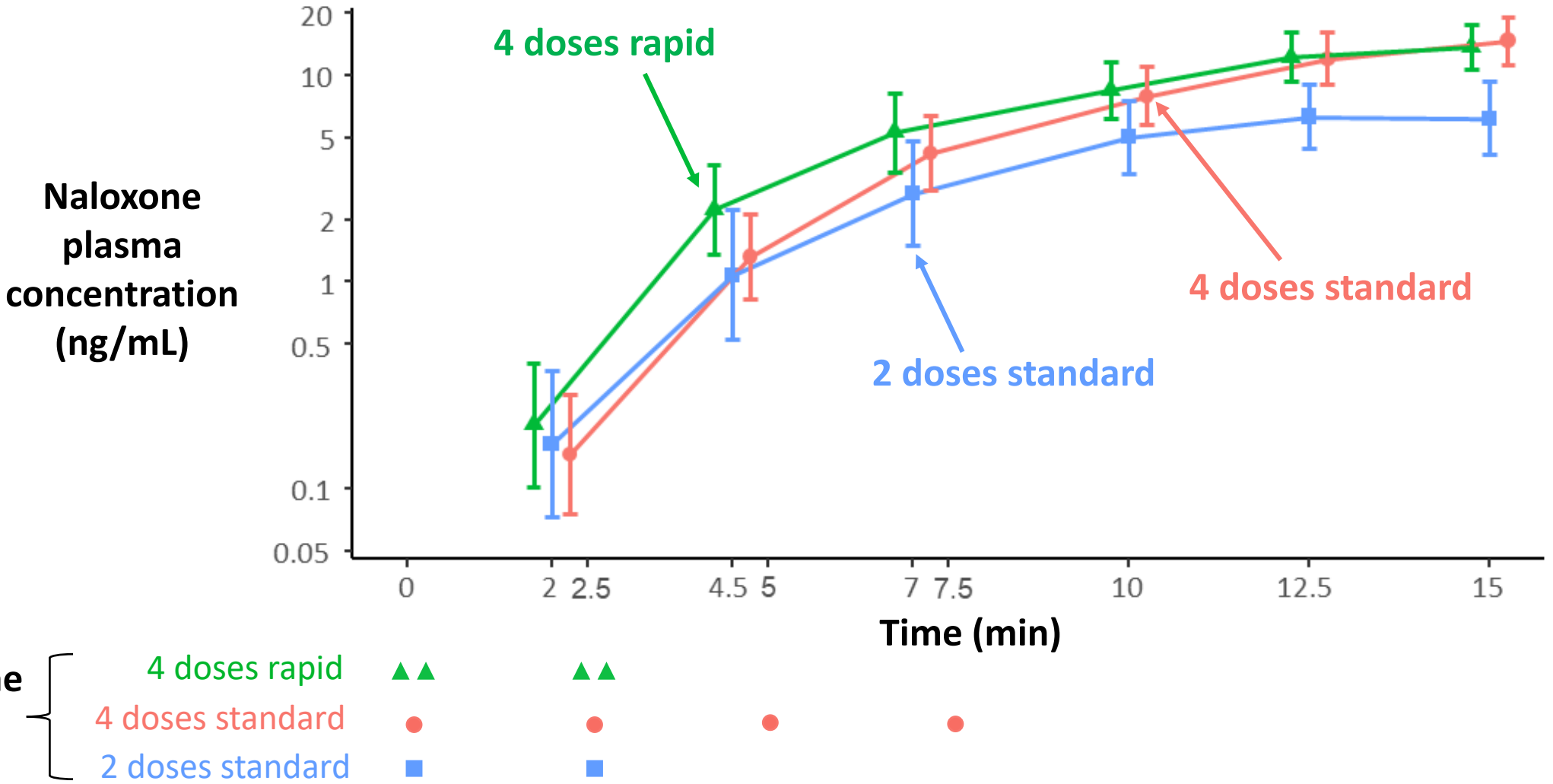
- Randomized crossover trial in 21 healthy participants to compare naloxone plasma concentration between different intranasal (IN) naloxone repeat dosing strategies
  - All IN naloxone doses 4 mg/0.1 mL (Narcan, Emergent BioSolutions)



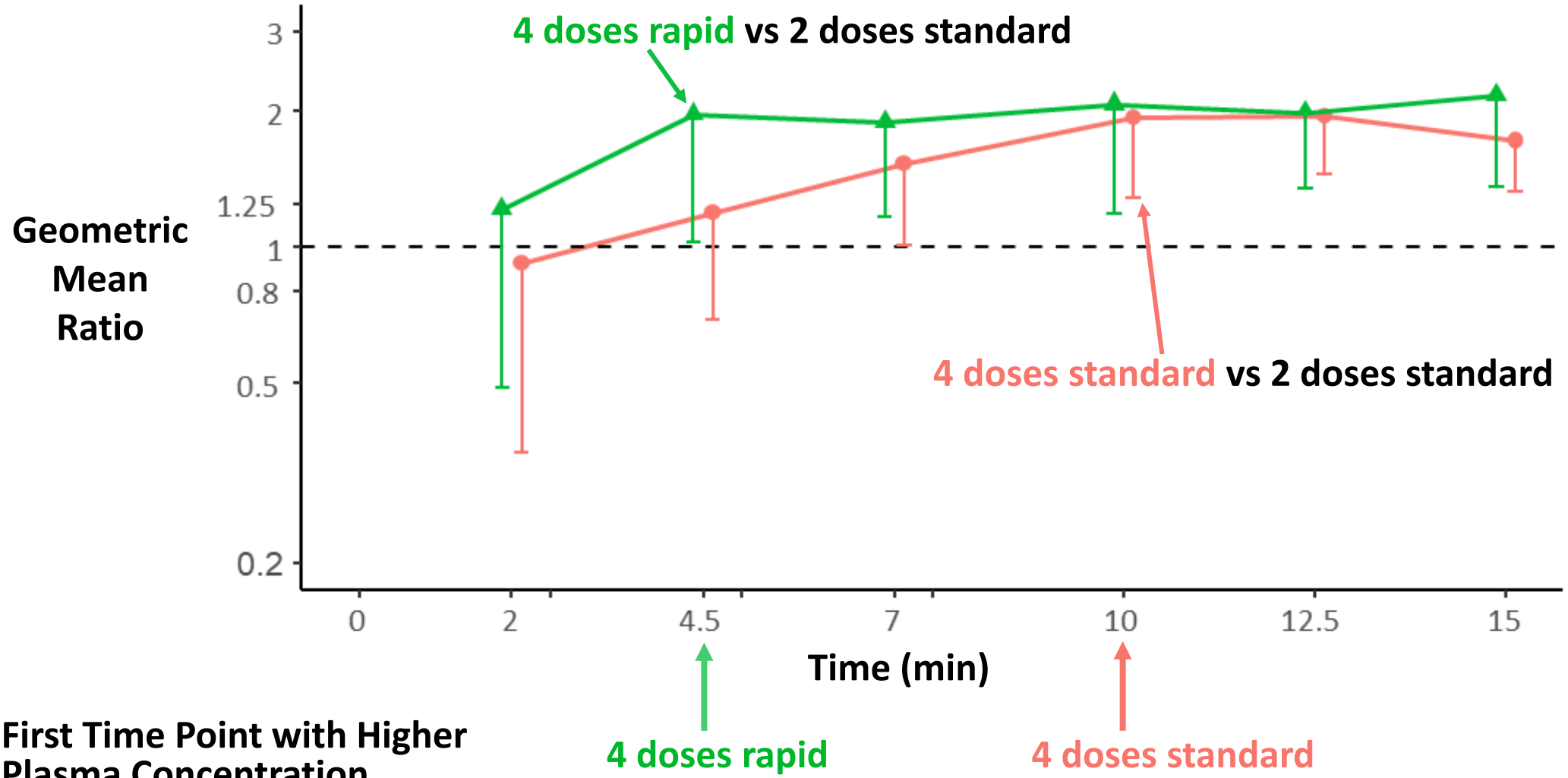
- Primary outcome: first time point when there was higher naloxone plasma concentration in the naloxone 4-dose groups compared to the 2-dose group
- Data used to predict the impact of each dosing strategy on brain hypoxia time and cardiac arrest following fentanyl or carfentanil overdoses with a previously developed and validated pharmacokinetic-pharmacodynamic model

ClinicalTrials.gov - NCT04764630

Clinical Trial Results: Naloxone Plasma Concentration



Comparison Between Naloxone Dosing Strategies



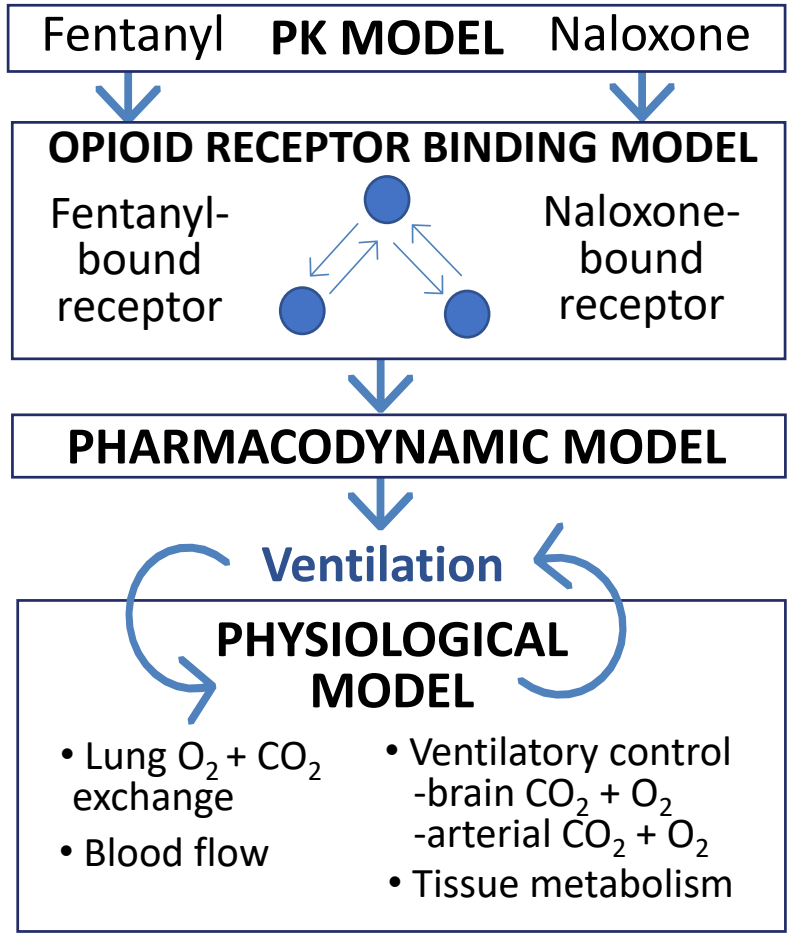
First Time Point with Higher Plasma Concentration

Previously Developed and Validated Model

Development of a Translational Model to Assess the Impact of Opioid Overdose and Naloxone Dosing on Respiratory Depression and Cardiac Arrest

John Mann[1], Mohammadreza Samieegohar[1], Anik Chaturbedi[1], Joel Zirkle[1], Xiaomei Han[1], S. Farzad Ahmadi[1], Amy Eshleman[2], Aaron Janowsky[2], Katherine Wolfrum[2], Tracy Swanson[2], Shelley Bloom[2], Albert Dahan[3], Erik Olofsen[3], Jeffry Florian[1], David G. Strauss[1] and Zhihua Li[1,*]

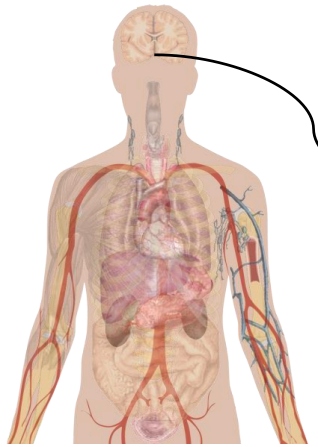
Clinical Pharmacology & Therapeutics 2022;112:1020-32.



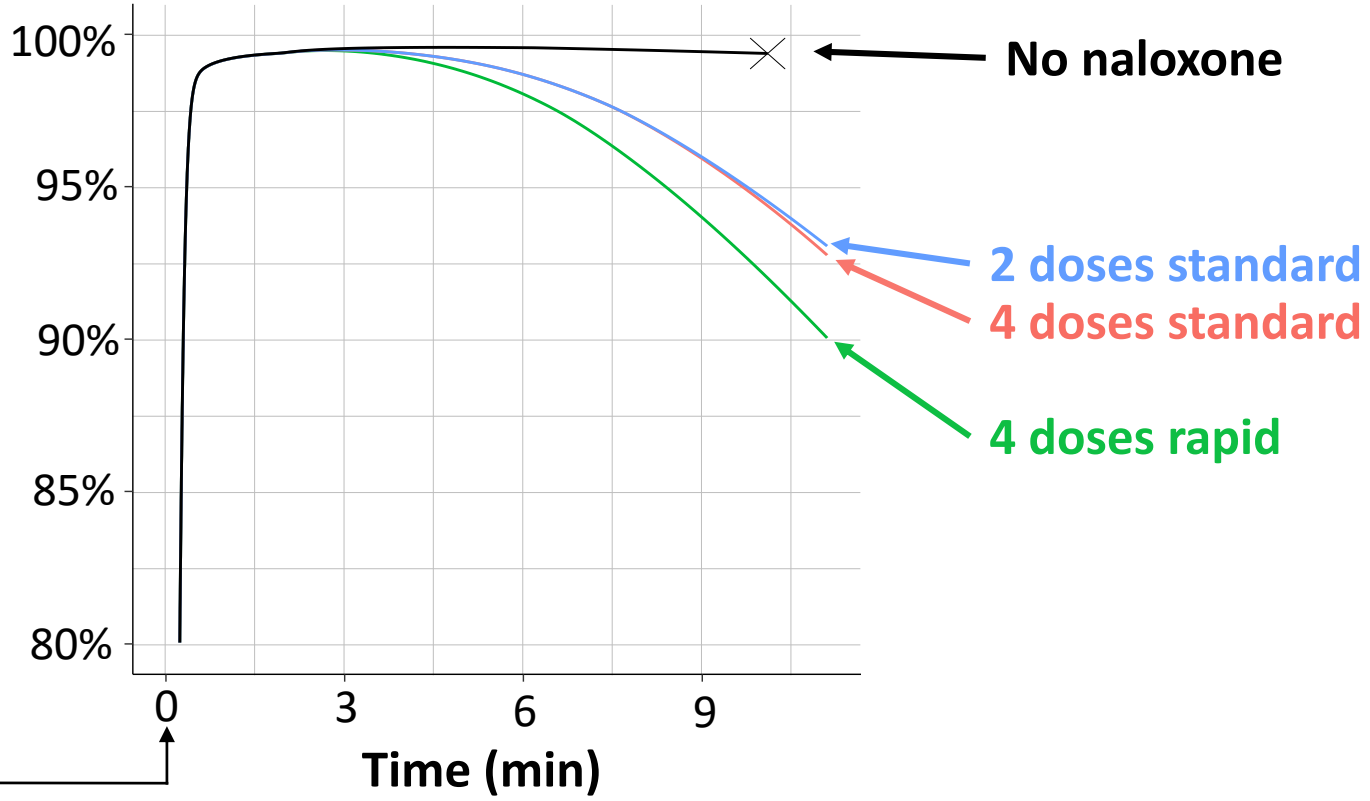
Overdose Simulations Methods

- Two fentanyl doses (1.63 mg and 2.97 mg) were selected based on simulating the intravenous doses that would result in the mean and 1 standard deviation above the mean plasma concentration from a prior study of approximately 500 unintentional fentanyl overdoses with postmortem data

Overdose Simulation Results: Opioid Receptor Binding

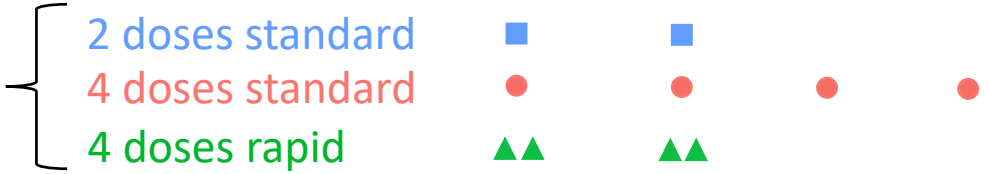


Percent of opioid receptors bound by fentanyl



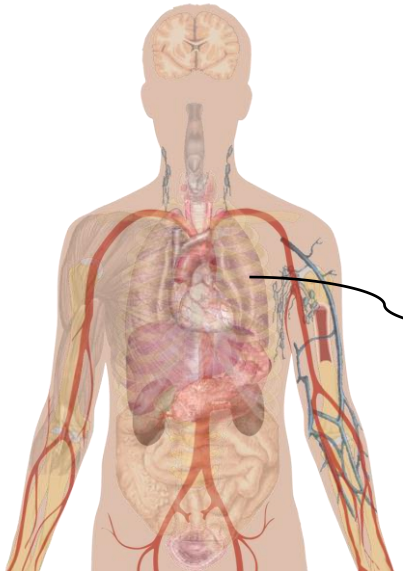
Fentanyl IV

Naloxone doses timing
(1st dose 1 min after ventilation <40% of baseline)

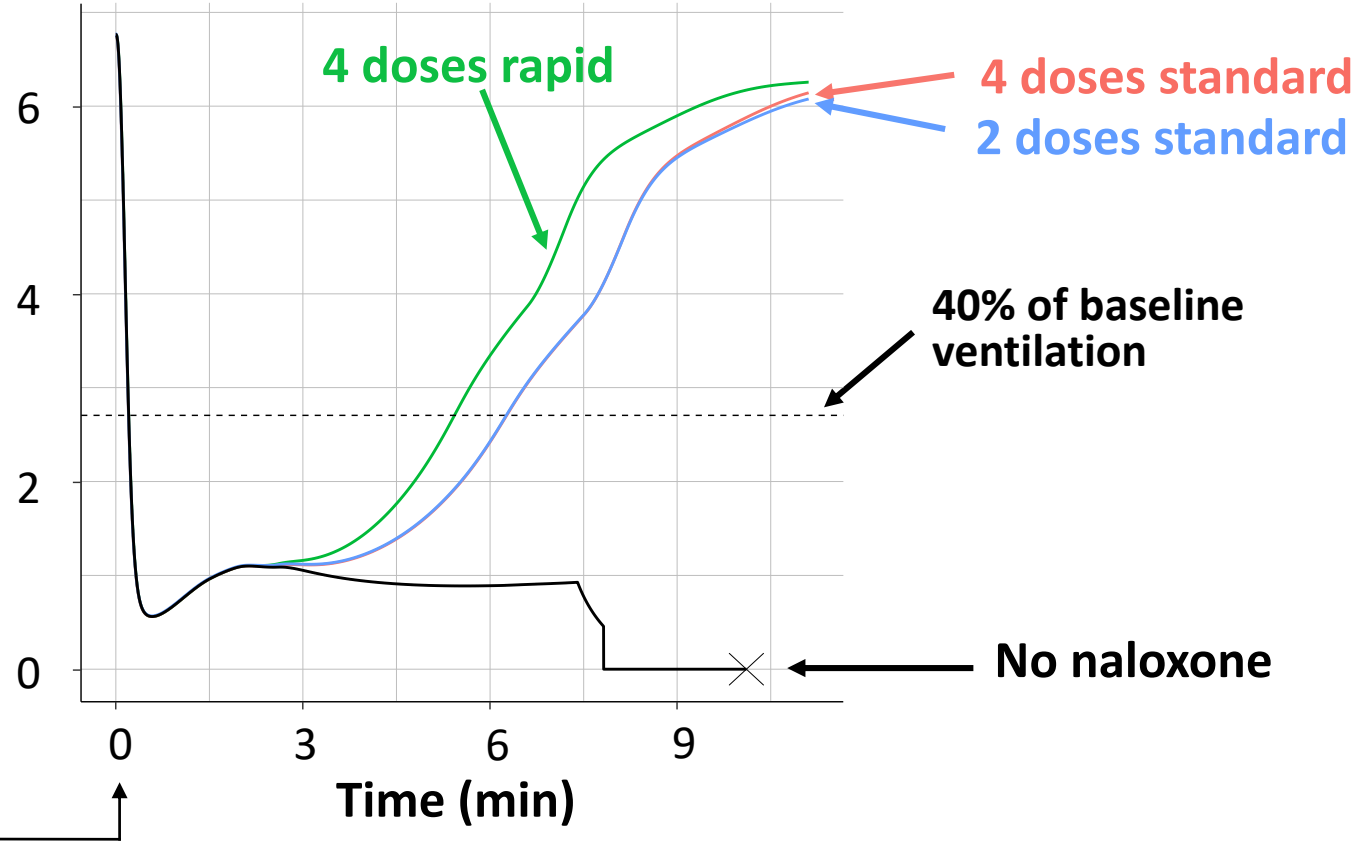


Fentanyl IV 2.97 mg
Naloxone IN 4 mg/0.1 mL

Ventilation



Ventilation (L/min)



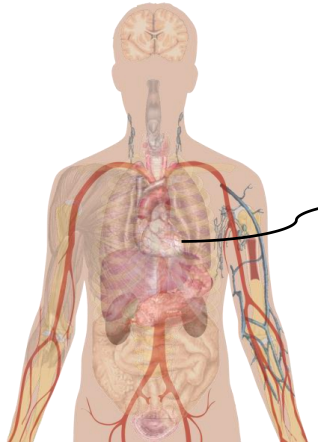
Fentanyl IV

Naloxone doses timing
(1st dose 1 min after ventilation <40% of baseline)

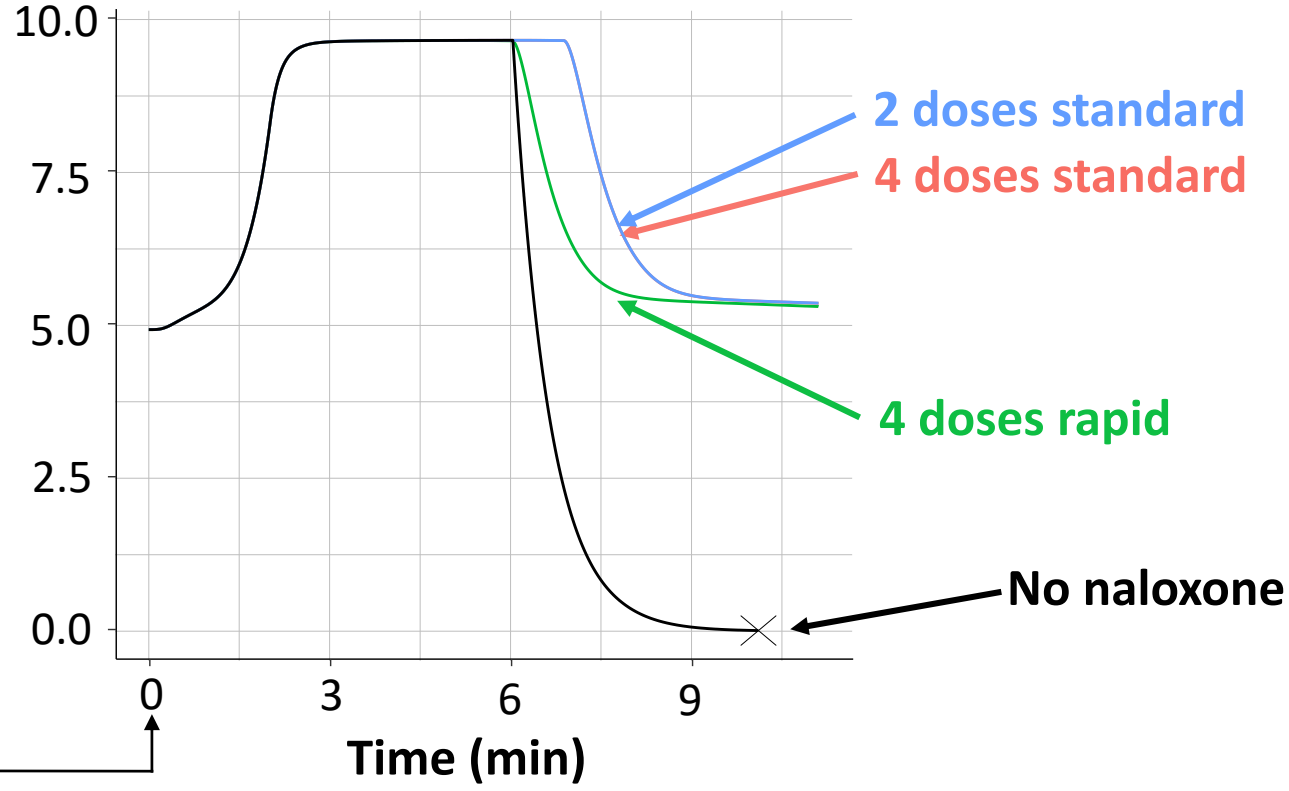
- 2 doses standard
- 4 doses standard
- 4 doses rapid

Fentanyl IV 2.97 mg
Naloxone IN 4 mg/0.1 mL

Cardiac Output



Cardiac output (L/min)



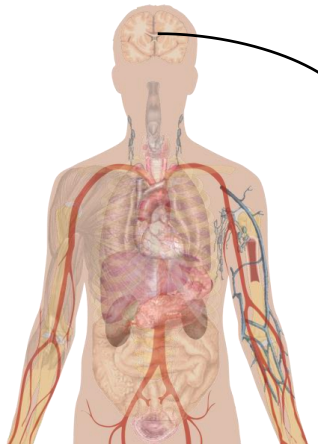
Fentanyl IV

Naloxone doses timing
(1st dose 1 min after ventilation <40% of baseline)

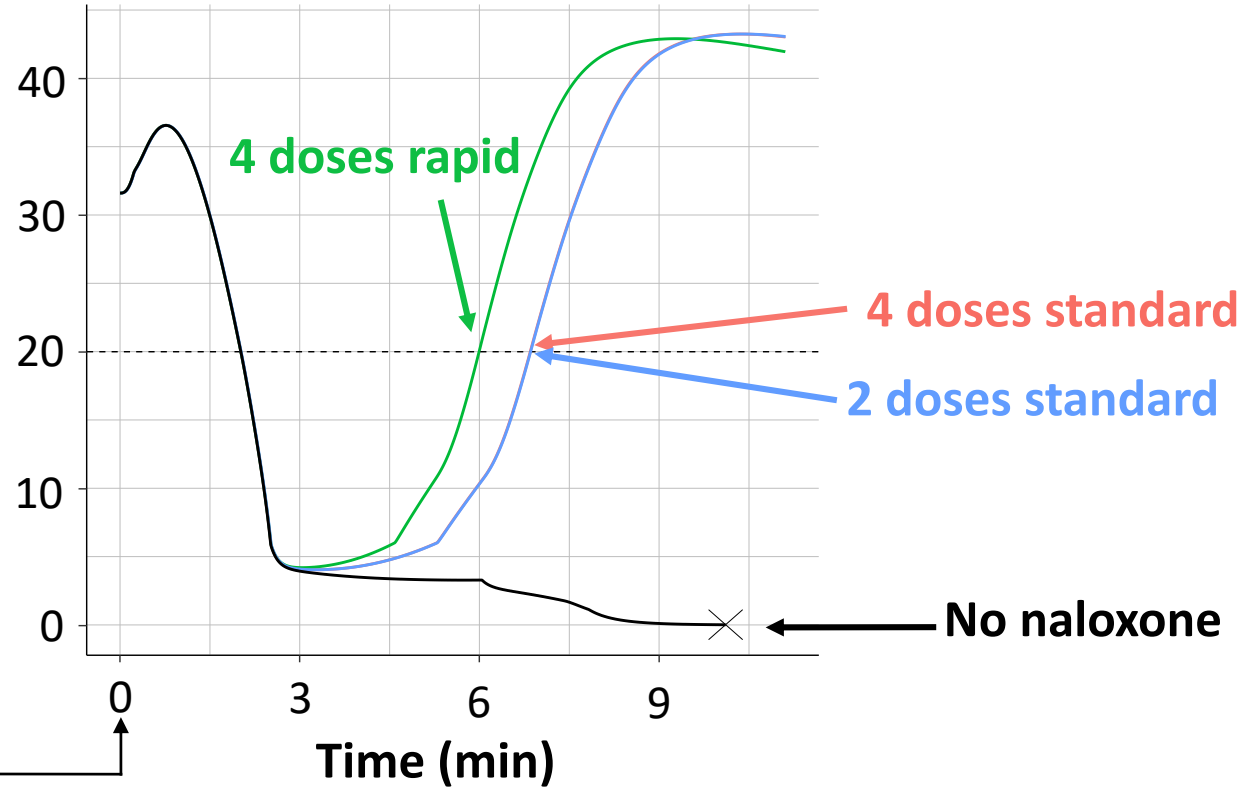
2 doses standard ■ ■
4 doses standard ● ● ● ●
4 doses rapid ▲▲ ▲▲

Fentanyl IV 2.97 mg
Naloxone IN 4 mg/0.1 mL

Brain Tissue Oxygen



Brain O_2 partial pressure (mm Hg)



Fentanyl IV

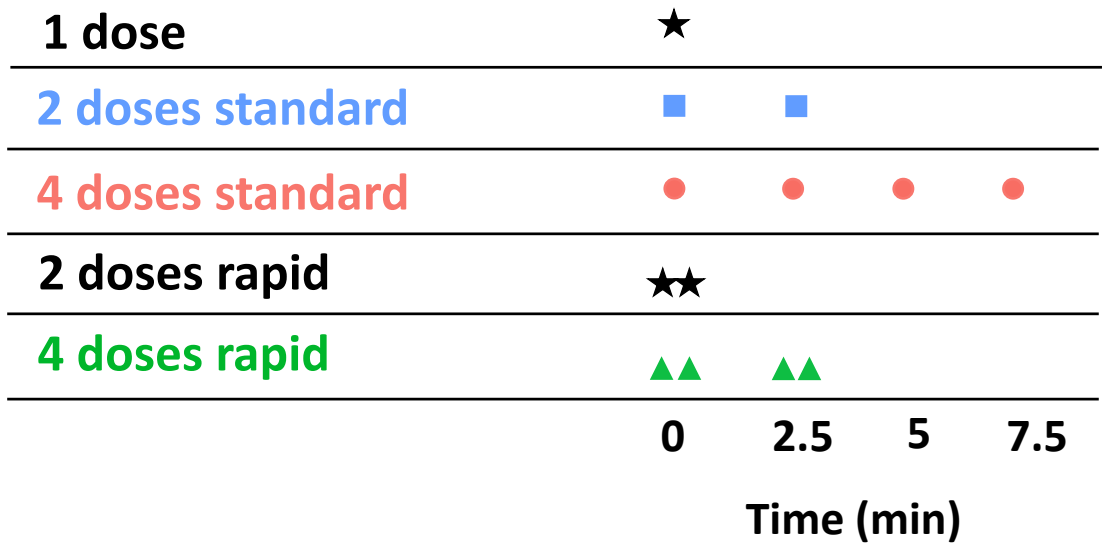
Naloxone doses timing
(1st dose 1 min after ventilation <40% of baseline)

- 2 doses standard ■ ■
- 4 doses standard ● ● ● ●
- 4 doses rapid ▲▲ ▲▲

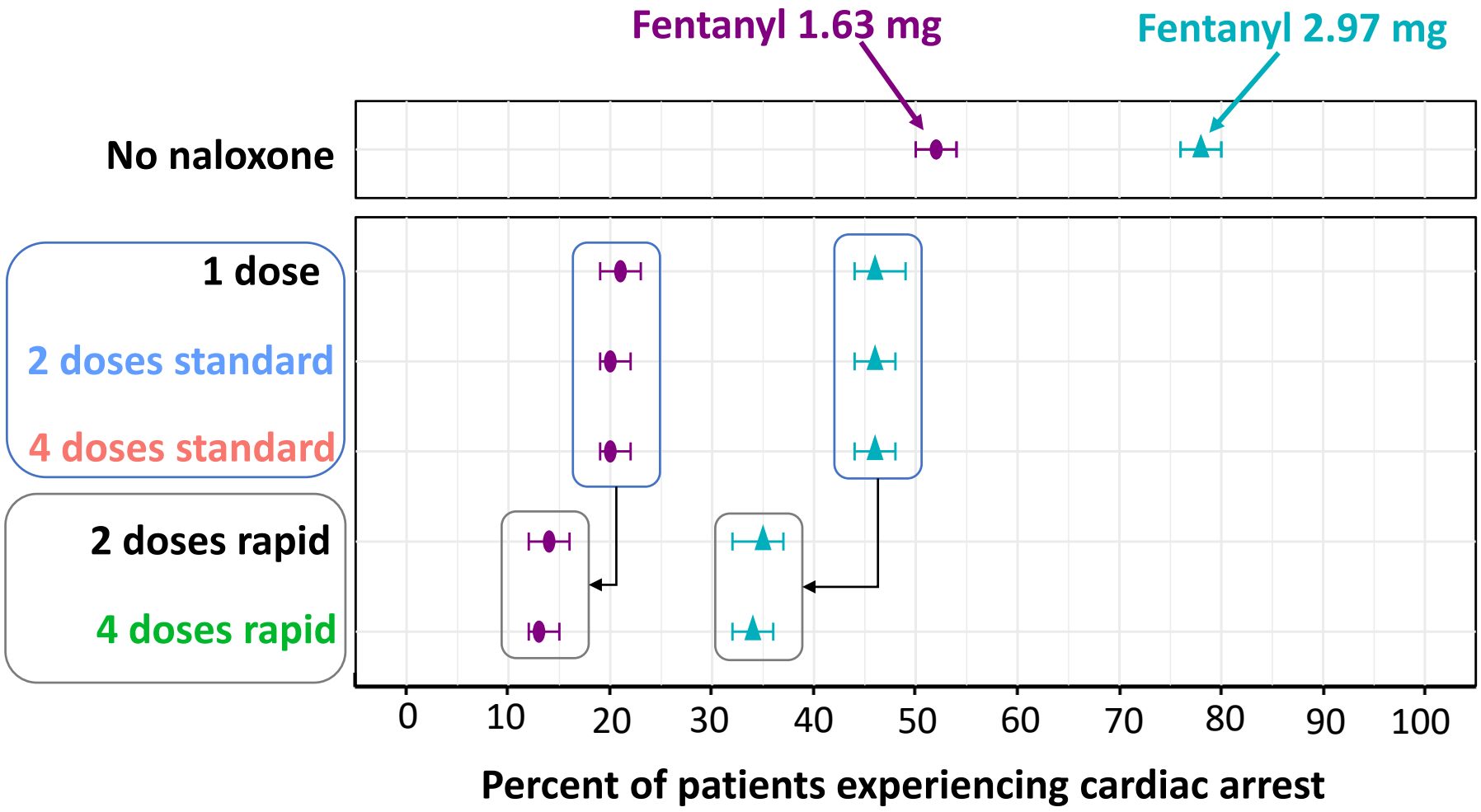
Fentanyl IV 2.97 mg
Naloxone IN 4 mg/0.1 mL

Overdose Simulations Methods

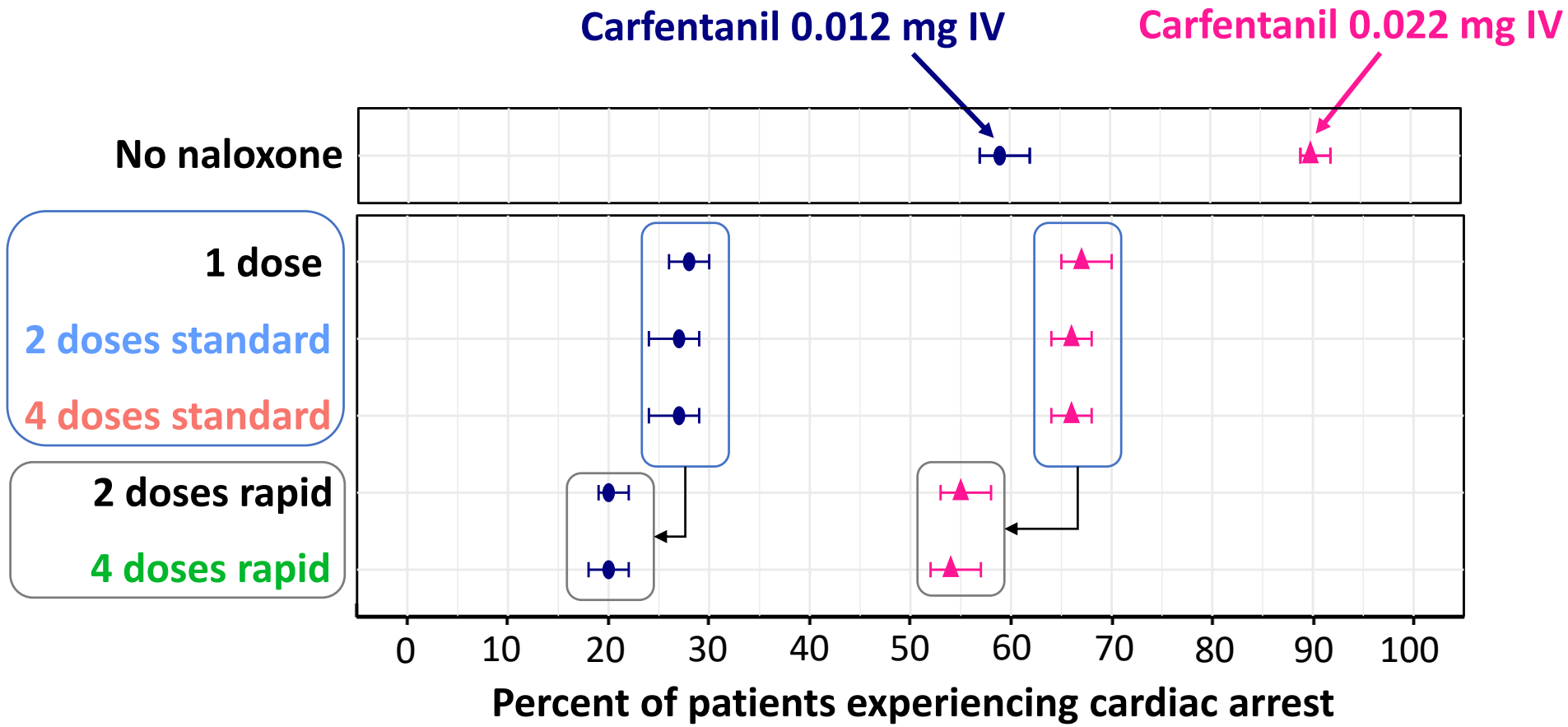
- Simulated 2000 patients with different pharmacokinetic and binding parameters
- In addition to the naloxone dosing strategies from the clinical trial, 2 additional doses were included:
  - 1 dose at 0 min
  - 2 doses at 0 min (2 doses rapid)



Percent of Simulated Patients Experiencing Cardiac Arrest (Fentanyl)



Percent of Simulated Patients Experiencing Cardiac Arrest (Carfentanil)



Comparison with IV Dosing of Naloxone

Boyer, NEJM 2012.

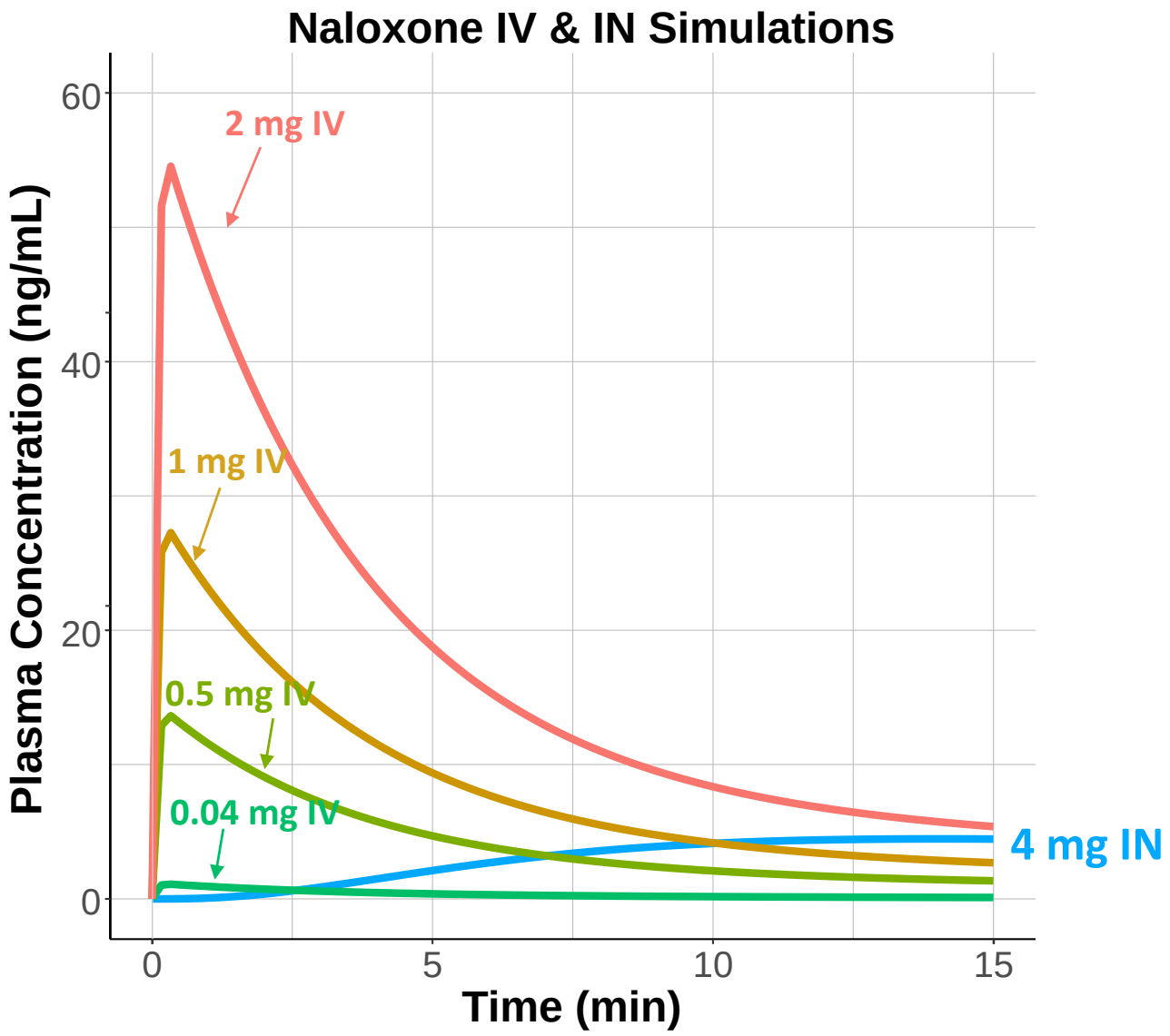
Support respiration with bag-valve mask before administering naloxone

Initial adult dose: 0.04 mg IV

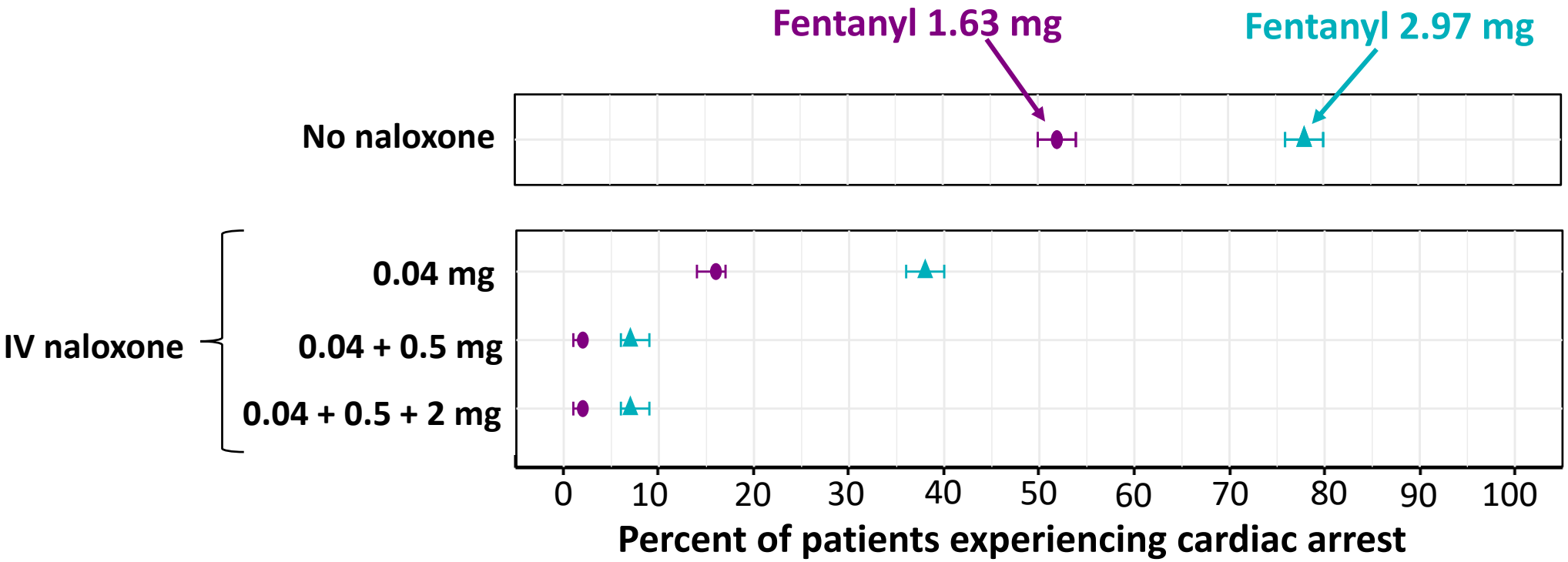
If an increase in respiratory rate does not occur in 2-3 min

- **0.5 mg IV naloxone**
- **2 mg IV naloxone**
- **4 mg IV naloxone**
- **10 mg IV naloxone**
- **15 mg IV naloxone**

[Management of Opioid Analgesic Overdose | NEJM]

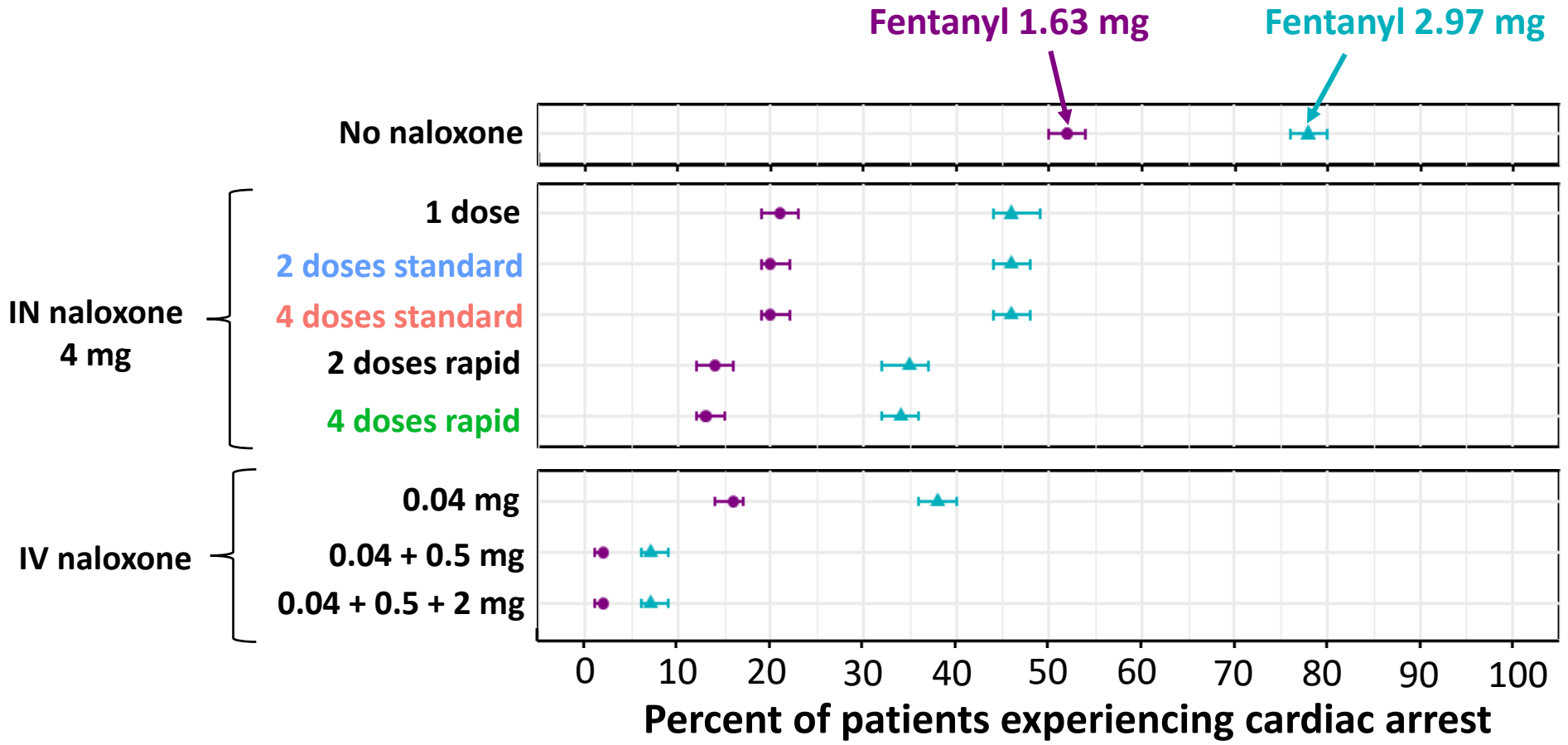


Percent of Simulated Patients Experiencing Cardiac Arrest (IV naloxone)



*Each IV dose was administered 2.5 minutes after the previous dose starting at 0 minutes

Percent of Simulated Patients Experiencing Cardiac Arrest (comparison of IN and IV naloxone)



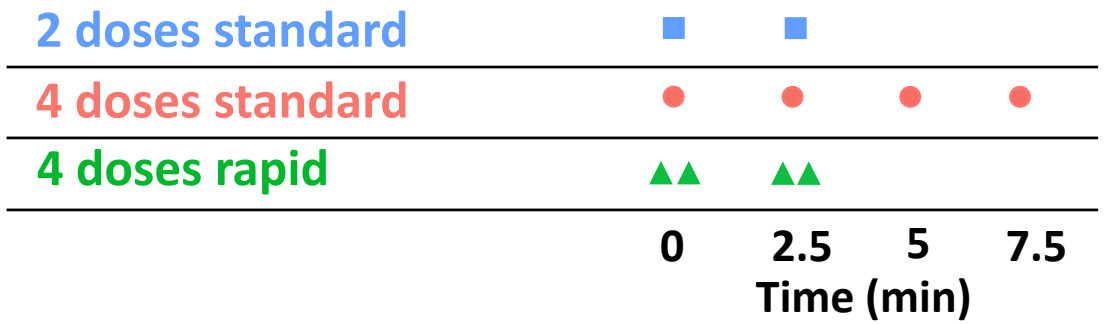
*Each IV dose was administered 2.5 minutes after the previous dose starting at 0 minutes

Summary: Background and Motivation

- Community use intranasal naloxone products contain 2 doses
- Approved for administration as a single dose with repeat doses every 2 to 3 minutes if needed
- Questions have emerged as to whether current naloxone dosing is adequate in the era of illicitly manufactured fentanyl(s)

Summary: Study Results

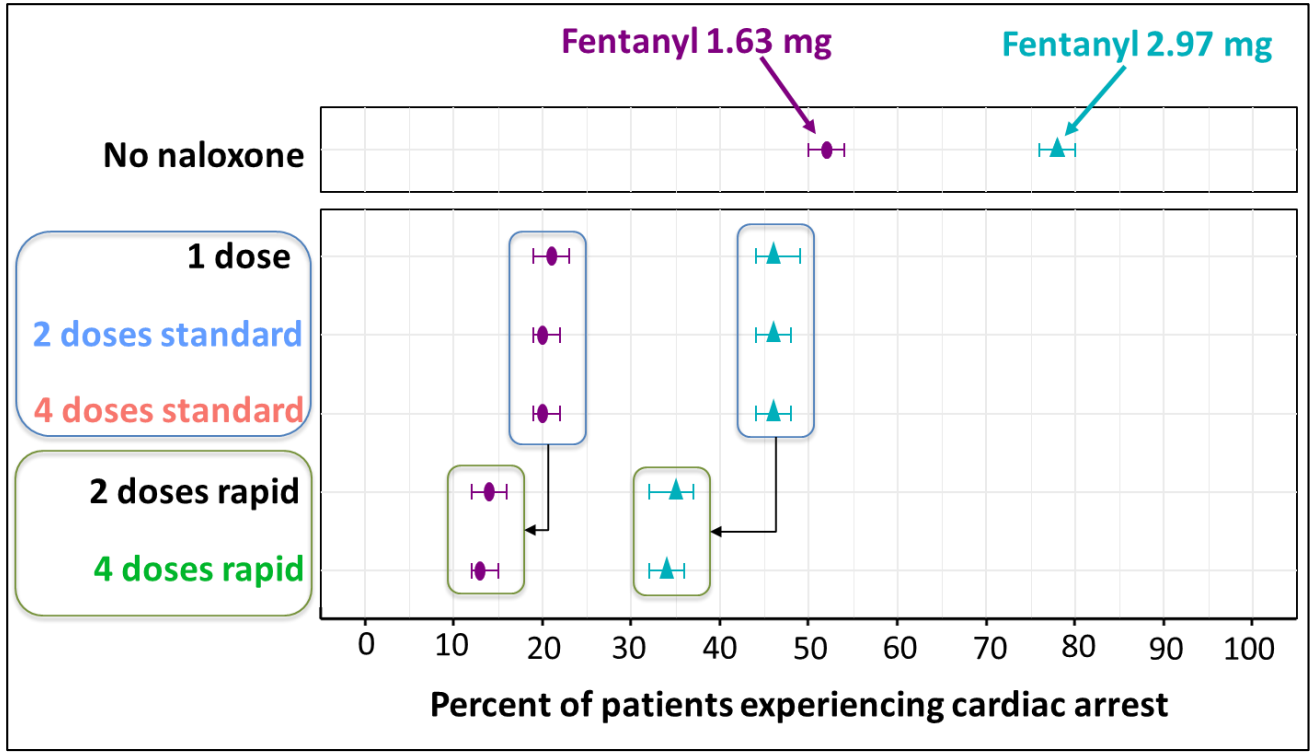
- Compared with 2 doses standard:
  - 4 doses standard first increased naloxone concentration at 10 minutes
  - 4 doses rapid first increased naloxone concentration at 4.5 minutes



- **In simulations of fentanyl and carfentanil overdoses**:
  - 4 doses standard compared to 2 doses standard did not rescue additional patients because sufficiently high naloxone concentrations were not reached prior to cardiorespiratory decompensation leading to cardiac arrest
  - 4 doses rapid did rescue additional patients

Additional Simulations Suggested …

- 2 doses rapid had a similar effect as 4 doses rapid
- Repeat dosing every 2.5 minutes did not further decrease cardiac arrest



Discussion

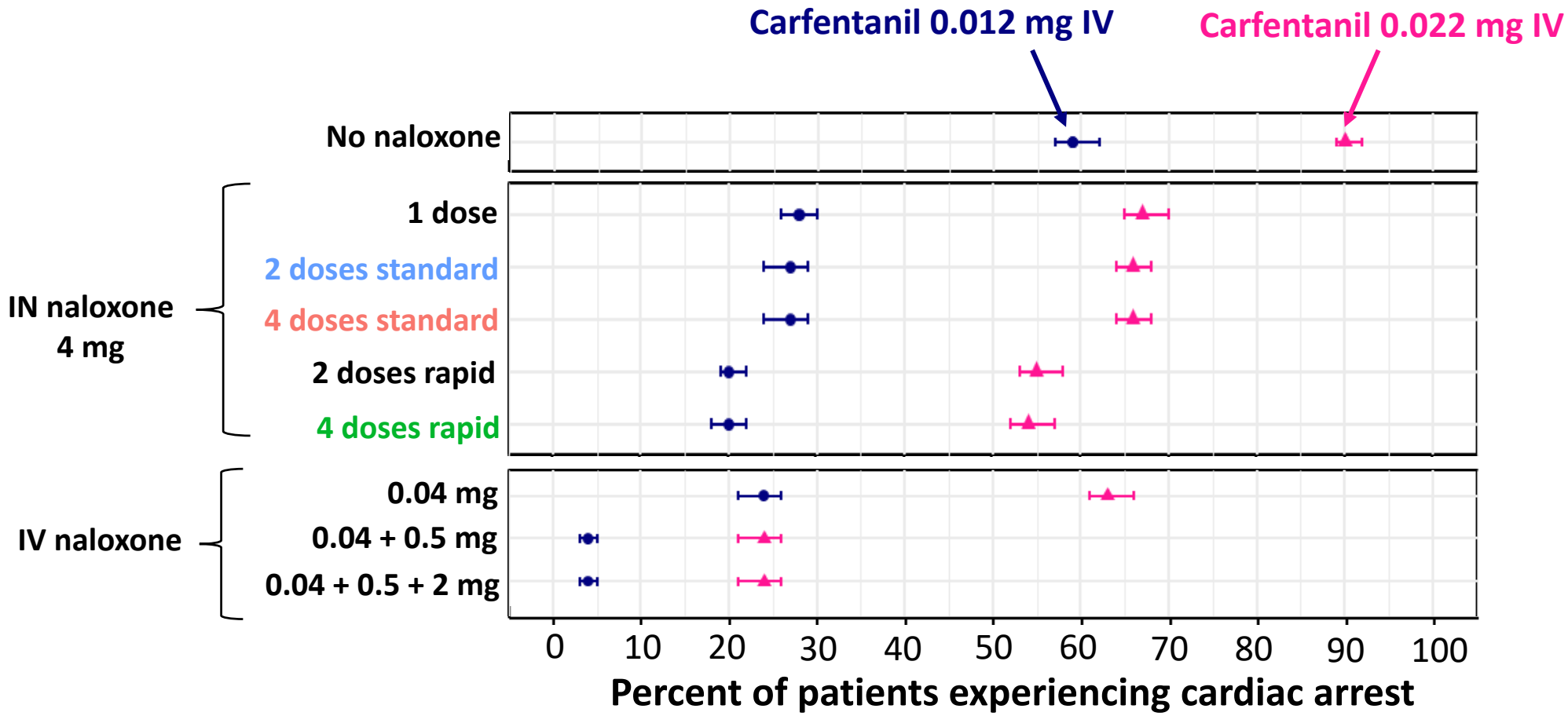
- In health care settings with adequate ventilatory support, naloxone can be titrated to reverse an opioid overdose and minimize the risk for precipitating acute withdrawal in opioid-tolerant individuals
- However, in the community setting without ventilatory support, there is a limited window before hypoxic injury is irreversible and cardiac arrest occurs
- This can occur extremely rapidly with fentanyl
- What is the ideal naloxone dosing strategy in the community setting?

Thank you

Zhihua Li
Anik Cahturbedi
Shilpa Chakravartula
Mohammedreza (Iman) Samieegohar
John Mann
Kristin Prentice
Aanchal Shah
Keith Burkhart
Jennifer Deering
Albert Dahan
Rutger Van der Schrier
Jeffry Florian

Spaulding Clinical Research
KCAS Bioanalytical and Biomarker Services

Percent of Simulated Patients Experiencing Cardiac Arrest (carfentanil + IN or IV naloxone)



*Each IV dose was administered 2.5 minutes after the previous dose starting at 0 minutes

Break until 3:30 pm (Eastern)

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FOUNDATION
FOR THE FDA

Session 3: Real-World Experiences Managing Opioid Overdose

REAGAN-UDALL FOUNDATION FOR THE FDA

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Session 3: Real-World Experiences in Rural Areas with Managing Opioid Overdose

Understanding Fatal Overdoses to Inform Product Development and Public Health Interventions

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Background

- West Virginia (WV) has had the highest rate of overdose death in the United States (US) for 20 consecutive years
  - In 2020 the age-adjusted overdose death rate per 100k was 28.3 in US compared to 81.4 in WV
  - In 2017, WV had the highest rate of overdose deaths involving psychostimulants
- Opioid overdoses cause respiratory depression & there is a significant risk of cerebral hypoxia if inadequate respiration persists > 4-5 minutes
  - Our team conducted the first systematic review of overdose-related brain injuries or cognitive impairments and while the incidence of such injuries is unknown, overdose-related brain injuries have been reported as early as 1973 across 21 countries
  - Case series have also reported the sudden onset of amnesia following fentanyl overdoses

SOURCES: Cano & Huang (2021) PMID: 33158665; Winstanley et al. 2021 PMID: 34271512; Barash et al. (2018) PMID: 29562161

Background

- Reversing opioid overdose-induced respiratory depression is critical to preventing mortality, as well as morbidity
- There is limited empirical data that directly compares different modes of naloxone administration:
  - Existing research conducted in Australia suggests that nasal administration is less effective when compared to intramuscular in terms of time to adequate respiration & requiring a second dose
  - The bioavailability of nasal naloxone was significantly lower (4%) compared to intramuscular (36%)

Table 1 Results of randomized studies comparing intranasal (i.n.) and intramuscular (i.m.) naloxone administration.

Study	*Time to adequate respiration*	*% Patients with adequate respiration*	*% Patients requiring second dose*
Kelly *et al.* 2005	i.m., 6 minutes, i.n., 8 minutes ($P = 0.01$)	i.m., 82%, i.n., 63% ($P = 0.02$)	i.m., 13%, i.n., 26% ($P = 0.06$)
Kerr *et al.* 2009	i.m., 7.9 minutes, i.n., 8.0 minutes (P = NS)	i.m., 77.5%, i.n., 72.3% (P = NS)	i.m., 4.5%, i.n., 18.1% ($P = 0.01$)

NS = not significant.

- We became increasingly concerned about anecdotal reports from community members & study participants about:
  - Need for multiple doses of nasal naloxone when reversing overdoses
  - Significant morbidity associated with non-fatal overdoses
- There is limited objective empirical data on overdose-related morbidity & naloxone dosing, hence we conducted a retrospective cohort study to address this gap

SOURCES: Winstanley (2016) PMID: 26995167; Kelly et al. (2005) PMID: 15651944; Kerr et al. (2009) PMID: 19922572

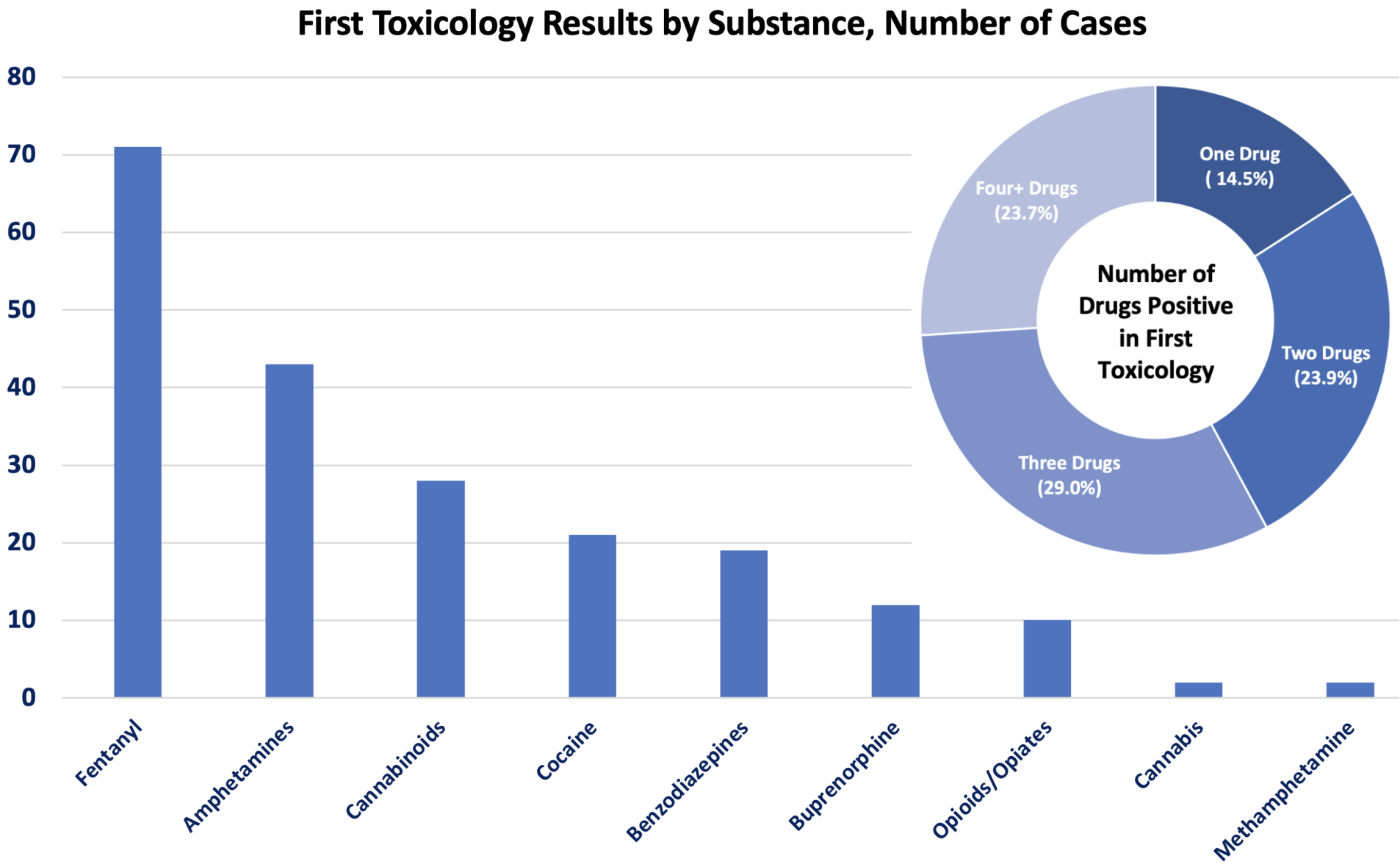
Research Aims & Methods

- The overall aim of the study was to determine the morbidity resulting from fentanyl overdoses
- We are conducting a retrospective cohort study of adult patients (n=394) that presented to a WVU medicine facility (emergency department or hospital) for a fentanyl-related overdose between November 2020 – October 2022
- Cases were identified by an electronic search of medical records for patients with a diagnosis of fentanyl overdose and by referral from clinicians
  - Cases were confirmed if toxicology performed at the time of the overdose was positive for fentanyl or if the overdose was suspected to involve fentanyl based on clinician, family member or friend reports
- Data was extracted from the electronic medical record (EMR) & entered into a chart extraction form in REDCap
- Preliminary data (n=83) will be presented from this ongoing study
  - Limited data was available on 3 cases that were dead upon arrival to the ED/hospital
- This study was approved by the WVU IRB

Results

- The majority of cases (62.9%) were treated at an ED/hospital in Morgantown or Parkersburg WV
- 84% (n=70) of cases had toxicology positive for fentanyl
- 67.5% were male, mean age was 38.5 (SD-11.9), and 95% were White
- 50.0% (n=41) had a current substance use disorder (SUD) diagnosis, 9.8% (n=8) had a history of SUD and 34.2% (n=28) had no SUD history noted in their EMR
- 25.6% (n=21) were presumed to be enrolled in a treatment program offering medications for opioid use disorder (MOUD) prior to their overdose
- 56.3% (n=45) had a current or history of at least one mental health diagnosis

Results: Toxicology Results



Results: Morbidity & Mortality

- Among individuals that were alive upon arrival to the ED/hospital (n=80):
  - 62.5% (n=50) stayed in the hospital 2+ days
  - 41.3% (n=33) cases were transferred to the ICU
  - Cases were medically complex involving multiple diagnoses such as cardiac arrest, acute kidney injury, anoxic brain injury, aspiration pneumonia and COPD
- 15.7% (n=13) of cases died
  - 12 expired during their hospitalization & 1 died 27 days after hospital discharge
  - 12/13 deaths appeared to be directly related to the overdose

Results: Naloxone Administration

- Data on naloxone administration in the pre-hospital setting was available for 60 cases:
  - Doses ranged from 0.2mg-16mg
  - Routes of naloxone administration included intranasal (n=22), IV (n=11), intramuscular (n=4)
- 27 cases were administered naloxone in the ED/hospital:
  - 6 cases were given an IV infusion of naloxone
  - 18 were administered IV naloxone
  - 14 cases were administered naloxone more than once

Length of time the individual was unconscious was only known for 11 cases

Results: Naloxone Administration

- 41 cases received more than 2mg of naloxone; however, it is unknown how much time elapsed between dosing
- 15 cases were administered naloxone in the prehospital & hospital settings
- The naloxone route of administration and dosing was variable

Route	Prehospital Administration			Hospital Administration
	Unknown	Bystander	First Responder/EMS	
Nasal	2mg-14mg	2mg	2mg-16mg	1mg-4mg
Intramuscular	6mg		2mg	
IV push	2mg-8mg		0.4mg-6mg	0.2mg-4mg
IV infusion				4mg-10mg
Unknown	0.2mg-2mg		2mg-12mg	

Conclusions

- Preliminary data from this retrospective cohort study suggests that there is significant morbidity requiring prolonged hospitalization (63%) & mortality (16%) associated with fentanyl overdoses in WV
- Among patients presenting to the ED/hospital for a fentanyl overdose, many required multiple doses of naloxone to reverse respiratory depression
- Individuals who successfully reverse fentanyl overdoses may never seek medical intervention
- Pre-hospital setting naloxone administration data may not be consistently reported in the EMR

Naloxone Access in WV

- Individuals may encounter **stigma** when attempting to access naloxone in pharmacies & not all pharmacies may sell it:
  - Unclear how OTC naloxone will impact this & whether it will be available in other retail settings
- **Free naloxone** is available on a limited basis
  - Nasal naloxone is more widely available whereas harm reduction programs may provide intramuscular naloxone (1 ml vials, two vials per kit)
  - Only about 54% of patients in our outpatient buprenorphine treatment program reported getting naloxone & only 1 received it without a prescription
- OTC nasal naloxone may be **unaffordable** for low-income individuals
- **Timely access** to the optimal formulation (nasal, intramuscular) & dose of naloxone is critical in rural areas, where cell phone coverage is limited/spotty & emergency response times are protracted and in some remote areas ambulance service may not even be available
- Current WV regulations require Naloxone dispensing data to be reported to the Prescription Drug Monitoring Program (**PDMP**)
  - Unclear whether WV will require tracking of OTC naloxone
- Empirical data is needed on how to optimize the management of overdoses involving both opioids and methamphetamine, as well as on how to manage methamphetamine induced-psychosis

SOURCES: Winstanley et al. (2022) PMID: 36844166; Thorton et al. (2016) PMID: 28163027

Acknowledgements

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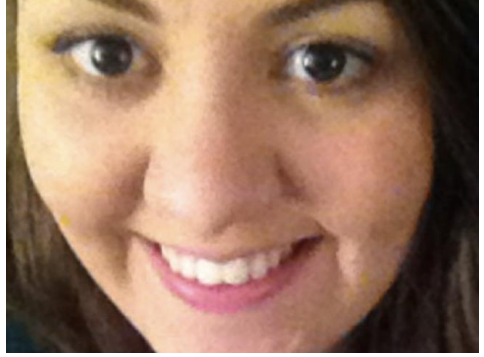

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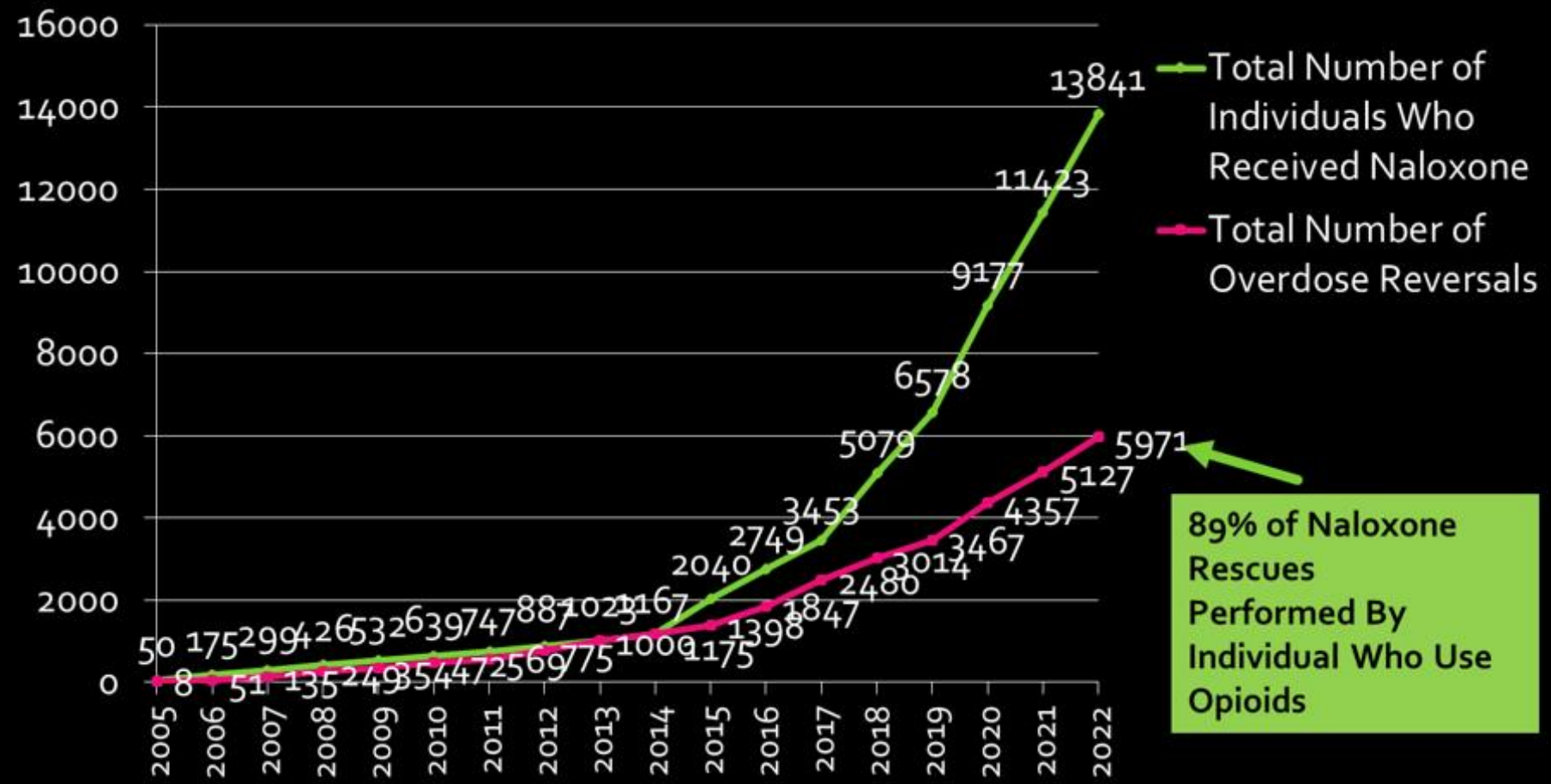
Prevention Point Pittsburgh

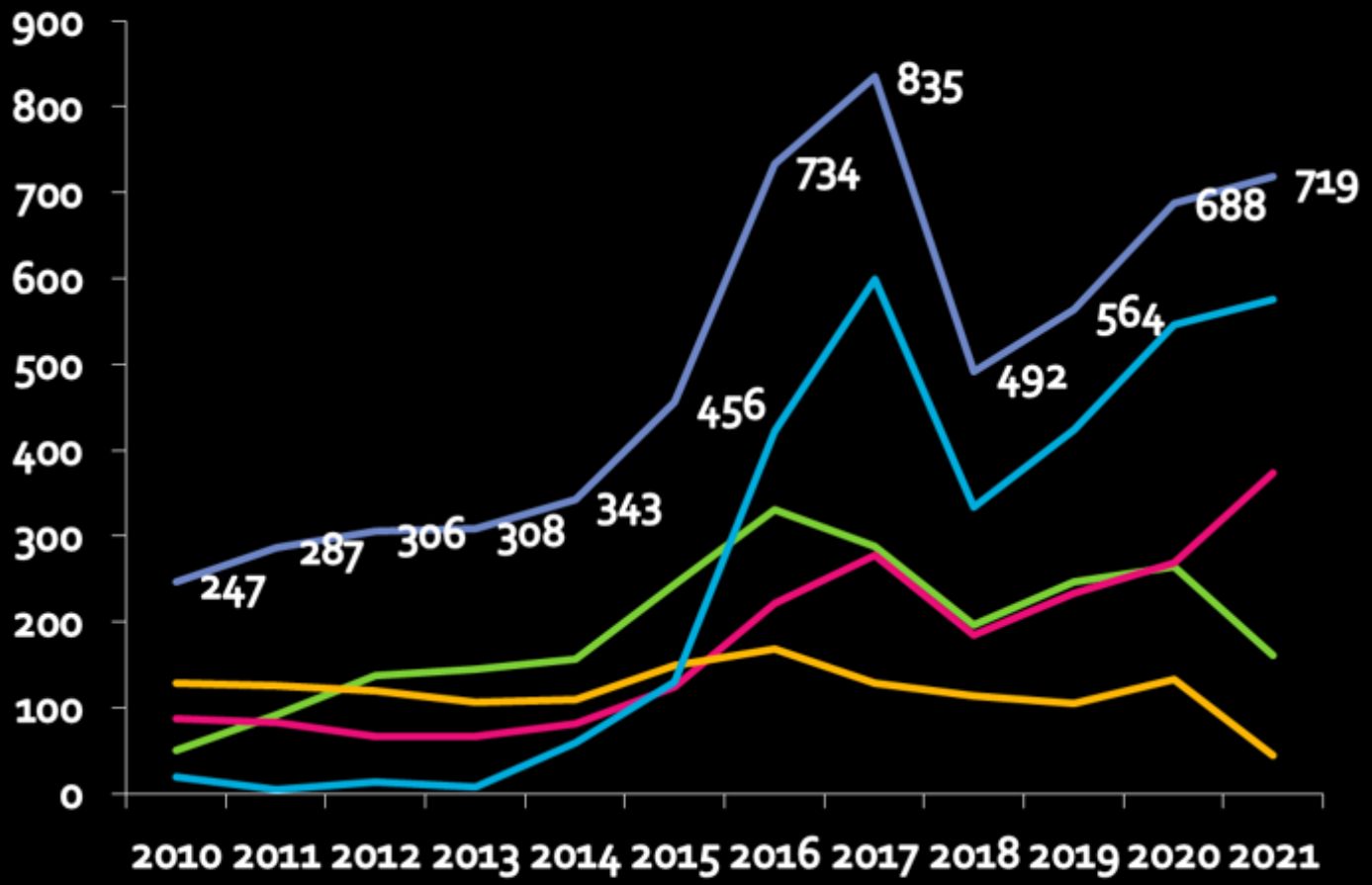
Harm Reduction Services

- Providing Sterile Injection Equipment to prevent HIV & Hep C since 1995.
- Testing for HIV and Hepatitis C
- Case Management, assistance to Tx
- Overdose Prevention & Response Training
- Naloxone Distribution since 2005.
- Statewide naloxone mailing project
- Wound Care Consultation Clinic
- Fentanyl test strips since 2017
- Medical Van/buprenorphine prescribing
- All Services Free of Charge
- Anonymous/Confidential

Prevention Point Pittsburgh Naloxone
CUMULATIVE DATA - July 2005- December 2022



Allegheny County, Pennsylvania
Accidental Drug Overdose Deaths
2000-2021



2022 on Track to match 2021

Heroin

Cocaine

Prescription Opioids

Fentanyl & Analogues

*Data from Allegheny County Medical Examiners Annual Reports. Includes all overdose deaths where these drugs were present at time of death, alone or in combination with other substances..

Zoom in (Ctrl+Plus)

Taylor & Francis
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Substance Abuse

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Amount of naloxone used to reverse opioid overdoses outside of medical practice in a city with increasing illicitly manufactured fentanyl in illicit drug supply

Alice Bell, Alex S. Bennett, T. Stephen Jones, Maya Doe-Simkins & Leslie D. Williams

In 2017, with rising rates of fentanyl deaths, in response to fears that fentanyl and other opiods might require additional doses of naloxone, we compared our data from 2013, when only 3% of deaths in our county involved fentanyl, to 2016 when 68% of overdose deaths involved fentanyl.

We did NOT find increase in the number of doses needed to reverse an overdose, in fact there was a slight decrease in average number of doses used from 1.62 to 1.52.

Number of Doses of Naloxone Used by PPP Participants to Reverse Opioid Overdoses 2013-2016

- 2013
  - 3.5% of 229 opioid overdose deaths in Allegheny County involved fentanyl.
  - 89.3% of reversals used 1 or 2 doses of naloxone. Mean doses per reversal 1.62
- 2016
  - 68.7% of 600 opioid overdose deaths involved fentanyl.
  - 92.8% of reversals used 1 or 2 doses.

    Mean doses per reversal **decreased** to 1.52

Number of Doses of Naloxone Used by PPP Participants to Reverse Opioid Overdoses

- 2020
  - 95% of 590 opioid overdose deaths involved fentanyl.
  - But still 91% of reversals used 1 or 2 doses of naloxone. Mean doses remained at 1.52.
- 2021
  - 92% of 625 opioid overdose deaths in Allegheny County involved fentanyl.
  - 87.5% of reversals used 1 or 2 doses of naloxone. Mean doses per reversal 1.64

Why Do People Use Additional Doses? (Additional = more than 2)

- When people report using more 2 doses, we ask some additional questions. The most consistent explanations have been that they gave additional doses without waiting 3-5 minutes for the initial dose/s to work, and/or there were other sedating drugs involved, like benzos, or more recently xylazine.

- We have recently been receiving numerous reports that person was breathing but still unconscious or unresponsive.

- The 3rd reason given has been that they found the person, didn't know how long they'd been out and they were too far gone to be revived with any amount of naloxone (so the occasional report of someone getting 10 doses for example, when they were already dead).

Concerns about high doses

- Most reports from people who reversed someone else's overdose, but people who received naloxone themselves report experience of multiple doses of 4mg nasal making them sick, so they ask for the standard IM 0.4mg injectable.
- When 911 is called, people sometimes receive ADDITIONAL doses from paramedics and hospital staff! Because nasal spray is so easy to administer, people seem uninhibited to continue giving additional doses.
- Concerns that if people have even higher dose products, people may end up with 10-20 times the necessary dose!
- We are very pleased that the ReVive product is a 3mg dose!!

In 18 years, NO reports of someone dying because they didn't have enough doses of naloxone.

- 2020-2022, we documented 1,569 overdose reversals.
- 167 EMS came to scene.
- 86 were hospitalized.
- Of the 23 people who died,
  - 18 cases they were found "too late,"
  - 3 cases paramedics told them there was "another cause" of death, not opioid overdose
  - 1 case the person said police would not let her use the naloxone she had and the person died
  - 1 case no information was reported.

Need for continued availability of inexpensive, injectable naloxone

- We offer IN or IM to people now, their choice.
- Half of doses requested continue to be for injectable
- Millions of Federal dollars would go SO much further in purchasing inexpensive injectable!
- Concerns that $ may dry up and want to make sure people always know how to use IM!

Impact of OTC Naloxone

- Less bureaucracy, reduced need for Dr. to sign paperwork
- Rural areas continue to experience stigmas in pharmacies and community settings, OTC may reduce barriers to individual access, depending on how it's marketed.
- Looking forward to 3mg dose!!
- Concerns about whether it will lead to reduced availability of IM.

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Day 2 of
Understanding Fatal Overdoses
begins at 1 PM (eastern) tomorrow

Thank You for joining us!

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