Understanding Fatal Overdoses to Inform Product Development & Public Health Interventions to Manage Overdose

The public meeting will begin shortly
Housekeeping

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

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)
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.

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
Overdose Death Trends
Current State of the Overdose Crisis – 1968 to 2021

Drug Overdose Death Rates in the U.S. from 1968 to 2021

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

Overdose Crisis Over Time at the County Level

Rate per 100,000 population

2003

2021

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
Substances Involved in Overdose Deaths, 2020-2022P

Source: CDC NVSS Wonder, 2022

2022 data are provisional
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

Source: SUDORS Dashboard: Fatal Overdose Data | Drug Overdose | CDC Injury Center
Place of Drug Overdose Death, 2021

- Medical Facility - Inpatient: 9.4%
- Medical Facility - Outpatient or ER: 11.4%
- Medical Facility - Dead on Arrival: 0.9%
- Decedent's home: 50.7%
- Hospice facility: 0.3%
- Nursing home/long term care: 0.1%
- Other: 27.1%
- Place of death unknown: 0.1%

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

Source: CDC NVSS Wonder, 2022

**Age-Adjusted Rate per 100K by Gender**

- Male
- Female

**Rate per 100K by Age Group**

- 15-24
- 25-34
- 35-44
- 45-54
- 55-64
- 65+

**Age-Adjusted Rate per 100K by Race/Ethnicity**

- AI/AN, NH
- Black, NH
- White, NH
- Hispanic
- NH/OPI, NH
- Asian, NH

**Rate per 100K by Urbanization**

- Large Central Metro
- Large Fringe Metro
- Medium Metro
- Small Metro
- Micropolitan Nonmetro
- NonCore Nonmetro
Drugs & Drug Classes Involved in Opioid-Involved Overdose Deaths

- Synthetic Opioids: 82.3% (2020), 87.8% (2021), 89.7% (2022P)
- Heroin: 19.2% (2020), 11.4% (2021), 7.9% (2022P)
- Natural & Semi-Synthetic Opioids: 19.6% (2020), 16.9% (2021), 15.0% (2022P)
- Methadone: 5.2% (2020), 4.6% (2021), 4.0% (2022P)
- Psychostimulants: 21.5% (2020), 26.6% (2021), 27.6% (2022P)
- Cocaine: 22.3% (2020), 23.9% (2021), 26.1% (2022P)
- Benzodiazepines: 15.7% (2020), 13.7% (2021), 11.9% (2022P)
- T42.7 (e.g. xylazine): 0.5% (2020), 3.2% (2021), 5.6% (2022P)

2022 data are provisional.
Stimulant-Involved Overdoses
Psychostimulant-Involved Overdose Deaths, U.S., 2009-2021

Source: NVSS Wonder, 2022

All Psychostimulant-Involved OD Deaths

With Opioids

Without Opioids

Percent involving Opioids 2018-2022P

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

2022 data are provisional
Cocaine-Involved Overdose Deaths, U.S., 2009-2021

Source: NVSS Wonder, 2022

2022 data are provisional
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.

2022 data are provisional.
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
Urine Drug Test Results Significantly and Strongly Correlate with Overdose Mortality

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

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

Geographical Analysis of Drug Use Trends

<table>
<thead>
<tr>
<th>U.S. Census Division</th>
<th>Methamphetamine UDT Positivity</th>
<th>Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2019</td>
<td>2022</td>
</tr>
<tr>
<td>Pacific</td>
<td>10.4%</td>
<td>12.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>U.S. Census Division</th>
<th>Prescription Opioids UDT Positivity</th>
<th>Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2019</td>
<td>2022</td>
</tr>
<tr>
<td>Pacific</td>
<td>11.6%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Mountain</td>
<td>3.6%</td>
<td>3.7%</td>
</tr>
<tr>
<td>West North Central</td>
<td>4.1%</td>
<td>6.4%</td>
</tr>
<tr>
<td>West South Central</td>
<td>4.3%</td>
<td>4.2%</td>
</tr>
<tr>
<td>East North Central</td>
<td>6.6%</td>
<td>4.2%</td>
</tr>
<tr>
<td>East South Central</td>
<td>9.0%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Mid Atlantic</td>
<td>5.4%</td>
<td>4.8%</td>
</tr>
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<td>7.2%</td>
<td>9.6%</td>
</tr>
<tr>
<td>New England</td>
<td>5.6%</td>
<td>3.3%</td>
</tr>
<tr>
<td>US Total</td>
<td>6.9%</td>
<td>5.5%</td>
</tr>
</tbody>
</table>

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

These geographical differences may have important clinical implications:

- 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%

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.

*Data from Q3/Q4 2022
## Top 10 Drug Combinations in Fentanyl-Positive Population

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug Combination</th>
<th>Specimens (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F, Cannabis</td>
<td>9.0%</td>
</tr>
<tr>
<td>2</td>
<td>F, Cocaine</td>
<td>8.2%</td>
</tr>
<tr>
<td>3</td>
<td>F, Gabapentin</td>
<td>6.2%</td>
</tr>
<tr>
<td>4</td>
<td>F, Methamphetamine</td>
<td>5.7%</td>
</tr>
<tr>
<td>5</td>
<td>F, Prescription Opioids</td>
<td>4.1%</td>
</tr>
<tr>
<td>6</td>
<td>F, Methamphetamine</td>
<td>2.5%</td>
</tr>
<tr>
<td>7</td>
<td>F, Gabapentin</td>
<td>2.1%</td>
</tr>
<tr>
<td>8</td>
<td>F, Prescription Opioids</td>
<td>2.0%</td>
</tr>
<tr>
<td>9</td>
<td>F, Cannabis</td>
<td>1.8%</td>
</tr>
<tr>
<td>10</td>
<td>F, Methamphetamine</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

* = Fentanyl  
= Cannabis  
= Methamphetamine  
= Cocaine  
= Gabapentin  
= Prescription Opioids

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.
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

CESAR: Center for Substance Use and Health Research, 2023
23% OR LESS OF SUSPECTED SYNTHETIC CANNABINOID OVERDOSE PATIENTS TESTED POSITIVE FOR THE DRUG

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

### Table: Percentage Positive for Likely Illicit Selected Drugs, By Site

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Prince George’s Hospital Center (N=108)</th>
<th>UMNC, Midtown Campus (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive by CDEWS Lab for:</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>1. Marijuana</td>
<td>69%</td>
<td>61%</td>
</tr>
<tr>
<td>2. Cocaine</td>
<td>22%</td>
<td>48%</td>
</tr>
<tr>
<td>3. OXY</td>
<td>47%</td>
<td>3%</td>
</tr>
<tr>
<td>4. Any New Psychoactive Substance (NPS)</td>
<td>22%</td>
<td>32%</td>
</tr>
<tr>
<td>5. Any Synthetic Cannabinoid (SC)</td>
<td>23%</td>
<td>20%</td>
</tr>
<tr>
<td>6. Any Fentanyl</td>
<td>4%</td>
<td>28%</td>
</tr>
<tr>
<td>7. 6-Monoacetylmorphine (6-MAM)</td>
<td>0%</td>
<td>13%</td>
</tr>
<tr>
<td>8. Methamphetamine</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Positive for Any (of 8)</td>
<td>91%</td>
<td>54%</td>
</tr>
<tr>
<td>Positive for Any (excluding marijuana)</td>
<td>74%</td>
<td>75%</td>
</tr>
</tbody>
</table>

**Number of Drugs/Drug Classes in Specimen (of 8):**

<table>
<thead>
<tr>
<th>Number of Drugs/Drug Classes</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td>9</td>
<td>26</td>
<td>38</td>
<td>14</td>
<td>8</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

**Mean Number of Drugs Found Positive (of 8):** 1.89 for Prince George’s Hospital Center, 2.06 for UMNC, Midtown Campus.

**Note:** LSD and Amphetamines 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 was 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 lacking the drug by perception were counted as negative in this analysis.

**p<0.01 based on Chi Square.**

**p<0.001 based on Fisher’s Exact Test or Chi Square.**
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)

- Opiates
- Cocaine
- Marijuana
- Benzodiazepines
- Methadone
- Amphetamines

Notes: UMMC—University of Maryland Medical Center; MTC—University of Maryland Medical Center- Medtown Campus.
Barbiturate and PCP results not shown because of low occurrence.
*Ns vary slightly because not all specimens were tested for all drugs each period.

Quarter (Number of Specimens Tested)
- 2 Quarter Moving Average
- Percent Testing Positive That Quarter
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

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

**Source:** CESAR, University of Maryland, College Park, October 2022

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

Notes from the Field

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

Zachary Dezman, MD1; Braddell Schwartz, MD1; Amy Billing, MSHA2; Dominick Massey, MA3; E. Eric Artigiani, MA4; Julie Factor3; Eric D. Wish, PhD1

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 fentanyl. A more recent study included 1,000 patients and found that 61% of the fentanyl positive specimens contained two or more drugs/drug classes in addition to fentanyl. 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 overdose. 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 cannabinoid metabolites. 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. A subsequent survey 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 61% of the fentanyl positive specimens contained two or more drugs/drug classes in addition to fentanyl.

Source: CESAR, University of Maryland, College Park, October 2022

CESAR: Center for Substance Use and Health Research, 2023

• 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, College Park, October 2022

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

Source: CESAR, University of Maryland, College Park, October 2022

CESAR: Center for Substance Use and Health Research, 2023
## Fentanyl/Norfentanyl EDDS Test Results, By Hospital’s Drug Screen Result
(N=1,663 Specimens Submitted by HCA Hospitals)

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Positive for Fentanyl/Norfentanyl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hospital found Positive for any drug</td>
</tr>
<tr>
<td>Grand Strand Medical Center, SC</td>
<td>(n=100) 28%</td>
</tr>
<tr>
<td>TriStar Skyline Medical Center, TN</td>
<td>(100) 25%</td>
</tr>
<tr>
<td>Riverside Community Hospital, CA</td>
<td>(100) 24%</td>
</tr>
<tr>
<td>Trident Medical Center, SC</td>
<td>(100) 16%</td>
</tr>
<tr>
<td>MountainView Hospital, NV</td>
<td>(101) 15%</td>
</tr>
<tr>
<td>HCA Florida West, FL</td>
<td>(100) 13%</td>
</tr>
<tr>
<td>HCA Florida Orange Park, FL</td>
<td>(106) 9%</td>
</tr>
<tr>
<td>HCA Florida Brandon Hospital, FL</td>
<td>(56) 7%</td>
</tr>
<tr>
<td>Memorial Satilla Health, GA</td>
<td>(100) 6%</td>
</tr>
<tr>
<td>Houston Healthcare Kingwood, TX</td>
<td>(100) 6%</td>
</tr>
<tr>
<td>HCA Florida Aventura, FL</td>
<td>(103) 4%</td>
</tr>
<tr>
<td>HCA Florida North Florida, FL</td>
<td>(45) 2%</td>
</tr>
</tbody>
</table>

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

• 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.

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

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](https://cesar.umd.edu/landing/EDDS)

CESAR: Center for Substance Use and Health Research, 2023
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

Source: CESAR, University of Maryland, College Park, October 2022

CESAR: Center for Substance Use and Health Research, 2023
### MD-EDDS Fentanyl Dipstick Study Results in 8 Hospitals

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

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.

**Too few cases to calculate meaningful statistics.**
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

<table>
<thead>
<tr>
<th>Hospital Found Positive for:</th>
<th>Positive for Fentanyl by Dipstick (N=48) %</th>
<th>Negative for Fentanyl by Dipstick (N=352) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>63***</td>
<td>24***</td>
</tr>
<tr>
<td>Marijuana (n=47)</td>
<td>43*</td>
<td>58*</td>
</tr>
<tr>
<td>Methadone (n=39)</td>
<td>39***</td>
<td>8***</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>21*</td>
<td>9*</td>
</tr>
<tr>
<td>Opiates</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Oxycodone (n=26)</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>PCP (n=29)</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Buprenorphine (n=10)</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

^AConsecutive 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.cesarerearch.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
CONTACT THE EDDS TEAM:

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www.cesar.umd.edu/landing/edds
@CESAResearch

CESAR: Center for Substance Use and Health Research, 2023
Session 2: Pharmacology of Opioids & Overdose Management Products

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
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?

\[ \mu \text{OR} = \text{mu OPIOID receptor} \]
How effective is naloxone in restoring respiratory activity? If not effective what to do next?

- **μOR** = mu OPIOID receptor
- **REC** = receptor
- Neuron
  - **μOR** = Opioid
  - **REC** = Xylazine
  - Xylazine receptor

**Diagram:**
- Neuron with μOR and REC
- Neuron icon
AMP receptors
Phosphodiesterase
Opioid receptors
Serotonin receptors
Rostral ventral Respiratory group
Caudal ventral Respiratory group
Respiratory excitatory receptor systems
Potassium channels
Retrotrapezoid nucleus
Bötzinger complex
PreBötzinger complex
Parabrachial-Kolliker Fuse
Carotid body
Nucleus tractus solitarius
Raphe
Mid line
Respiratory motoneurons
Opioids have a dual mechanism of OIRD at the pre-Bötzinger complex:
- Impairment of excitatory presynaptic neurotransmission,
- Intrinsic hyperpolarization of respiratory neurons.
Opioid overdose - Respiratory phenotype 1

Exhaled carbon dioxide (CO₂)

Irregular breathing

Cyclic breathing

Apnea

vd Schrier 2023
Opioid overdose - Respiratory phenotype 2

Exhaled carbon dioxide (CO$_2$)

Resuscitation started
Opioid overdose - Respiratory phenotype 3

Exhaled carbon dioxide (CO\textsubscript{2})

Oxygen saturation (SpO\textsubscript{2})
Fentanyl Overdose

- Decline in respiration
- Loss of consciousness
- Bradycardia
- Cardiac arrest
- Death

Questions to ask

Is the individual still breathing?
More important: does the individual still have a pulse?
Fentanyl Overdose

Decline in respiration
Loss of consciousness
Bradycardia
Cardiac arrest
Death

Questions to ask
Is the individual still breathing?
More important: does the individual still have a pulse?
Fentanyl Pharmacology

OR = Opioid Receptor

Drug disposition | Biophase distribution | Receptor kinetics | Signal transduction | Effect

K_{OFF}

CP | BBB | CNS | MOP receptor | Respiratory network | Phrenic nerve | Ventilation
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.

### Receptor Kinetics

<table>
<thead>
<tr>
<th>Opioid</th>
<th>$K_i$</th>
<th>$K_{OFF}$</th>
<th>$t_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone</td>
<td>26</td>
<td>40 min</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1.35</td>
<td>0.004</td>
<td>5 min</td>
</tr>
<tr>
<td>Morphine</td>
<td>1.1</td>
<td>0.002</td>
<td>60 min</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.22</td>
<td>0.0002</td>
<td>75 min</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.14</td>
<td>0.001</td>
<td>5 min</td>
</tr>
<tr>
<td>Carfentanil</td>
<td>0.05</td>
<td>0.00025</td>
<td>5 min</td>
</tr>
<tr>
<td>Naloxone</td>
<td>1.1</td>
<td>0.04</td>
<td>&lt; 1 min</td>
</tr>
</tbody>
</table>

$v$ 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)

Infusion duration (min)

Fentanyl
Sufentanil
Remifentanil
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 (CO₂)
Exhaled carbon dioxide (CO₂)

Time (min)

End-tidal PCO₂ (kPa)

Sufentanil infusion

4 mg intranasal naloxone

5-10 min

30 min

0  60  120  180

4.0  4.5  5.0  5.5  6.0

30  35  40  45

End-tidal PCO₂ (mmHg)
Exhaled carbon dioxide (CO₂)

- End-tidal PCO₂ (kPa)
- End-tidal PCO₂ (mmHg)
- Time (min)

4 mg intranasal naloxone

5-10 min

30 min

Sufentanil infusion

Renarcotization
Exhaled carbon dioxide (CO₂)
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?

\[ \mu\text{OR} = \text{mu OPIOID receptor} \]

\[ \text{REC} = \text{receptor} \]
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
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)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>2.5</th>
<th>5</th>
<th>7.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 doses standard</td>
<td>■</td>
<td>■</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 doses standard</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>4 doses rapid</td>
<td>▲▲</td>
<td>▲▲</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 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

Naloxone plasma concentration (ng/mL)

Time (min)

Naloxone doses timing
- 4 doses rapid
- 4 doses standard
- 2 doses standard

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

Graph showing the plasma concentration of naloxone over time for different dosing regimens.
Comparison Between Naloxone Dosing Strategies

- **First Time Point with Higher Plasma Concentration**
  - 4 doses rapid vs 2 doses standard
  - 4 doses standard vs 2 doses standard

**Geometric Mean Ratio**

**Time (min)**
0 2 4.5 7 10 12.5 15

- **4 doses rapid**
- **4 doses standard**
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 Mann1, Mohammadreza Samieegohar1, Anik Chaturbedi3, Joel Zirkle1, Xiaomei Han1, S. Farzad Ahmad1, Amy Eshleman2, Aaron Janowsky2, Katherine Wolfrum3, Tracy Swanson3, Shelley Bloom2, Albert Dahan4, Erik Olafsen2, Jeffry Florian1, David G. Strauss1, and Zhihua Li1

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

OPIOID RECEPTOR BINDING MODEL

• Fentanyl-bound receptor
• Naloxone-bound receptor

PHARMACODYNAMIC MODEL

• Ventilatory control
  - brain CO2 + O2
  - arterial CO2 + O2
• Tissue metabolism

PHYSIOLOGICAL MODEL

• Lung O2 + CO2 exchange
• Blood flow

Ventilation

Fentanyl PK MODEL Naloxone
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

Fentanyl IV

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

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

Percent of opioid receptors bound by fentanyl

Time (min)

No naloxone

Fentanyl IV 2.97 mg
Naloxone IN 4 mg/0.1 mL
Ventilation

Ventilation (L/min)

40% of baseline ventilation

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

No naloxone

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

Time (min)

Fentanyl IV 2.97 mg
Naloxone IN 4 mg/0.1 mL

No naloxone
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)

<table>
<thead>
<tr>
<th>Dosing Strategy</th>
<th>0</th>
<th>2.5</th>
<th>5</th>
<th>7.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 dose</td>
<td>⭐</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 doses standard</td>
<td></td>
<td>■</td>
<td>■</td>
<td></td>
</tr>
<tr>
<td>4 doses standard</td>
<td></td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>2 doses rapid</td>
<td></td>
<td>★★</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 doses rapid</td>
<td></td>
<td>▲▲</td>
<td>▲</td>
<td>▲</td>
</tr>
</tbody>
</table>

Time (min)
Percent of Simulated Patients Experiencing Cardiac Arrest (Fentanyl)

No naloxone

1 dose
2 doses standard
4 doses standard

2 doses rapid
4 doses rapid

Percent of patients experiencing cardiac arrest

Fentanyl 1.63 mg
Fentanyl 2.97 mg
Percent of Simulated Patients Experiencing Cardiac Arrest (Carfentanil)

- No naloxone
- 1 dose
- 2 doses standard
- 4 doses standard
- 2 doses rapid
- 4 doses rapid

Graph showing the percent of patients experiencing cardiac arrest for different dosages and administration times of Carfentanil 0.012 mg IV and Carfentanil 0.022 mg IV.
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

Naloxone IV & IN Simulations

Plasma Concentration (ng/mL)

Time (min)

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

<table>
<thead>
<tr>
<th></th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 doses standard</td>
<td></td>
</tr>
<tr>
<td>4 doses standard</td>
<td>▪ ▪</td>
</tr>
<tr>
<td>4 doses rapid</td>
<td>▲▲ ▲▲</td>
</tr>
</tbody>
</table>

• 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

![Graph showing the percent of patients experiencing cardiac arrest with different dosing strategies and fentanyl doses.](image)
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)

No naloxone

IN naloxone
4 mg

IV naloxone

0.04 mg
0.04 + 0.5 mg
0.04 + 0.5 + 2 mg

Carfentanil 0.012 mg IV

Carfentanil 0.022 mg IV

*Each IV dose was administered 2.5 minutes after the previous dose starting at 0 minutes
The meeting will resume in ten minutes at 3:30 PM ET.

Learn more about the Reagan-Udall Foundation for the FDA at reaganudall.org.

Break until 3:30 pm (Eastern)

Learn more about the Foundation reaganudall.org
Session 3: Real-World Experiences Managing Opioid Overdose

Presenters

Erin Winstanley, PhD
West Virginia University School of Medicine

Alice Bell, LCSW
Prevention Point Pittsburgh

Reactor Panel

Sessi K. Blanchard
Community Access

Justin Strickland, PhD
Johns Hopkins University

Zachary Dezman, MD, MS
U.S. Food and Drug Administration
Session 3: Real-World Experiences in Rural Areas with Managing Opioid Overdose

Understanding Fatal Overdoses to Inform Product Development and Public Health Interventions
March 8, 2023

Erin L. Winstanley, Ph.D.
Associate Professor; West Virginia University, Department Behavioral Medicine & Psychiatry; Department of Neuroscience
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>
<thead>
<tr>
<th>Study</th>
<th>Time to adequate respiration</th>
<th>% Patients with adequate respiration</th>
<th>% Patients requiring second dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelly et al. 2005</td>
<td>i.m., 6 minutes, i.n.</td>
<td>i.m., 82%, i.n.</td>
<td>i.m., 13%, i.n.</td>
</tr>
<tr>
<td></td>
<td>8 minutes (P = 0.01)</td>
<td>63% (P = 0.02)</td>
<td>26% (P = 0.06)</td>
</tr>
<tr>
<td>Kerr et al. 2009</td>
<td>i.m., 7.9 minutes, i.n.</td>
<td>i.m., 77.5%, i.n.</td>
<td>i.m., 4.5%, i.n.</td>
</tr>
<tr>
<td></td>
<td>8.0 minutes (P = NS)</td>
<td>72.3% (P = NS)</td>
<td>18.1% (P = 0.01)</td>
</tr>
</tbody>
</table>

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

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

First Toxicology Results by Substance, Number of Cases

Number of Drugs Positive in First Toxicology

- One Drug (14.5%)
- Two Drugs (23.9%)
- Three Drugs (29.0%)
- Four+ Drugs (23.7%)
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

<table>
<thead>
<tr>
<th>Route</th>
<th>Prehospital Administration</th>
<th>Hospital Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unknown</td>
<td>Bystander</td>
</tr>
<tr>
<td>Nasal</td>
<td>2mg-14mg</td>
<td>2mg</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>6mg</td>
<td></td>
</tr>
<tr>
<td>IV push</td>
<td>2mg-8mg</td>
<td></td>
</tr>
<tr>
<td>IV infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0.2mg-2mg</td>
<td></td>
</tr>
</tbody>
</table>
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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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

- Total Number of Individuals Who Received Naloxone
- Total Number of Overdose Reversals

89% of Naloxone Rescues Performed by Individual Who Use Opioids
Allegheny County, Pennsylvania
Accidental Drug Overdose Deaths
2000-2021

2022 on Track to match 2021

*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.
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 opioids 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.
Alice Bell, L.C.S.W.
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Prevention Point Pittsburgh
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Thank You for joining us!

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

https://reaganudall.org/