



Understanding Fatal  
Overdoses to Inform  
Product Development  
and Public Health  
Interventions to Manage  
Overdose  
**PUBLIC MEETING SUMMARY**  
JULY 2023



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## ONE: INTRODUCTION

The Reagan-Udall Foundation for the FDA, in partnership with the U.S. Food and Drug Administration (FDA) and the Substance Abuse and Mental Health Services Administration (SAMHSA), hosted a two-day virtual public meeting on March 8 and 9, 2023, titled “Understanding Fatal Overdoses to Inform Product Development and Public Health Interventions to Manage Overdose.” Speakers and participants represented people with lived experience, harm reduction programs, clinicians, academic researchers, and federal agencies. This document summarizes the presentations and discussions from the meeting. This document does not represent the official views of FDA or SAMHSA.

### BACKGROUND

Drug overdose persists as a major public health issue in the United States, with over 105,000 fatal overdoses occurring in the 12-month period ending in December 2022.<sup>1</sup> Synthetic opioids, such as fentanyl and its analogs, are the primary driver of the increase in overdose deaths.<sup>2</sup> Other controlled substances, including benzodiazepines and stimulants (particularly methamphetamine), are also being used in combination with opioids. To support efforts to develop products and approaches to treat overdose and prevent fatalities, stakeholders – including people with lived experience, their families, harm reduction programs, clinicians, academic researchers, and federal partners – explored the evolving context surrounding fatal overdoses. Participants discussed epidemiological trends, drug supply changes, public health interventions to manage overdose, and product development opportunities.

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<sup>1</sup> Ahmad FB, Cisewski JA, Rossen LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. 2023. <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>

<sup>2</sup> Jones, CM. The Drug Overdose Crisis in the U.S.: What the Latest Data Tell Us. Presented at: Understanding Fatal Overdoses to Inform Product Development and Public Health Interventions to Manage Overdose; March 8, 2023. <https://reaganudall.org/news-and-events/events/understanding-fatal-overdoses-inform-product-development-and-public-health>

## TWO: THE PUBLIC HEALTH LANDSCAPE

Drug overdose affects people in all regions of the United States. Despite efforts by public health, health care, harm reduction, and governmental organizations, overdose deaths remain the leading cause of injury-related death in this country.<sup>3</sup> The dramatic increase in fatal overdoses since 2018 has led to an epidemic that does not distinguish among age, sex, race, or location.<sup>4</sup> While drug overdoses increased among all demographics, the increase was larger among certain subpopulations (Figure 1). Between 2018 and 2021, overdose deaths increased in all age groups from 15 years to 65 and older. The greatest increase occurred for those aged 35-44 years, closely followed by people 25-34 and 55-64 years old.<sup>5</sup> Fatal overdoses have increased for both sexes over the same period, with rates rising more rapidly in males versus females. Non-Hispanic American Indian and Alaska Native populations experienced the greatest age-adjusted rate increase of fatal overdose from approximately 30 per 100,000 deaths in 2018 to almost 60 per 100,000 deaths in 2021. Age-adjusted rate increases were also seen for Non-Hispanic Black, Non-Hispanic White, Hispanic, and Non-Hispanic Pacific Islander populations during this same time frame. The largest rises in fatal overdose across all metropolitan, micropolitan, and rural geographies occurred in 2020 and 2021.

The current drug crisis is driven by changes in the supply of illicit drugs and people unintentionally ingesting or injecting adulterated drugs. The most recent rise in overdose deaths is primarily driven by fentanyl and fentanyl analogs, contaminating both opioid and non-opioid products. Per CAPT Christopher Jones from the Centers for Disease Control and Prevention (CDC): “The overdose crisis continues to be dominated by illicit synthetic opioids such as illicitly made fentanyl 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. The 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.”

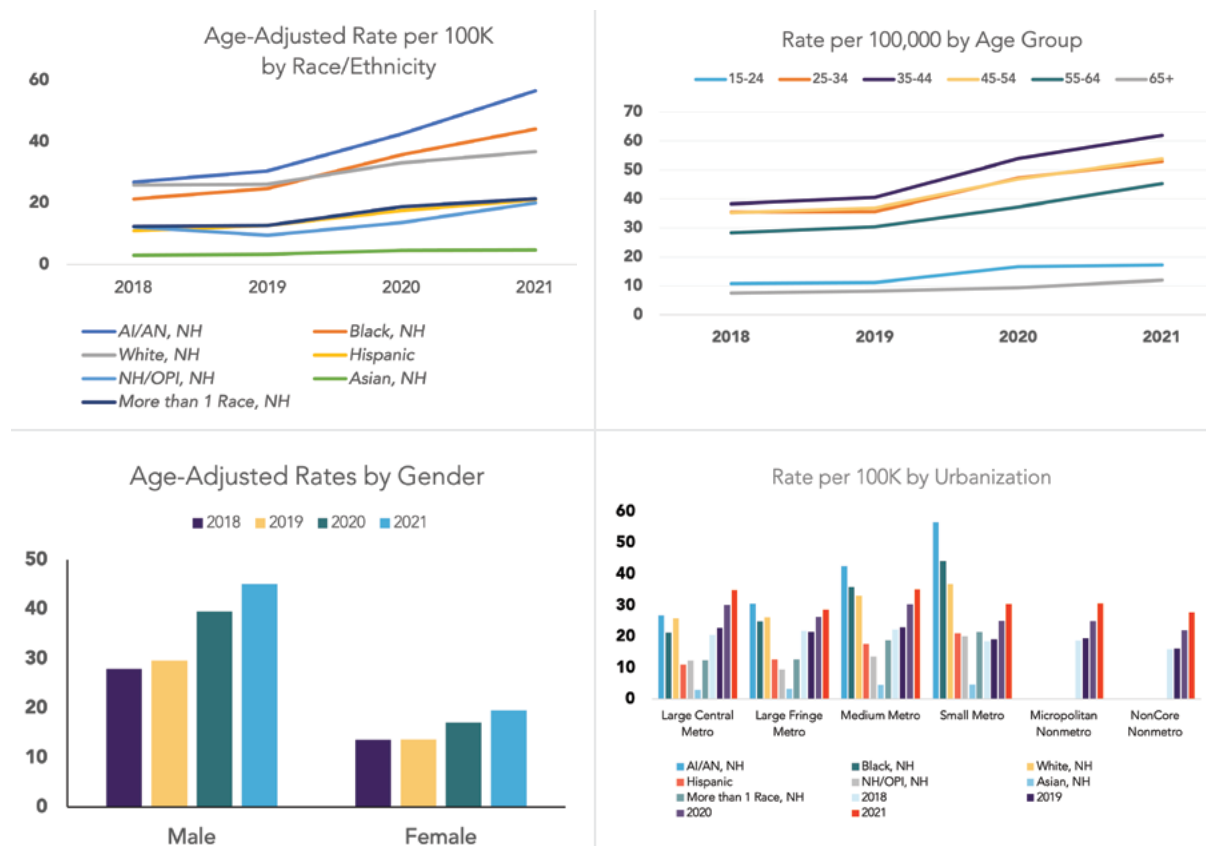
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<sup>3</sup> Understanding drug overdoses and deaths. Centers for Disease Control and Prevention. <https://www.cdc.gov/drugoverdose/epidemic/index.html>. Published February 14, 2022. Accessed April 26, 2023.

<sup>4</sup> Ibid.

<sup>5</sup> CDC NVSS Wonder 2022. Jones, CM. The Drug Overdose Crisis in the U.S.: What the Latest Data Tell Us. Presented at: Understanding Fatal Overdoses to Inform Product Development and Public Health Interventions to Manage Overdose; March 8, 2023. <https://reaganudall.org/news-and-events/events/understanding-fatal-overdoses-inform-product-development-and-public-health>

**FIGURE 1: DRUG OVERDOSE DEATHS BY DEMOGRAPHICS<sup>6</sup>**



NCHS Urban-Rural Classification Scheme for Counties: Metropolitan counties: Large central metro counties are counties in metropolitan statistical areas (MSA) of 1 million or more population that 1) contain the entire population of the largest principal city of the MSA, or 2) are completely contained in the largest principal city of the MSA, or 3) contain at least 250,000 residents of any principal city of the MSA. Large fringe metro counties are counties in MSAs of 1 million or more population that do not qualify as large central. Medium metro counties are counties in MSAs of 250,000 to 999,999 population. Small metro counties are counties in MSAs of less than 250,000 population. Nonmetropolitan counties: Micropolitan counties are counties in micropolitan statistical areas. Non-core counties are nonmetropolitan counties that are not in a micropolitan statistical area. [https://www.cdc.gov/nchs/data\\_access/urban\\_rural.htm](https://www.cdc.gov/nchs/data_access/urban_rural.htm)

Polysubstance<sup>7</sup> overdose is the most common. Psychostimulant-involved overdose deaths involving opioids increased from 50.5% in 2018 to 66.9% in July 2022 (based on preliminary data).<sup>8</sup> Drug testing and surveillance data presented by Dr. Angela Huskey from Millennium Health support the multi-substance nature of both nonfatal and fatal overdose. Urine drug test results significantly and strongly correlate with overdose mortality.<sup>9</sup> Fentanyl use continues to rise across the country, and fentanyl and methamphetamine were the top drugs found among those receiving care in substance use disorder (SUD) treatment settings in 2022 (Figures 2,3).<sup>10</sup>

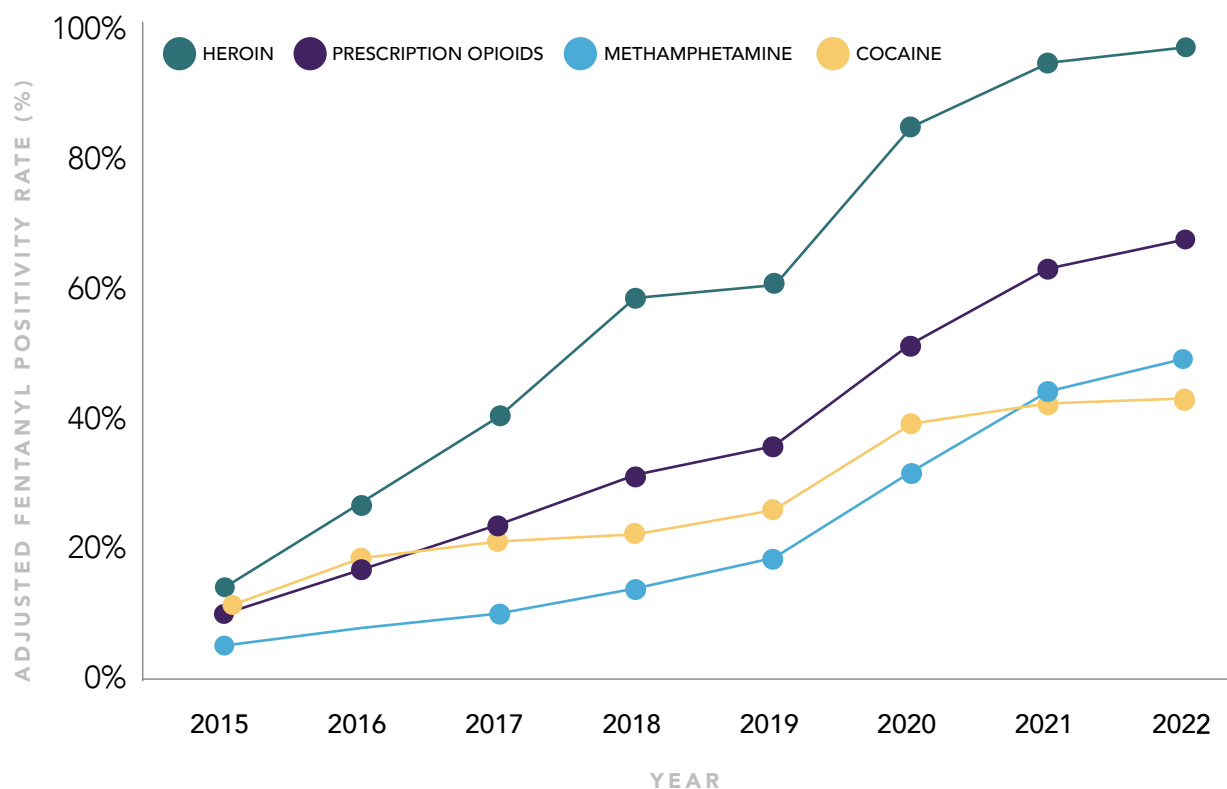
<sup>6</sup> Ibid.

<sup>7</sup> Polysubstance use refers to use of more than one type of drug, such as a stimulant and an opioid.

<sup>8</sup> CDC NVSS Wonder 2022. Jones, CM. The Drug Overdose Crisis in the U.S.: What the Latest Data Tell Us. Presented at: Understanding Fatal Overdoses to Inform Product Development and Public Health Interventions to Manage Overdose; March 8, 2023. <https://reaganudall.org/news-and-events/events/understanding-fatal-overdoses-inform-product-development-and-public-health>

<sup>9</sup> 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.

**FIGURE 2: THE PROPORTION OF FENTANYL-POSITIVE SPECIMENS AMONG INDIVIDUALS POSITIVE FOR HEROIN, PRESCRIPTION OPIOIDS, METHAMPHETAMINE, OR COCAINE FROM 2015 THROUGH 2022.11**



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.

It is critical to maintain awareness of current drug use trends because patterns of polysubstance use vary over time and geographically.<sup>12</sup> Dr. Angela Huskey stated, “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 for other drugs. More than 60% of fentanyl-positive specimens contained one or more fentanyl analogs 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.”

<sup>10</sup> Millennium Health LLC. Fentanyl in Focus: Perspectives on Polysubstance Use in 2022. Millennium Health Signals Report™, Volume 5. <https://www.millenniumhealth.com/signalsreport/>. Published February, 2023. Included urine specimens collected from substance use disorder treatment health care practices 2015-2022.

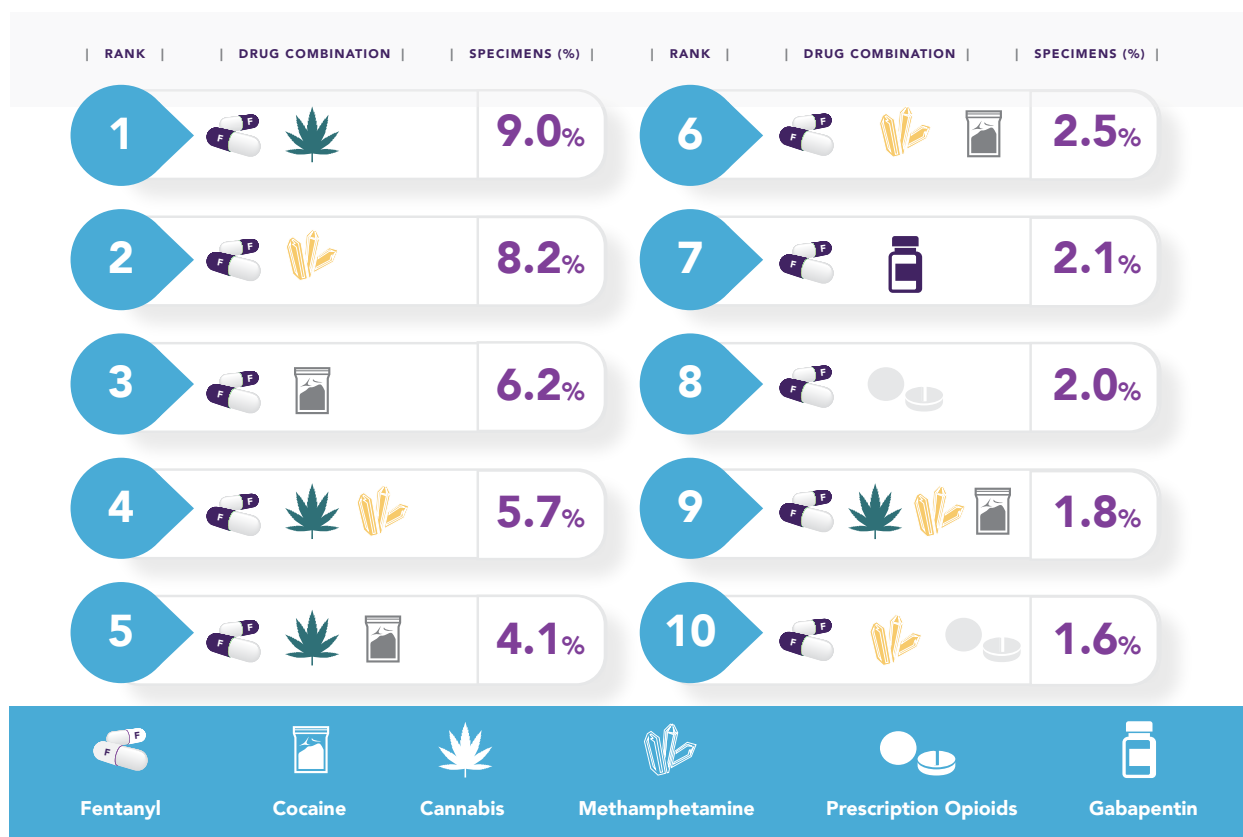
<sup>11</sup> Ibid.

<sup>12</sup> Huskey, A. Applying Clinical Drug Testing Data For Real-Time Surveillance of Drug Use. Trends. Presented at: Understanding Fatal Overdoses to Inform Product Development and Public Health Interventions to Manage Overdose; March 8, 2023. <https://reaganudall.org/news-and-events/events/understanding-fatal-overdoses-inform-product-development-and-public-health>



Despite the high rate of fentanyl presence in other opioid and non-opioid drugs, fentanyl is not included in the standard urinalysis (UA) panel run by many hospitals and is likely underreported in statistics as a result. Further, the omission of fentanyl in standard UA panels may affect whether patients are properly treated, using incomplete information about the drugs to which the patient was exposed. In his presentation, Dr. Eric Wish from the University of Maryland highlighted the critical need for fentanyl to be added to standard UA panels and the need for a CLIA<sup>13</sup>-approved rapid fentanyl test. He also called for a national epidemiologic system for collecting and analyzing hospital patients' UA results in order to monitor drug epidemics.

**FIGURE 3: FENTANYL PRESENCE IN THE DRUG SUPPLY<sup>14</sup>**



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

In this current landscape, organizations and health care systems need a menu of options for overdose reversal to be effective and to tailor treatment to individual situations. Clinical and public health expertise often lags behind the emergence of new illicit drugs. An important question addressed during the two-day public meeting was, “How can public health agencies at all levels do more to meet the needs of the moment?”

<sup>13</sup> Clinical laboratory Improvement Amendments (CLIA)

<sup>14</sup> Ibid.



## THREE: THE ROLE OF REVERSAL AGENTS AND COMMUNITY INTERVENTIONS IN OVERDOSE

### CURRENT REVERSAL AGENTS

Approved opioid antagonist drugs in the United States include naloxone, nalmefene, and naltrexone. Naloxone and nalmefene (**TABLE 1**) are indicated for the management of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. Naltrexone is used for the prevention of relapse in persons diagnosed with opioid use disorder, following opioid detoxification, and is not indicated for rapid reversal of opioid overdose.

Naloxone and nalmefene antagonize opioid effects by binding to opioid receptors and can reverse and block the effects of full opioid agonists such as fentanyl, heroin, morphine, and oxycodone.<sup>15,16</sup> Naloxone is the primary drug used in community and hospital settings to reverse opioid overdose. Both the intranasal and injection formulations of naloxone reverse respiratory and central nervous system (CNS) depression following an opioid overdose. Neither formulation affects cardiac symptoms (**Figure 4**), and both carry a risk of inducing precipitated withdrawal.

**TABLE 1: APPROVED OPIOID ANTAGONIST DRUGS FOR EMERGENCY TREATMENT OF OPIOID OVERDOSE**

	Naloxone	Nalmefene
<b>Indication</b>	Indicated in the management of known or suspected opioid overdose	Indicated in the management of known or suspected opioid overdose
<b>Mechanism of Action</b>	Complete or partial reversal of opioid drug effects, including respiratory depression	Complete or partial reversal of opioid drug effects, including respiratory depression
<b>Formulations Available</b>	Injection, nasal spray	Injection, nasal spray
<b>Routes of Administration</b>	IV, IM, SC, IN	IV, IM, SC, IN
<b>Initial Dose</b>	IV/IM/SC: 0.4 mg to 5 mg IN: 3-8 mg administered as a single dose	IV: Recommended initial dose for non-opioid dependent patients is 0.5 mg/70 kg IM/SC: 1 mg IN: 2.7 mg administered as a single dose <sup>17</sup>
<b>Repeated Dosing</b>	Adjusted doses may be repeated at two- to three-minute intervals	If needed, this may be followed by a second dose, two to five minutes later

IV: Intravenous, IM: Intramuscular, SC: subcutaneous, IN: Intranasal

<sup>15</sup> Naloxone. SAMHSA. <https://www.samhsa.gov/medications-substance-use-disorders/medications-counseling-related-conditions/naloxone>. Accessed April 26, 2023. Product Package Inserts

<sup>16</sup> Nalmefene Hydrochloride Injection. U.S. Food and Drug Administration. <https://www.accessdata.fda.gov/spl/data/5b7a6101-5382-476a-a45e-32c032c757d7/5b7a6101-5382-476a-a45e-32c032c757d7.xml>. Accessed June 27, 2023.

<sup>17</sup> FDA approves prescription nasal spray to reverse opioid overdose. FDA News Release. U.S. Food and Drug Administration. Accessed June 4, 2023. <https://www.fda.gov/news-events/press-announcements/fda-approves-prescription-nasal-spray-reverse-opioid-overdose>.

## NALOXONE DOSING/TIMING IN THE AGE OF FENTANYL<sup>18,19</sup>

Questions have emerged as to whether current naloxone dosing is adequate in the era of illicitly manufactured fentanyl(s). Fentanyl and its analogs have a high affinity for opioid receptors and due to its lipophilicity, fentanyl accumulates in the body, extending the duration of its effect.

In a fentanyl overdose, ventilation initially declines, followed by cessation of breathing (apnea) and loss of consciousness. Cardiac events then occur secondary to compensatory mechanisms in response to hypoxia (Figure 4). The timing of these effects varies and depends on the dose of fentanyl and opioid tolerance. In community settings without ventilatory support, there is a limited window before the hypoxic injury is irreversible and cardiac arrest occurs, which may happen extremely rapidly with fentanyl.

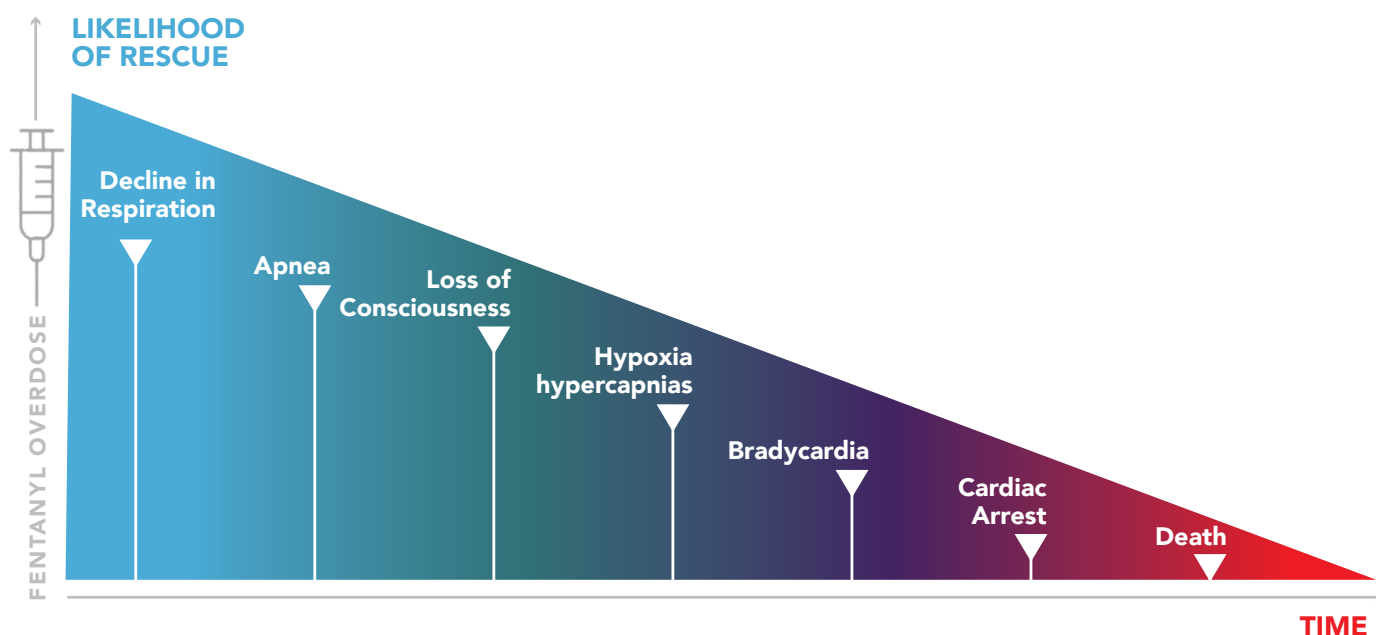
Pharmacologic data presented at the meeting suggested that fentanyl overdose is difficult to reverse because of slow receptor kinetics and fentanyl accumulation. It is more difficult for naloxone to displace fentanyl due to the high receptor affinity of the drug; therefore, higher naloxone doses (4-8mg) may be required for an initial reversal of respiratory depression. Even more important than the dose is timing – delivering the dose early in the cascade depicted in Figure 4. Higher dose naloxone may reverse respiratory depression early, but because of fentanyl accumulation in the body and the short duration of action of intranasal and IM naloxone, re-narcotization (recurrence of respiratory and CNS depression due to re-saturation of opioid receptors by fentanyl) may occur and result in ineffective opioid reversal.

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<sup>18</sup> Dahan A. Reversal of Opioid-Induced Respiratory Depression: Fentanyl and Congeners. Presented at: Understanding Fatal Overdoses to Inform Product Development and Public Health Interventions to Manage Overdose; March 8, 2023. <https://reaganudall.org/news-and-events/events/understanding-fatal-overdoses-inform-product-development-and-public-health>

<sup>19</sup> Strauss, D. Assessment of Intranasal Naloxone Repeat Dosing Strategies. Presented at: Understanding Fatal Overdoses to Inform Product Development and Public Health Interventions to Manage Overdose; March 8, 2023. <https://reaganudall.org/news-and-events/events/understanding-fatal-overdoses-inform-product-development-and-public-health>

FIGURE 4: PHYSIOLOGIC EFFECTS OF FENTANYL OVERDOSE<sup>20</sup>



### REAL-WORLD EXPERIENCES

Overdose management is a complicated process; it is not just about reversing the overdose and restoring respiration. A successful overdose reversal requires many steps. First, a bystander must be present to recognize that an overdose is occurring. Substance use can be isolating; solitary drug use puts people at higher risk for fatal overdose. Further, bystanders may have concerns about administering naloxone, and concerns about withdrawal or legal action may prevent a person witnessing an overdose from using a second or third naloxone dose or seeking further medical care.

The danger is not over once the initial respiratory depression is reversed. A person may require hours of supportive care, yet refuse emergency medical services (EMS) or other medical care. Opioid effects can be reversed by naloxone, but the person may still be sedated for hours due to other substances that cannot be reversed by an opioid antagonist (e.g., benzodiazepines, xylazine). Adverse outcomes from reversal also need to be considered, including psychomotor agitation, precipitated withdrawal, and the emergence of stimulant effects in a polysubstance overdose.

<sup>20</sup> Dahan A. Reversal of Opioid-Induced Respiratory Depression: Fentanyl and Congeners. Presented at: Understanding Fatal Overdoses to Inform Product Development and Public Health Interventions to Manage Overdose; March 8, 2023. <https://reaganudall.org/news-and-events/events/understanding-fatal-overdoses-inform-product-development-and-public-health>



Dr. Carin King Malley from the University of Pittsburgh Medical Center described components of “ideal” overdose management, including:

1. Bystanders are present
2. Bystanders recognize that this is a drug overdose
3. Someone has naloxone
4. Someone knows how to administer naloxone (many are afraid of hurting people with administration)
5. Able to connect to EMS services and EMS is called
6. EMS is able to obtain IV access
7. Person accepts additional medical care

### NALOXONE HESITANCY AND PRECIPITATED WITHDRAWAL

Hesitancy to use naloxone is another important factor in the complicated process of overdose reversal. Table 2 details reasons for reluctance to administer and receive naloxone.

Both clinicians and persons with lived experience cited precipitated withdrawal as a real concern associated with naloxone use. Precipitated withdrawal occurs when withdrawal symptoms are caused by medications used to reverse the effects of opioids. Symptoms are generally intense and seriously distressing and can include excessive vomiting and diarrhea, intense sweating, cramping, muscle aches and pains, agitation, restlessness, and anxiety. Precipitated withdrawal symptoms can last for hours to days. Persons with lived experience stated that they would do anything to avoid experiencing severe precipitated withdrawal again, even if it means increasing the risk they will die – an important consideration for the community, clinical settings, and research approaches to treating opioid overdose.

**TABLE 2: REASONS FOR NALOXONE USE HESITANCY**

PERSON ADMINISTERING NALOXONE	PERSON RECEIVING NALOXONE
<ul style="list-style-type: none"> <li>▶ Fear of hurting the patient while administering the drug</li> <li>▶ Legal liability</li> <li>▶ The person experiencing overdose is not known to the person administering naloxone and does not know what to expect</li> <li>▶ The person experiencing an overdose may need hours of supportive care after reversal</li> </ul>	<ul style="list-style-type: none"> <li>▶ Fear of withdrawal symptoms and precipitated withdrawal</li> <li>▶ Fear of legal charges for personal drug possession in states where it is illegal</li> <li>▶ EMS not called for fear of arrest or police involvement</li> </ul>

## FOUR: PUBLIC HEALTH APPROACHES FOR OVERDOSE PREVENTION

The current drug overdose crisis is driven by the changes in the illicit drug supply, and public health expertise often lags behind the emergence of new drugs in the illicit supply (e.g., xylazine), leaving health care and public health professionals to approach overdoses without fully understanding the evolving situation.

### PUBLIC HEALTH AND HARM REDUCTION OUTREACH

Methods used for overdose education and prevention in the community include naloxone distribution and drug-checking services. Drug-checking services (where people who use drugs can test their supplies to determine whether unknown substances, such as fentanyl, are present) provide opportunities for education about contaminated or adulterated drugs in the illicit drug supply. They also provide a tactile process that aids in overcoming barriers to understanding the presence of fentanyl and fentanyl analogs in opioid, benzodiazepine, and stimulant products being used.

Obstacles to the full implementation of such services include socioeconomic and legal barriers. Gaps in socioeconomic disparities are increasing. People most at risk for overdose are least likely to receive harm reduction services. Phillip Fiuty from the Mountain Center stated, “We have fantastic tools for overdose prevention, but we haven’t figured out how to get them in all the places that they need to be.”

Speakers noted that paraphernalia laws and criminalization of drug possession also interfere with public health and harm reduction efforts. Paraphernalia laws prevent state and county health departments from providing drug-checking services. Criminalization of drug possession may contribute to an underlying fear of arrest in the person experiencing an overdose. Decriminalization of drug possession for personal use allays fears of legal repercussions and opens a safe space for people using drugs to ask questions and seek assistance. People who feel safe are also less likely to use drugs alone, lessening the risk for fatal overdose.

## NALOXONE ACCESS

Naloxone access remains a considerable barrier to overdose prevention. Naloxone decreases morbidity and mortality associated with opioid overdose. The ultimate goal is community saturation of naloxone, similar to the distribution of defibrillators for use during cardiac arrest. During the meeting, experts emphasized the need to get naloxone into the hands of people using drugs and the communities in which they reside. While nonprescription naloxone will expand access, it will not address all the barriers to obtaining the medication.<sup>21</sup> The potential price of nonprescription naloxone, insurance coverage, and willingness of pharmacies and other retailers to sell the product remain to be seen. In addition, harm reduction organizations expressed concerns that nonprescription nasal naloxone may lead to decreased availability of injectable naloxone, which would be detrimental to their work and leave them without an important item on their spectrum of overdose treatment options.

## NOVEL/INNOVATIVE APPROACHES TO OVERDOSE PREVENTION

Speakers and panelists presented innovative strategies to overcome barriers to naloxone access and overdose prevention. Innovations included:

1. Low-barrier naloxone access programs, mobile vans, and naloxone vending machines
  - ▶ Examples: The DOPE Project (<https://harmreduction.org/our-work/action/dope-project-san-francisco/>), Impact Exchange Vending Machines (<https://www.harmreductioncenterlv.com/impact-exchange-vending-machines>), NEXT Distro (<https://nextdistro.org/>), Remedy Alliance (<https://remedyallianceftp.org/>)
2. Combined services – Naloxone distribution plus kits to check for adulterated drug supply, syringe exchange programs, and HIV/Hepatitis C testing
  - ▶ Examples: Access Point Georgia (<https://www.accesspointga.org/>), Dance Safe (<https://dancesafe.org/>), North America Syringe Exchange Network (NASEN) (<https://www.nasen.org/>)<sup>22</sup>
3. Nonprescription naloxone<sup>23</sup> – intranasal naloxone available without a prescription from a health care provider

<sup>21</sup> The FDA Foundation report on “Naloxone: Economic Impact” explores potential economic factors impacting nonprescription naloxone: <https://reaganudall.org/sites/default/files/2023-03/Naloxone%20Report%20FINAL%203.10.23.pdf>

<sup>22</sup> Lambdin BH, Bluthenthal RN, Wenger LD, Wheeler E, Garner B, Lakosky P, Kral AH. Overdose Education and Naloxone Distribution Within Syringe Service Programs - United States, 2019. *MMWR Morb Mortal Wkly Rep.* 2020 Aug 21;69(33):1117-1121. doi: 10.15585/mmwr.mm6933a2. PMID: 32817603; PMCID: PMC7439981.

<sup>23</sup> Naloxone Economic View Summary Report; <https://reaganudall.org/sites/default/files/2023-03/Naloxone%20Report%20FINAL%203.10.23.pdf>

4. Overdose prevention centers (OPCs) – OPCs are medically supervised and legally sanctioned facilities that provide a hygienic environment and safe space in which people are able to consume illicit recreational drugs. The presence of trained staff allows for the prevention of deaths due to drug overdose.<sup>24</sup> OPCs are also known as supervised consumption services (SCS), supervised injection facilities/sites (SIFs), or drug consumption rooms (DCRs).
  - ▶ Examples: ONPOINT NYC (<https://onpointnyc.org/>), Prevent Overdose RI (<https://preventoverdoseri.org/>), Supervised consumption sites and services in Canada (<https://www.canada.ca/en/health-canada/services/substance-use/supervised-consumption-sites/explained.html>)
  - ▶ Legislation is pending to authorize overdose prevention centers in Colorado, Connecticut, Illinois, Maryland, Massachusetts, New Mexico, New York, and Vermont.
5. Safe drug supply initiatives – “safer supply” refers to providing prescribed medications as a safer alternative to the toxic illegal drug supply to people who are at high risk of overdose<sup>25</sup>
  - ▶ Canada – Responding to Canada’s Opioid Crisis, Safer Supply (<https://www.canada.ca/en/health-canada/services/opioids/responding-canada-opioid-crisis/safer-supply.html>)
  - ▶ European programs – by providing a reliable drug supply these programs are also shrinking the illicit opioid market; heroin programs in Switzerland have led to a reduction in the illegal supply

## FEDERAL TECHNICAL ASSISTANCE

SAMHSA supports the scaling of innovative services and technical assistance through various grant programs which include, but are not limited to:

1. Grants to Prevent Prescription Drug/Opioid Overdose-Related Deaths - <https://www.samhsa.gov/grants/grant-announcements/sp-21-002>
2. First Responders-Comprehensive Addiction and Recovery Act grants - <https://www.samhsa.gov/grants/grant-announcements/ti-21-009>
3. Block grants - <https://www.samhsa.gov/grants/block-grants>
4. Harm Reduction grants - <https://www.samhsa.gov/grants/grant-announcements/sp-22-001>

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<sup>24</sup> Overdose prevention centers - [drugpolicy.org](https://drugpolicy.org). [https://drugpolicy.org/sites/default/files/overdose-prevention-centers\\_0.pdf](https://drugpolicy.org/sites/default/files/overdose-prevention-centers_0.pdf). Accessed April 26, 2023.

<sup>25</sup> Canada H. Government of Canada. Prescribed medications as a safer alternative to toxic illegal drugs - [Canada.ca](https://www.canada.ca/en/health-canada/services/opioids/responding-canada-opioid-crisis/safer-supply.html). <https://www.canada.ca/en/health-canada/services/opioids/responding-canada-opioid-crisis/safer-supply.html>. Published April 25, 2023. Accessed April 26, 2023.



## FIVE: INNOVATION AND PRODUCT DEVELOPMENT CONSIDERATIONS

Many opportunities exist for innovation in product development for the prevention and treatment of overdose. Presenters and panelists provided many recommendations for naloxone and ideal products to manage opioid and polysubstance overdoses.

During the meeting, harm reductionists and people who nonmedically use opioids emphasized that high dose naloxone is not a high priority for them. Patients, community members, and clinicians indicated a preference for products allowing for a more titratable dose without requiring IV access that results in a milder, more gradual reversal. People with lived experience and some professionals advocated for a variable dosing mechanism product in order to titrate to a dose reversing respiratory depression without causing severe withdrawal. They also noted that people with lived experience are often comfortable using products requiring the use of a needle and syringe. Because of the precipitated withdrawal concerns, many people who use opioids would rather have access to a titratable injectable (i.e., a formulation permitting administration of partial doses titrated to effect) rather than formulations that deliver the entire dose at once (e.g., nasal sprays, autoinjectors) because of a lower risk for precipitated withdrawal.

### OPPORTUNITIES FOR INNOVATION IN OVERDOSE MANAGEMENT PRODUCTS

Clinicians, harm reduction professionals, researchers, and people with lived experience expressed the desire for a variety of options to tailor overdose reversal to individual situations.

#### Desired products include:

- Pre-use agents to prevent respiratory depression (i.e., use a small dose of naloxone or nalmefene prior to ingesting the opioid)
- A titratable overdose reversal agent with selective reversal of respiratory depression
  - ▶ Including the ability to identify when the dosage is adequate or not enough, for example, alerting the administrator when there is a respiratory rate of ~ 8 breaths/minute

- Partial agonists for reversal
- Automated overdose detection/alert devices and devices that signal a person is heading toward an overdose
- Devices that allow lay people to administer assisted ventilation
- Preassembled drug-device products for quick use and prevention of administration mistakes
- Products for use in all age groups (pediatrics included)
- Affordable, practical, and simple devices to aid in airway management & oxygenation

**Speakers suggested the ideal overdose reversal agent would possess the following characteristics:**

- Titratable
- Partial opioid receptor agonist and/or selective for reversal of respiratory depression
- Methods or devices allowing for closer titration of the reversal agent without IV access
- Self-administration of a reversal/partial reversal agent when a person realizes they may have overdosed
- Low or no-cost price
- Community acceptance

**Ideal naloxone formulations would include:**

- Methods/devices allowing for closer titration without IV access
- Mild, gradual reversal
- Greater tolerability

**Innovative ideas for overdose prevention and treatment that were presented include:**

- Pulse oximetry paired to a smartphone plus canned oxygen
- Digital health technologies
  - ▶ Acute overdose sensing
  - ▶ A wearable device with the ability to detect parameters (for example, respiratory depression) and then signal for intervention

## SIX: HUMAN FACTORS

Substance use can be very isolating, and many people who use drugs do so alone. Solitary drug use puts people at high risk for fatal overdose. Stigma, criminalization of personal drug possession, and focus on the behavior rather than the individual furthers seclusion.

Speakers and panelists underscored the importance of respect and the need to consider the ethics of overdose reversal in all aspects of care, from harm reduction and clinical care efforts to research and product development. In the realm of substance use and overdose, it is important to center the conversation around treating people rather than around drugs or a disorder. Person-centered care includes honoring patient choice and obtaining consent for steps in overdose reversal, when able. Meeting people where they are puts the needs and priorities of people with lived experience front and center.

At the core of harm reduction is a commitment to the rights and autonomy of people who use drugs. Examples of honoring the choice and consent of a person who uses drugs include:

- Naloxone dose and route of administration preference
- Whether to administer additional naloxone
- Whether to call 911
- The use of medications for opioid use disorder (MOUD) when the person is ready – until that time, support safer drug use

Meeting people where they are also means educating where education is needed. Communities where people frequently use opioids are generally familiar with how to use naloxone. Education and outreach efforts should be prioritized based on where they are likely to have the highest impact.

## SEVEN: OPIOID OVERDOSE-RELATED RESEARCH

Primary themes regarding opioid overdose-related research included the need to integrate people with lived experience at all stages and in all areas of substance use and overdose research, as well as to build evidence for the effectiveness of public health innovations. To achieve progress and improve response time to emerging changes in the drug supply, there must be a coordinated effort between research, development, and regulatory pathways.

### 1. **Greater inclusion of those with lived experience**

In general, there is systematic exclusion of people with lived experience from substance use and overdose research. More effort is needed to engage people with lived experience in product and drug development. People with first-hand involvement in reversing and experiencing overdose must be included in all phases of research via qualitative methods and the use of focus groups. The exclusion of this population results in a disconnect between research objectives and needs identified by professionals and the substance use community.

### 2. **Build evidence for the effectiveness of public health interventions**

Research priorities should not solely focus on products. As stated earlier, safe and effective options to reverse opioid overdose are not getting to the people who need them. To avoid duplication of efforts, evidence generation should occur across substance use disorder interventions (e.g., drug checking services, safe supply, safe consumption). It is also important to look forward and avoid creating interventions that quickly become obsolete because of changes in the drug supply, in drug-use behavior, or other evolution. Data and funding are needed to support program implementation and evaluation and ensure that programs are doing what they should be doing or that the method of service delivery is having the expected impact.



## EIGHT: CONCLUSION AND FUTURE DIRECTIONS

Public health efforts often lag behind changes in the drug supply. It can take years for trends to show up in federal data, yet public health agencies at all levels need to do more to meet the needs of front-line professionals in real time.

More research is needed to explore opioid antagonist dosing in different settings. Pharmacologic data suggest the need for higher naloxone doses to reverse some opioid overdoses, especially in the setting of fentanyl. Those who have experienced or reversed opioid overdose often prefer lower, more titratable naloxone doses that induce a milder, more gradual reversal. Taken together, these findings highlight the need for collaborative solutions in developing optimal interventions to prevent fatal overdose.

Progress and improvement require a multi-modal approach; there is no single solution to tackling the challenge of fatal overdose. It is important to think about substance use and overdose holistically, not drug by drug.<sup>26</sup> Innovation is needed at the system level, not just at the molecular or pharmacological level. The product development community needs to do more to engage people with lived experiences. Every clinician, advocate, and person with lived experience asked for more patient involvement in the design process for drug development to ensure end-user acceptability of the product.

In addition, it is important to continue and build on efforts to expand naloxone access, ensure the safety of the non-prescribed drug supply, and address regulatory considerations for future action and innovation.

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<sup>26</sup> Jones, CM. The Drug Overdose Crisis in the U.S.: What the Latest Data Tell Us. Presented at: Understanding Fatal Overdoses to Inform Product Development and Public Health Interventions to Manage Overdose; March 8, 2023. <https://reaganudall.org/news-and-events/events/understanding-fatal-overdoses-inform-product-development-and-public-health>



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