

# WELL BEING TRUST BRIEF

## NALOXONE FOR OVERDOSE REVERSAL: CHALLENGES & OPPORTUNITIES



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## NALOXONE FOR OVERDOSE REVERSAL: CHALLENGES & OPPORTUNITIES



### Introduction

Naloxone is a widely used medication to reverse opioid overdoses and a mainstay of harm reduction strategies of every U.S. government agency combating the opioid epidemic. At a time when the effects of the pandemic have greatly increased overdose rates, however, there are glaring inconsistencies in U.S. naloxone policies and practices from one region, health system, and community to another. The purpose of this Well Being Trust policy brief is to illustrate those inconsistencies and to make policy recommendations to optimize the benefits of this key life-saving tool. It is informed by a rigorous review of research literature from multiple disciplines, as well as interviews with policymakers, administrators, clinicians, harm-reduction advocates, and pharmacologists.

## What is Naloxone?

Developed in the 1960s by a cancer researcher seeking a treatment for constipation from chronic opiate use, naloxone is an evidence-based, FDA-approved opioid antagonist that binds with high affinity to mu-opioid receptors in the brain, the primary binding site for opioids. When it binds the receptor, it quickly displaces heroin, fentanyl, and other opioid agonists that can cause overdose and respiratory depression resulting in death. Its primary side effect for individuals with physical dependence on opioids is precipitated opioid withdrawal with symptoms including body aches and stomach pain. In the 1970s, the use of naloxone for overdose reversal was limited to hospitals and emergency rooms. It wasn't until the 1990s that the Chicago Recovery Alliance began distributing it to community organizations around the country to give to individuals at syringe exchanges and other harm reduction events (Campbell, 2019). Today, it is commonly carried and administered by individuals who use opioids, family and community members, physical and mental health providers, and first responders, such as police, fire, and emergency medical services.

### Naloxone is currently available in multiple formulations:

#### **Intramuscular (IM)**

- 0.4 mg vials available from several companies as a generic drug.
- 5 mg ZIMHI produced by Adamis Pharmaceuticals. It was approved by the FDA in October 2021 as a single-dose pre-filled syringe. It can be administered IM and subcutaneously.

#### **Intranasal (IN)**

- 2 mg naloxone atomizer.
- 4 mg Narcan nasal spray produced by Emergent BioSolutions, and two recent 4 mg generic naloxone nasal sprays (launched in December 2021) from Sandoz and Teva.
- 8 mg Kloxxado nasal spray produced by Hikma Pharmaceuticals.

These formulations are distributed in a variety of ways. Some are available through local pharmacies by prescription or, if the state has a Standing Order, without prescription. State, county, and municipal public health departments also purchase large amounts of naloxone products, often funded by federal or other grants, to distribute to local and regional organizations and agencies, such as harm reduction advocacy groups, health systems, and first responders. Remedy Alliance's Opioid Safety and Naloxone Network Buyers Club—a collective of 104 harm reduction organizations throughout the country—purchases low-cost generic IM naloxone in bulk to divvy up and distribute to individuals who use opioids.

All formulations, except for ZIMHI, are available in two-dose kits. People who are given these kits are instructed to always carry them with them or store them in a place where they can be quickly retrieved. If someone in possession of a naloxone kit encounters an individual who has suffered an overdose, these are the actions they should take:

- Administer the first dose of naloxone immediately.
- Call 911.
- Start rescue breathing while waiting for emergency services.
- If the overdose victim does not resume breathing within 3-4 minutes of receiving the first dose of naloxone, administer the second dose. (Unfortunately, not all those who have been given two-dose kits will carry both doses with them.)



## Literature Review

Our unstructured literature review focused on identifying guidance on effectiveness of different naloxone formulations, especially in geographic areas of high fentanyl prevalence. Specifically, we sought to understand:

- What are the recommended criteria for choosing a specific naloxone formulation by prescribers, family and community members, and individuals who use opioids?
- Are higher doses of naloxone needed for individuals experiencing an overdose caused by fentanyl or fentanyl analogues?
- How has the distribution of naloxone in community settings impacted the rate of death from opioid overdose?

We used the Google Scholar and PubMed search engines to find pertinent quantitative and qualitative studies, most post-2017, in the fields of Toxicology, Public Health, Social Work, Addiction Medicine, and Emergency Medicine from peer-reviewed academic, practitioner and multidisciplinary journals. Our search included key words and phrases and excluded any studies funded in part or wholly by a pharmaceutical company.

### Findings

Results were inconsistent and inconclusive, sometimes reaching opposite inferences. For example, the authors of one 2018 study from *Substance Abuse* “refute the notion that high potency synthetic opioids like illicitly manufactured fentanyl require increased doses of naloxone to successfully treat an overdose” (Bell, et. Al., 2018). But the authors of a 2017 study from *Prehospital Emergency Care* found that the need for multiple naloxone doses had increased since the advent of fentanyl (Faul, et. Al. 2017).

Others highlighted the “human factor” challenge, regardless of the naloxone formulation, faced by lay users under the high stress of an overdose emergency. For instance, in a study of 207 randomly selected adults “without training in naloxone administration, even the easiest to use devices are still administered incorrectly approximately a third of the time. Public health officials and pharmacists should ensure that training resources are available to the public, especially if naloxone receives over-the-counter status” (Eggleston 2019).

Given such concerns, it is not surprising that one researcher concluded that there is “an urgent need for more comprehensive studies to determine optimal naloxone dosing and routes of administration” (Mayer, 2018).

## Interview Process

Short interviews were conducted over several months from 2021–2022 with 20 professionals representing all facets of the delivery system, from those who make policies to those who implement the policies. View the list of interviewees on page 11.

## Barriers & Challenges

Despite the decades-long history of effective naloxone use, interviewees described the many barriers that still exist for disseminating it more broadly and reversing more overdoses:

- **There is too little naloxone available** to meet the need for overdose reversal. According to a recent study in *Lancet Public Health*, “almost all U.S. states have underdeveloped naloxone distribution efforts, and few are able to avert 80 percent of witnessed deaths due to opioid overdose with naloxone” (Irvine, 2022).
- **Fear of legal repercussions** for intervening with naloxone. Good Samaritan laws are not universal, and even if they are present, drug users and their friends/family may not be aware of them. As of 2017, 40 states and the District of Columbia have enacted some form of Good Samaritan law to protect those trying to help.

- **Stigma still exists** toward people who use drugs. Stigma causes barriers at multiple levels: institutional stigma results in the lack of top-down policies to supply people with naloxone and train them in its use in overdose situations, while individual stigma causes people from the bottom-up to be disinterested or even actively eschew such efforts. Consequently, some agencies haven't embraced harm reduction techniques. According to Ryan Hampton, the director of Voices Project, a Las Vegas-based harm reduction advocacy group, law enforcement officers and EMTs in various parts of the country still don't routinely carry naloxone while on duty.
- **There is fear of precipitated opioid withdrawal.** Some individuals who use opioids fear being suddenly wracked by withdrawal symptoms after using naloxone. Some first responders and other family members fear individuals whose overdoses have been reversed will become severely agitated, violent, and unmanageable.
- **There have been occasional shortages** of naloxone in the last decade because of manufacturing problems. In April 2021, Pfizer experienced manufacturing difficulties that greatly delayed delivery of IM naloxone to harm reduction organizations for the rest of that year.
- For those given or prescribed IM naloxone, **there may be fear of using needles or general fear of safety.**

## Clinical Practice

As more naloxone formulations have become available for prescribers to prescribe, there appears little consensus among physicians about the right approach. There are two primary areas of disagreement:

### Prescriptions versus Take-Home Kits

While many prescribers of opioid pain medications are still not prescribing accompanying naloxone, those who do frequently give patients prescriptions rather than take-home kits. The available data, however, suggests that most of those prescriptions are never filled. According to Steve Aks, DO, an emergency room physician and Toxicology Director for Cook County Health in Chicago, only 18 percent of naloxone prescriptions provided in his hospitals'

emergency rooms are filled; he believes the cause is likely cost and stigma. Less than 2 percent were filled by individuals prescribed IM naloxone upon discharge from two Seattle emergency rooms (Lebin, 2017). Many physicians seem unaware of these low fill rates. Others have been prevented from handing out take-home kits by regulatory or policy barriers. Some emergency departments have tried to get around these barriers by asking patients to fill their naloxone prescriptions at the hospital pharmacy immediately upon discharge. A recent *Annals of Emergency Medicine* article, co-written by a consortium of emergency room providers from seven Chicago-area hospitals, describes the challenges of and makes recommendations for establishing a take-home naloxone program (Eswaran, 2020).

### Need for Higher Doses of Naloxone for Fentanyl?

There is an ongoing debate among prescribers about the need for higher doses of naloxone to counter fentanyl-induced overdoses. There are several reasons for the difficulty in reversing an overdose, including the dose of the opioid the person used or the drug being contaminated. "Too much naloxone is always enough," said Daniel Brooks, MD, an emergency room physician and Co-Director of the Center for Toxicology and Pharmacology Education and Research for Banner Health in Phoenix. "The 4 mg formulation is better than the 2 mg formulation. The 8 mg formulation is better than the 4." Many prescribers such as Dr. Brooks have anecdotes about the patients who needed more than 10 mgs to reverse fentanyl-induced overdoses. They usually dismiss concerns that higher doses of naloxone will cause more precipitated withdrawal, saying that saving lives is the highest priority.

*"If a patient needs more than one to two doses of lower-dose naloxone, then something else is going on—for instance, the patient is using other drugs besides opioids."*

But other physicians differ strongly about the dosing. "When fentanyl started increasing, we took a really close look at our naloxone data and we didn't see any change in its use for reversing overdoses," said Jennifer Plumb, MD, MPH, a pediatric emergency room physician at Intermountain Healthcare

and Associate Professor at the University of Utah Department of Pediatrics. “If a patient needs more than one to two doses of lower-dose naloxone, then something else is going on—for instance, the patient is using other drugs besides opioids.”

As noted in the “Literature Review” section above, there is insufficient empirical evidence yet to justify the use of specific naloxone doses. “Although there is discussion in peer reviewed literature that people on fentanyl need higher doses of naloxone, the data is inconsistent,” said Shannon Robinson, MD, a psychiatrist and addiction medicine specialist, former director of the Alcohol and Drug Treatment Program at San Diego Veterans Affairs, and currently a consultant with Health Management Associates. “Additional consideration should be given to binding properties beyond the mu opioid receptor and the contributions those play in relationship to fentanyl related fatalities.”

“We have limited data to work from about the perfect dose,” said Elizabeth Salisbury-Afshar, MD, a specialist in family, addiction, preventive medicine who is also an Associate Professor at the University of Wisconsin-Madison. “We need to give people the formulation they are willing and able to use.”



## Community Distribution & Harm Reduction

There is consensus in one regard among state, county, and municipal decision-makers that provide naloxone to community groups to distribute to their members. They have nearly all opted to purchase large quantities of IN formulations, generally by tapping grant funds, such as federal State Opioid Response (SOR) grants. Most are paying approximately \$72 per two-dose kit and then distributing for free, often through online ordering, the 4 mg Narcan nasal spray. Some are still distributing the 2 mg naloxone atomizer because, at approximately \$50 per two-dose kit, it is less expensive and because they believe that the 4 mg dose isn't necessary to reverse even fentanyl-induced overdoses. While some states have added 8 mg Kloxxado to their Medicaid formularies, few, if any of them, are using that IN formulation for community distribution.

### IN vs. IM

When asked why they chose IN rather than IM formulations, most decision-makers cite consumer preference. According to Linda A. Mahoney, LCDS, CAADC, an administrator for Rhode Island's Department of Behavioral Healthcare, Developmental Disabilities, and Hospitals (BHDDH), a 2020 state survey about naloxone to which 300 individuals responded found that 73 percent preferred IN, 13 percent preferred IM, and the rest had no preference. A 2017 social media survey, published in the journal *Addictive Behaviors*, also found a clear preference for noninjectable forms of naloxone among patients who had been prescribed opioid pain medications (Dunn, Barrett, Bigelow, 2018).

But the decision-makers appear to be at odds with harm reduction advocacy groups which strongly prefer the IM formulation. Their highest priority is increasing access to naloxone because they believe there is not enough available to meet the current need. “Saturation is key,” said Alice Bell, Director of Prevention Point Pittsburgh which distributes IM kits. “The cost of a kit, including syringe, alcohol wipes, etc., is only \$15 to \$18.” Purchasing and distributing less expensive naloxone, she and others argue, means more of it reaches the community. Said Dr. Jennifer Plumb, “IN kits should only be given to people who are needle phobic.”

The harm reduction advocates also disagree with the conclusion drawn by decision-makers about consumer preference.

“Most people who are given naloxone and are the reversers are other users who are comfortable using needles,” said Maya Doe-Simkins, Co-Director of Remedy Alliance whose Buyers Club purchased and distributed 1.3 million IM kits in 2020. Her assertion about who the reversers are seems to be supported by statistics from California Department of Health Services’ Naloxone Distribution Program (NDP). In 2020, this program gave out approximately one-third of the 450,000 4 mg Narcan kits it distributed to harm reduction groups. But nearly three-quarters of overdose reversals were reported that year by individuals, presumably including many who use opioids, to whom the Narcan kits had been given.

A few governmental agencies, such as the Philadelphia Department of Public Health Division of Substance Use Prevention and Harm Reduction and the California Department of Health Services’ NDP, will pay for and distribute both the Narcan nasal spray and IM naloxone. They cite significantly lower cost and the preferences of harm reduction groups as the reasons for offering IM as well as IN formulations.

### Need for Higher Doses?

Certain harm reduction advocates also push back on the notion that higher fentanyl prevalence requires higher naloxone dosing. “From 2013 to 2016, deaths due to fentanyl rose from 3 to 63 percent of all overdose deaths in Allegheny County, Pennsylvania,” said Alice Bell. “But there has been no increase in the need for more than one to two doses of lower-dose naloxone to reverse a fentanyl-induced overdose.” The advocates also say that IM allows those who are administering it to titrate the dose up slowly as needed and thereby reduce the likelihood that the overdose victim will suffer precipitated withdrawal. (Technically, only licensed prescribers should be titrating naloxone doses using their medical knowledge and experience.)

## Policy Recommendations

The greatest opportunities for optimizing the benefits of naloxone and reducing overdose doses are through conducting additional research, creating practice standards, and changing federal and state policies to increase access to these life-saving medications. Here are four recommendations to improve our country’s use of naloxone.



### Recommendation 1. Data Collection and Analysis

For as much as we have learned about naloxone since it was created more than 50 years ago, there is an absence of information about some important aspects of the national efforts to increase its availability, especially in community settings. Additional insight on the following would help inform decision-making at local, state, and national levels related to naloxone:

- a. What is the quantifiable impact of naloxone on the rate of opioid-related overdose deaths?
  - How effective are current clinical programs (prescriptions and take-home kits)?
  - How effective are current programs for distributing naloxone to community stakeholders?
  - What percentage of distributed naloxone has been used for overdose reversal?
    - > How willing are naloxone carriers to administer it?
    - > How well prepared are Good Samaritan naloxone carriers to administer naloxone?
    - > Are there effective strategies for decreasing “bystander hesitancy”?
- b. What is the experience of naloxone users?
  - This includes those who have been given Naloxone/Narcan to reverse an overdose and should include their reports on the effects of naloxone and higher dose antagonist medications.



## **Recommendation 2. Increase & Improve the Availability of Antagonist Medications**

- a. Much more naloxone in any form needs to be made available to individuals with OUD, their supporters, first responders, EDs, etc.
- All distribution programs should focus on making available naloxone formulations people are willing and able to use.
  - The formulations people are willing and able to use are dependent on social acceptability and cost, which must be considered in efforts to expand availability and access.

- b. In January 2019, the FDA called for naloxone to become available over the counter (OTC). This was reiterated during a March 2022 webinar sponsored by the Reagan-Udall Foundation.
- Naloxone meets all FDA requirements for OTC status. Making it available OTC would improve access and help alleviate concerns with regard to inconsistent state standing orders and liability for those administering or possessing the medication. Unfortunately, labeling that ensures that consumers know how to use naloxone safely, and provides the manufacturers protection from lawsuits, continues to be a barrier to OTC authorization.

Because of this, it is likely that the IN formulation would be available OTC sooner than the IM version, simply because there is less concern from manufacturers related to consumer safety when administering intranasally as opposed to the use of syringes.

- Pocket Naloxone is creating naloxone nasal swab to market OTC and will be seeking FDA approval.
- As per Ryan Hampton, naloxone should be as readily available in pharmacies as condoms so that no individual is deterred from purchasing it out of fear of needing to ask a pharmacist for it.

- A letter in Integrated Pharmacy Research and Practice (Evoy, Hill, Davis, 2021) explores pros and cons of over-the-counter naloxone availability and concludes that over-the-counter distribution would increase naloxone access more than the current patchwork of state Standing Orders.
  - Similar to other OTC medications available at no-cost through the Medicaid program, Centers for Medicare & Medicaid Services (CMS) must establish processes to help ensure those with Medicaid coverage have equitable access to naloxone if it becomes available OTC.
- c. Federal and state governments should take steps to increase distribution of naloxone:
- The federal government should consider distribution of naloxone kits through the USPS upon requests, as it has done with COVID test kits.
  - CMS should seek congressional authority for 100% federal medical assistance percentage (FMAP) to create an Opioid Overdose Elimination Program (OOEP) and encourage states to seek an 1115 Demonstration Waiver to develop and test the effectiveness. Parameters of the OOEP should include requiring data collection on the following metrics:
    - > Number and type of naloxone kits purchased.
    - > Number and type of naloxone kits distributed statewide by provider/organization, date, zip code.
    - > Opioid overdose rates and overdose death rates.
    - > Consumer feedback.

HHS & CMS should establish regulations requiring 100% insurance coverage for naloxone (including without a prescription) in:

- Medicaid programs in states that seek an 1115 Demonstration Waiver for the Opioid Overdose Elimination Program.
- ACA health plans.
- Medicare Advantage plans.

d. Consider novel means of distributing naloxone to the community.

- Vending machines (as per Marin County, California, Nevada, Rhode Island, Michigan).
- First responder programs.
- In AED units.
- On every airplane.
- In every school.

e. States should review all administrative procedures for naloxone distribution that may inadvertently pose barriers to its dissemination.



### **Recommendation 3. Create clinical best practices for administering antagonist medications**

- a. For prescribers, greater research is needed to determine the risks of lower versus higher naloxone doses. Specifically, research is needed in the following areas:
- Risk of mortality.
  - Risk of precipitated withdrawal.
  - Algorithm of right dose, given fentanyl prevalence in community.
- b. For prescribers and first responders, the following is needed:
- Reduce professional stigma.
  - Mandated annual OUD/naloxone stigma reduction training.
  - Mandate that law enforcement and EMS carry naloxone.



### **Recommendation 4. Create best practices for community naloxone distribution programs**

- a. Many in the harm reduction arena believe that state programs should offer both IM and IN (in most instances, Narcan 4 mg) to meet the needs of different populations.
- IM can be provided directly to harm reduction organizations.
    - > Because it is preferred by them because of “smoother withdrawal”.
    - > Because it is significantly less expensive.
  - Allay decision-makers’ concerns about needle sticks from IM naloxone by researching its likelihood. (There is no current data.)
  - Offer train-the-trainer courses in IN/IM use and rescue breathing to all CBOs to train community members.
  - Emphasize rescue breathing will likely save additional lives from overdose.
- b. HHS should set minimum training requirements that states must comply with if authorized to receive a 100% FMAP rate for purchase/dispensation of naloxone.
- Requirements should be modeled after the American Heart Association’s training for CPR certification.

## **Conclusion**

In conclusion, the greatest opportunities for optimizing the benefits of naloxone and reducing overdoses are through conducting additional research, in the way naloxone is used, its effectiveness and ideal formulation; creating practice standards; and changing federal and state policies to increase access to these life-saving medications.

## Interviewees

Interviews were conducted with professionals representing all facets of the delivery system from those who make policy to those who implement the policies.

### Providers:

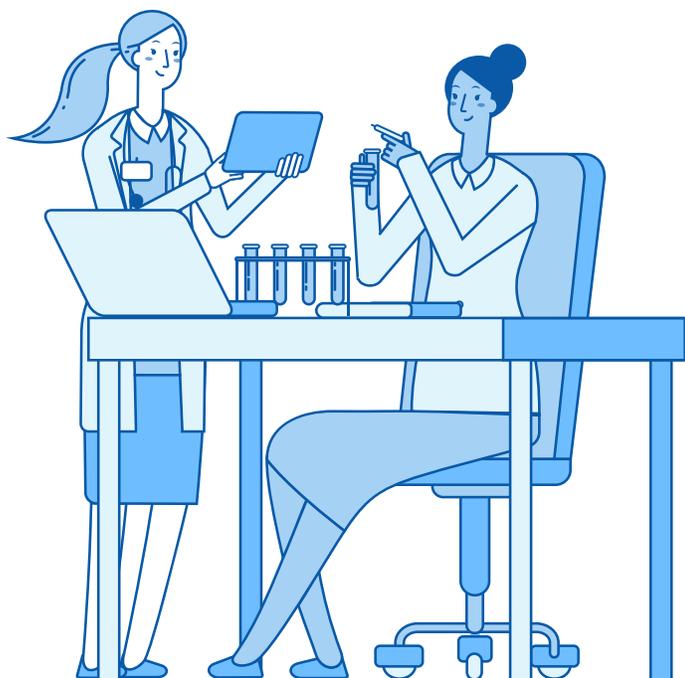
**Steven Aks**, DO, Toxicology Director, Department of Emergency Medicine, Cook County Health System, Chicago IL

**Daniel Brooks**, MD, Emergency Medicine Physician and Toxicologist, Banner Health; Co-Director of Center for Toxicology and Pharmacy Education and Research; Medical Director, Banner Poison and Drug Information Center; Phoenix, AZ

**Margaret Jarvis**, MD, Chief of Addiction Medicine, Department of Psychiatry, Geisinger Health System, PA

**Jennifer Plumb**, MD, MPH, Pediatric Emergency Medicine Physician at Intermountain Healthcare, Salt Lake City, UT; Associate Professor of Pediatrics, University of Utah

**Shannon Robinson**, MD, Principal, Health Management Association; formerly Director of the Alcohol and Drug Treatment Program, San Diego VA, San Diego, CA



**Elizabeth Salisbury-Afshar**, MD, MPH, Associate Professor, University of Wisconsin-Madison, Madison, WI

### Decision-makers:

IL: **Kathleen Monahan**, IL State Opioid Response Project Director, IL DHS, Division of Substance Use Prevention and Recovery

CA: **Sheari Narayan**, Department of Health Care Services; **Chelsea Kelleher**, **Madison Royer**, Aurrera Health Group

PA: **Ellen DiDomenico**, Deputy Secretary, Department of Drug and Alcohol Programs, Pennsylvania; **David Kelley**, MD, MPA, Chief Medical Officer, Pennsylvania Department of Human Services' Office of Medical Assistance Programs, **Dale Adair**, MD, Medical Director, Office of Mental Health and Substance Abuse Services, Department of Human Services

Philadelphia: **Kendra Viner**, (formerly) Director, Division of Substance Use Prevention and Harm Reduction, Department of Public Health, City of Philadelphia

RI: **Linda Mahoney**, LCDS, CAADC, Administrator II, State Opioid Treatment Authority, Behavioral Health, Developmental Disabilities, and Hospitals

### Advocates:

**Alice Bell**, Director, Pittsburgh Prevention Point, Pittsburgh, PA

**Maya Doe-Simkins**, Co-Director, Remedy Alliance, OSNN Naloxone Buyers Club

**Ryan Hampton**, Director, The Voices Project, Las Vegas, NV

### Pharmacology

**Lucas G. Hill**, Pharm.D., BCACP, Director of Pharmacy Addictions Research & Medicine Program, University of Texas at Austin

### First Responders (Police & EMT)

**Claire Zagorski**, MS, paramedic; Program Director and Harm Reduction Instructor, PhARM Program, University of Texas at Austin

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