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More Is Not Always Better: Challenging Calls for High-Dose Naloxone

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The opioid antagonist, naloxone, is an especially important harm reduction tool in today's landscape. Naloxone binds to opioid receptors in the brain, preventing other opioids, such as fentanyl or heroin, from binding to and activating them.

Introduction

Overdose deaths have skyrocketed across the United States in recent years, increasing by 622 percent between 2000 and 2020, with more than 112,000 lives lost in 2023.[1] This crisis has been largely driven by the proliferation of potent synthetic opioids such as illicitly manufactured fentanyl, which is up to 50 times stronger than heroin.[2]

The opioid antagonist, naloxone, is an especially important harm reduction tool in this landscape. Naloxone binds to opioid receptors in the brain, preventing other opioids, such as fentanyl or heroin, from binding to and activating them.[3] The U.S. Food and Drug Administration (FDA) first approved the medication for the reversal of opioid overdoses in 1971.[4] When administered in a timely manner, naloxone can restore breathing within minutes and successfully reverse 75 to 100 percent of overdoses.[5]

Consequently, lawmakers and government agencies across the country have taken steps to improve access to naloxone. State legislatures have passed laws providing immunity to laypeople who administer the medication, authorized statewide standing orders to facilitate prescription-free pharmacy access, and purchased naloxone in bulk for direct distribution and to pass along to community-based organizations and first responders.[6] Last year, the FDA approved intranasal naloxone products for over-the-counter sale for the first time.[7]

The U.S. Food and Drug Administration (FDA) first approved naloxone for the reversal of opioid overdoses in 1971.

However, with novel, increasingly potent synthetic opioids dominating the illicit supply, some medical experts worry that naloxone as we know it is simply not good enough anymore.[8] In fact, in 2021, the FDA approved both higher-dose naloxone products and new, longer-lasting opioid antidotes, and some government agencies have begun purchasing these products for distribution in their communities.[9]

This policy study aims to inform legislators and public health decision-makers about how high-dose naloxone fits into federal, state, and local efforts to combat the opioid overdose crisis. We examine the research on naloxone efficacy—in laboratory and medical settings and in the real world—and assess potential drawbacks associated with alternatives to standard-dose naloxone.

Reversing Opioid Overdoses: Evaluating Standard Naloxone Doses in the Era of Fentanyl

Naloxone: Defining "Standard"

The FDA first approved naloxone as an antidote to opioid overdoses in 1971, during an era when heroin dominated the U.S. illicit opioid market. It was originally available in an injectable formulation intended for administration by medical professionals. However, by the 1990s, grassroots harm reduction organizations had begun distributing the medication—either with syringes for injection or with an adapter that allowed for intranasal administration—directly to people who use drugs as part of overdose education and prevention trainings.[10] It soon became apparent that lay bystanders were extremely adept overdose rescuers.[11]

Since then, a variety of products and policies have been developed to facilitate naloxone access for people who use drugs and the friends and family members who make up their social networks. In 2001, New Mexico passed the nation's first naloxone-access law authorizing trained responders to administer the medication.[12] States began removing prescription barriers to naloxone for lay bystanders in the late aughts, introducing standing orders; these efforts have surged since 2013 in response to fentanyl's proliferation in the market. As of late 2023, every state has some sort of legislation that reduces prescription barriers to naloxone, although the reach and strength of these laws varies considerably.[13] In 2015, the FDA approved the first intranasal naloxone product that was purpose-designed for lay responders. Last year, several intranasal naloxone products were granted federal approval for retail over-the-counter sale.[14]

Today, injection and nasal sprays remain the two primary ways to administer naloxone, and a range of branded and generic products are available through pharmacists and on drug store shelves. The standard dose recommendations for overdose reversal range from 0.4 mg injected to 4 mg delivered via nasal spray.[15] Many naloxone manufacturers and healthcare professionals recommend administering subsequent doses every two to three minutes until respiration rebounds, although some note that if a patient exhibits no response after delivery of 10 mg of naloxone, the overdose likely involves non-opioid depressant drugs.[16]

Fentanyl vs. Heroin

In the more than 50 years since naloxone's approval, the opioid supply has changed dramatically.[17] Potent synthetic opioids such as illicitly manufactured fentanyl drive the current overdose crisis—more than two-thirds of overdose deaths in 2023 involved these types of substances.[18] Thus, to understand and evaluate claims that the standard doses of naloxone may no longer be sufficient to reverse an opioid overdose, one must first understand the differences between heroin and fentanyl.

The risk of overdosing on fentanyl is estimated to be roughly twice that of heroin.[19] This is in large part because of fentanyl's considerably higher potency: The drug is approximately 50 times stronger than heroin, and 100 times stronger than morphine.[20] Furthermore, due to the lack of quality control and transparency, which characterize the illicit drug market, people may not know that their supply contains fentanyl, let alone how much.[21]

Naloxone Timeline

1971
The U.S. Food and Drug Administration (FDA) approves naloxone for the reversal of opioid overdoses

1990s
Grassroot harm reduction organizations begin distributing naloxone

2001
New Mexico passed the nation's first naloxone-access law authorizing trained responders to administer the medication

2015
FDA approved the first intranasal naloxone product that was purpose-designed for lay responders

2023
Every state has some sort of legislation that reduces prescription barriers to naloxone

In addition to increasing the risk of overdose, fentanyl consumption is associated with a higher likelihood that an overdose will result in death.[22] While high potency is certainly one contributor to this elevated risk, other characteristics of the drug play a role as well.[23] For example, compared to heroin, the onset of respiratory depression is faster with fentanyl, as is progression to cardiac arrest.[24] This accelerated timeline drastically narrows the window available for bystanders to administer an opioid antidote or call for emergency medical services.[25] Furthermore, fentanyl overdoses are sometimes accompanied by "wooden chest syndrome," a complication in which sufferers involuntarily hold their breath and tense muscles, resulting in a locked jaw, tight abdomen, and stiff arms and legs, further inhibiting breathing and hindering respiratory rebound.[26]

Beyond potency, another factor that people worry about with overdose is the potential for respiratory depression to return after the antidote—which works for 30 to 90 minutes—wears off.

Beyond potency, another factor that people worry about with overdose is the potential for respiratory depression to return after the antidote—which works for 30 to 90 minutes—wears off.[27] While fentanyl and heroin stay in the body for roughly the same amount of time, fentanyl's "duration of action" is estimated at 30 to 60 minutes when injected, compared to 4 to 6 hours for heroin.[28] Indeed, people who use fentanyl generally report that its desired effects wear off relatively quickly, leaving them in withdrawal much sooner than they would expect with heroin.[29] The need to use more frequently in turn contributes to an increased likelihood of engaging in risky behaviors like sharing injection equipment, and may also contribute to the drug's higher overdose potential.[30] However, fentanyl's shorter effect window may have one benefit: Animal studies suggest that its effects on respiration also wear off more quickly than heroin's, which could ultimately lead to better outcomes if appropriate opioid antidotes are delivered swiftly.[31] Nonetheless, given the variations in possible duration of action for both naloxone and individual opioids, as well as the fact that lack of transparency on the illicit market means that bystanders are unlikely to know the dose taken, overdose recurrence is possible. Therefore, experts recommend calling emergency medical services and monitoring individuals for at least two hours after administering naloxone.[32]

These differences lead some individuals to question whether naloxone is sufficient to successfully reverse fentanyl overdoses, especially in doses and administration protocols that were originally intended for the reversal of heroin overdoses. In the following sections, we review the extant research to assess whether standard naloxone doses are effective in the era of fentanyl.

Naloxone Dosing and Fentanyl: Findings from Laboratory and Real-World Studies

Fentanyl's potency and rapid binding to opioid receptors in the brain are at the core of questions about whether standard naloxone can outcompete the drug and successfully reverse overdoses.[33] Although research consistently shows that naloxone is effective at reversing fentanyl overdoses, some data from animal and laboratory studies have challenged standard dosing protocols. For example, in mice, higher doses of opioid agonists were found to require correspondingly higher doses of naloxone.[34] In addition, human studies in hospital settings revealed mixed outcomes when it comes to the relative efficacy of standard versus high-dose naloxone in preventing

or reducing overdose recurrence.[35] Similarly, real-world studies have found that medical professionals, first responders, and lay bystanders are administering higher baseline doses and more standard doses of naloxone now that fentanyl has spread throughout the illicit drug supply.[36]

These findings have been used to justify the development of higher-dose naloxone products, which have become available alongside standard-dose options in recent years (Table 1).

Table 1: Naloxone Product Breakdown

	Route of Administration	Dose and Recommended Administration
Standard Naloxone HCL	Nasal Spray	4 mg (follow-up dose may be delivered after 2-3 minutes if needed)
	Nasal Spray	3 mg (follow-up dose may be delivered after 2-3 minutes if needed)
	Injectable (intravenous, intramuscular, or subcutaneous)	0.4 mg to 2 mg (follow-up dose may be delivered after 2-3 minutes if needed)
High-Dose Naloxone HCL	Nasal spray	8 mg (follow-up dose may be delivered after 2-3 minutes if needed)
	Injectable (prefilled syringe for intramuscular injection)	5 mg (follow-up dose may be delivered after 2-3 minutes if needed)

Source: "Naloxone (Nasal Route)." https://www.mayoclinic.org/drugs-supplements/naloxone-nasal-route/proper-use/drg-20165181; "naloxone hydrochloride injection, USP-VIAL Dosage and Administration." https://www.pfizermedicalinformation.com/naloxone/dosage-admin; Chou et al. https://www.ncbi.nlm.nih.gov/books/NBK487479/table/methods.t1; "naloxone (Rx)." https://reference.medscape.com/drug/zimhi-naloxone-343741; "naloxone intranasal (Rx, OTC)." https://reference.medscape.com/drug/narcan-nasal-spray-kloxxado-naloxone-intranasal-1000057.

Despite research indicating that people administer more doses of naloxone in the fentanyl era, it is not clear that this practice is necessary or beneficial.

The real-world studies above examined changes in rescuer behavior but were not able to explore motivations for these behavior changes or compare overdose reversal outcomes. However, an examination of related research on the rising prevalence of fentanyl and the current landscape of the illicit drug market reveals the possible reasons that people may give more naloxone.

First, in the past decade, the omnipresence of fentanyl has become a serious cause for concern among people who use drugs. Research indicates that many people—including first responders, people who predominately use stimulants, and those who have been using opioids for a long time—fear fentanyl's potency and the associated increased risk of overdose.[37]

Furthermore, in the stressful environment associated with an overdose, individuals may forget the specifics of their overdose response training and, knowing naloxone is a safe medication, default to giving multiple doses, sometimes without waiting the recommended time between doses.[38] Delayed overdose response times—due to physical separation from the person, intoxication, or failure to recognize early symptoms of overdose, for example—may also lead people to give more doses of naloxone once they begin a rescue effort.[39]

Another important factor that could be leading people to administer multiple doses of naloxone is the rise in polysubstance use and associated overdoses.[40] In qualitative studies, overdose rescuers have sometimes attributed their decision to administer additional doses of naloxone to the fact that the victim appeared non-responsive.[41] Because naloxone is an opioid antagonist—not an all-cause overdose antidote—the presence of non-opioid sedatives such as benzodiazepines, alcohol, or xylazine would increase the likelihood of respiratory depression persisting even after naloxone administration.[42]

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Given the complexity of factors that affect both the overdose context and rescuers' decisions about naloxone administration, it is not clear that higher doses of naloxone are warranted, even in an environment saturated with fentanyl. Nonetheless, high-dose naloxone products have now entered the market. While harm reductionists have widely opposed the adoption of such products, their growing presence provides an opportunity to assess their impact in the real world.[43]

Assessing the Impact of High-Dose Naloxone

A study published in February of this year became the first real-world comparison of high-dose and standard-dose naloxone administration. Based on 354 New York State Patrol naloxone administration reports submitted between March 2022 and August 2023, the comparison revealed "no benefits to administration of 8-mg intranasal naloxone compared with 4-mg product."[44] Results are outlined in Table 2, below.

Table 2: Comparison of Administration of Standard and High-Dose Naloxone by New York State Patrol

	4 mg Intranasal Naloxone	8 mg Intranasal Naloxone
Number of Recipients (out of 354)	253	101
Average Number of Doses Administered Per Interaction	1.67	1.58
Average Total Amount of Naloxone Administered Per Interaction	6.7 mg	12.6 mg
Law Enforcement Officer Reported Post-Naloxone Combativeness	10.9 percent of interactions	7.9 percent of interactions
Survival Rate	99.2 percent	99.0 percent
Percent of Recipients Experiencing Opioid Withdrawal Signs and Symptoms	19.4	37.6

Source: Emily R. Payne et al. https://www.cdc.gov/mmwr/volumes/73/wr/mm7305a4.htm?s_cid=mm7305a4_w.

The fact that survival rates were comparable whether recipients were given standard- or high-dose naloxone aligns with prior emergency department research that found no relationship between fentanyl blood concentration and the dose of naloxone administered for successful reversal.[45]

The New York State study's findings regarding withdrawals are also important and align with concerns expressed by scholars and harm reductionists that higher doses of naloxone will lead to more, and potentially more severe, withdrawal symptoms. Indeed, recipients of the 8 mg dose of naloxone were 2.5 times more likely to experience precipitated withdrawal compared to those who received the 4 mg dose(s).[46] Precipitated withdrawals "whether caused by naloxone in the pre-hospital or emergency department setting or by naloxone or naltrexone during a medically supervised withdrawal treatment, can lead to hospital admission or even require intensive care."[47]

The experience of being put into withdrawal may undermine people's trust in the medical providers and harm reduction communities that seek to help them stay healthier and alive.[48] Furthermore, research shows that post-naloxone withdrawals increase the likelihood that people will take opioids again to treat their symptoms, thereby increasing their risk of subsequent overdose.[49]

Implications for Decision Makers

Our review of the current research challenges the notion that higher doses of naloxone are necessary or beneficial at this time, even in a fentanyl-dominated drug environment. Rather than focusing on high-dose naloxone products, lawmakers, public health agencies, and other decision makers should turn their attention to the following recommendations.

Policy Recommendation 1

- **Continue to improve access to a variety of standard-dose naloxone products:**

  While naloxone access has improved significantly in recent years, barriers still exist among those who are most likely to need it—people who use drugs.[50] In particular, many communities still lack syringe services programs (the primary distributors of naloxone); pharmacists and the public are not sufficiently knowledgeable about naloxone access laws; stigma persists at pharmacies; and the retail price of over-the-counter naloxone remains cost prohibitive for many.[51] Furthermore, potential overdose rescuers and recipients have varied preferences when it comes to which product they want, with some prioritizing the relative ease-of-use of intranasal products and others wanting the ability to titrate doses (to better prevent inducing withdrawals) with injectable formulations.[52]

Policy Recommendation 2

- **Provide potential rescuers with clear, accurate information about overdose identification and reversal:**

  Research suggests that overdose rescuers—including lay bystanders and law enforcement officers—do not always administer naloxone according to best practices.[53] The stress of an overdose coupled with uncertainties about what to expect after administering naloxone may increase the likelihood that responders will give more naloxone than necessary, exacerbating the risk of precipitated withdrawals. Furthermore, education about overdose and naloxone has been shown to improve access to the medication and willingness to administer it.[54]

- **Strengthen Good Samaritan laws to encourage follow-up care by emergency medical services and health care professionals:**

  The constant influx of novel adulterants in the illicit drug market, coupled with a rise in polysubstance use, means that opioid antagonists—regardless of dose—may not always be sufficient to fully reverse an overdose.[55] Therefore, it is more important than ever that people who use drugs, and people who act as overdose rescuers, feel safe to call emergency services for follow-up medical care. Broad Good Samaritan Laws, especially when paired with naloxone access and immunity laws, improve willingness to call 911 and have been shown to decrease overdose fatalities at the population level.[56]

Policy Recommendation 3

- **Ensure research and development efforts consider the priorities and concerns of people who use drugs:**

  People who use opioids are both the most likely individuals to administer naloxone and the most likely to be recipients of the medication.[57] As such, their needs should be prioritized to ensure novel products are as relevant as possible.

Policy Recommendation 4

Conclusion

The proliferation of potent synthetic opioids throughout the U.S. illicit drug market has led to concerns that standard-dose naloxone products are no longer adequate to prevent overdose deaths. Consequently, high-dose products have emerged on the market in recent years. In this study, we examined the existing research on the potential need for high-dose naloxone, and assessed the nascent research on the real-world impact of these new products. We conclude that high-dose naloxone is not currently warranted and is associated with considerable risks for people who use opioids. As such, we recommend that decisionmakers focus their attention on efforts that will improve the access and safe use of standard-dose naloxone; encourage people to engage emergency medical professionals; and support research efforts to better address the concerns of people directly affected.

We conclude that high-dose naloxone is not currently warranted and is associated with considerable risks for people who use opioids.

About the Author

Stacey McKenna is a resident senior fellow in Integrated Harm Reduction at the R Street Institute. In her research and writing, she focuses on the ways that policy affects drug use, related risks, and people who use drugs' right to protect their health.

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