



5-29-2019

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Weiner, Janet; Murphy, Sean M.; and Behrends, Czarina. Expanding Access to Naloxone: A Review of Distribution Strategies. LDI Issue Briefs. 2019; 23 (4). <https://ldi.upenn.edu/brief/expanding-access-naloxone-review-distribution-strategies>

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Abstract

Amidst an ongoing opioid crisis that claimed 47,600 lives in 2017, increasing the availability of the rescue medication naloxone is a high priority. Naloxone reverses an opioid overdose when given intranasally or intramuscularly. But to be effective, naloxone must be available at the time of overdose. Naloxone distribution to laypeople can save a life when first responders are not immediately available, or when people witnessing overdoses are unwilling or unable to call 911. Naloxone is increasingly available through some pharmacies under a standing order; however, even when available, cost and stigma barriers persist. This Issue Brief reviews recent evidence on the outcomes and cost-effectiveness of naloxone distribution strategies in community, pharmacy, and other health care settings.

Keywords

naloxone, opioid use disorder, opioid crisis

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Expanding Access to Naloxone: A Review of Distribution Strategies

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Amidst an ongoing opioid crisis that claimed 47,600 lives in 2017, increasing the availability of the rescue medication naloxone is a high priority. Naloxone reverses an opioid overdose when given intranasally or intramuscularly. But to be effective, naloxone must be available at the time of overdose.

The U.S. [Department of Health and Human Services](#) identifies naloxone distribution as one of the top three strategies for addressing the opioid epidemic. Last year, the U.S. [Surgeon General](#) called naloxone a “safe antidote” to a suspected overdose, and urged more individuals to carry naloxone, including family, friends, community members, and those who are personally at risk.

Naloxone distribution to laypeople can save a life when first responders are not immediately available, or when people witnessing overdoses are unwilling or unable to call 911. Naloxone is increasingly available through some pharmacies under a standing order; however, even when available, cost and stigma barriers persist. This Issue Brief reviews recent evidence on the outcomes and cost-effectiveness of naloxone distribution strategies in community, pharmacy, and other health care settings.

Naloxone use and availability

Naloxone is currently available in three forms: injection formulations, auto-injectors, and nasal sprays. Despite the surge in deaths related to opioid overdoses, the market for naloxone remains small. One [industry analyst](#) estimated the entire naloxone market has about \$290 million in annual sales. A recent [analysis](#) conducted for the Food and Drug Administration (FDA) estimated that national naloxone sales to all settings of care doubled from 2013 to 2017, with the majority being the injection formulation. About 83% of naloxone units were sold to non-retail settings of care, such as hospitals and clinics, health departments, and institutions that supply first responders, emergency medical services, and community groups. Seventeen percent of sales were to retail and mail-order/specialty pharmacies, up from 3% of total sales in 2013. The retail setting accounted for a small but growing proportion of total naloxone dispensing. The number of naloxone prescriptions filled at U.S. retail pharmacies more than doubled from 134,000 prescriptions in 2016 to 330,000 prescriptions in 2017. More than 70% of the naloxone prescriptions filled in retail pharmacies in 2017 were for the nasal spray Narcan[®], followed by 20% for the autoinjector Evzio[®]. This is not surprising given the differences in [list price](#) between the two products (about \$150 per two pack of Narcan[®] and over \$4,000 per two pack of Evzio[®].) Injection formulations are much less expensive, but retail sales are dominated by the branded products specifically designed for bystander use.

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OBSERVATIONAL STUDIES AND ECONOMIC MODELS SUGGEST THAT OVERDOSE EDUCATION AND NALOXONE DISTRIBUTION (OEND) PROGRAMS PREVENT DEATHS AND ARE COST-EFFECTIVE.

The potential need for naloxone is large, given that about 2.1 million people 12 and older in the U.S. have an opioid use disorder. Ultimately, the goal of naloxone distribution strategies is to make this life-saving medication available to people most likely to observe an opioid overdose, in time to reverse respiratory depression. These strategies must go beyond health care providers and health system settings, to reach people at risk, their social networks, and the communities in which they live.

Community-based and pharmacy naloxone distribution

Naloxone is available to laypeople through two basic channels: as part of overdose education and naloxone distribution (OEND) programs for those at risk of overdose (and people in their social networks), and through pharmacies. A wide variety of organizations participate in OEND efforts, such as syringe exchange programs, homeless shelters, emergency medical services, social service agencies, libraries, emergency departments, health care providers, and substance use disorder treatment programs. Little is known about how well different types of OEND programs reach individuals most likely to witness an overdose, as well as the cost of providing services. Depending on state law, some pharmacies distribute naloxone through a standing order or through direct pharmacist prescribing. Pharmacy availability, consumer acceptance, and out-of-pocket costs vary across jurisdictions. The FDA is considering converting individual naloxone products to over-the-counter (OTC) status.

Opioid Education and Naloxone Distribution (OEND) programs

[Observational studies and economic models](#) suggest that OEND programs prevent deaths and are cost-effective. [Walley, Xuan, Hackman, et al.](#) (2013) found that Massachusetts communities with an OEND had lower opioid overdose death rates than communities without an OEND. In that study, OEND programs trained 2,912 potential bystanders between 2006 and 2009, who reported 327 rescues. [Bird, McAuley, Perry, & Hunter](#) (2016) found that a national program in Scotland to distribute naloxone to people released from prison (a time of high risk for overdose) was associated with a 36% reduction in the proportion of opioid-related deaths that occurred in the four weeks following release from prison. In this pre-post study, the distribution of 12,000 naloxone kits was associated with 42 fewer prison-release overdose deaths during 2011-13. A followup commentary by [Bird and McAuley](#) (2019) noted that by 2016, the goal of distributing 9,000 rescue kits (20 times Scotland's average number of yearly opioid-related deaths) had been met, and such deaths in the four weeks after prison release had been halved since 2011.

Economic modelling studies find that OEND programs for people who use heroin are cost-effective, when using a standardized measure of the length of life adjusted for the quality of life (quality-adjusted life-years, or QALYs). [Coffin & Sullivan](#) (2013) estimated that 6% of overdose deaths among heroin users could be prevented with distribution, or one death for every 277 naloxone kits distributed. Naloxone distribution increased costs by \$53 and produced a gain of 0.12 QALYs, for an incremental cost-effectiveness ratio of \$438 per QALY gained. These results have been replicated in other studies of heroin users by [Uyei et al.](#) (2017) in the U.S., [Coffin & Sullivan](#) (2013) in Russia, and [Langham et al.](#) (2018) in the United Kingdom, with similar incremental cost-effectiveness ratios of \$323, \$94, and £899 (about \$1,144)/QALY, respectively. All are well within established parameters for cost-effective interventions.

In contrast, an [economic model](#) by [Cipriano & Zaric](#) (2018) found that a plan to equip all Toronto high schools with naloxone kits would not be cost-effective in many scenarios, if the frequency of overdose in a Toronto high school was low. This points out the importance of distributing naloxone in places and to people at a high level of risk.

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[Keane, Egan, & Hawk \(2018\)](#) used qualitative data and agent-based modeling to simulate the effects of different community distribution strategies to high-risk people. Over six months, a single community distribution site (i.e., pharmacy, urgent care center, or hospital), when giving up to 10 kits per visit to an individual, decreases overdose deaths by 8.3% relative to baseline. Adding in secondary distribution (where the individual distributes kits to their social network) decreases overdose deaths by 42.5%, more than the effect of increasing the number of sites tenfold without secondary distribution. Distributing naloxone to an individual at syringe exchange sites decreases deaths by about 65%, an effect that is unchanged by secondary distribution.

Pharmacy distribution

Pharmacies are another way to expand naloxone distribution to laypeople. Most states have passed laws that allow pharmacists to dispense naloxone under a standing order, which does not require a physician's prescription. [At least 23 states](#) have issued statewide standing orders by a physician-official, while 24 others allow jurisdictions to pass standing order laws. Nine states give pharmacists direct authority to prescribe and sell naloxone to the public. In a national evaluation of these laws between 2005 and 2016, [Abouk, Pacula, & Powell \(2019\)](#) found that states granting pharmacists direct authority saw a significant decrease in overdose deaths, an effect that grew stronger over time. Three years after the passage of such laws, overdose deaths fell by an average of 34%, and nonfatal emergency department visits increased by 15%. States allowing or issuing standing orders—what the investigators termed “indirect authority” for pharmacists—had little effect.

Other studies have assessed the relationship between state laws expanding naloxone access and opioid deaths, and reached different conclusions. Concerns have been raised that these laws encourage riskier behaviors around opioid use, because rescue is more likely. Potentially, this so-called risk compensation could offset or even swamp the reduction in deaths due to naloxone's wider use. Three prior studies have evaluated state laws as a package, and two found that the laws were associated with a reduction in opioid deaths in the range of 9% ([Rees et al., 2017](#)) to 14% ([McClellan et al., 2018](#)). However, a recent study by [Doleac & Mukherjee \(2019\)](#) found that state laws expanding naloxone distribution were associated with more opioid-related emergency department visits and more opioid-related theft, with no reduction in opioid-related deaths. The paper created controversy in the scientific community as well as in the lay press; while space does not permit a full examination of this issue, [Frank, Pollack, and Humphreys \(2018\)](#) capture the debate well.

Recent audit studies in individual states provide insight into how poor implementation might limit the effectiveness of state laws in reducing overdose deaths. [Puzantian & Gasper \(2018\)](#) conducted a “secret shopper” study of a random sample of all pharmacies in California, which has issued a statewide standing order. Just 23.5% of 1,147 pharmacies indicated that naloxone was available and could be dispensed without a prescription. Similarly, in a secret shopper study by [Graves et al. \(2018\)](#) in Pennsylvania, which also has a statewide standing order, 45% of 682 pharmacies said that naloxone was available. Less than two-thirds of pharmacy staff members correctly answered questions about the standing order, and quotes of out-of-pocket costs ranged from \$50 to \$4,000. A *New York Times* [investigation](#) revealed that of the 720 pharmacies on New York City's list of pharmacies that sell naloxone under the state's standing order, only 38% had it in stock and were willing to dispense it without a prescription. These studies and articles suggest that a standing order, in itself, is not enough to overcome supply, knowledge, and cost barriers to expanded naloxone availability in pharmacies.

AN ECONOMIC MODEL
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Over-the-counter (OTC) naloxone

Given that naloxone is non-addictive and safe to use, advocates and policymakers have called for it to be sold over the counter. Earlier this year, the [FDA](#) took the unprecedented step of developing and validating model Drug Facts Labels for naloxone as a nasal spray and an autoinjector to encourage companies to enter the OTC market. The model labels can be used by sponsors to obtain OTC approval for naloxone.

What might happen to sales and prices if naloxone became available over the counter? In a recent study, [Murphy and other CHERISH investigators](#) (2019) modeled supply and demand factors to predict the effects of converting naloxone to OTC status.

First, they used a nationwide prescription claims dataset for 2010-2017 (covering 80% of retail pharmacies and including out-of-pocket prices) to estimate how sensitive naloxone buyers are to price. They found that buyers of naloxone are not very price-sensitive: on average, a 10% increase in out-of-pocket price would produce a 2.7% decrease in sales. Then they looked to the literature to find estimates on the price and demand effects of conversion to OTC status for other drugs. In particular, they focused on nicotine replacement therapies as the only other substance use disorder medication that had converted from prescription to OTC status. The authors used these estimates in their models to predict the change in naloxone sales, given the relative price insensitivity of naloxone buyers. If, for example, naloxone out-of-pocket prices increase after conversion at the estimated level of nicotine patches (26%) or nicotine gum (33%), the authors predict a 71% to 171% increase in naloxone sales.

All else being equal, greater sales of naloxone should increase the opportunities to reverse opioid overdoses. But the public health impact of increased sales will depend on how the purchasers of OTC naloxone differ from current purchasers in their likelihood of observing an overdose and using the product.

Health system distribution: co-prescribing

Another strategy to improve naloxone distribution is to co-prescribe naloxone to patients with opioid prescriptions who are at risk for opioid use disorder. [The Centers for Disease Control and Prevention](#), the [Substance Abuse and Mental Health Services Administration](#), and the [American Medical Association](#) all recommend that physicians consider co-prescribing naloxone and opioids for patients at high risk, such as those with a history of overdose, history of substance use disorder, higher opioid dosages, or concurrent benzodiazepine use. Earlier this year, an FDA advisory council recommended labeling changes to encourage co-prescribing. A systematic review by [Behar, Bagnulo, & Coffin](#) (2018) found a growing willingness to prescribe naloxone among primary care providers, although co-prescribing remains relatively infrequent, especially in the absence of a formal program.

In a recent study of nearly 140,000 commercially insured patients at high risk of opioid overdose, [Follman, Arora, Lyttle, et al.](#) (2019) found that only 1.5% of high-risk patients, including individuals with prior opioid overdose or opioid misuse or dependence, were prescribed naloxone, despite numerous interactions with the health care system.

There is little information on the effectiveness and cost-effectiveness of co-prescribing. In an observational study in community health centers, [Coffin et al.](#) (2016) found that co-prescribing naloxone to chronic pain patients was associated with fewer opioid-related emergency department visits, but did not assess opioid overdose deaths. While improving distribution in clinical settings to high-risk patient populations is recommended, further studies are needed to understand how to identify the populations who would benefit the

WHILE NALOXONE ALONE CANNOT ADDRESS THE MAGNITUDE OF THE OPIOID CRISIS, IT IS ONE PART OF A MULTIPRONGED STRATEGY TO PREVENT IMMEDIATE DEATHS AND LINK PEOPLE WITH OPIOID USE DISORDERS TO EFFECTIVE TREATMENTS.

most in these settings and the economic impact to the health care system of using these strategies.

Distribution to non-medical first responders

Communities are increasingly training and equipping police and firefighters with naloxone. Police, rather than paramedics, are often the first to respond to overdose emergencies, particularly in more rural areas. Nationwide, nearly 2,500 law enforcement agencies [report](#) that their officers carry naloxone, although comprehensive data on the number of rescues by police first responders do not exist, and the effectiveness of these programs is unknown. [Rando et al.](#) (2015) studied opioid overdose deaths before and after a police naloxone training program in one Ohio county and found that the program was associated with a decrease in opioid overdose mortality in the year after implementation.

Conclusion

As opioid deaths continue to mount, there is a clear need for strategies that maximize the likelihood that naloxone will be on hand at the right time to reverse an overdose. The cost-effectiveness of all strategies will depend on reaching high-risk people and their social networks, and reducing access and cost barriers to use. Agent-based modeling suggests that optimal distribution involves targeting the highest-risk people (for example, in syringe-exchange programs) and encouraging secondary distribution among social networks in other settings.

This review reveals that OEND programs on a national and local basis are effective and cost-effective in reducing opioid overdose deaths in people who use heroin and other opioids; that giving direct authority to pharmacists to dispense naloxone is more effective than “standing orders” (although the latter has been adopted by far more states); and that the effectiveness of co-prescribing remains uncertain.

Eliminating the need for a prescription holds some promise, and the FDA has actively encouraged naloxone manufacturers to apply for OTC status. An economic model predicts that naloxone sales could double if sold over the counter, although the ultimate public health impact depends on whether these new buyers are likely to observe an overdose.

Further research is needed to understand the economic impact of the wide variety of OEND programs, and whether widespread distribution of naloxone to laypeople is cost-effective. While naloxone alone cannot address the magnitude of the opioid crisis, it is one part of a multipronged strategy to prevent immediate deaths and link people with opioid use disorders to effective treatments.

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This Issue Brief is supported by Center for Health Economics of Treatment Interventions for Substance Use Disorder, HCV, and HIV (CHERISH), a National Institute on Drug Abuse-funded Center of Excellence (P30DA040500).

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About CHERISH: The Center for Health Economics of Treatment Interventions for Substance Use Disorders, HCV, and HIV (CHERISH) is a multi-institutional Center of Excellence, funded by the National Institute on Drug Abuse. The Center's mission is to develop and disseminate health economic research on health care utilization, health outcomes, and health-related behaviors that informs substance use disorder treatment policy and HCV and HIV care of people who use substances. The Center is a collaboration among Weill Cornell Medicine, Boston Medical Center, the University of Pennsylvania, and the University of Miami Miller School of Medicine. For additional information on CHERISH, contact Jared Leff (email: jal2033@med.cornell.edu).
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