

JAMA Insights

Intranasal Naloxone for Opioid Overdose

Jessica L. Taylor, MD; Karen E. Lasser, MD, MPH

In 2021, opioid overdose deaths exceeded 80 000 in the US.¹ Naloxone, a competitive opioid receptor antagonist that reverses symptoms of opioid intoxication and overdose by displacing opioids from μ -opioid receptors, is a safe and effective medication for preventing opioid overdose death. Naloxone meets US Food



CME at jamacmelookup.com

and Drug Administration (FDA) criteria for approval without a prescription: its benefits outweigh risks, it treats a condition that can be identified by people in the community, it has a low potential for misuse, and it can be labeled to facilitate correct administration.

In 2015, the FDA approved a 4-mg/0.1 mL intranasal naloxone formulation available by prescription. In March 2023, the FDA approved 4-mg/0.1 mL intranasal naloxone for availability without prescription. In July 2023, a generic form of naloxone 4-mg/0.1 mL nasal spray and a 3-mg/0.1 mL naloxone formulation became available without prescription.

Indications for Naloxone Administration

Naloxone is recommended for people with signs and symptoms of opioid overdose, such as sedation or coma, nonresponsiveness, respiratory depression, abnormal respirations (eg, gurgling or snoring), cool or clammy skin, miosis, and cyanosis. Naloxone, often packaged as 2 doses, is typically administered as a single initial 4-mg/0.1 mL intranasal dose and has a half-life of approximately 2 hours. For correct administration, the nozzle must be fully inserted inside the nostril rather than adjacent to it. Individuals administering naloxone should also call 911 and if appropriate, administer artificial ventilation or chest compressions. If spontaneous breathing is not restored 3 minutes after initial naloxone administration, an additional dose should be administered.

Naloxone for Opioid Overdose

Intranasal naloxone at currently recommended doses has not been studied in randomized clinical trials because withholding overdose treatment is unethical. A recent randomized clinical trial reported that 800 μ g of naloxone was less effective for opioid overdose reversal when administered intranasally, compared with intramuscular administration.² Participants randomized to receive intramuscular naloxone ($n = 96$) were less likely to require a second dose of naloxone after initial treatment, consisting of intramuscular naloxone hydrochloride (800 μ g) 10 minutes after the initial treatment, compared with those randomized to receive intranasal naloxone ($n = 104$) (8 [8.6%] with intramuscular administration required a second dose after initial treatment vs 24 [23.1%] with intranasal administration; odds ratio, 0.35 [95% CI, 0.15-0.66]; $P = .002$). Intranasal naloxone at 4-mg/0.1 mL and 3-mg/0.1 mL doses achieves clinically effective bioavailability.

Observational and quasiexperimental studies demonstrated that education about opioid overdose and naloxone distribution was associated with lower rates of opioid overdose fatality.³ In

a meta-analysis of 4 epidemiologic studies that included 66 overdose events, bystander naloxone administration was associated with increased odds of recovery from overdose (odds ratio, 8.58 [95% CI, 3.90-13.25]; absolute rates not available) compared with no naloxone administration.⁴

In Massachusetts, 2912 people in the community, including people who used opioids, their family and friends, and social service agency staff, received education in opioid overdose and naloxone distribution. Compared with communities that did not receive this training, communities that trained 1 to 100 people per 100 000 population and those that trained more than 100 people per 100 000 population had significant reductions in opioid overdose death rates, adjusting for demographics, addiction treatment engagement, and high-risk opioid prescriptions (adjusted rate ratio for 1-100 people/100 000, 0.73 [95% CI, 0.57-0.91]; and adjusted rate ratio for >100 people/100 000, 0.54 [95% CI, 0.39-0.76]; absolute rates not available).⁵

A nonrandomized study of 1985 adults receiving long-term opioid therapy reported that patients who received a naloxone prescription had fewer opioid-related emergency department (ED) visits per month during the following year (incident rate ratio, 0.37 [95% CI, 0.22-0.64]; $P < .001$) compared with patients who did not receive naloxone.⁶ Patients had a mean of 6% fewer opioid-related ED visits with each additional month since receiving a naloxone prescription.

Safety

Among people without recent opioid exposure, naloxone does not have adverse effects. In patients with opioid overdose, naloxone has minimal risk, and it may prevent fatalities from opioid overdose. The potential risks of naloxone administration are rarely life-threatening and include opioid withdrawal symptoms such as nausea, vomiting, agitation, tachycardia, and hypertension. More serious complications, including cardiac events in the setting of catecholamine surge due to opioid withdrawal and pulmonary edema, are rare and have been reported in case series; prevalence data are not available.⁷ Naloxone-induced pulmonary edema can be difficult to distinguish from opioid-induced pulmonary edema.⁸ Adverse effects are mitigated by administering the minimum dose necessary to restore breathing and calling 911 for transport to emergency care.

Preventing Opioid Overdose

Individuals at risk for opioid overdose, as well as their friends and family, should carry naloxone. People at risk include those with opioid use disorder or a history of prior opioid overdose; people using other substances, including stimulants such as methamphetamine or cocaine and nonprescribed benzodiazepines, which may be contaminated with opioids; and people using nonprescribed opioids, prescribed opioids and central nervous system depressants (eg, benzodiazepines) concurrently, or prescribed opioids for chronic pain.

Among those taking opioids for chronic pain, the Centers for Disease Control and Prevention recommends a naloxone prescription when daily morphine milligram equivalents meet or exceed 50 mg, when opioids are coprescribed with benzodiazepines, and when patients have other overdose risk factors such as sleep-disordered breathing, prior opioid overdose, or recent loss of opioid tolerance. Many health systems have implemented naloxone coprescribing.⁹

Children in environments where opioid access is unsecured are also at increased risk for accidental exposure and may safely receive adult naloxone doses. Although symptoms of opioid overdose, including sedation and respiratory depression, can develop over minutes, precluding naloxone self-administration, carrying naloxone helps make it available for bystander administration. People at risk for opioid overdose may administer naloxone if they witness overdose in others.

The prevalence of opioid use disorder in the US was estimated to be between 2.04% and 2.77% in 2019.¹⁰ First responders, such as law enforcement officers, firefighters, and emergency medical services personnel, as well as those working in locations with public bathrooms (eg, public libraries, health care settings) or in other places where drug use is common, should consider having naloxone available.

Availability of Naloxone Without a Prescription

Availability of naloxone without a prescription may reduce stigma and communicate that naloxone is safe and effective. Naloxone without prescription may be available in pharmacies, gas stations, grocery stores, other businesses, or via online sale. This accessibility may be particularly important for people residing in rural parts of the US.

Barriers to Naloxone Use

The cost of intranasal naloxone without prescription, approximately \$45, is expected to remain a barrier to use. The approval of

a generic product and a 3-mg/0.1 mL dose may reduce cost over time. However, if insurance companies reduce coverage of prescribed naloxone, costs for individual patients could increase.

The effect of naloxone availability without prescription is projected to increase the quantity of naloxone sold at pharmacies. This increase raises the possibility of naloxone drug shortages, which could affect community programs involved in direct naloxone distribution to individuals at highest risk.

Naloxone in Patients With Fentanyl Overdose

The optimal dose of intranasal naloxone for patients with fentanyl overdose remains uncertain. There have been reports of fentanyl overdose events requiring more than the 2 naloxone doses contained in a standard kit. However, identifying the optimal dose of naloxone is complicated by rising rates of polysubstance overdose, as naloxone does not reverse sedation or respiratory depression due to non-opioid substances such as xylazine or benzodiazepines. Because of the possibility of nonopioid respiratory depression, in addition to administering naloxone in patients with suspected fentanyl overdose, responders should activate emergency services and provide ventilation or chest compressions consistent with their level of training.

There are potential harms associated with administering more naloxone than necessary to restore breathing, including severe precipitated opioid withdrawal and patient refusal of acute care after opioid overdose reversal. An 8-mg intranasal naloxone formulation is available by prescription, but there are insufficient data to support use without prescription.

Conclusions

Intranasal naloxone is safe and effective for reversing opioid overdose and is now available without prescription. Physicians and other licensed clinicians should prescribe naloxone to those who may benefit.

ARTICLE INFORMATION

Author Affiliations: Grayken Center for Addiction, Boston Medical Center, Boston, Massachusetts (Taylor); Section of General Internal Medicine, Department of Medicine, Boston University Chobanian and Avedisian School of Medicine and Boston Medical Center, Boston, Massachusetts (Taylor, Lasser); Senior Editor, *JAMA* (Lasser).

Corresponding Author: Karen E. Lasser, MD, MPH, Section of General Internal Medicine, Boston Medical Center, 801 Massachusetts Ave, Second Floor, Boston, MA 02118 (karen.lasser@bmc.org).

Published Online: December 21, 2023.
doi:10.1001/jama.2023.23248

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by the National Institutes of Health (NIH) and the Substance Abuse and Mental Health Services Administration (SAMHSA) through the NIH HEAL (Helping to End Addiction Long-Term) Initiative under award UM1DA049412.

Role of the Funder/Sponsor: NIH and SAMHSA had no role in the preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent

the official views of the NIH, SAMHSA, or the NIH HEAL Initiative. Dr Lasser is a Senior Editor of *JAMA* but was not involved in any of the decisions regarding review of the manuscript or its acceptance.

REFERENCES

1. National Institute on Drug Abuse. Drug overdose death rates. Published February 9, 2023. Accessed June 13, 2023. <https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates>
2. Dietze P, Jauncey M, Salmon A, et al. Effect of intranasal vs intramuscular naloxone on opioid overdose: a randomized clinical trial. *JAMA Netw Open*. 2019;2(11):e1914977. doi:10.1001/jamanetworkopen.2019.14977
3. Razaghizad A, Windle SB, Filion KB, et al. The effect of overdose education and naloxone distribution: an umbrella review of systematic reviews. *Am J Public Health*. 2021;111(8):1516-1517. doi:10.2105/AJPH.2021.306306a
4. Giglio RE, Li G, DiMaggio CJ. Effectiveness of bystander naloxone administration and overdose education programs: a meta-analysis. *Inj Epidemiol*. 2015;2(1):10. doi:10.1186/s40621-015-0041-8
5. Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ*. 2013;346:f174. doi:10.1136/bmj.f174
6. Coffin PO, Behar E, Rowe C, et al. Nonrandomized intervention study of naloxone coprescription for primary care patients receiving long-term opioid therapy for pain. *Ann Intern Med*. 2016;165(4):245-252. doi:10.7326/M15-2771
7. Kummer RL, Kempainen RR, Olives TD, Leatherman JW, Prekker ME. Naloxone-associated pulmonary edema following recreational opioid overdose. *Am J Emerg Med*. 2022;53:41-43. doi:10.1016/j.ajem.2021.12.030
8. Rzasz Lynn R, Galinkin JL. Naloxone dosage for opioid reversal: current evidence and clinical implications. *Ther Adv Drug Saf*. 2018;9(1):63-88. doi:10.1177/2042098617744161
9. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC clinical practice guideline for prescribing opioids for pain—United States, 2022. *MMWR Recomm Rep*. 2022;71(3):1-95. doi:10.15585/mmwr.rr7103a1
10. Keyes KM, Rutherford C, Hamilton A, et al. What is the prevalence of and trend in opioid use disorder in the United States from 2010 to 2019? using multiplier approaches to estimate prevalence for an unknown population size. *Drug Alcohol Depend Rep*. 2022;3:100052. doi:10.1016/j.dadr.2022.100052