

## CONCEPTS

# MASS OPIOID EXPOSURE: ENHANCING MEDICAL COUNTERMEASURE PREPAREDNESS

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## ABSTRACT

The feasibility of using opioids to intentionally cause mass casualties has been demonstrated to horrific effect in the past 25 years, and the current wide availability of high-potency synthetic opioids in the United States raises the risk of their use as a weapon of mass effect on the civilian population. These facts highlight the pressing need to prepare for future events with easily and quickly administered, fast onset, durable medical countermeasures. The recently FDA-approved intranasal nalmeferene was developed to those requirements. Intranasal nalmeferene can increase availability, access, and treatment capacity for emergency response to a mass exposure to synthetic opioids and expand first responders' ability to treat certain opioid overdose patients. Emergency responders and local supplies of naloxone and nalmeferene serve as the first line of defense against a mass opioids incident, with government stock of nasal nalmeferene spray available for resupply to prevent depletion of opioid receptor antagonist products in the community.

## INTRODUCTION

The proliferation of opioids, both illicit and prescribed, has led those who plan for chemical disasters, disaster medicine, and mass casualty incidents to worry about mass dispersal of opioids in a closed environment as well as other potential mass exposure routes (Morrell, 2017). Methods to reverse the incapacitating effects of highly potent synthetic opioid exposure quickly and effectively are essential. The evolution of synthetic classes of opioids that are highly potent and capable of causing life-threatening respiratory depression necessitates opioid receptor antagonists that simultaneously are potent enough to reverse the effects of synthetic opioids with a rapid onset of action and last long enough to protect patients from "renarcotizing" into unconsciousness with inadequate breathing. Importantly, for a mass casualty incident, they must also be administered easily without the use of needles (Gold et al., 2025).

The mass release of a highly potent synthetic opioid (fentanyl, alfentanil, carfentanil, or other derivatives) was carried out in-

tentionally in Moscow in 2002 to aid Russian authorities in ending a hostage siege at the Dubrovka Theater (Riches et al., 2012). The event unfolded when 40 Chechen separatists took more than 900 theater-goers hostage, demanding that Russian authorities withdraw troops from Chechnya. After four days, the Russian authorities pumped an “aerosolized anesthetic” into the theater to put everyone to sleep. While the siege did end, the cost was horrific. The aerosolized drugs were all too effective, severely intoxicating everyone in the theater with the exception of a few terrorists who donned gas masks. At least 132 hostages died from exposure to the aerosolized synthetic opioids pumped into the building (BBC News, 2002). There were reports that ambulance personnel attempted to use naloxone to revive some patients but did not have enough—despite authorities later insisting that emergency personnel had 1,000 doses (Chemical and Biological Weapons Nonproliferation Program, 2002). What is unclear is how many patients received even a single dose of naloxone, much less multiple doses.

This event was the first known use of an aerosolized synthetic opioid release with the intent to sedate many people simultaneously. Multiple-victim opioid overdose incidents involving fentanyl are increasingly being reported (Desai, 2024; KOAA NEWS5, 2025; Moreno-Paz & Nguyen, 2024). In the U.S., counterfeit prescription pills contaminated with opioids have threatened public health and emergency systems, exemplified by the 2016 Norco counterfeit drug exposure in California and, more recently, by the 75 overdoses and 9 fatalities during a 2024 opioid overdose outbreak in Austin, Texas (Moreno-Paz & Nguyen, 2024; Vo, 2016). Counterfeit pills are no longer confined to tainted drugs purchased on the “street” or to illicit drug users. Deaths of children and adolescents from illicit fentanyl have increased (Tanz et al., 2022). The Centers for Disease Control and Prevention (CDC) issued a statement in October 2024 warning of the potential public health risk of counterfeit prescription medications sold by illegal online pharmacies (CDC, 2024; U.S. Attorney's Office [USAO], 2024). As synthetic opioids have become more common, the use of aerosolized or fine particulate formulations—either as a weapon of mass effect or as a potential additive to counterfeit pills and aerosolized drugs of abuse—is also becoming more likely. Public health and emergency response authorities need the ability to deploy an overdose rescue treatment capable of rapidly and lastingly reversing the respiratory effects of synthetic opioids. The rising risk of intentional use of opioids to cause harm has not gone unnoticed by federal government planners and medical countermeasure experts. Use of more powerful fentanyl analogs and emergence of other classes of synthetic opioids, including nitazenes, means that as naloxone becomes less effective, renarcotization will continue to become more common (Laffont et al., 2024).

## CONCEPT DESCRIPTION

In an effort to address the first surge of fentanyl overdose and to prepare for a mass opioid overdose scenario, the Biomedical Advanced Research and Development Authority (BARDA) within the Administration for Strategic Preparedness and Response, along with the National Institute on Drug Abuse (NIDA) at the National Institutes of Health, both part of the U.S. Department of Health and Human Services, undertook pharmaceutical development of a repurposed, long-lasting opioid receptor antagonist in a new form amenable to rapid administration to many patients. The goal was to develop a rapid-onset opioid receptor antagonist that is easily administered via a nasal spray device with fast onset and long lasting enough to reduce the capacity requirements needed to frequently reevaluate patients for renarcotization and readminister treatment during a

mass exposure response. A mass casualty incident in this context is considered an emergency event in which patient count exceeds local resources and capabilities in a short time, overwhelming the local emergency response and/or hospital healthcare system.

Currently, the predominant opioid receptor antagonist used for reversing opioid overdose is naloxone. In the management of individual patients, naloxone is effective, but due to the shorter half-life of its effect, requires continued vigilance of the patient's respiratory status to ensure that re-narcotization does not occur, especially in the presence of synthetic opioid overdoses.

To address the growing concern of synthetic opioids and their potential weaponization, BARDA and NIDA, with the U.S. Food and Drug Administration's (FDA) guidance and fast track designation, supported the development of a previously approved pharmaceutical product that met the requirement for a long-lasting and potent opioid receptor antagonist—nalmefene—but in an efficacious intranasal formulation. A durable opioid receptor antagonist in a familiar nasal spray device was developed to support effective deployment and use in the out-of-hospital environment by first responders. New clinical data from pharmacokinetic studies supported by BARDA and NIDA demonstrated the long half-life of the intranasal form of nalmefene (Crystal et al., 2024; Opiant Pharmaceuticals, 2023). In May of 2023, the FDA approved nalmefene nasal spray in a single-use intranasal administration device for the known or suspected treatment of opioid exposure, including synthetic opioids, such as fentanyl, with a half-life of about 11 hours that provides sustained reversal effects (FDA, 2023; Opiant Pharmaceuticals, 2023). In addition, BARDA funded a pharmacodynamic clinical Phase 2 study required by the FDA that showed the effectiveness of intranasal nalmefene in reversing remifentanyl-induced respiratory depression longer than naloxone in healthy, non-dependent but opioid experienced volunteers (Ellison et al, 2024; Opiant Pharmaceuticals, 2023).

The challenge that first responders will face in a mass opioid exposure incident will be two-fold: availability of opioid receptor antagonists in quantities sufficient to reverse the respiratory depression effects on multiple victims, and the need for responders to continually re-evaluate patients for re-narcotization, readministration of treatment, and/or additional resuscitative measures for respiratory failure, such as positive pressure ventilation. This two-fold challenge could be alleviated, in part, by using a potent, long-lasting reversal agent like nasal-administered nalmefene, giving this type of treatment an important place in mass opioid overdose preparations. It is well understood that to enable improved preparedness, medical countermeasures must be readily available and preferably in use day-to-day and "flexed" to support mass care operations. This principle is why nalmefene, particularly the easily administered intranasal form, can be a "force multiplier" in prehospital emergency mass care operations.

## DISCUSSION

In patients who have opioid use disorder histories and are susceptible to precipitated withdrawal, naloxone may remain the better treatment (Stolbach et al., 2023). Both naloxone and nalmefene should be available so that the first responder can use the product best suited for the emergency situation. In patients who are naïve to opioids or are occasional users, current evidence indicates that nalmefene can be a better treatment as its long-lasting effect will decrease the likelihood of re-narcotization (Laffont, 2024). The

half-life of intranasal nalmeferene, which was determined to be approximately 11 hours in clinic research, is longer than that of naloxone, and this more sustained time in the body to maintain opioid reversal effects decreases the likelihood of readministration to treat fentanyl overdose (Crystal et al., 2024; Opiant Pharmaceuticals, 2023). This may prove critical for patient transport, particularly over longer distances, and during mass care efforts. Clinical results from the pharmacodynamic study on reversal of remifentanyl-induced respiratory depression showed that intranasal nalmeferene (2.7 mg) had a faster onset of action compared to intranasal naloxone (4 mg) widely used by first responders. Additionally, nalmeferene, particularly in the nasal spray form, will provide additional capacity for mass opioid exposure incidents thereby expanding the operational capability of the responders and improving the survivability of patients. Timing of emergency treatment is critical for any opioid overdose scenario, but in a mass opioid exposure incident, the availability of a large number of treatment doses is also crucial.

Stockpiled opioid overdose treatments may take too much time to distribute into the field, so the standard availability and use of naloxone by first responders for daily operations coupled with commercially available nalmeferene nasal spray represent the first line of emergency response in a mass casualty opioids incident. The uptake of nasal nalmeferene spray in the commercial market ensures the availability and additional capacity of an additional countermeasure for daily and mass care use in patients 12 years and older. However, the adoption of nasal nalmeferene spray since its commercial launch has been hampered by barriers including higher cost per unit dose than naloxone, initial shelf life, required approvals for adding to medication lists and pharmacy formularies, and, likely, lack of established guidelines and patient protocols. There are anecdotal concerns raised by certain harm reduction and emergency medicine communities that nalmeferene may precipitate an untoward reaction of withdrawal in the opiate dependent patient (Stolbach et al., 2023). This concern has also influenced the adoption of nalmeferene. However, in a mass exposure event, the vast majority of victims will likely be opioid naïve, and nalmeferene poses no risk of withdrawal and provides a substantial reduction in risk of “renarcotization”. Unlike for nasal nalmeferene spray, prehospital protocols exist for naloxone, the current standard of care in the prehospital environment, and two formulations of intranasal naloxone can now be purchased over-the-counter by individuals. Because nasal nalmeferene spray is an additional medical countermeasure with important use cases that augments, but does not replace naloxone, it is critical to increase awareness and include the new drug in prehospital training and education as well as into field protocols.

Nasal nalmeferene spray is currently being stocked in the U.S. government inventory under vendor management and can be deployed to supplement and resupply local emergency opioid overdose antidote stocks preventing depletion of local and neighboring emergency caches (BARDA, 2024). Unlike nerve agent antidotes, nasal nalmeferene spray has potential everyday life-saving use in the local community (along with naloxone) as well as for responses to mass exposure incidents. Deployment strategies for each EMS system must be based upon their operational environments, including prevalence of risk, available resources (i.e., number of response units), first responder utilization of opioid medical countermeasures (i.e., quantity of nasal opioid antagonist available outside of EMS units), and financial impact of stocking a new medication. By evaluating these and other operational variables, EMS systems and their medical directors can determine their needs for a longer acting opioid antagonist such as nalmeferene. Implementing a standard

operating procedure (SOP) for utilization of a longer acting opioid receptor antagonist might include the determination of patient opioid dependency at the individual patient and/or community setting (e.g., severe opioid use disorder in unhoused populations versus poisonings from adulterated pills in a school/university environment). Having this determination process embedded in a SOP will benefit the patients and enable the availability of a long acting opioid antagonist for the multiple patient scenario.

Future real world clinical studies comparing nasal nalmeferene spray and naloxone in the field are needed to provide data for developing or enhancing SOPs for nalmeferene use in the prehospital setting. Although FDA-required clinical studies in the laboratory setting demonstrated the non-inferiority of nalmeferene with superior pharmacokinetic and pharmacodynamic readouts, as well as durability of opioid reversal, real world assessment in a variety of environments and types of opioids is critical (Ellison et al, 2024; Opiant Pharmaceuticals, 2023). In addition, a pediatric study for intranasal nalmeferene use in patients under 12 years old is planned. Nalmeferene nasal spray was initially developed to address a critical treatment gap for fentanyl overdose when it emerged as the predominant opioid in the public health crisis. Since its approval, the shelf-life of nasal nalmeferene spray has been extended to 4 years, equivalent to nasal naloxone spray. As nasal nalmeferene spray is a new opioid reversal product that can augment naloxone in certain opioid overdose emergencies, it is critical to increase awareness through paramedicine training and education for community use and emergency planning as well as additional field research. With the emergence of the more potent and longer acting fentanyl analog, carfentanil, and an entirely different class of even stronger synthetic opioids, nitazenes, the need for nalmeferene for first responder use has become clear.

## REFERENCES

- BBC News. (2002, October 27). Gas “killed Moscow hostages.” *BBC News World Edition*. <http://news.bbc.co.uk/2/hi/europe/2365383.stm>
- Biomedical Advanced Research and Development Authority [BARDA]. (2024, August 26). BARDA procures emergency opioid overdose treatment OPVEE nasal nalmeferene spray from Indivior Inc. under Project BioShield contract. *U.S. Department of Health & Human Services, Administration for Strategic Preparedness and Response*. <https://www.medicalcountermeasures.gov/newsroom/2024>
- Centers for Disease Control and Prevention [CDC]. (2024, October 2). *Potential public health risk among individuals ordering counterfeit prescription medications from online pharmacies*. <https://www.cdc.gov/media/releases/2024/s1002-counterfeit-prescription-online-pharmacies.html>
- Chemical and Biological Weapons Nonproliferation Program. (2002, November 4). The Moscow theater hostage crisis: Incapacitants and chemical warfare. *Middlebury Institute of International Studies at Monterey, James Martin Center for Nonproliferation Studies*. <https://nonproliferation.org/the-moscow-theater-hostage-crisis-incapacitants-and-chemical-warfare>
- Crystal, R., Ellison, M., Purdon, C., & Skolnick, P. (2023). Pharmacokinetic properties of an FDA-approved intranasal nalmeferene formulation for the treatment of opioid overdose. *Clinical Pharmacology in Drug Development*, 13(1). <https://doi.org/10.1002/cpdd.1312>

- Desai, I. (2024, February 12). 3 men, 1 woman found dead at South Lake Tahoe home are identified. Authorities suspect fentanyl. *Sacramento Bee*. <https://www.sacbee.com/news/local/article285399977.html>
- Ellison, M., Hutton, E., Webster, L., & Skolnick, P. (2024). Reversal of opioid induced respiratory depression in healthy volunteers: comparison of intranasal nalmefene and intranasal naloxone. *Journal of Clinical Pharmacology*, 64(7). <https://doi.org/10.1002/jcph.2421>
- Gold, M.S., Milas, B., Cutchins, C., Walsh, S.L., Piotrowski, J., & Boyer, E.W. (2025). Overdose reversal challenges and priorities in the era of synthetic opioids: Insights from the respire expert forum. *Current Addiction Reports*, 12(39), 12:39. <https://doi.org/10.1007/s40429-025-00648-5>
- KOAA News (2025, June 10). Organizers shut down Southern Colorado arts festival due to fentanyl-laced substances. *KOAA News 5*. <http://www.koaa.com/news/covering-colorado/organizers-shut-down-southern-colorado-arts-festival-due-to-fentanyl-laced-substances>
- Laffont, C.M., Purohit, P., Delcamp, N., Gonzalez-Garcia, I., & Skolnick, P. (2024). Comparison of intranasal naloxone and intranasal nalmefene in a translational model assessing the impact of synthetic opioid overdose on respiratory depression and cardiac arrest. *Frontiers in Psychiatry*, 15. <https://doi.org/10.3389/fpsyt.2024.1399803>
- Morell, M.J. (2017, September 3). The opioid crisis becomes a national security threat. *The Cipher Brief*. [https://www.thecipherbrief.com/column\\_article/opioid-crisis-becomes-national-security-threat](https://www.thecipherbrief.com/column_article/opioid-crisis-becomes-national-security-threat)
- Moreno-Paz , B., & Nguyen, T. (2024, May 2). Officials say opioid “outbreak” in Austin, Texas, linked to 9 deaths and 75 overdoses. *USA Today*. <https://www.usatoday.com/story/news/nation/2024/05/02/austin-texas-opioid-overdose-outbreak/73548183007>
- Opiant Pharmaceuticals. (2023). OPVEE (nalmefene) nasal spray [label]. *U.S. Food and Drug Administration*. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2023/217470Orig1s000.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217470Orig1s000.pdf)
- Riches, J.R., Read, R.W., Black, R.M., Cooper, N.J., & Timperley, C.M. (2012). Analysis of clothing and urine from Moscow theatre siege casualties reveals carfentanil and remifentanil use. *Journal of Analytical Toxicology*, 36(9), 647–656. <https://doi.org/10.1093/jat/bks078>
- Stolbach, A.I., Mazer-Amirshahi, M., Nelson, L.S., & Cole, J.B. (2023, September 28). ACMT & AACT joint position statement on nalmefene should not replace naloxone as the primary opioid antidote at this time. *American College of Medical Toxicology*. <https://www.acmt.net/news/acmt-aact-joint-position-statement-on-nalmefene-should-not-replace-naloxone-as-the-primary-opioid-antidote-at-this-time>
- Tanz, L.J., Dinwiddie, A.T., Mattson, C.L., O'Donnell, J., & Davis, N.L. (2022). Drug overdose deaths among persons aged 10-19 years—United States, July 2019-December 2021. *Morbidity and Mortality Weekly Report*, 71(50). <https://doi.org/10.15585/mmwr.mm7150a2>
- U.S. Attorney's Office, Southern District of New York. (2024, September 30). U.S. Attorney announces charges against 18 defendants in scheme to manufacture and distribute millions of deadly counterfeit pharmaceuticals through fake online pharmacies. <https://www.justice.gov/usao-sdny/pr/us-attorney-announces-charges-against-18-defendants-scheme-manufacture-and-distribute>

- U.S. Food and Drug Administration [FDA]. (2023, May 22). FDA approves prescription nasal spray to reverse opioid overdose. <https://www.fda.gov/news-events/press-announcements/fda-approves-prescription-nasal-spray-reverse-opioid-overdose>
- Vo, K.T., van Wijk, X.M.R., Lynch, K.L., Wu, A.H.B., & Smollin, C.G. (2016). Counterfeit norco poisoning outbreak—San Francisco Bay Area, California, March 25–April 5, 2016. *Morbidity and Mortality Weekly Report*, 65(16), 420–423. <https://doi.org/10.15585/mmwr.mm6516e1>