NCPD
2.0
ANCC
Contact
Hours

Opioid-Associated Emergencies

A Review of Their Management and the Utility of Naloxone

Danielle M. Candelario ▼ Roberta Dume ▼ Nimrah Khan

Although pain is most effectively treated through a multimodal approach, opioids remain a mainstay of treatment for chronic pain despite their considerable adverse effect profile and associated risks. Through modulation of the μ-opioid receptors, opioids can cause respiratory depression, which may result in death if not treated. When used in conjunction with other sedative substances, the risk of respiratory depression is potentiated. If an opioid emergency is suspected, responders should activate the emergency response system as outlined by the American Heart Association. Prompt and appropriate naloxone administration is vital to appropriate emergency care. As a preventative measure, naloxone should be recommended to individuals who are at higher risk of an opioid overdose. Naloxone is available at most pharmacies, can be billed through an individual's insurance, and is now available over the counter without a prescription.

Background

Pain is a complex process with profound clinical, psychological, and social consequences. Although pain is most effectively treated through a multimodal approach, opioids remain a mainstay of treatment despite their considerable adverse effect profile and associated risks. Significant public awareness in conjunction with the recent publication of federal agency guidelines has affected overall opioid prescribing with decreases in overall prescriptions since the initial surge in the 1990s (American Medication Association, 2021). According to the Federal Pain Management Best Practices Inter-Agency Task Force, this shift in opioid prescribing practices has negatively impacted patients; in many cases providers were urged to suddenly stop prescribing opioids, which led to patients resorting to unguided self-tapering, medication misadventures, and misuse (2019). In 2020, prescription opioids were the most commonly misused prescription drug in the United States (Substance Abuse and Mental Health Services Administration [SAMHSA], 2021a). Among persons aged 12 years and older, 9.5 million reported misuse of opioids within the past year with 1.2 million initiating in the past year (SAMHSA, 2021a). This prevalence has declined since 2015 when 12.5 million reported misuse. Among those reporting misuse during the past year, 64.6% reported their main reason for misuse was to "relieve physical pain" compared with 11.3% to "feel good or get high" (SAMHSA, 2021a). Opioid deprescribing has also contributed to the rise in the use of illicit drugs for pain control, such as fentanyl and heroin, quickly creating a fentanyl crisis. This has increased the demand for illicit synthetic opioids as well as other substances and negatively correlates with a fourfold increase in the rate of death from heroin since 2010 (Federal Pain Management Best Practices Inter-Agency Task Force, 2019). Nationwide, nearly half of all opioid overdose deaths in 2017 involved illicitly manufactured fentanyl.

The Centers for Disease Control and Prevention (CDC) recognizes the need for a national guidance on pain management to improve appropriate opioid prescribing while minimizing opioid misuse, overdose, and death for persons living with pain. The 2022 CDC Clinical Practice Guideline for Prescribing Opioids for Pain aims to enhance clinician–patient communication and offer recommendations for improving the quality of pain treatment while reducing the risks associated with treatment (Dowell et al., 2022).

Characteristics of an Opioid Overdose

The opioid effect on pain response, stress, and affect is complex and contributes to the powerful analgesic and addictive properties of opioids. Although opioids affect three distinct receptors, μ, κ and δ, the downstream effect on γ-aminobutyric acid (GABA) is primarily

Danielle M. Candelario, PharmD, BCPS, Associate Professor, Department of Pharmacy Practice, College of Pharmacy, Rosalind Franklin University, North Chicago, IL.

Roberta Dume, PharmD, BCPP, Assistant Professor, Department of Pharmacy Practice, College of Pharmacy, Rosalind Franklin University, North Chicago, IL.

Nimrah Khan, PharmD, PGY-1 Community-Based Resident, Jewel-Osco Pharmacies/Albertsons, Itasca, IL, and Rosalind Franklin University, North Chicago, IL.

The authors have no conflicts of interest to disclose or ethical consideration that may compromise the integrity of this article.

Correspondence: Roberta Dume, PharmD, BCPP, Department of Pharmacy Practice, College of Pharmacy, Rosalind Franklin University, North Chicago, IL 60064 (Roberta.Dume@rosalindfranklin.edu).

DOI: 10.1097/NOR.0000000000001002

responsible for the most concerning adverse effect, respiratory depression, which often results in death if not treated (Valentino & Volkow, 2018). Opioids have differing potencies and affinity for these three receptors, causing a variable effect on respiratory depression. However, the concomitant use of other sedative substances that also potentiate GABA can lead to a synergistic effect on respiratory depression. Most opioid-associated out-of-hospital cardiac arrests involve coadministration and use of multiple sedatives (Dezfulian et al., 2021). Table 1 describes the most common signs and symptoms associated with an opioid emergency (SAMHSA, 2018). If an opioid overdose is suspected, initiate the emergency response system and consider administration of naloxone.

Responding to an Opioid-Associated Emergency

The 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care provide the most comprehensive review of evidence-based recommendations for opioid-associated emergencies (AHA, 2020a). Guidelines offer two algorithms, one for laypersons and one for healthcare providers, both emphasizing the need for training and activation of the emergency response system by all who may encounter such emergencies (AHA, 2020b, 2020c). The two algorithms reflect the spectrum of poisoning, from respiratory depression to cardiac arrest, and highlight the need for prompt emergency response. Responders should begin by checking responsiveness, shouting for help, activating the emergency response system, getting naloxone, and identifying automated external defibrillator (AED) availability. In the event of a suspected cardiac arrest, additional resuscitative measures may be required. In a patient with a definite pulse but abnormal breathing, it is reasonable for responders to administer naloxone in addition to providing standard basic life support care. Naloxone administration in a suspected overdose should not be delayed. In the event a pulse is unable to be established, responders should initiate CPR with a focus on high-quality chest compressions. Naloxone may still be administered; however, standard resuscitative measures should take priority over naloxone administration (AHA, 2020a).

Table 1. Signs And Symptoms of An Opioid Overdose

Miosis or small, constricted "pinpoint pupils"
Sedation or inability to awaken
Slow, shallow breathing
Choking or gurgling sounds
Altered mental status
Vomiting
Limp body
Pale, blue, or cold skin, fingernails or lips
Seizure if coadministration with medications like tramadol, benzodiazepines
May lead to cardiac arrest

Out-of-hospital cardiac arrest can be complicated by aspiration, pulmonary edema, and rhabdomyolysis. Therefore, all patients experiencing an opioid-associated emergency with or without cardiac arrest will require hospital observation and postresuscitation care to prevent further deterioration. This ensures best practice care to prevent secondary brain injury (Dezfulian et al., 2021).

Comparing Naltrexone and Naloxone

Although both naltrexone and naloxone are classified as opioid antagonists and bind to the μ-opioid receptors, naloxone is the only U.S. Food and Drug Administration (FDA)-approved antidote for opioid-related emergencies (Patel & Dickenson, 2022). Naltrexone is reserved for the treatment of both alcohol use disorder (AUD) and opioid use disorder (OUD) depending on the formulation. By blocking μ-opioid activity, naltrexone prevents intoxication when other opioid agonists (i.e., prescription opioids) attempt to bind to those same receptors (Singh & Saadabadi, 2023). Additionally, naltrexone works to modify the hypothalamic–pituitary–adrenal axis to suppress cravings for alcohol and opioids, which is the pathway associated with "reward" in substance use disorders (Singh & Saadabadi, 2023).

Despite its appropriateness for use in OUD, naltrexone should not be used in an acute opioid-related emergency. The reasoning lies in its pharmacokinetic profile. Unlike naloxone, which has a quick onset and short half-life ideal for a life-threatening opioid overdose, naltrexone has a longer half-life and onset of action (Lexicomp, n.d.a, n.d.b). Although naloxone's time to peak concentration is 15 minutes, naltrexone takes 60 minutes to achieve peak concentration for the oral formulation, limiting its use in an emergency situation (Lexicomp, n.d.a, n.d.b).

Another significant difference between naltrexone and naloxone that should be noted is that naltrexone has special dosing considerations (SAMHSA, 2021b). Naltrexone should only be administered to someone who has been opioid-free for at least 7–10 days, as to prevent a precipitated opioid withdrawal (Lexicomp, n.d.b).

Naloxone Administration

Naloxone as an opioid antagonist acts quickly to reverse and block the effects of the opioids, especially respiratory depression. Naloxone can restore normal breathing in someone whose breathing has slowed down or stopped (National Institute on Drug Abuse [NIDA], 2022a).

The two FDA-approved formulations of naloxone include injectable and prepackaged nasal spray (NIDA, 2022a/b). However, naloxone is also available in subcutaneous and intravenous injectable forms used in inpatient settings. The onset of action depends on the dosage form but it works within a matter of minutes. Table 2 provides a summary of the available dosage forms (Adamis Pharmaceutical Corp, 2021; Emergent

Table 2. Available Naloxone Formulation

Route of Administration	Starting Dose	Standard Dose	Maximum Dose
Inpatient			
Naloxone IV, IM, SUBQ	0.4 mg	0.4–2 mg	10 mg
Outpatient			
Naloxone IM or SUBQ (ZIMHI)	5 mg	5–10 mg	Repeat 5 mg every 2–3 minutes until medical help arrives
Naloxone intranasal (Narcan, Kloxxado)	4–8 mg	4–8 mg	Repeat 4–8 mg every 2–3 minutes in alternating nostrils until medical help arrives

Note. IM = intramuscular; IV = intravenous; SUBQ = subcutaneous.

BioSolutions Inc, 2020; Hikma Specialty USA Inc, 2021; Lexicomp, n.d.a).

Table 3 summarizes the proper use and administration of various naloxone formulations (Adamis Pharmaceutical Corp, 2021; Emergent BioSolutions Inc, 2020; Hikma Specialty USA Inc, 2021; Jordan & Morrisonponce, 2023; Lexicomp, n.d.a). The patient should be monitored until emergency care arrives to make sure their breathing does not slow down or stop again. Due to the short half-life of naloxone, withdrawal effects may return. These symptoms are not life-threatening but can be unpleasant for patients. Withdrawal symptoms can include agitation,

Table 3. Proper Use and Administration of Various Naloxone Dosage Forms

	Proper Use and Administration	
Naloxone IV	Continuous IV infusion	
	• Dilute naloxone 2 mg in 500 ml of normal saline or dextrose 5% in water to make a final concentration of 4 mcg/ml • One-third of the dose is given as a bolus ○ Remaining two-thirds of the dose is given as a hourly infusion or split bolus dose in two and give the second-half of the bolus 15 minutes after the start of the continuous infusion	
Naloxone SUBQ	Autoinjector	Vial with syringe
	• Place patient in a supine position • Remove safety guard • Pinch the skin of the desired area (upper arm, shoulder, thigh) • Insert the needle into the skin of the outer thigh at a 45° angle • Press plunger until it clicks and hold for 2 seconds before removing • Pull the safety guard down with one hand with fingers behind the needle • Place used syringe into the blue case, close it, and call 911 • Monitor patient closely, repeat dose in 2–3 minutes if no response	• Assemble the vial and syringe • Withdraw 1 ml of 0.4 mg/ml naloxone from vial • Clean the injection site • Pinch the skin of the desired area (upper arm, shoulder, thigh, outer buttocks, or abdomen) • Insert the needle into the skin at a 45° angle • Inject naloxone solution • Monitor patient closely, repeat dose in 2–3 minutes if no response
Naloxone IM	Autoinjector	Vial with syringe
	• Place patient in a supine position • Remove safety guard • Press needle into outer thigh (can be injected through clothing) • Press plunger until it clicks and hold for 2 seconds before removing • Pull the safety guard down with one hand with fingers behind the needle • Place used syringe into the blue case, close it and call 911 • Monitor patient closely, repeat dose in 2–3 minutes if no response	• Open cap of naloxone vial • Remove cap of needle and insert into the vial • With the vial upside down, pull back plunger and draw up 1 ml of naloxone • Using a needle at least 1-inch long, inject into muscle in the upper arm or outer thigh • Get medical help right away • Monitor patient closely • If needed, can administer more doses every 2–3 minutes until the patient responds or medical assistance arrives
Naloxone intranasal	• Requires no assembly or priming • Lay patient on their back • Support the patient's neck with your hand and let the head tilt back • Gently insert the tip of the nozzle into one nostril and press plunger • Remove the nasal spray from the patient's nose • Move the patient on their side in the recovery position • Get medical help right away • Monitor patient closely • If needed, can administer more doses every 2–3 minutes in alternating nostrils until the patient responds or medical help arrives	

Note. IM = intramuscular; IV = intravenous; SUBQ = subcutaneous.

anxiety, hypertension, hyperventilation, and tachycardia. Nausea, vomiting, and diarrhea can also occur leading to peristalsis. Symptoms resolve between 3 and 10 days depending on the offending opioid used and its pharmacokinetic profile (i.e., short-acting vs. long-acting). The Clinical Opiate Withdrawal Scale has been developed to manage symptoms of withdrawal in inpatient and outpatients settings (Powell & Peters, 2019).

Naloxone Access

Although the utilization of naloxone in the emergency department and even out in the field by law enforcement officers may appear ubiquitous, barriers to access for patients persist. Unfortunately, the stigma around building robust and equitable naloxone access programs in the community still exists (Martignetti & Sun, 2022). More specifically, there is widespread belief that naloxone access programs would only facilitate continued and riskier opioid use in the future. In many cases, healthcare providers appear to hold a stigma around the access of naloxone and poorer outcomes (Freeman et al., 2017; Green et al., 2013). It is not surprising that patients who may have initially pursued seeking naloxone are now faced with potential ridicule, shame, and perceived legal repercussions given the polarizing viewpoints among healthcare workers (Bessen et al., 2019). Additionally, some patients encounter a financial barrier, as access to naloxone may be cost prohibitive depending on insurance status (Gatewood et al., 2016).

It is clear that stigma is the driving barrier for patient access to naloxone. Therefore, patient education with the utilization of motivational interviewing techniques is key to ensure patient buy-in. The CDC recommends a multistep approach that begins with thorough patient education around how naloxone works and its life-saving potential (CDC, n.d.). They include recommendations around asking open-ended questions when discussing opioid use and naloxone, and also include a chart reviewing the preferred language to use when discussing with patients to avoid unintended stigma.

Naloxone is recommended to be dispensed to individuals who use heroin, or are taking high-dose opioid medications, which is usually defined by ≥50 morphine milligram equivalents per day (CDC, 2023). Additionally, naloxone should be offered to individuals who concomitantly use opioids and benzodiazepines (BZDs), given the combination of these drug classes increases the risk of respiratory depression (CDC, 2023). In fact, at least 17 states have passed laws requiring naloxone to be dispensed to patients who pose an overdose risk, including the documented concomitant use of BZDs and opioids (Dowell et al., 2022). Naloxone is also recommended to individuals who are around others who are at risk of overdose, including healthcare workers.

Naloxone is available at most pharmacies, and can be billed through an individual's insurance similarly to other prescription medications with a prescription. Further, a patient may also be able to receive naloxone without a prescription as many states have a standing order for naloxone, which allows pharmacists to dispense directly to the patient. In March 2023, the FDA approved the first nonprescription Narcan spray, followed by the first generic nonprescription naloxone in July 2023 as a more cost-effective option (FDA, 2023). Over-the-counter formulations will begin shipment to stores in September 2023. Depending on locality, there are many community-based distribution programs, local health departments, or other health groups that distribute naloxone at no cost for those with financial hardship (NIDA, 2022b).

Summary

Despite the seemingly exponential increase in opioid-related overdose deaths year after year, there is an intervention that healthcare providers can do in response. Identifying patients who are at high risk for an opioid-related emergency and providing education around signs and symptoms of opioid overdose are essential. Additionally, providing patients with naloxone access and education on how and when to use it appropriately can potentially save a life. There are both national and local efforts to increase naloxone access to the public.

References

Adamis Pharmaceutical Corp. (2021). *Zimhi®* [prescribing information]. Adamis Pharmaceuticals Corporation.

American Heart Association. (2020a). 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*, *142*(16, Suppl. 2), S337–S357. https://doi.org/10.1161/CIR.0000000000000918

American Heart Association. (2020b). *Opioid-Associated Emergency for Lay Responders Algorithm*. Retrieved August 25, 2023, from https://cpr.heart.org/-/media/CPR-Files/CPR-Guidelines-Files/Algorithms/AlgorithmOpioidLay_Responder_200615.pdf

American Heart Association. (2020c). *Opioid-Associated Emergency for Healthcare Providers Algorithm*. Retrieved August 25, 2023, from https://cpr.heart.org/-/media/CPR-Files/CPR-Guidelines-Files/Algorithms/AlgorithmOpioidHC_Provider_200615.pdf

American Medication Association. (2021). *2021 Overdose Epidemic Reports*. Retrieved August 25, 2023, from https://end-overdose-epidemic.org/wp-content/uploads/2021/09/AMA-2021-Overdose-Epidemic-Report_92021.pdf

Bessen, S., Metcalf, S. A., Saunders, E. C., Moore, S. K., Meier, A., McLeman, B., Walsh, O., & Marsch, L. A. (2019). Barriers to naloxone use and acceptance among opioid users, first responders, and emergency department providers in New Hampshire, USA. *The International Journal on Drug Policy*, *74*, 144–151. https://doi.org/10.1016/j.drugpo.2019.09.008

Centers for Disease Control and Prevention. (2023). *Lifesaving naloxone*. Retrieved September 19, 2023, from https://www.cdc.gov/stopoverdose/naloxone/index.html#:~:text=People%20who%20are%20taking%20high,heroin%20should%20all%20carry%20naloxone

Centers for Disease Control and Prevention. (n.d.). *Naloxone: Talking about Naloxone with Patients Prescribed Opioids*. Retrieved September 19, 2023, from https://www.cdc.gov/opioids/naloxone/factsheets/pdf/conversation-starter_naloxone_clinician.pdf

Dezfulian, C., Orkin, A. M., Maron, B. A., Elmer, J., Girotra, S., Gladwin, M. T., Merchant, R. M., Panchal, A. R., Perman, S. M., Starks, M. A., van Diepen, S., & Lavonas, E. J.; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and

Resuscitation; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Council on Clinical Cardiology. (2021). Opioid-associated out-of-hospital cardiac arrest: Distinctive clinical features and implications for health care and public responses: A scientific statement from the American Heart Association. *Circulation*, *143*(16), e836–e870. https://doi.org/10.1161/CIR.0000000000000958

Dowell, D., Ragan, K. R., Jones, C. M., Baldwin, G. T., & Chou, R. (2022). CDC clinical practice guideline for prescribing opioids for pain—United States, 2022. MMWR. Recommendations and reports: Morbidity and mortality weekly report. *Recommendations and Reports*, *71*(3), 1–95. https://doi.org/10.15585/mmwr.rr7103a1

Emergent BioSolutions Inc. (2020). *Narcan® (naloxone HCl) Nasal Spray* [prescribing information]. Emergent BioSolutions Inc.

Federal Pain Management Best Practices Inter-Agency Task Force. (2019). *Pain Management Best Practices Inter-Agency Task Force Report*. Retrieved August 25, 2023, from https://www.hhs.gov/sites/default/files/pain-mgmt-best-practices-draft-final-report-05062019.pdf

Freeman, P. R., Goodin, A., Troske, S., Strahl, A., Fallin, A., & Green, T. C. (2017). Pharmacists' role in opioid overdose: Kentucky pharmacists' willingness to participate in naloxone dispensing. *Journal of the American Pharmacists Association*, *57*(2S), S28–S33. https://doi.org/10.1016/j.japh.2016.12.064

Gatewood, A. K., Van Wert, M. J., Andrada, A. P., & Surkan, P. J. (2016). Academic physicians' and medical students' perceived barriers toward bystander administered naloxone as an overdose prevention strategy. *Addictive Behaviors*, *61*, 40–46. https://doi.org/10.1016/j.addbeh.2016.05.013

Green, T. C., Bowman, S. E., Zaller, N. D., Ray, M., Case, P., & Heimer, R. (2013). Barriers to medical provider support for prescription naloxone as overdose antidote for lay responders. *Substance Use & Misuse*, *48*(7), 558–567. https://doi.org/10.3109/10826084.2013.787099

Hikma Specialty USA Inc. (2021). *Kloxxado® (naloxone HCl) Nasal Spray* [prescribing information]. Hikma Specialty USA Inc.

Jordan, M. R., & Morrisonponce, D. (2023). Naloxone. In *StatPearls*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK441910/

Lexicomp. (n.d.a). Naloxone: Drug information. *UpToDate*. Retrieved August 25, 2023, from https://www-uptodate-com.rosalindfranklin.idm.oclc.org/contents/naloxone-drug-information?source=auto_suggest&selectedTitle=1~4—1~4—naloxone&search=naloxone

Lexicomp. (n.d.b). Naltrexone: Drug information. *UpToDate*. Retrieved August 25, 2023, from https://www-uptodate-com.rosalindfranklin.idm.oclc.org/contents/naltrexone-drug-information?source=auto_suggest&selectedTitle=1~3—1~3—naltrex&search=naltrexone

Martignetti, L., & Sun, W. (2022). Perspectives of stakeholders of equitable access to community naloxone programs: A literature review. *Cureus*, *14*(1), e21461. https://doi.org/10.7759/cureus.21461

National Institute on Drug Abuse. (2022a). *Naloxone DrugFacts*. Retrieved September 1, 2023, from https://nida.nih.gov/publications/drugfacts/naloxone

National Institute on Drug Abuse. Advancing Addiction Science. (2022b). *Naloxone Drug Facts*. Retrieved September 19, 2023, from https://nida.nih.gov/publications/drugfacts/naloxone#:~:text=How%20is%20naloxone%20given%3F,skin%2C%20or%20into%20the%20veins

Patel, R., & Dickenson, A. H. (2022). Neuropharmacological basis for multimodal analgesia in chronic pain. *Postgraduate Medicine*, *134*(3), 245–259. https://doi.org/10.1080/00325481.2021.1985351

Powell, H., & Peters, G. (2019). Managing opioid overdose in the hospital setting. *US Pharm*, *44*(3). https://www.uspharmacist.com/article/managing-opioid-overdose-in-the-hospital-setting

Singh, D., & Saadabadi, A. (2023). Naltrexone. In *StatPearls*. Retrieved August 25, 2023, from https://www.ncbi.nlm.nih.gov/books/NBK534811/

Substance Abuse and Mental Health Services Administration. (2018). *SAMHSA Opioid Overdose Prevention TOOLKIT*. Retrieved August 25, 2023, from https://store.samhsa.gov/sites/default/files/d7/priv/sma18-4742.pdf

Substance Abuse and Mental Health Services Administration. (2021a). *Key substance use and mental health indicators in the United States: results from the 2020 National Survey on Drug Use and Health*. US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. Retrieved August 25, 2023, from https://www.samhsa.gov/data/sites/default/files/reports/rpt35325/NSDUHFFRPDFWHTMLFiles2020/2020NSDUHFFR1PDFW102121.pdf

Substance Abuse and Mental Health Services Administration. (2021b). *Medications for Opioid Use Disorder. Treatment Improvement Protocol (TIP) Series 63*. Publication No. PEP21-02-01-002. Retrieved August 25, 2023, from https://store.samhsa.gov/sites/default/files/pep21-02-01-002.pdf

U.S. Food and Drug Administration. (2023). *FDA Approves Second Over-the-Counter Naloxone Nasal Spray Product*. Retrieved September 19, 2023, from https://www.fda.gov/news-events/press-announcements/fda-approves-second-over-counter-naloxone-nasal-spray-product#:~:text=The%20agency%20approved%20the%20first,opportunities%20for%20nonmedical%20use%2C%20accidental

Valentino, R. J., & Volkow, N. D. (2018). Untangling the complexity of opioid receptor function. *Neuropsychopharmacology*, *43*(13), 2514–2520. https://doi.org/10.1038/s41386-018-0225-3

The test for this nursing continuing professional development activity can be taken online at www.NursingCenter.com/CE/ORTHO.