

UConn

AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

- After completing the continuing education activity, pharmacists and pharmacy technicians will be able to
- DISCUSS naloxone nasal spray's shift to over-the-counter (OTC) availability
 - DESCRIBE how to use naloxone nasal spray safely and effectively
 - IDENTIFY the pharmacist's role in OTC naloxone access



The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this application-based activity and will receive up to 0.1 CEU (1 contact hour) for completing the activity, passing the post-test with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

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You Asked for It! CE



An Over-The-Counter Lifesaver: Increased Intranasal Naloxone Accessibility

TARGET AUDIENCE: Pharmacists and pharmacy technicians who work in settings that will sell OTC naloxone.

ABSTRACT: Recently, the US Food and Drug Administration approved an over-the-counter naloxone product. This is a welcome change that will hopefully reduce the number of opioid-related deaths in the United States, which have escalated over the last two decades. Used appropriately, naloxone can be lifesaving. In addition, its wide margin of safety contributed to the FDA's decision to move this medication from prescription status to over-the-counter (OTC) status. This continuing education (CE) activity covers important information about naloxone, signs of overdose, and naloxone use by bystanders who observe potential opioid overdoses. It also discusses the legal repercussions of using OTC naloxone. Finally, this CE covers counseling tips that are critical for laypeople who purchase OTC naloxone.

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FACULTY DISCLOSURE: Dr. Giara has no financial relationships with an ineligible company.

DISCLOSURE OF DISCUSSIONS of OFF-LABEL and INVESTIGATIONAL DRUG USE: This activity may contain discussion of off label/unapproved use of drugs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of the University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

INTRODUCTION

The opioid epidemic has gripped the United States (U.S.) for more than two decades.¹ Opioid overdose is the number one cause of death for adults aged 25 to 64 years old, which significantly contributes to the decline in the average lifespan.¹ The rise of synthetic opioids (primarily fentanyl) augments the uptick in overdoses, referred to as the "3rd wave" of the opioid epidemic.^{1,2} In fact, 8 in 10 fatal opioid overdoses in the U.S. now involve synthetics.¹ Non-fatal overdose is also significant; for every opioid-induced fatality, up to 8.4 non-fatal overdoses occur.¹

Prescription opioids are also a noteworthy contributor to the rise in opioid overdose deaths.² Healthcare providers started prescribing opioids for chronic, non-cancer pain (e.g., arthritis, back pain) in the 1990s.³ In the decades since, patients started receiving increasingly higher doses of prescription opioids for long-term chronic pain management.^{2,3} In 2015, the amount of opioids prescribed per person was three times higher than it was in 1999.³ Even when patients take opioids as prescribed, they are still at risk of accidental overdose and drug-drug (e.g., benzodiazepines) or drug-alcohol interactions.² Their household contacts are also at risk.

Naloxone—an opioid antagonist—is the only approved treatment to reverse opioid overdose.⁴ The drug competes for the same receptor sites opioids use, effectively and rapidly reversing their effects (i.e., respiratory depression, sedation, and hypotension).⁴ Naloxone is available in intranasal, subcutaneous, and intramuscular formulations for outpatient use and intravenous formulations for inpatient use.^{5,6} Naloxone is a safe antidote for suspected overdose, and its use has caused the number of opioid overdose deaths to decrease in communities where it is readily available.²

The U.S. Food and Drug Administration (FDA) has undertaken a series of measures to increase accessibility to this lifesaving medication.⁷ Until recently, naloxone was only available via prescription. In March 2023, the FDA approved the first naloxone product for over-the-counter (OTC), nonprescription use.^{6,7} This aims to improve access to naloxone, increase the number of locations where it is available (e.g., drug stores, convenience stores, grocery stores, the Internet), and help reduce opioid overdose deaths across the country.

INCREASED ACCESSIBILITY

The FDA first approved naloxone in 1971 as a prescription drug.⁶ It wasn't until 2014 that the agency approved the first naloxone auto-injector for use outside of a healthcare setting, followed by a nasal spray formulation in 2015.⁸ Its status as a prescription-only medication made initial access difficult and inconsistent across the country and various high-risk groups.

In the mid-1990s, community-based programs implemented efforts to increase distribution to high-risk individuals.⁶ Consequently, naloxone dispensing from retail pharmacies increased substantially from 2010 to 2015, with a 1170% increase between 2013 and 2015.⁶ Naloxone dispensing remains inadequate, however, with only one naloxone prescription dispensed for every 70 high-dose opioid prescriptions.

Pharmacist Naloxone Prescribing

It's common knowledge that pharmacists are highly accessible, trusted healthcare professionals, so their role in naloxone distribution is not surprising. Their accessibility, medication expertise,

access to patients' medical records, and regular patient interaction are valuable tools for increasing naloxone availability.⁶

Many states across the U.S. have enacted naloxone access laws (NALs) to expand pharmacists' scope of practice through standing orders or collaborative practice agreements, allowing them to distribute naloxone without a patient-specific prescription.⁶ Studies show that NALs significantly increased naloxone prescribing, but not enough.⁶ Despite NALs, many pharmacists remain uncomfortable dispensing the drug without a patient-specific order given limited training, lack of understanding state laws, and lack of reimbursement for patient education. Some evidence also exists that pharmacists are afraid of potential legal ramifications.⁶

Shifting to the Other Side of the Counter

The FDA has a specific process for shifting from prescription to OTC approval.⁹ Prescription products can undergo a full switch or partial switch. A full switch converts the drug product covered under a New Drug Application (NDA) to nonprescription marketing status entirely. A partial switch only converts some of the conditions of use (e.g., indications) to nonprescription status and retains others within prescription status. A full switch requires a sponsor to submit an efficacy supplement to an approved NDA or a 505(b)(2) application, but a partial switch requires an entirely new NDA.⁹ Ultimately, approval of a prescription-to-OTC switch application depends on the FDA deciding that prescription status is “not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and...the drug is safe and effective for use in self-medication as directed in proposed labeling.”⁹

The FDA has been working to authorize an OTC version of naloxone since 2019 by prioritizing applications and assisting manufacturers pursuing OTC naloxone approval.⁸ The agency announced in January 2019 that preliminary assessment showed that consumers understood a model drug facts label well for OTC naloxone nasal spray and manufacturers found the label acceptable, a slow but steady step in the right direction.⁸ In late 2022, the FDA issued a Federal Register notice indicating that certain naloxone products—up to 4 mg nasal spray and up to 2 mg intramuscular or subcutaneous autoinjector—may be approvable for nonprescription use.¹⁰ This did not immediately approve naloxone products for safe and effective OTC use, but it did provide the framework for manufacturers to pursue approval.

The FDA granted priority review status to the application to approve branded naloxone nasal spray (Narcan) for OTC use.¹¹ It was then the subject of an advisory committee meeting in February 2023 where the committee voted unanimously to approve naloxone for nonprescription marketing.¹¹

What's Next?

It's important to note that the prescription to OTC switch does not automatically apply to all forms of naloxone. Only branded Narcan 4 mg nasal spray is now granted OTC status, not its generic counterparts.⁷ Manufacturers of generic products with Narcan listed as their reference listed drug product will need to submit a supplemental application to switch their products to OTC status. Other brand name naloxone nasal spray products of 4 mg or less must also update labeling and apply individually for a switch to OTC status.⁷

Pharmacy teams should also be aware that the drug will not be available on drug store shelves immediately.¹² The manufacturer will need to implement manufacturing and supply chain changes to support nonprescription packaging requirements. According to the drug's manufacturer, pharmacies can expect the OTC formulation to be available in late summer 2023. Until then, the prescription product will be readily available through current access channels.¹²

Cost is also important to consider. The drug's manufacturer has yet to reveal pricing plans for the OTC version, but it plans to work with public interest groups who are now charging about \$47.50 per box.¹³ Health economists predict that the price of OTC Narcan could land somewhere between \$35 and \$65, plus a retailer's markup.¹³ Unfortunately, this price could be prohibitive for many individuals, especially those who misuse opioids. Some also fear that this could encourage individuals to shoplift the drug, forcing locations to move the product behind the pharmacy counter or behind glass and creating a barrier to those who can afford it but are uncomfortable asking for it.¹³

As for accessing the drug outside of a pharmacy setting (e.g., convenience stores, gas stations), additional barriers may exist. Some states require a special license for non-pharmacy businesses to sell OTC medications, which can effectively create "naloxone deserts" where the drug is not available for purchase. In the state of Connecticut, for example, 28 towns currently do not have stores with permits to sell OTC medications, causing residents to travel to obtain the lifesaving antidote.¹⁴ Pharmacy teams should check their state's law regarding OTC sales to direct interested individuals on where to obtain the drug.

NEW OPPORTUNITIES FOR THE PHARMACY TEAM

Naloxone shift to OTC availability may seem to take the load off pharmacy teams when it comes to collaborative practice agreements and NALs, but the pharmacy team should remain heavily involved in naloxone distribution. OTC medications are often not covered by insurance, so pharmacists should stay vigilant about active NALs and collaborative practice agreements to prescribe the drug for people with cost concerns.



Assessing Overdose Risk

Prescription or not, a crucial role for pharmacy staff is identifying patients for whom naloxone is appropriate. Anyone exposed to opioids, regardless of the source, is at risk of overdose and should be considered for naloxone.¹⁵ This applies to people taking opioids for pain with or without other medications and those who misuse opioids. As the drug is bystander-administered, caregivers of individuals at risk of overdose may also request naloxone and should be educated about its use.¹⁵

Paying attention to opioid dosing is important when considering patients for naloxone. A dose of 50 morphine milligram equivalents (MME) per day doubles the risk of fatal opioid overdose compared to 20 MME or less.³ Patients taking 90 MME or more daily are 10-times more likely to die from an overdose.³ Other overdose risk factors include¹⁵

- concurrent benzodiazepine and/or alcohol use
- history of substance use disorder, including opioid addiction
- comorbid mental illness (e.g., depression, anxiety)
- filling prescriptions at multiple pharmacies and/or from multiple prescribers
- receiving a methadone prescription
- recent emergent medical care for opioid poisoning, intoxication, or overdose
- recent period of abstinence (e.g., release from incarceration, discharge from an opioid detox or abstinence-based program)
- renal or hepatic dysfunction
- comorbid respiratory conditions (e.g., smoking, chronic obstructive pulmonary disease, emphysema, asthma, sleep apnea)

Counseling on Naloxone Nasal Spray Use

The FDA deemed naloxone nasal spray safe enough for OTC use, but that doesn't preclude the need to counsel individuals on its safe and appropriate use. Pharmacists should counsel all patients buying OTC naloxone nasal spray about signs of an opioid overdose, how to administer naloxone, and other important clinical pearls. Signs of an opioid overdose include¹⁵

- pale and/or clammy skin
- limp body
- pinpoint pupils
- blue or purple lips, nose, and/or fingernails
- vomiting or making gurgling noises
- unconscious or unarousable
- breathing very slow or not at all

Pharmacists should advise individuals to administer naloxone in the event of suspected overdose even if they are not 100% sure the victim is in fact suffering from an overdose.¹⁶ Administering naloxone to someone who is not actually suffering from opioid overdose is better than withholding care from an overdose victim based on uncertainty. See [Sidebar: Saving a Life is Scary](#) for additional information to ease concerns regarding naloxone administration.

Naloxone nasal spray is available in a two-pack of single-use, pre-filled devices that cannot be reused.^{4,5} The device should not be primed. Pharmacists should advise people buying OTC naloxone nasal spray about the following administration steps^{4,16}:

- 1) Check for a suspected overdose (i.e., yell "wake up," shake the person gently)
- 2) If the individual does not wake up, lay them on their back
- 3) Hold the nasal spray device with a thumb on the bottom of the plunger
- 4) Insert the nozzle into one nostril and press firmly to administer the dose
- 5) Call 911 immediately
- 6) Stay until medical assistance arrives, even if the person wakes up
- 7) Give another dose if the person does not wake up after 2 to 3 minutes or they become very sleepy again initial arousal
- 8) Continue giving doses every 2 to 3 minutes until the person wakes up or medical assistance arrives (it is safe to keep giving doses)

Naloxone is a relatively safe drug, but it still comes with risks and clinical pearls that cannot be ignored. Abrupt opioid reversal in physically dependent individuals can cause acute withdrawal.^{4,7} Signs and symptoms include body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, and tachycardia.⁴ Patients may also become aggressive upon sudden reversal of opioids. Naloxone is only effective in reversing

SIDEBAR: Saving a Life Is Scary^{15,17}

Often, individuals are trained and ready to perform lifesaving first-aid procedures like CPR or the Heimlich maneuver, but they are afraid of the implications if things take a turn for the worse. Naloxone administration is subject to these same liability concerns. Individuals may also be concerned about legal repercussions when calling for help at the scene of an overdose. Ensure that individuals know about supporting laws and regulations that protect them to increase comfort and confidence with administering the drug:

- **Good Samaritan***: Protects people who call for emergency medical assistance at the scene of an overdose from being arrested for drug possession.
- **Liability protection/third party administration**: Protects naloxone prescribers and bystanders who administer the drug and allows bystanders to obtain naloxone for use on opioid overdose victims.

*Some states have Good Samaritan laws that differ from general ones. For example, Ohio places limits on the number of times someone can be granted Good Samaritan immunity and requires that overdose victims seek referral for addiction treatment within 30 days. Pharmacy teams should stay current with state-specific Good Samaritan laws regarding naloxone.

opioid overdoses, not in treating other types of overdoses, so it is crucial that individuals seek emergency medical attention following naloxone administration.

CONCLUSION

Naloxone is a vital tool for preventing fatal opioid overdose. Pharmacists should be prepared to identify people at risk of overdose and assess their need for this lifesaving drug, make all individuals aware of its OTC availability, and counsel on its safe and appropriate use.



Figure 1. Safety and Counseling Related to Naloxone Administration

Best

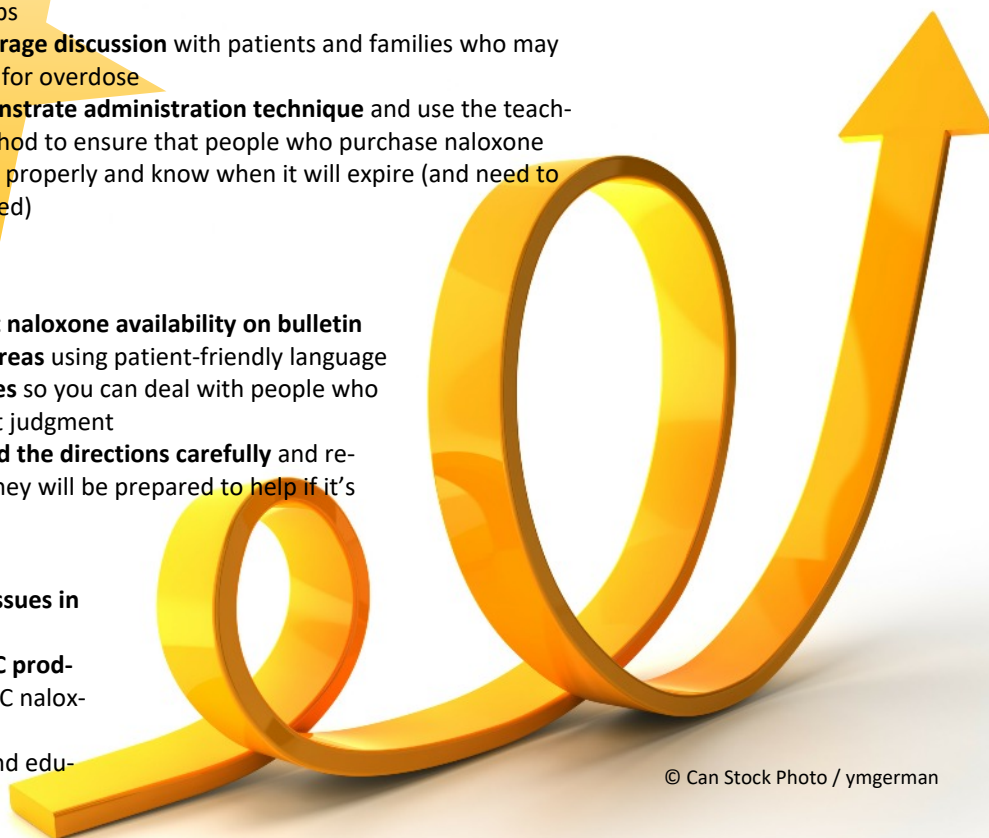
- 1 **Be COMMUNITY CHAMPIONS** and whenever possible, present classes on how and when to use OTC naloxone to community groups
- 2 **Encourage discussion** with patients and families who may be at risk for overdose
- 3 **Demonstrate administration technique** and use the teach-back method to ensure that people who purchase naloxone can use it properly and know when it will expire (and need to be replaced)

Better

- 1 **Post information about naloxone availability on bulletin boards in patient waiting areas** using patient-friendly language
- 2 **Examine your own biases** so you can deal with people who ask about naloxone without judgment
- 3 **Remind patients to read the directions carefully** and review them periodically so they will be prepared to help if it's ever necessary

Good

- 1 **Acquaint yourself with the opioid issues in your location**
- 2 **Know how your state regulates OTC products** and if your pharmacy will stock OTC naloxone
- 3 **Anticipate naloxone availability** and educate yourself about this drug's actions



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