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Opioid Overdose: What Every Family Physician Needs to Know

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Learning Objectives

- Increase knowledge in recognizing the signs and symptoms of opioid overdose, particularly those associated with synthetic opioids, such as fentanyl, to enhance early intervention and improve patient outcomes.
- Demonstrate competence in transitioning from acute overdose management to long-term opioid use disorder (OUD) treatment using FDA-approved medications, including new pharmacological approaches such as extended-release injectable partial opioid receptor agonists/antagonists.
- Increase competence and confidence in addressing barriers to effective opioid overdose response and treatment, such as stigma and limited access to care, by integrating harm reduction strategies and collaborating with community-based programs.

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Introduction to and Epidemiology of the Opioid Crisis

Opioid overdose remains a critical public health issue in the United States and has gone through many phases over the past several decades. Initially fueled by overprescription of opioid pain relievers in the late 1990s, the crisis transitioned to heroin use (second phase). Although overdose mortality from heroin and prescription opioids has plateaued and even decreased (CDC), in 2021, synthetic opioids, especially fentanyl (third phase), were involved in more than 80 percent of opioid overdose deaths.[1] Recently, deaths from the combined use of synthetic opioids and stimulants (fourth phase) has sharply risen.[2]

Opioid Overdose: Who is At Risk?

Providers should prescribe naloxone to those who are at an elevated risk for opioid overdose. According to CDC guidelines, individuals on long-term opioid therapy at or above a 50 morphine milligram equivalent (MME) daily have a higher risk of fatal overdose and qualify for a co-prescription of naloxone.[3] Unfortunately, only one naloxone prescription is filled for every 70 high-dose opioid prescriptions nationally.[4]

Additional risk factors include concurrent benzodiazepine or other central nervous system depressant use, a history of OUD or prior overdose, and conditions such as sleep-disordered breathing or impaired renal/hepatic function.[3] A US Surgeon General's Advisory strongly urges clinicians to prescribe or dispense naloxone to high-risk patients and their friends and family who may witness an overdose.[3] Naloxone also should be offered to patients who use stimulants; more than 12 percent of methamphetamine and nearly 15 percent of cocaine samples contain fentanyl, posing a significant danger to people who are unaware of exposure.[5] Naloxone prescription by third parties without a prescriber-patient relationship is legal in most states through standing orders or by pharmacists.[6]

Opioid Overdose Recognition and Management

Opioid Overdose Recognition

Opioid overdose typically presents with a characteristic triad of symptoms, including respiratory depression, pinpoint pupils (miosis), and decreased consciousness. Individuals may report feelings of extreme drowsiness or euphoria before losing consciousness (Table 1). Some may describe sensations of heaviness, confusion, or dizziness. Early warning signs include difficulty staying awake or speaking and a profound sense of weakness. People with a history of opioid use may recognize these signs in themselves or others but may fail to seek help due to fear, stigma, or a desire to avoid medical authorities.[7] The subjective experience of opioid overdose often varies with the type and quantity of opioids used and use of any co-occurring substances.

Symptoms can progress to profound central nervous system and respiratory depression, which rapidly can lead to life-threatening complications, such as bradycardia due to enhanced vagal tone and direct suppression of cardiac pacemaker activity.[8–10] Hypotension may follow, resulting from peripheral vasodilation and reduced sympathetic outflow, further exacerbating decreased perfusion to vital organs.[9,10]

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Table 1. Opioid Overdose Triad of Symptoms

Respiratory Depression	A dangerous effect of opioid toxicity is slowed or stopped breathing due to suppression of the brainstem's respiratory centers, leading to fatal outcomes if untreated.
Pinpoint Pupils (Miosis)	Constricted pupils are a hallmark of opioid intoxication, although in severe cases, anoxia may lead to fixed and dilated pupils.
Unconsciousness or Unresponsiveness	Patients experiencing an overdose often exhibit deep sedation or unconsciousness, making timely intervention critical.

Severe respiratory depression advances to respiratory arrest—the most immediate and direct cause of death in opioid overdose cases—as opioids inhibit brainstem respiratory centers.[11,12] Without rapid intervention, this cascade can culminate in irreversible hypoxic injury and cardiac arrest.[11,13]

Opioid Receptor Antagonists and Immediate Intervention

Opioid receptor antagonist (OA) treatment has been the gold standard for opioid overdose reversal. Available in intravenous (IV), intramuscular (IM), and intranasal (IN) formulations, OAs such as naloxone rapidly displace opioids from receptor sites, restoring normal respiration. In May 2023, nalmefene received FDA approval for acute opioid overdose as a nasal spray,[14] and in August 2024, nalmefene was approved as an auto-injector.[15] Future strategies may include naloxone-loaded nanoparticles, enhancing drug absorption, and duration of action.[16] Naltrexone, another FDA-approved OA with oral and long-acting injectable forms, is used for opioid and alcohol use disorder maintenance, not for overdose.[13]

With the rise of fentanyl use and its analogs, traditional dosing may be insufficient due to fentanyl's high receptor affinity and slow release from adipose tissue with chronic use, mimicking a long half-life. Multiple naloxone doses or continuous infusions may be required to prevent overdose reccurrence.[12] OAs should be administered for suspected respiratory suppression; 'The dose is titrated to increase the patient's respiratory drive and allow for adequate spontaneous respiration and oxygenation, but not full reversal.'[17] Intranasal naloxone is given in an initial 4mg dose, with additional doses given every 2 to 3 minutes as necessary, determined by the monitoring of vital signs.[17]

Following initial resuscitation, post-overdose management includes observation for the return of opioid toxicity, as OA effects can wear off before the opioids.[18] Naloxone has a short half-life (from 60–120 minutes, depending on route of administration), whereas nalmefene's half-life is approximately 11 hours,[19] which may be better suited for long-acting opioids but potentially prolongs withdrawal (Table 2).

Adulterants in fentanyl, such as xylazine ('tranq'), and medetomidine, an alpha-2 adrenergic agonist, complicate overdose management. In some regions, exposure is commonplace. In Philadelphia, medetomidine was found in 29 percent of analyzed fentanyl samples in May 2024, and in 87 percent of samples by November 2024.[20] These adulterants cause profound central nervous system depression, bradycardia, hypotension, and hypoventilation. Treatment is supportive, as naloxone does not reverse adulterants' effects, but administering treatment remains critical due to difficulty in clinically determining overdose etiology.

FDA-Approved OUD Treatment Approaches

Long-term treatment for OUD typically involves FDA-approved medications, including buprenorphine (partial opioid receptor agonist/antagonist), methadone, or long-acting injectable naltrexone (LAI NTX).[21] Evidence supporting the clinical benefit of naltrexone for OUD is limited to the long-acting injectable formulation as opposed to oral naltrexone.[22] Evidence supports methadone and buprenorphine as first-line treatments (with a substantial mortality benefit) and LAI NTX as a second-line treatment.[23–25] Counseling, mental health treatment, and/or 12-step programs can be helpful. Newer approaches, including extended-release injectable buprenorphine, show promise in reducing overdose risk and improving adherence compared to sublingual formulations, leading to fewer overdoses and better treatment retention.[26,27] Pharmacological treatments help prevent withdrawal symptoms and cravings. Buprenorphine, given in conscious patients after naloxone rescue, can stabilize withdrawal by increasing mu-opioid receptor (MOR) agonism, but patients should be cautious with concurrent sedative use (potential respiratory depression) or methadone use (as overdose is not an automatic indication to start buprenorphine instead of methadone).[28] Buprenorphine also may protect against fentanyl-induced overdose and respiratory depression.[29,30] Practitioners with Schedule III DEA prescribing authority can prescribe

Table 2. Summary of Standard and Emerging Therapies for Opioid Overdose

	Examples	Formulations	Key Features
Standard therapies	Naloxone	IV, IM, IN	Rapidly reverses opioid effects by displacing them from receptors and restoring breathing; multiple doses or infusions may be needed with fentanyl analogs
	Nalmefene hydrochloride	Nasal spray	FDA approved (May 2023) for acute opioid overdose; potential benefits in fentanyl cases
Emerging therapies (investigational)	Naloxone-loaded nanoparticles	Intranasal or other investigational	Enhanced absorption and prolonged action

buprenorphine for OUD, but state laws may have additional requirements.[31,32]

Barriers to Care and Community-Based Interventions

Barriers to opioid overdose and OUD treatment remain substantial despite efforts to address these. Stigma surrounding opioid use often prevents individuals from seeking help for overdose and addiction treatment.[33] Fear of legal consequences, particularly law enforcement at overdose sites, discourages emergency service involvement.[7,34] In rural and underserved areas, treatment facility shortages and the complexity of medication-assisted treatments create significant gaps in care.[35,36] Logistical barriers include lack of access to naloxone[37] and costs,[38] despite availability without a prescription in all states through standing orders.[4] Many pharmacists are unwilling to dispense it, and out-of-pocket cost can be prohibitive.[39]

Integrating overdose response programs into community settings enhances harm-reduction strategies, such as combining pharmacologic and non-pharmacologic interventions, beginning with test doses, and the use of fentanyl test strips.[40] Harm-reduction support is lacking, particularly in rural areas and for older and unemployed individuals.[41] Community-based interventions, such as post-overdose outreach teams, effectively connect individuals to treatment services and reduce repeat overdoses.[42,43] Overdose prevention centers (OPCs) are an evidence-based and emerging legal option in the United States, eg OnPoint NYC.[44] Programs such as the Recovery Opioid Overdose Team (ROOT) incorporate community engagement and facilitate treatment entry following non-fatal overdoses,[42] focusing on proactive, patient-centered approaches.[43]

Expanding naloxone distribution and integrating overdose education reduces mortality and improves community readiness.[45] Bystander-administered naloxone is feasible and effective, with evidence that untrained laypersons successfully deliver pre-stationed intranasal naloxone correctly in simulated overdose scenarios.[46] It was found that naloxone delivered to overdose victims by drones could be retrieved and administered by bystanders, supporting the practicality of public access and use in real-world emergencies.[47] Brief education of patients and family on overdose and naloxone delivery is an important and effective tool to prevent overdose mortality. Educational initiatives that address barriers, such as stigma and fear of legal repercussions, increase bystander willingness to administer naloxone.[7,48] Community-wide naloxone programs have been linked to improved survival outcomes and reduced overdose-related deaths.[49]

Conclusions

Addressing the opioid crisis requires a comprehensive approach that integrates rapid overdose reversal using opioid antagonists such as naloxone, long-term treatment strategies prioritizing access to Medication for Opioid Use Disorder (MOUD), and robust community-based interventions. Expanding harm reduction programs, naloxone distribution, and support services in community and healthcare settings reduces mortality, breaks stigma, and enhances care engagement. By combining innovative pharmaceutical advances with collaborative, patient-centered community strategies, healthcare systems can improve patient outcomes and build greater resilience against future surges in opioid-related health burden and mortality.

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