

THE OPIOID CRISIS: OVERVIEW AND PREVENTION STRATEGIES

JEFF GOLDBERG, PharmD, BCPP

Jeff Goldberg is a graduate of the University of Montana, Skaggs School of Pharmacy Doctor of Pharmacy program. He has clinical experience working in inpatient acute care and psychiatric hospitals and is a board-certified psychiatric pharmacist. He has also worked in community pharmacy settings. Jeff spends most of his free time exploring with his wife and kids and enjoys attending concerts and sports events.

Topic Overview

Opioids are a diverse class of medications most commonly used to treat various types of pain. They are used in several medical scenarios, including the short-term treatment of acute pain, chronic pain caused by significant injuries or illnesses, such as cancer, and during invasive procedures, such as surgery and intubation. In addition to being used for legitimate medical purposes, opioids are among the most commonly misused substances, with over two million people in the United States having an opioid use disorder. More people die from opioid overdose than from overdoses from all other substances combined. When used under the guidance of healthcare professionals, opioids can be used safely, and serious adverse events can generally be avoided. However, when opioids are misused, they pose a significant danger and can lead to respiratory depression and death.

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Target Audience: This educational activity is for pharmacists.

How to Earn Credit: From January 16, 2023, through January 16, 2026, participants must:

- 1) Read the “learning objectives” and “author and planning team disclosures;”
- 2) Study the section entitled “educational activity;” and
- 3) Complete the Course Test and Evaluation form. The Course Test will be graded automatically. Following successful completion of the Course Test with a score of 70% or higher, a statement of participation will be made available immediately. (No partial credit will be given.)

Learning Objectives: Upon completion of this educational activity, participants should be able to:

1. **Review** the history of the current opioid epidemic
2. **Identify** key developments that exacerbated the opioid epidemic
3. **Identify** people at risk for opioid misuse and overdose
4. **Review** strategies for combating the opioid epidemic

Disclosures

The following individuals were involved in developing this activity: Jeff Goldberg, PharmD, Amanda Mayer, PharmD, and Susan DePasquale, MSN, PMHNP-BC. There are no financial relationships relevant to this activity to report or disclose by any of the individuals involved in the development of this activity.

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Introduction

The misuse of prescription opioids, and the overdoses and deaths associated with misuse, have risen to crisis levels during the past decades. This crisis has been worsened by the rise of synthetic opioids, such as fentanyl and fentanyl analogs, which have now overtaken as the leading causes of overdose and death. Opioid use disorder and overdose have become public health emergencies that require a multifaceted approach to help patients affected by them. These approaches cover a series of responses that involve prevention strategies, harm reduction, treatment of substance use disorders, and recovery support.

Brief History of Opioids

Opium has been used (and subsequently misused) by various cultures throughout the world for thousands of years. Beginning with its isolation from the opium poppy in the early 1800s to its chemical structure being identified in 1947, morphine has become the benchmark by which all subsequent opioids have been compared.⁵ Since this time, several different opioids and formulations have been developed with unique properties, making them useful in treating acute and chronic pain.^{6,7} However, the use of opioids for treating chronic noncancer pain remains controversial.⁶ Morphine continues to be the benchmark by which all subsequent opioids are compared.⁷

In the late 19th and early 20th century, opioids were commonly used for various conditions, and their addictive properties were largely unknown by the general public.⁸ Diacetylmorphine, commonly known as heroin, was marketed as an over-the-counter cough suppressant for adults and children.⁸ Beginning in 1914, with the passage of the Harrison Narcotic Act, the production, sale, and use of opioids began to be restricted.⁸

Over the next several decades, prescription opioids were mainly used for acute pain, cancer pain, or end-of-life pain.⁹ Before the 1980s, there was minimal research on the effectiveness of opioids for chronic, non-cancer pain, and most providers generally avoided prescribing them in this situation for

fear of their addictive properties outweighing the potential benefits they may provide.⁸

The Opioid Crisis

In 1987, pain management experts began to call attention to the possibility of opioids being used for chronic, non-cancer pain.⁸ That same year, MS Contin, a long-acting formulation of morphine, received FDA approval. Long-acting opioids were thought to decrease the likelihood of abuse and subsequent addiction. In addition, Duragesic transdermal patch, a long-acting formulation of fentanyl, and OxyContin, a long-acting form of oxycodone, also received FDA approval in 1990 and 1995, respectively.⁹

Over the several years that followed the FDA approval of MS Contin, the use of opioids for chronic, non-cancer pain increased dramatically as pharmaceutical companies and pain experts began to encourage their use in this population. Societal perception also shifted, and chronic pain management became a focus of patients' overall health. The American Pain Society even went so far as to label "pain as the fifth vital sign" in 1996, implying that pain should be assessed as frequently as the other traditional vital signs.⁸

By the early 2000s, overdoses and deaths associated with prescription opioids began to increase dramatically. Over the next two decades, regulatory measures were slowly implemented to help curb the rise in opioid-related overdoses and deaths.⁹ Some of these measures include the following:

- Black box warnings were added to opioids, providing a visible warning alerting providers and patients of the potential dangers associated with using these products.¹⁰
- Medication guides, which help keep patients informed of the risks of opioids, and clearer FDA-approved indications, which help guide providers when selecting patients who are appropriate to prescribe opioids, were also implemented.⁹

- Drug manufacturers were warned by the FDA for misleading healthcare providers and patients.⁹
- Some drug manufacturers even faced litigation for helping fuel the opioid epidemic, such as Purdue Pharma (the manufacturer of OxyContin), which was forced into bankruptcy after being levied a several billion dollar fine.¹¹
- A number of pieces of legislation have been passed to help combat the damage caused by opioid abuse. Many of these will be discussed in greater detail below.¹²
- Prescription drug monitoring programs allow healthcare providers to monitor trends in the use of controlled substances by individual patients.^{13,14}

Despite these measures, overdoses and deaths continue to rise. Since 1999, nearly one million people have died from drug overdoses, including over 100,000 people in 2021 alone.¹ Opioids have emerged as the most common drug class involved in drug overdose deaths.^{1,2} In 2021, greater than 75% of drug overdose deaths in the United States involved opioids, and synthetic opioids (such as fentanyl and carfentanil) accounted for nearly 90% of all opioid-involved deaths.² Excluding methadone, synthetic opioid overdose deaths increased 97-fold from 1999 to 2021.³ Synthetic opioids are often very potent, which decreases the dose that will lead to respiratory depression and death.¹⁵ For example, fentanyl is estimated to be 100 times as potent as morphine, and carfentanil is estimated to be 10,000 times as potent as morphine.⁴

Synthetic opioids, such as fentanyl and fentanyl analogs, are often made illicitly, making regulatory measures much more difficult. Synthetic opioids are added to other illicit substances, such as heroin or counterfeit prescription tablets, to increase the product's potency. In many cases, individuals are unaware that they are taking a synthetic opioid or how potent the substance is that they are ingesting.¹⁵

Combating the Opioid Crisis

In 2017, the U.S. Department of Health and Human Services (HHS) initiated a 5-point strategy to help combat the opioid epidemic. The initial 5-points include the following:^{16,17}

- 1) Access: Improved access to prevention, treatment, and recovery services.
- 2) Data: Improved efficiency in sharing data to help combat the opioid epidemic.
- 3) Pain Management: Improved pain management strategies.
- 4) Overdoses: Improved access to life-saving overdose reversal medications.
- 5) Research: More research on pain and addiction.

Currently, the HHS now breaks down its strategy for combating the opioid epidemic and preventing overdoses into four categories. Each of these categories will be discussed in greater detail below, but they include:³

- 1) Primary Prevention
- 2) Harm Reduction
- 3) Evidence-Based Treatment
- 4) Recovery Support

Primary Prevention

Primary prevention is a multitiered approach to preventing individuals from misusing and subsequently becoming addicted to opioids. Decreasing the number of people who abuse and become addicted to opioids is key to decreasing the number of overall overdoses and deaths. Primary prevention includes large-scale strategies to decrease overall opioid abuse as well as individualized interventions on high-risk patients.³

The Helping to End Addiction Long-term (HEAL) Initiative is a National Institute of Health (NIH) program that researches opioid abuse prevention strategies. The goal is to provide healthcare providers with evidence-based opioid abuse prevention strategies, better pain management strategies, and better opioid use disorder treatments and addiction services.³

One area of focus is the ability to efficiently identify patients with a high risk for opioid abuse, with the goal of providing access to preventative measures to these patients. Studying socioeconomic determinants and their role in access to opioid abuse prevention services is also a focus. Providing prevention measures during periods of time when the risk of beginning to abuse opioids is high (such as when a patient is initially started on prescription opioids or during the transitions experienced during puberty and into adulthood) is highlighted in the program as well. The Adolescent Brain Cognitive Development (ABCD) Study is another NIH program aimed at studying the changes that occur during brain development, which could help researchers to understand drug abuse better and develop preventative strategies.³

Some common risk factors for developing an opioid use disorder include the following:¹⁸

- History of substance abuse
- Untreated mental health condition
- Young age
- Social or family situations that promote substance abuse

Another aspect of the primary prevention of opioid abuse is developing safer, more effective treatments for pain. The increased use of opioids in chronic, non-cancer pain may have helped fuel the opioid epidemic, but it also drew attention to a drastically undertreated condition.³ In 2022, the Centers for Disease Control (CDC) provided updated guidelines for prescribing opioids for pain. The updated guidelines are designed to help healthcare providers do the following:¹⁹

- 1) Decide whether to start opioids in a patient
- 2) After deciding whether opioid treatment is appropriate for a patient, selecting specific opioids and dosages
- 3) Determining the duration of opioid treatment and follow up
- 4) Determining the risks and potential negative impacts of initiating opioid treatment

Primary prevention also includes avoiding medications that may contribute to a patient overdosing on opioids.³ Certain medications are known to have additive or synergistic effects with opioids, and avoiding prescribing these medications simultaneously helps to minimize the risk of overdose. Benzodiazepines, when combined with opioids, significantly increase the risk of overdose and death. It is quite common for a patient to have both opioids and benzodiazepines in their system at the time of death following an overdose. In addition to those taking both opioids and benzodiazepines knowingly, benzodiazepines are often found in illicit opioid products, meaning these patients may be unaware that they are taking both substances.²⁰

Harm Reduction

Harm reduction is another important factor in combating the opioid epidemic and preventing overdoses. Harm reduction strategies aim to minimize the damage caused by the abuse of drugs, such as opioids, both for the individual and from a public health perspective. Continuing to provide help and healthcare to all individuals, even those who abuse drugs (including opioids), and attempting to eliminate the stigma regarding substance abuse are also keys to harm reduction. There are several different strategies to attempt to decrease the harm caused by drug abuse.³

One strategy in harm reduction is the use of fentanyl testing strips.³ Fentanyl (and other potent synthetic opioids) are increasingly the culprit in overdose cases. People may unknowingly ingest fentanyl as it is a common adulterant in illicit drug products.¹ Providing fentanyl testing strips for people who abuse opioids and other drugs could potentially allow them to avoid unknowingly ingesting fentanyl and may decrease overdoses.

Syringe services programs are another harm reduction approach that has become more widespread. These programs provide people with clean syringes and safe places to dispose of used syringes. They do not reduce harm from overdose but instead decrease the likelihood that blood-borne pathogens (such as HIV and Hepatitis C) can spread to people who would share needles if these programs were not available. Syringe services programs may also work with programs that provide blood-borne pathogen testing and treatment for people infected with blood-borne pathogens to reduce the risk of these diseases spreading further.³

If not treated promptly, an opioid overdose can lead to respiratory depression and death. Naloxone, an opioid antagonist, is a safe and extremely effective medication that reverses the effects of the opioid and can restore breathing.²¹ Increasing access and availability to naloxone for first responders and other people who are at high risk of coming into contact with someone overdosing on opioids (such as family members or friends of people taking opioids) is a vital component of the harm reduction aspect of combating the opioid epidemic.³ Many states have a standing order that allows healthcare professionals (including pharmacists) to provide naloxone to anyone that requests it. Several states also allow third-party prescribing, where a healthcare provider prescribes naloxone to someone other than the intended recipient of the medication. For example, the parent of a child who abuses opioids could obtain a prescription for naloxone to use on their child in the event of an opioid overdose.²²

Evidence-Based Treatment

Medication-Assisted Treatment

Medication-Assisted Treatment (MAT) is a treatment approach that uses prescription medications to treat opioid use disorder.¹² It is used in combination with counseling to help patients stay in recovery. The Drug Addiction Treatment Act of 2000 (DATA 2000) was the initial legislation that laid the framework for the current use of MAT. Prior to DATA 2000, the only option for patients to get access to MAT was from outpatient treatment

facilities, which would dispense small supplies of medications (such as methadone) to help patients in their recovery. These facilities were approved by the Narcotic Addict Treatment Act of 1974 and remained the only option for patients until DATA 2000 was signed into law.¹²

DATA 2000 allows qualified healthcare providers that have met the requirements set forth in the legislation to prescribe schedule III-V controlled substances to treat opioid use disorder. Providers wanting to prescribe these medications for opioid use disorder must complete training outlined by the U.S. Department of Health and Human Services Substance Abuse and Mental Health Services Administration (SAMHSA). Healthcare professionals that have completed the required training and have obtained the waiver from SAMHSA to prescribe schedule III-V controlled substances for opioid use disorder can be identified by the presence of an "X" as the first letter in their DEA number on the prescription.¹²

Subsequent legislation has further expanded the use of MAT for opioid use disorder. In 2016, the Comprehensive Addiction and Recovery Act was signed into law. Some aspects of the law include the following:²³

- Increased prevention and educational initiatives
- Increased accessibility of naloxone for first responders to aid in the reversal of overdoses
- Increased resources for people in correctional settings
- Increased sites to dispose of medications no longer being used
- Expanded access to opioid use disorder treatment, including MAT
- Reinforce the importance of prescription drug monitoring programs

The Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) of 2018 further expanded access to MAT. It allows more providers (including nurse practitioners, physician assistants, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives) to prescribe MAT. It also expands the ability of each healthcare provider to treat more patients with MAT.¹²

Currently, the only controlled substance that can be prescribed and dispensed to a patient for MAT in opioid use disorder is buprenorphine.¹² Methadone is also FDA-approved for MAT in opioid use disorder; however, it must be administered by a healthcare provider in an outpatient treatment facility on a daily basis, and only long-term, stable patients are ever allowed to take the medication at home.²⁴ Buprenorphine is available in several different formulations approved for use in opioid use disorder, including sublingual film, sublingual tablet, subcutaneous injection, and subdermal implant. Buprenorphine is sometimes formulated in combination with naloxone in an effort to deter misuse. If taken appropriately, there is minimal naloxone absorption. If taken by a non-prescribed route (such as intravenously), the naloxone will block some of the effects of buprenorphine.²⁵

Buprenorphine is a mu-opioid receptor partial agonist, a kappa-opioid receptor antagonist, a delta-opioid receptor agonist, and an ORL-1 receptor partial agonist. Activation of mu-receptors leads to analgesia and euphoria, as well as respiratory depression and opioid dependence. Buprenorphine has a high affinity for mu-opioid receptors, only partially activates opioid receptors, and slowly detaches from the receptor, allowing it to compete for opioid receptor sites with full mu-opioid receptor agonists.²⁵ This can be beneficial in the event that a patient relapses and takes a full opioid while being treated with buprenorphine. In this situation, the buprenorphine will compete with the full opioid for the limited opioid receptors and decrease the effects that the full opioid will have, including analgesia, euphoria, and respiratory depression.²⁶ Treatment with either buprenorphine or methadone for opioid use disorder has been shown to decrease the risk of death.²⁷

Treatment strategies to combat the opioid epidemic will continue to evolve over time. Increasing access to treatment of opioid use disorder for all patients is vital in this fight. Developing strategies that increase patients' willingness to accept treatment and retain these patients once they are actively receiving treatment are also important future goals.³

Neonatal Opioid Withdrawal Syndrome

Another important treatment aspect of combating the opioid crisis is developing a better understanding of neonatal opioid withdrawal syndrome (NOWS).³ As the opioid epidemic has continued to surge, its use has increased in pregnant women. There was a greater than four-fold increase in the incidence of NOWS from 2004 to 2014.²⁸ There is very little information concerning the long-term effects of patients born with NOWS. The Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW) Program is a large-scale program involving numerous research hospitals throughout the United States that is part of the NIH HEAL initiative discussed above. The goal of this program is to improve the treatment of patients exposed to opioids in the womb and accumulate data on the long-term effects of NOWS to help guide treatment in the future.³

Some of the symptoms of NOWS include tremors, irritability, diarrhea, sweating, a high-pitched cry, nasal congestion and sneezing, sleep disturbances, fever, increased yawning, and skin excoriation.²⁸ Many of these symptoms are common in adult patients experiencing opioid withdrawal as well. Pharmacological and nonpharmacological measures are necessary to support a patient diagnosed with NOWS.²⁸ Allowing the mother and infant to stay in the same room may decrease the severity of NOWS. Increasing the frequency of feeds and decreasing the amount given to the infant during each feeding session may also help with NOWS. The decision to breastfeed should be made on a case-by-case basis, but breastfeeding should not be withheld strictly because the mother is receiving MAT.²⁸ Pharmacological treatment should be individualized based on the patient's severity of symptoms. Morphine and methadone are traditionally the most common opioids used in the treatment of NOWS. Buprenorphine is also an option, but more research is needed regarding its use in NOWS. Other medications used to manage symptoms, such as clonidine and phenobarbital, are sometimes used in refractory cases.²⁸

Recovery Support

Once patients are actively receiving treatment for opioid use disorder, it is important that they continue to receive services to help in their overall recovery. Recovery will be a lifelong process, and recovery support services are an essential component of the patient's treatment. Peer support groups and assistance with housing and employment help patients overcome some of the challenges they may face while in recovery. Improving access to recovery support services and improving the overall quality of these services will help more patients on their path to recovery.³

An example of a recovery support service is the Peer Recovery Center of Excellence.²⁹ It is led by other patients in recovery and is funded by the Substance Abuse and Mental Health Administration (SAMHSA). It provides training and support for substance use disorder and patients in recovery.²⁹

Pharmacogenomics

Pharmacogenomics is an evolving research branch that studies how an individual patient's genetic sequence affects their response to different medications.³⁰ Recent research has focused on whether specific genetic deviations may be risk factors for opioid abuse and overdose.³¹ Genetic variations can play a role in pharmacodynamics and pharmacokinetics and affect how patients respond to medications, including opioids. If further research into pharmacogenomics can identify all genes associated with an increased risk of opioid abuse and overdose, these patients can be monitored more closely, or an alternative treatment can be selected to help minimize the risk to the patient.³¹ As pharmacogenomics evolves, each patient's treatment will be much more individualized to a plan that is most likely to provide them benefits while minimizing the risk of harm.³¹

Summary

Opioids are an extremely useful class of medications most commonly used to treat pain. They are used in several different clinical situations,

including the short-term treatment of acute pain, and chronic pain caused by significant injuries or illnesses such as cancer. Opioids are vital in helping to make invasive procedures, such as surgery and intubation, possible. Despite their benefits, they are also one of the most misused substances and account for the majority of fatal drug overdoses in the United States. Opioid use disorder and overdose have become a public health emergency that will require a multifaceted approach to help patients affected by it. Primary prevention, harm reduction, evidence-based treatment, and recovery support are four key areas that can help address the different aspects of the opioid crisis.

Course Test

1. Which opioid has become the benchmark by which all subsequent opioids have been compared?

- a. Oxycodone
- b. Hydrocodone
- c. Morphine
- d. Methadone

2. Which of the following accounts for the majority of opioid-related overdose deaths?

- a. Fentanyl (and other synthetic opioids)
- b. Morphine
- c. Heroin
- d. Oxycodone

3. Common risk factors for developing an opioid use disorder include

- a. young age.
- b. history of substance misuse or an untreated mental health condition.
- c. social or family situations that promote substance misuse.
- d. All of the above

4. True or False: Benzodiazepines, when combined with opioids, significantly increase the risk of overdose and death.

- a. True
- b. False

5. Harm reduction strategies include which of the following?

- a. Increasing naloxone availability
- b. Syringe service programs
- c. Fentanyl testing programs
- d. All of the above

6. Which two medications are FDA-approved as Medication Assisted Treatment (MAT) for opioid use disorder?

- a. Methadone and oxycodone
- b. Methadone and buprenorphine
- c. Oxycodone and buprenorphine
- d. Methylphenidate and buprenorphine

7. True or False: If an infant is born with neonatal opioid withdrawal syndrome, the mother cannot breastfeed the infant if the mother is receiving MAT.

- a. True
- b. False

8. Healthcare professionals that have completed the required training and have obtained the waiver from SAMHSA to prescribe schedule III-V controlled substances for opioid use disorder can be identified by the presence of what letter as the first letter in their DEA number on a prescription.

- a. D
- b. B
- c. X
- d. Z

9. Buprenorphine is available to treat opioid use disorder in all of the following formulations except

- a. sublingual film.
- b. sublingual tablet.
- c. intravenously.
- d. subcutaneous injection.

10. Which of the following are examples of recovery support?

- a. Peer support groups
- b. Assistance with housing
- c. Assistance with employment
- d. All of the above

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