

# Opioid-Related Disorders

Chapter 467 | Part 13: Neurologic Disorders | Part 13 – Neurologic Disorders | DETAILED EDITION

## KEY CLINICAL POINTS

1. Opioid Use Disorder (OUD) is defined in DSM-5 (2022) as repeated use of the opiate during a 12-month period while producing problems in two or more areas including tolerance, withdrawal, use of greater amounts of opioids than intended, craving, and use despite adverse consequences.
2. In 2022, 8.9 million United States residents misused pain relievers and >76,000 overdose deaths involved opioids, nearly half combined with stimulants.
3. Naloxone dosing for fentanyl overdoses may need to be twice that needed for other opioids; recent rescue preparations contain twice the traditional dosing.
4. Methadone prolongs QT interval at rates as high as 16% above rates in non-methadone-maintained, drug-injecting patients.
5. Buprenorphine is a partial opioid agonist; overdose is nearly impossible because as the dose increases, it has greater opioid antagonist than agonist activity.
6. Withdrawal symptoms begin 8–10 h after the last dose; acute course lasts 7–10 days; protracted abstinence lasts 26–30 weeks.
7. Clonidine and lofexidine are alpha-adrenergic agonists used for detoxification to suppress NE neuronal activation during withdrawal.
8. Naltrexone must be administered only after detoxification from opioids to avoid precipitating withdrawal.
9. Intravenous opioid use carries risk of hepatitis B, HIV/AIDS, septic complications (meningitis, osteomyelitis, abscesses), and necrosis with xylazine addition.
10. Routes of administration that slowly increase opioid blood and brain levels (oral, transdermal) are effective for analgesia but do not produce an opioid high.

## FIGURES IN THIS CHAPTER

1. Normal mu-receptor activation by endogenous opioids...

## 1. DEFINITION & OVERVIEW

- Opioid analgesics have been used since at least 300 b.c.
- Nopenthe (Greek for 'free from sorrow') helped the hero of the Odyssey.

- Widespread opium smoking in China and the Near East has caused harm for centuries.
- Since the first chemical isolation of opium and codeine 200 years ago, a wide range of synthetic opioids have been developed.
- Opioid receptors were cloned in the 1990s.
- Two of the cycles most important adverse effects of all these agents are the development of opioid use disorder and overdose.
- Prescription opioids are primarily used for pain management, but due to ease of availability individuals procure and misuse these drugs with dire consequences.
- In 2022, for example, 8.9 million United States residents misused pain relievers and >76,000 overdose deaths involved opioids, nearly half combined with stimulants.
- These numbers continue to increase and have accelerated due to mixing of high-potency fentanyl derivatives with other opioids and stimulants.
- The accelerating death rates are partially because reversal of fentanyl overdoses can require severalfold larger doses of naloxone than the doses in the intranasal devices used for nonmedical street resuscitations.
- Fentanyl-associated deaths also increased during the COVID-19 pandemic.
- The World Drug Report attributes the greatest global burden of morbidity and mortality to opioid misuse, including disease transmission, increased health care, crime, law enforcement, family distress, and lost productivity.

### 1.1 Diagnostic Criteria

---

- The terms dependence and addiction have been replaced with opioid use disorder, opioid intoxication, and opioid withdrawal.
- *Opioid use disorder is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; 2022) as the repeated use of the opiate during a 12-month period while producing problems in two or more areas including tolerance, withdrawal, use of greater amounts of opioids than intended, craving, and use despite adverse consequences.*
- This new definition reduces the diagnostic criteria from three problem areas to two.
- This reduction has not changed the rates of these disorders because most opioid-using individuals meet more than three criteria.

## 2. EPIDEMIOLOGY

---

- A striking recent aspect of illicit opioid use has been its marked increase as the gateway to illicit drugs in the United States.
- Since 2007, prescription opiates have surpassed marijuana as the most common illicit drug that adolescents initially use, although overall rates of opioid use are far lower than marijuana.
- The most used opioids had been diverted prescriptions for oxycodone and hydrocodone until about 2015, when fentanyl misuse and lethal overdose rose exponentially.
- Two opioid maintenance treatment agents—methadone and buprenorphine—are also misused, but at substantially lower rates.
- The partial opioid agonists such as butorphanol, tramadol, and pentazocine are misused even less frequently.
- Because the chemistry and general pharmacology of these agents are covered in major pharmacology texts, this chapter focuses on neurobiology and pharmacology relevant to opioid use disorder and its treatments.

### 3. ETIOLOGY & PATHOPHYSIOLOGY

- After binding to mu opioid receptors, opioids downregulate intracellular messenger systems and activate potassium ion channels, as summarized in Table 467-1.
- All opioid receptors are G protein–linked and coupled to the cyclic adenosine monophosphate (cAMP) second messenger system and to G protein–coupled inwardly rectifying potassium channels (GIRKs).
- The GIRKs increase permeability to potassium ions, causing hyperpolarization and inhibiting action potential production.
- Thus, opioids inhibit the activity of all neurons with opioid receptors in and induce analgesia, sedation, and drug reinforcement through various brain pathways.
- Relevant pathways for the reinforcing euphoric effects of opioids appear to act include the mesolimbic dopaminergic pathway from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), where opioids indirectly increase synaptic levels of dopamine through inhibition of GABAergic neurons that inhibit both the VTA and the NAc.
- The positive subjective effects of opioid drugs also include mu receptor desensitization and internalization, potentially related to stimulation of  $\beta$ -arrestin signaling pathways.
- However, the 'high' only occurs when the rate of change in dopamine is fast.
- Large, rapidly administered doses of opioids block  $\gamma$ -aminobutyric acid (GABA) inhibition and produce a burst of VTA dopamine neuron activity that is associated with a 'high' in commonly misused substances.
- Therefore, routes of administration that slowly increase opioid blood and brain levels, such as oral and transdermal routes, are effective for analgesia and sedation but do not produce an opioid 'high' that follows smoking and intravenous routes.
- Other acute effects such as analgesia and respiratory depression involve opioid receptors located in other brain areas such as the periaqueductal grey for pain and medulla oblongata for respiration.
- Opioid tolerance and withdrawal are related to genetic polymorphisms that impact several proteins and that after chronic opioid dosing affect the functioning of the cAMP–protein kinase A (PKA)–cAMP response-element binding protein (CREB) intracellular cascade within the locus coeruleus (LC) (Fig. 467-1).
- Up to 50% of the risk for withdrawal is related to specific functional polymorphisms including one in the mu opioid receptor gene producing a threefold increase in this receptor's affinity for opioids and the endogenous ligand  $\beta$ -endorphin.
- Epigenetic DNA methylation changes in the mu receptor gene also act as compensation by inhibiting gene transcription and reducing the number of mu receptors.
- After chronic opioid dosing and its sustained inhibition of the cAMP molecular cascade as shown in Fig. 467-1, a compensation occurs in this cascade within the LC neurons that mediate opioid tolerance and withdrawal.
- Noradrenergic (NE) neurons in the LC activate the cerebral cortex.
- When large opioid doses saturate and activate all of the LC's mu receptors, action potentials cease.
- When this direct inhibitory effect is sustained over weeks and months of opioid use, a secondary set of adaptive changes occur to upregulate cyclic AMP enzyme activity.
- When the inhibiting opioid is abruptly discontinued, overactivity occurs in NE neurons of the LC that contribute to withdrawal symptoms (Fig. 467-1).
- This molecular model of NE neuronal activation during withdrawal has had important treatment implications, such as the use of the presynaptic  $\alpha$ -agonists clonidine and lofexidine to treat opioid withdrawal by again suppressing NE neuronal activation through feedback inhibition of this neuronal activity.
- Other contributors to withdrawal include deficits within the dopamine reward system and overactive neurotransmission within the glutamatergic system.

### 3.1 Receptor Actions

- Table 467-1 summarizes the actions of opioid receptors.

**Table 1** Table 467-1 Actions of Opioid Receptors

RECEPTOR TYPE	ACTIONS
Mu ( $\mu$ ) (e.g., morphine, buprenorphine)	Analgesia, reinforcement euphoria, cough and appetite suppression, decreased respirations, decreased GI motility, sedation, hormone changes, dopamine and acetylcholine release
Kappa ( $\kappa$ ) (e.g., butorphanol)	Dysphoria, decreased GI motility, decreased appetite, decreased respiration, psychotic symptoms, sedation, diuresis, analgesia
Delta ( $\delta$ ) (e.g., etorphine)	Analgesia, euphoria, physical dependence, hormone changes, appetite suppression, dopamine release
Nociceptin/orphanin FQ	Analgesia, appetite, anxiety, tolerance to opioids, hypotension, decreased GI motility, 5-HT and NE release

### 3.2 Molecular Cascade

- Figure 467-1 illustrates the normal mu-receptor activation by endogenous opioids inhibiting the cAMP-PKA-CREB cascade in noradrenergic neurons within the locus coeruleus (A) through inhibitory Gi/o protein influence on adenylyl cyclase (AC).
- Similarly, acute exposure to opioids (e.g., morphine) inhibits this system.
- Chronic exposure to opiates (B) leads to upregulation of the cAMP pathway in an attempt to oppose opioid-induced inhibitory influence.
- Upregulation of this system is involved in opioid tolerance.
- When the opioid is removed, unopposed noradrenergic neurotransmission is involved in opioid withdrawal.
- Upregulated PKA phosphorylates CREB, initiating the expression of various genes such as tyrosine hydroxylase (TH) and brain-derived neurotrophic factor (BDNF).
- BDNF is implicated in long-term neuroplastic changes in response to chronic opioids.

## 4. CLINICAL FEATURES

- The clinical features of opioid misuse are tied to the route of administration and rapidity of the drug reaching the brain.
- Intravenous and smoked administration rapidly produces high drug concentrations in the brain.
- This produces a 'rush,' followed by euphoria, a feeling of tranquility, and sleepiness ('the nod').
- Heroin produces effects that last 3–5 h, and several doses a day are required to forestall manifestations of withdrawal in chronic users.
- Symptoms of opioid withdrawal begin 8–10 h after the last dose.
- Lacrimation, rhinorrhea, yawning, and sweating appear first.
- Restless sleep followed by weakness, chills, gooseflesh ('cold turkey'), nausea and vomiting, muscle aches, involuntary movements ('kicking the habit'), hyperpnea, hyperthermia, and hypertension occur in later stages of the withdrawal syndrome.
- The acute course of withdrawal may last 7–10 days.

- A secondary phase of protracted abstinence lasts for 26–30 weeks and is characterized by hypotension, bradycardia, hypothermia, mydriasis, and decreased responsiveness of the respiratory center to carbon dioxide.
- Besides the brain effects of opioids on sedation and euphoria and the combined brain and peripheral nervous system effects on analgesia, a wide range of other organs can be affected.
- The release of several pituitary hormones is inhibited, including corticotropin-releasing factor (CRF) and luteinizing hormone, which reduces levels of cortisol and sex hormones and can lead to impaired stress responses and reduced libido.
- An increase in prolactin also contributes to the reduced sex drive in males.
- Two other hormones affected are thyrotropin, which is reduced, and growth hormone, which is increased.
- Respiratory depression results from opioid-induced insensitivity of brainstem neurons to increases in carbon dioxide, and in patients with pulmonary disease, this can result in clinically significant complications.
- In overdoses, aspiration pneumonia is common due to loss of the gag reflex.
- Opioids reduce gut motility, which is helpful for treating diarrhea but can lead to nausea, constipation, and anorexia with weight loss.
- Deaths occurred in early methadone maintenance programs due to severe constipation and toxic megacolon.
- Opioids such as methadone may prolong QT intervals and lead to sudden death in some patients.
- Orthostatic hypotension may occur due to histamine release and peripheral blood vessel dilation, which is an opioid effect usefully applied to managing acute myocardial infarction.
- During opioid maintenance, interactions with other medications are of concern; these include inducers of the cytochrome P450 system (usually CYP3A4) such as rifampin and carbamazepine.
- Heroin users, in particular, tend to use opioids intravenously and are likely to be polydrug users, also using alcohol, sedatives, cannabinoids, and stimulants.
- None of these other drugs are substitutes for opioids, but they have desired additive effects.
- Therefore, one needs to be sure that the person undergoing a withdrawal reaction is not also withdrawing from alcohol or sedatives, which might be more dangerous and more difficult to manage.
- Intravenous opioid use carries with it the risk of serious complications.
- The common sharing of hypodermic syringes can lead to infections with hepatitis B and HIV/AIDS, among others.
- Bacterial infections can lead to septic complications such as meningitis, osteomyelitis, and abscesses in various organs.
- Off-target effects or additions of other agents to opioids synthesized in illicit drug labs can lead to serious toxicity.
- For example, attempts to illicitly manufacture meperidine in the 1980s produced a parkinsonism-inducing neurotoxin, MPTP (Chap. 446).
- More recently, adding xylazine to illicit fentanyl markedly increased fentanyl's respiratory suppression, leading to overdose deaths.
- Individuals who inject fentanyl and xylazine also can develop necrosis and have an increased risk of limb amputation.

#### 4.1 Overdose Signs

---

- The diagnosis is based on recognition of characteristic signs and symptoms.
- Shallow and slow respirations.

- Pupillary miosis (mydriasis does not occur until significant brain anoxia supervenes).
- Bradycardia.
- Hypothermia.
- Stupor or coma.

## 4.2 Withdrawal Timeline

---

- Onset: 8–10 h after the last dose.
- Early symptoms: Lacrimation, rhinorrhea, yawning, sweating.
- Later symptoms: Restless sleep, weakness, chills, gooseflesh, nausea, vomiting, muscle aches, involuntary movements, hyperpnea, hyperthermia, hypertension.
- Acute course duration: 7–10 days.
- Protracted abstinence: 26–30 weeks (hypotension, bradycardia, hypothermia, mydriasis, decreased responsiveness to CO<sub>2</sub>).

## 5. DIFFERENTIAL DIAGNOSIS

---

- Polydrug use (alcohol, sedatives, cannabinoids, stimulants) can mimic or complicate opioid withdrawal.
- Xylazine addition to illicit fentanyl can mimic opioid overdose but with increased respiratory suppression and necrosis.
- MPTP neurotoxin can cause parkinsonism.
- Precipitated withdrawal in patients dependent on fentanyl or on maintenance doses of methadone (>80 mg daily) when starting buprenorphine.

## 6. INVESTIGATIONS & DIAGNOSIS

---

- Blood or urine toxicology studies can confirm a suspected diagnosis.
- Immediate management must be based on clinical criteria.
- If naloxone is not administered, progression to respiratory and cardiovascular collapse leading to death occurs.
- With fentanyl overdoses, the naloxone dose may be twice that needed for other opioids.
- Recent rescue preparations contain twice the traditional dosing.

### 6.1 Diagnostic Criteria

---

- DSM-5 criteria: Repeated use of the opiate during a 12-month period while producing problems in two or more areas including tolerance, withdrawal, use of greater amounts of opioids than intended, craving, and use despite adverse consequences.

## 7. MANAGEMENT & TREATMENT

---

- The acute treatment of opioid overdose with naloxone or nalmefene is a medical emergency.
- After reversal of that life-threatening complication, clinicians have two general treatment options: opioid maintenance or detoxification.
- Opioid agonist and partial agonist medications are commonly used for both maintenance and detoxification purposes.
- $\alpha$ -Adrenergic agonists are primarily used for detoxification.
- Antagonists are used to accelerate detoxification and then continued after detoxification to prevent relapse.

- The residential medication-free programs have had some success but generally less than the medication-based programs.
- Success of the various treatment approaches is assessed as retention in treatment and reduced opioid and other drug use.
- Secondary outcomes, such as reduced HIV risk behaviors, crime, psychiatric symptoms, medical comorbidity, and overdoses, also indicate successful treatment.
- Potentially lethal overdoses require rapid recognition and treatment with naloxone or nalmefene, two highly specific reversal agents that are relatively free of complications.
- The diagnosis is based on recognition of characteristic signs and symptoms, including shallow and slow respirations, pupillary miosis (mydriasis does not occur until significant brain anoxia supervenes), bradycardia, hypothermia, and stupor or coma.
- Blood or urine toxicology studies can confirm a suspected diagnosis, but immediate management must be based on clinical criteria.
- If naloxone is not administered, progression to respiratory and cardiovascular collapse leading to death occurs.
- With fentanyl overdoses, the naloxone dose may be twice that needed for other opioids, and recent rescue preparations contain twice the traditional dosing.
- Additionally, nalmefene has recently become available for treatment of overdose and has higher potency and lasts longer than naloxone.
- Opioids generally do not produce seizures except for unusual cases of polydrug use with the opioid meperidine, with high doses of tramadol, or in the newborn.
- In addition to naloxone, management of overdose requires support of vital functions, including intubation if needed (Table 467-2).
- If the overdose is due to buprenorphine or fentanyl, then naloxone might be required at total doses of 10 mg or greater, but primary buprenorphine overdose is nearly impossible because this agent is a partial opioid agonist, meaning that as the dose of buprenorphine is increased, it has greater opioid antagonist than agonist activity.
- Thus, a 0.2-mg buprenorphine dose leads to analgesia and sedation, while a hundred times greater 20-mg dose produces profound sedation.
- Because naloxone only lasts a few hours and most opioids last considerably longer, an IV naloxone drip with close monitoring is frequently employed to provide a continuous level of antagonism for 24–72 h depending on the opioid used in the overdose (e.g., morphine vs methadone).
- Whenever naloxone has only a limited effect, other sedative drugs that produce significant overdoses must be considered.
- The most common are benzodiazepines, which have produced overdoses and deaths in combination with buprenorphine.
- A specific antagonist for benzodiazepines, flumazenil at 0.2 mg/min can rapidly reverse overdoses, but it may precipitate seizures and increase intracranial pressure.
- Like naloxone, administration for a prolonged period is usually required because most benzodiazepines remain active for considerably longer than flumazenil.
- Support of vital functions may include oxygen and positive-pressure breathing, IV fluids, pressor agents for hypotension, and cardiac monitoring to detect QT prolongation, which might require specific treatment.
- Activated charcoal and gastric lavage may be helpful for oral ingestions, but intubation will be needed if the patient is stuporous.
- Methadone maintenance substitutes a once-daily oral opioid dose for three to four times daily heroin.

- Methadone saturates the opioid receptors and, by inducing a high level of opioid tolerance, blocks the euphoria from additional opioids.
- Buprenorphine, a partial opioid agonist, also can be given once daily at sublingual doses of 4–32 mg daily, and in contrast to methadone, it can be given in an office-based primary care setting.
- Methadone's slow onset of action when taken orally, long elimination half-life (24–36 h), and production of cross-tolerance at doses from 80 to 150 mg are the basis for its efficacy in treatment retention and reductions in IV drug use, criminal activity, and HIV risk behaviors and mortality.
- Methadone can prolong the QT interval at rates as high as 16% above rates in non-methadone-maintained, drug-injecting patients, but it has been used safely in the treatment of opioid use disorder for >40 years.
- Unlike the full agonist methadone, buprenorphine is a partial agonist of mu-opioid receptors with a slow onset and long duration of action.
- Its partial agonism reduces the risk of unintentional overdose but limits its efficacy to patients who need the equivalent of only 60–70 mg of methadone, and many patients in methadone maintenance require higher doses of up to 150 mg daily.
- Buprenorphine is combined with naloxone at a 4:1 ratio to reduce its abuse liability.
- Because of pediatric exposures and diversion of buprenorphine to illicit use, mucosal films are now used rather than sublingual pills that can be crushed and snorted.
- A long-acting buprenorphine injection that lasts a month is also available to prevent illicit diversion and to enhance compliance.
- Primary care physicians often prescribe buprenorphine for opioid use disorder, which has reduced opioid-related deaths and drug-injection-related medical morbidity with treatment retention as high as 70% over a 6-month follow-up period.
- Buprenorphine does not appear to lead to better outcomes than methadone but is superior to clonidine in reducing symptoms of withdrawal, in retaining patients in a withdrawal protocol, and in completing treatment, although it can precipitate withdrawal in patients dependent on fentanyl or on maintenance doses of methadone (>80 mg daily).
- Several  $\alpha$ -adrenergic agonists have relieved opioid withdrawal by suppressing hyperactivity.
- Clonidine relieves some signs and symptoms of opioid withdrawal such as lacrimation, rhinorrhea, muscle pain, joint pain, restlessness, and gastrointestinal symptoms.
- Related agents are lofexidine, guanfacine, and guanabenz acetate.
- Lofexidine can be dosed up to ~2 mg/d and appears to be associated with fewer adverse effects.
- Clonidine or lofexidine is typically administered orally, in three or four doses per day, with dizziness, sedation, lethargy, and dry mouth as the primary adverse side effects.
- Outpatient-managed withdrawal regimens require close follow-up, often with naltrexone maintenance to prevent relapse.
- The opioid antagonist naltrexone, typically combined with an  $\alpha$ -adrenergic agonist, has been purported to shorten the duration of withdrawal without increasing patient discomfort.
- Completion rates using naltrexone and clonidine range from 75 to 81% compared to 40 to 65% for methadone or clonidine alone.
- Ultrarapid opioid detoxification is an extension of this approach using anesthetics but is highly controversial due to the medical risks and mortality associated with it.
- Stopping opioid use is much easier than preventing relapse.
- Long-term relapse prevention for individuals with opioid use disorder requires combined pharmacologic and psychosocial approaches.
- Chronic users tend to prefer pharmacologic approaches; those with shorter histories of drug use are more amenable to detoxification and psychosocial interventions.

- Most opioid users enter medication-free treatments in inpatient, residential, or outpatient settings, but 1- to 5-year outcomes are very poor compared to pharmacotherapy except for residential settings lasting 6–18 months.
- The residential programs require full immersion in a regimented system with progressively increasing levels of independence and responsibility within a controlled environment.

## 7.1 Opioid Overdose Management

- Establish airway. Intubation and mechanical ventilation may be necessary.
- Naloxone 0.4–2.0 mg (IV, IM, or endotracheal tube). Onset of action with IV is ~1–2 min.
- Repeat doses of naloxone if needed to restore adequate respiration or a continuous infusion of naloxone can be used.
- One-half to two-thirds of the initial naloxone dose that reversed the respiratory depression is administered on an hourly basis (note: naloxone dosing is not necessary if the patient has been intubated).
- If the overdose is due to buprenorphine or fentanyl, then naloxone might be required at total doses of 10 mg or greater.
- Primary buprenorphine overdose is nearly impossible because this agent is a partial opioid agonist, meaning that as the dose of buprenorphine is increased, it has greater opioid antagonist than agonist activity.
- Thus, a 0.2-mg buprenorphine dose leads to analgesia and sedation, while a hundred times greater 20-mg dose produces profound sedation.

**Table 2 Table 467-2 Management of Opioid Overdose**

INTERVENTION	DETAILS
Airway	Establish airway. Intubation and mechanical ventilation may be necessary.
Naloxone	0.4–2.0 mg (IV, IM, or endotracheal tube). Onset of action with IV is ~1–2 min.
Repeat Dosing	Repeat doses of naloxone if needed to restore adequate respiration or a continuous infusion of naloxone can be used.
Hourly Maintenance	One-half to two-thirds of the initial naloxone dose that reversed the respiratory depression is administered on an hourly basis (note: naloxone dosing is not necessary if the patient has been intubated).

## 7.2 Detoxification

- The principles of detoxification are the same for all drugs: to substitute a longer-acting, orally active, pharmacologically equivalent medication for the substance being used, stabilize the patient on that medication, and then gradually withdraw the substituted medication.
- Methadone and buprenorphine are the two principal medications used to treat opioid use disorder.
- Clonidine, a centrally acting sympatholytic agent, has also been used for detoxification in the United States.
- By reducing central sympathetic outflow, clonidine mitigates many of the signs of sympathetic overactivity but typically requires augmentation with other agents.
- Clonidine has no narcotic action and is not addictive.

- Lofexidine, a clonidine analogue with fewer hypotensive effects, was approved for use in the United States in 2018 for management of opioid withdrawal symptomology.
- Methadone for Detoxification: Dose-tapering regimens for detoxification using methadone range from 2–3 weeks to as long as 180 days, but this approach is controversial given the relative effectiveness of methadone maintenance and the low success rates of detoxification.
- Unfortunately, most patients tend to relapse to heroin or other opioids during or after the detoxification period, indicative of the chronic and relapsing nature of opioid use disorder.
- Buprenorphine for Detoxification: Buprenorphine does not appear to lead to better outcomes than methadone but is superior to clonidine in reducing symptoms of withdrawal, in retaining patients in a withdrawal protocol, and in completing treatment, although it can precipitate withdrawal in patients dependent on fentanyl or on maintenance doses of methadone (>80 mg daily).
- $\alpha$ -Adrenergic Agonists for Detoxification: Several  $\alpha$ -adrenergic agonists have relieved opioid withdrawal by suppressing hyperactivity.
- Clonidine relieves some signs and symptoms of opioid withdrawal such as lacrimation, rhinorrhea, muscle pain, joint pain, restlessness, and gastrointestinal symptoms.
- Related agents are lofexidine, guanfacine, and guanabenz acetate.
- Lofexidine can be dosed up to ~2 mg/d and appears to be associated with fewer adverse effects.
- Clonidine or lofexidine is typically administered orally, in three or four doses per day, with dizziness, sedation, lethargy, and dry mouth as the primary adverse side effects.
- Rapid and Ultrarapid Opioid Detoxification: The opioid antagonist naltrexone, typically combined with an  $\alpha$ -adrenergic agonist, has been purported to shorten the duration of withdrawal without increasing patient discomfort.
- Completion rates using naltrexone and clonidine range from 75 to 81% compared to 40 to 65% for methadone or clonidine alone.
- Ultrarapid opioid detoxification is an extension of this approach using anesthetics but is highly controversial due to the medical risks and mortality associated with it.

### 7.3 Maintenance Therapy

---

- Methadone maintenance substitutes a once-daily oral opioid dose for three to four times daily heroin.
- Methadone saturates the opioid receptors and, by inducing a high level of opioid tolerance, blocks the euphoria from additional opioids.
- Methadone's slow onset of action when taken orally, long elimination half-life (24–36 h), and production of cross-tolerance at doses from 80 to 150 mg are the basis for its efficacy in treatment retention and reductions in IV drug use, criminal activity, and HIV risk behaviors and mortality.
- Methadone can prolong the QT interval at rates as high as 16% above rates in non-methadone-maintained, drug-injecting patients, but it has been used safely in the treatment of opioid use disorder for >40 years.
- Buprenorphine, a partial opioid agonist, also can be given once daily at sublingual doses of 4–32 mg daily, and in contrast to methadone, it can be given in an office-based primary care setting.
- Buprenorphine is combined with naloxone at a 4:1 ratio to reduce its abuse liability.
- Because of pediatric exposures and diversion of buprenorphine to illicit use, mucosal films are now used rather than sublingual pills that can be crushed and snorted.
- A long-acting buprenorphine injection that lasts a month is also available to prevent illicit diversion and to enhance compliance.
- Primary care physicians often prescribe buprenorphine for opioid use disorder, which has reduced opioid-related deaths and drug-injection-related medical morbidity with treatment retention as high as 70% over a 6-month follow-up period.

- Buprenorphine does not appear to lead to better outcomes than methadone but is superior to clonidine in reducing symptoms of withdrawal, in retaining patients in a withdrawal protocol, and in completing treatment, although it can precipitate withdrawal in patients dependent on fentanyl or on maintenance doses of methadone (>80 mg daily).

## 7.4 Antagonist Therapy

- Antagonist therapy blocks the action of self-administered opioids and should eventually extinguish the habit, but this therapy is poorly accepted by patients.
- Naltrexone, a long-acting pure opioid antagonist, can be given orally three times a week, or by monthly injection, which markedly improves adherence, reduces brain retention, and drug use.
- Because it is an antagonist, the patient must first be detoxified from opioids before starting naltrexone.
- It is safe even when taken chronically for years, is associated with few side effects (headache, nausea, abdominal pain), and can be given to patients infected with hepatitis B or C without producing hepatotoxicity.
- However, most providers refrain from prescribing naltrexone if liver function tests are three times above normal levels.
- Naltrexone maintenance combined with psychosocial therapy is effective in reducing heroin use.

## 8. PROGNOSIS & COMPLICATIONS

- Success of the various treatment approaches is assessed as retention in treatment and reduced opioid and other drug use.
- Secondary outcomes, such as reduced HIV risk behaviors, crime, psychiatric symptoms, medical comorbidity, and overdoses, also indicate successful treatment.
- Most opioid users enter medication-free treatments in inpatient, residential, or outpatient settings, but 1- to 5-year outcomes are very poor compared to pharmacotherapy except for residential settings lasting 6–18 months.
- The residential programs require full immersion in a regimented system with progressively increasing levels of independence and responsibility within a controlled environment.
- Intravenous opioid use carries with it the risk of serious complications.
- The common sharing of hypodermic syringes can lead to infections with hepatitis B and HIV/AIDS, among others.
- Bacterial infections can lead to septic complications such as meningitis, osteomyelitis, and abscesses in various organs.
- Off-target effects or additions of other agents to opioids synthesized in illicit drug labs can lead to serious toxicity.
- For example, attempts to illicitly manufacture meperidine in the 1980s produced a parkinsonism-inducing neurotoxin, MPTP (Chap. 446).
- More recently, adding xylazine to illicit fentanyl markedly increased fentanyl's respiratory suppression, leading to overdose deaths.
- Individuals who inject fentanyl and xylazine also can develop necrosis and have an increased risk of limb amputation.
- Deaths occurred in early methadone maintenance programs due to severe constipation and toxic megacolon.
- Opioids such as methadone may prolong QT intervals and lead to sudden death in some patients.
- Orthostatic hypotension may occur due to histamine release and peripheral blood vessel dilation, which is an opioid effect usefully applied to managing acute myocardial infarction.

## 9. SPECIAL CONSIDERATIONS

- During opioid maintenance, interactions with other medications are of concern; these include inducers of the cytochrome P450 system (usually CYP3A4) such as rifampin and carbamazepine.
- Heroin users, in particular, tend to use opioids intravenously and are likely to be polydrug users, also using alcohol, sedatives, cannabinoids, and stimulants.
- None of these other drugs are substitutes for opioids, but they have desired additive effects.
- Therefore, one needs to be sure that the person undergoing a withdrawal reaction is not also withdrawing from alcohol or sedatives, which might be more dangerous and more difficult to manage.
- Naltrexone can be given to patients infected with hepatitis B or C without producing hepatotoxicity.
- However, most providers refrain from prescribing naltrexone if liver function tests are three times above normal levels.

## 10. KEY PEARLS & CLINICAL TRAPS

- Routes of administration that slowly increase opioid blood and brain levels, such as oral and transdermal routes, are effective for analgesia and sedation but do not produce an opioid 'high' that follows smoking and intravenous routes.
- The 'high' only occurs when the rate of change in dopamine is fast.
- Large, rapidly administered doses of opioids block  $\gamma$ -aminobutyric acid (GABA) inhibition and produce a burst of VTA dopamine neuron activity that is associated with a 'high' in commonly misused substances.
- With fentanyl overdoses, the naloxone dose may be twice that needed for other opioids, and recent rescue preparations contain twice the traditional dosing.
- Primary buprenorphine overdose is nearly impossible because this agent is a partial opioid agonist, meaning that as the dose of buprenorphine is increased, it has greater opioid antagonist than agonist activity.
- Thus, a 0.2-mg buprenorphine dose leads to analgesia and sedation, while a hundred times greater 20-mg dose produces profound sedation.
- Methadone can prolong the QT interval at rates as high as 16% above rates in non-methadone-maintained, drug-injecting patients.
- Buprenorphine is superior to clonidine in reducing symptoms of withdrawal, in retaining patients in a withdrawal protocol, and in completing treatment, although it can precipitate withdrawal in patients dependent on fentanyl or on maintenance doses of methadone (>80 mg daily).

## FIGURES & ILLUSTRATIONS — FROM HARRISON'S

A striking recent aspect of illicit opioid use has been its marked increase as the gateway to illicit drugs in the United States. Since 2007, prescription opiates have surpassed marijuana as the most common illicit drug that adolescents initially use, although overall rates of opioid use are far lower than marijuana. The most used opioids had been diverted prescriptions for oxycodone and hydrocodone until about 2015, when fentanyl misuse and lethal overdose rose exponentially. Two opioid maintenance treatment agents—methadone and buprenorphine—are also misused, but at substantially lower rates, and the partial opioid agonists such as buprenorphine, tramadol, and pentazocine are misused even less frequently. Because the chemistry and general pharmacology of these agents are covered in major pharmacology texts, this chapter focuses on neurobiology and pharmacology relevant to opioid use disorder and its treatments. Although the neurobiology of misuse involves all four of the known opioid receptors—mu, kappa, delta, and nociceptin/orphanin—the mu receptor is the most clinically related to opioids.

#### NEUROBIOLOGY

After binding to mu opioid receptors, opioids downregulate intracellular messenger systems and activate potassium ion channels, as summarized in Table 467-1. All opioid receptors are G protein-linked and coupled to the cyclic adenosine monophosphate (cAMP) second messenger system and to G protein-coupled inwardly rectifying potassium channels (GIRKs). The GIRKs increase permeability to potassium ions, causing hyperpolarization and inhibiting action potential production. Thus, opioids inhibit the activity of all neurons with opioid receptors and induce analgesia, sedation, and drug reinforcement through various brain pathways.

Relevant pathways for the reinforcing euphoric effects of opioids include the mesolimbic dopaminergic pathway from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), where opioids indirectly increase synaptic levels of dopamine through inhibition of GABAergic neurons that inhibit both the VTA and the NAc. The positive subjective effects of opioid drugs also include mu receptor desensitization and internalization, potentially related to stimulation of  $\beta$ -arrestin signaling pathways. However, the "high" only occurs when the rate of change in dopamine is fast. Large, rapidly administered doses of opioids block  $\gamma$ -aminobutyric acid (GABA) inhibition and produce a burst of VTA dopamine neuron activity that is associated with a "high" in commonly misused substances. Therefore, routes of administration that slowly increase opioid blood and brain levels, such as oral and transdermal routes, are effective for analgesia and sedation but do not produce an opioid "high" that follows smoking and intravenous routes. Other acute effects such as analgesia and respiratory

TABLE 467-1 Actions of Opioid Receptors	
RECEPTOR TYPE	ACTIONS
Mu ( $\mu$ ) (e.g., morphine, buprenorphine)	Analgesia, reinforcement euphoria, cough and appetite suppression, decreased respirations, decreased GI motility, sedation, hormone changes, dopamine and acetylcholine release
Kappa ( $\kappa$ ) (e.g., butorphanol)	Dysphoria, decreased GI motility, decreased appetite, decreased respiration, psychotic symptoms, sedation, diuresis, analgesia
Delta ( $\delta$ ) (e.g., etorphine)	Analgesia, euphoria, physical dependence, hormone changes, appetite suppression, dopamine release
Nociceptin/orphanin (e.g., buprenorphine)	Analgesia, appetite, anxiety, tolerance to opioids, hypotension, decreased GI motility, 5-HT and NE release

Abbreviations: GI, gastrointestinal; 5-HT, serotonin; NE, norepinephrine.

depression involve opioid receptors located in other brain areas such as the periaqueductal grey for pain and medulla oblongata for respiration.

Opioid tolerance and withdrawal are related to genetic polymorphisms that impact several proteins and that after chronic opioid dosing affect the functioning of the cAMP-protein kinase A (PKA)-cAMP response-element binding protein (CREB) intracellular cascade within the locus coeruleus (LC) (Fig. 467-1). Up to 50% of the risk for withdrawal is related to specific functional polymorphisms including one in the mu opioid receptor gene producing a threefold increase in this receptor's affinity for opioids and the endogenous ligand  $\beta$ -endorphin. Epigenetic DNA methylation changes in the mu receptor gene also appear to act as compensation by inhibiting gene transcription and reducing the number of mu receptors.

After chronic opioid dosing and its sustained inhibition of the cAMP molecular cascade as shown in Fig. 467-1, a compensation occurs in this cascade within the LC neurons that mediate opioid tolerance and withdrawal. Noradrenergic (NE) neurons in the LC activate the cerebral cortex. When large opioid doses saturate and activate all of the LC's mu receptors, action potentials cease. When this direct inhibitory effect is sustained over weeks and months of opioid use, a secondary set of adaptive changes occur to upregulate cyclic AMP enzyme activity. When the inhibiting opioid is abruptly discontinued, overactivity occurs in NE neurons of the LC that contribute to withdrawal symptoms (Fig. 467-1). This molecular model of NE neuronal activation during withdrawal has had important treatment implications, such as the use of the presynaptic  $\alpha_2$ -agonists clonidine and lofevodine to treat opioid withdrawal by again suppressing NE neuronal activation

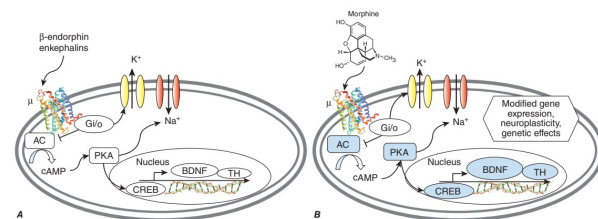


FIGURE 467-1 Normal mu-receptor activation by endogenous opioids inhibits the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA)-cAMP response-element binding protein (CREB) cascade in noradrenergic neurons within the locus coeruleus (A) through inhibitory Gi/o protein influence on adenylyl cyclase (AC). Similarly, acute exposure to opiates (e.g., morphine) inhibits this system, whereas chronic exposure to opiates (B) leads to upregulation of the cAMP pathway in an attempt to oppose opioid-induced inhibitory influence. Upregulation of this system is involved in opioid tolerance, and when the opioid is removed, unopposed noradrenergic neurotransmission is involved in opioid withdrawal. Upregulated PKA phosphorylates CREB, initiating the expression of various genes such as tyrosine hydroxylase (TH) and brain-derived neurotrophic factor (BDNF). BDNF is implicated in long-term neuroplastic changes in response to chronic opioids.

### Harrison's 22e · Figure 1

FIGURE 467-1 Normal mu-receptor activation by endogenous opioids inhibits the element binding protein (CREB) cascade in noradrenergic neurons within the locus Similarly, acute exposure to opioids (e.g., morphine) inhibits this system, whereas chronic to oppose opioid-induced inhibitory influence. Upregulation of this system is involved neurotransmission is involved in opioid withdrawal. Upregulated PKA phosphorylates and brain-derived neurotrophic factor (BDNF). BDNF is implicated in long-term — Figure 467-1: Normal mu-receptor activation by endogenous opioids inhibits the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA)-cAMP response-element binding protein (CREB) cascade in noradrenergic neurons within the locus coeruleus (A) through inhibitory Gi/o protein influence on adenylyl cyclase (AC). Similarly, acute exposure to opioids (e.g., morphine) inhibits this system, whereas chronic exposure to opiates (B) leads to upregulation of the cAMP pathway in an attempt to oppose opioid-induced inhibitory influence. Upregulation of this system is involved in opioid tolerance, and when the opioid is removed, unopposed noradrenergic neurotransmission is involved in opioid withdrawal. Upregulated PKA phosphorylates CREB, initiating the expression of various genes such as tyrosine hydroxylase (TH) and brain-derived neurotrophic factor (BDNF). BDNF is implicated in long-term neuroplastic changes in response to chronic opioids.