OPIOID USE CONSIDERATIONS

OPIOID PROPERTIES

- Receptor Activity
- Formulation and Half-Life
- Route of Administration
- Potency
- Source: Illicit vs Prescription
- Mixtures/Hidden Ingredients/ Potentiation
- Reversal of Opioid Overdose
- Evaluating for Presence of Opioids

Understanding Patient Opioid Use

Opioid use is a complex clinical scenario. Identified here are some considerations when screening for opioid use.

PATIENT FACTORS

- Comorbidities
- Demographic and Environmental Factors
- Medical History
- Body Composition
- Duration of Use and Tolerance
- Disclosure
- Stigma
- Diagnosis of Opioid Use Disorder

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Receptor Activity

Full Agonists

A **full agonist** binds to and fully activates the opioid receptor, by causing the largest conformational change which results in a maximal response, in a dose-dependent manner.

- Examples: heroin, morphine, codeine, oxycodone, meperidine, and fentanyl.

Partial Agonists

A **partial agonist** also binds to the opioid receptor but only causes a submaximal conformational change and, consequently, a submaximal response. The effect of a partial agonist is limited and further increases in the drug doses does not lead to an increase in response.

- Examples: levorphanol, tramadol, and oliceridine.

Antagonists

An **antagonist** binds to the opioid receptor without activating it and blocks the agonist activity, by preventing it from binding to the receptor and producing its effects.

- Examples: naloxone, naltrexone, and methylnaltrexone.

Receptor activity of opioid agonists and antagonists are presented in the **Table**.

Edinoff AN et al. *Anesth Pain Med*. 2021;11(4):e119156; Gress K et al. *Best Pract Res Clin Anaesthesiol*. 2020;34(3):449-461; Theriot J et al. *StatPearls [Internet]*. 2026; Comer SD, Cahil CM. *Neurosci Biobehav Rev*. 2019;106:49-57; Doi S et al. *Mol Pain*. 2016;12:1744806916654146; Olson KM et al. *PLoS One*. 2019;14(6):e0217371; Eastlack SC et al. *Pain Ther*. 2020;9(1):55-69; Dhesi M et al. *StatPearls [Internet]*. 2026; Jordan MR et al. *StatPearls [Internet]*. 2026; Kyhl LB et al. *Br J Clin Pharmacol*. 2016;81(2):290–300; Yasaei R et al. *StatPearls [Internet]*. 2026; Trescot AM et al. *Pain Physician*. 2008;11:S133-S153.

Examples of Opioids by Receptor Activity

Receptor Activity	
Full Agonists	
Morphine	μ receptor agonist
Codeine	
Hydrocodone	
Oxycodone	
Meperidine	
Fentanyl	μ receptor agonist other opioid receptor agonist (weaker affinity)
Hydromorphone	
Methadone	
Partial Agonist	
Tramadol	Opioid receptor agonist norepinephrine and serotonin reuptake inhibitor
Partial Agonist-Antagonist	
Buprenorphine	μ receptor partial agonist k receptor antagonist
Kratom, an herbal supplement	μ receptor agonist δ receptor antagonist
Antagonists	
Naloxone	highest affinity for blockade of μ opioid receptor blockade of k and δ opioid receptors
Nalmefene	μ and δ receptor antagonist partial κ receptor agonist
Naltrexone	highest affinity for blockade of μ opioid receptor

δ, delta; k, kappa; μ, mu.

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Formulation and Half-life

Opioid drugs can be classified as short- or long-acting medications. Both the half-life and administration formulation of an opioid medication contribute to the length of time that the medication may actively bind to opioid receptors.

Formulations and half-lives of select opioids are presented in the **Table**. Opioid pharmacokinetic and pharmacodynamic properties may be altered in states of physiological dysfunction, such as renal insufficiency or hepatic impairment. Properties of illicit street drugs containing opioids (e.g., illicit fentanyl and heroin) vary and may be unknown.

Chen YH et al. *Expert Rev Clin Pharmacol.* 2023;16(9):813–823; Malonne H et al. *Br J Clin Pharmacol.* 2004;57(3):270-278; Knotkova H et al. *J Pain Symptom Manage.* 2009;38(3):426-439; Shover CL et al. *Int J Drug Policy.* 2025;145:104977; Patel P et al. *StatPearls [Internet].* 2026; Trescot AM et al. *Pain Physician.* 2008;11:S133-S153; WHO. WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain. 2018; Ramos-Matos CF et al. *StatPearls [Internet].* 2026; Argoff CE et al. *Mayo Clin Proc.* 2009;84(7):602-612; Cofano S et al. *StatPearls [Internet].* 2026; Abi-Aad KR et al. *StatPearls [Internet].* 2026; Yasaei R et al. *StatPearls [Internet].* 2026; Sobieraj DM et al. Agency for Healthcare Research and Quality; 2019; Sadiq NM et al. *StatPearls [Internet].* 2026; Eastlack SC et al. *Pain Ther.* 2020;9(1):55-69; Dhesi M et al. *StatPearls [Internet].* 2026; Kumar et al. *StatPearls [Internet].* 2026; Taylor KP et al. *StatPearls [Internet].* 2026; Durrani M et al. *StatPearls [Internet].* 2026; MORPHINE SULFATE Prescribing Information; MORPHABOND ER Prescribing Information; Mugabure Bujedo B. *Pain Res Treat.* 2012;2012:612145; OXYCONTIN Prescribing Information; BUTRANS Prescribing Information; BRIXADI Prescribing Information; SUBLOCADE Prescribing Information.

Properties of Representative Short-acting and Long-acting Opioid Agonists, Partial Agonists, and Mixed Agonists-Antagonists

	Formulation(s)	Half-life	Duration of Action[a]
SHORT-ACTING			
Agonists			
Codeine	Oral solution, oral tablet	3 h	3-6 h
Fentanyl	IM, IV, TM	3.7 h	IV: 0.5-1 h TM: 2-4 h
Hydrocodone	Oral tablet	2.5-4 h	4-8 h
Hydromorphone IR	IV, IM, oral tablet, oral solution SQ, suppository	2-3 h	4-5 h
Meperidine	IM, IV, oral tablet, SQ, syrup	3-4 h	2-4 h
Morphine IR	IM, IV, oral capsule	2-3.5 h	3-5 h
Oxycodone IR	Oral capsule, oral solution, oral tablet	3-5 h	3-4 h
Partial Agonist			
Tramadol IR	Oral capsule, oral solution	5-7 h	1.6-1.9 h
Partial Agonist-Antagonist			
Buprenorphine	Buccal film, IM, IV, SL tablet	Varies with dose: 25-70 h	SL: 6-8 h
Kratom, an herbal supplement	Various	3 h	Varies
LONG-ACTING			
Agonists			
Fentanyl ER	TD patch	13-22 h	TD: 72 h
Hydromorphone ER	Oral tablet	8-15 h	13 h
Methadone	IM, IV, IT, oral solution, oral tablet, SQ	24 h	8-12 h
Morphine sulfate CR, ER	Oral capsule, oral tablet, epidural	11-13 h	Injection: 18-24 h Epidural: 48 h
Oxycodone CR, ER	Oral tablets	4.5 h	8-12 h
Partial Agonist			
Tramadol ER	Oral capsule	5-7 h	24 h
Partial Agonist-Antagonist			
Buprenorphine TD	TD patch	26 h	Formulation dependent (72-168 h)
Buprenorphine XR	SQ	Brixadi weekly: 3-5 days Brixadi monthly:19-26 days Sublocade: 43-60 days	Brixadi weekly: 1 week Brixadi monthly and Sublocade: 1 month

CR, controlled release; ER, extended release; h, hour; IM, intramuscular; IN, intranasal; IR, immediate release; IV, intravenous; IT, intrathecal; m, minute; SL, sublingual; SQ, subcutaneous; TD, transdermal; TM, transmucosal; XR, extended release.

[a]Dependent in part on severity of pain and on dose – often longer-lasting in very elderly and those with renal impairment.

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Route of Administration

Routes of administration for prescription opioids include:

See the **Table** for examples of opioids and routes of administration.

Oral, IV, and IN administration are the most common routes of administration for illicit prescription opioids.

NCI. PDQ Cancer Information Summaries. *Cancer Pain*. 2002; Young AM et al. *Harm Reduct J*. 2010;7:24; Patel P et al. *StatPearls [Internet]*. 2026; Ramos-Matos CF et al. *StatPearls [Internet]*. 2026; Cofano S et al. *StatPearls [Internet]*. 2026; Abi-Aad KR et al. *StatPearls [Internet]*. 2026; Yasaei R et al. *StatPearls [Internet]*. 2026; Sobieraj DM et al. Agency for Healthcare Research and Quality; 2019; Sadiq NM et al. *StatPearls [Internet]*. 2026; Eastlack SC et al. *Pain Ther*. 2020;9(1):55-69; Dhesi M et al. *StatPearls [Internet]*. 2026; Kumar et al. *StatPearls [Internet]*. 2025; Taylor KP et al. *StatPearls [Internet]*. 2025; Durrani M et al. *StatPearls [Internet]*. 2026; MORPHINE SULFATE Prescribing Information; Mugabure Bujedo B. *Pain Res Treat*. 2012;2012:612145; OXYCONTIN Prescribing Information; BUTRANS Prescribing Information; BRIXADI Prescribing Information; SUBLOCADE Prescribing Information.

Examples of Opioids by Receptor Activity

	Formulation(s)
SHORT-ACTING	
Agonists	
Codeine	Oral solution, oral tablet
Fentanyl	IM, IV, TM
Hydrocodone	Oral tablet
Hydromorphone IR	IV, IM, oral tablet, oral solution, SQ, suppository
Meperidine	IM, IV, oral tablet, SQ, syrup
Morphine IR	IM, IV, oral capsule
Oxycodone IR	Oral capsule, oral solution, oral tablet
Partial Agonist	
Tramadol IR	Oral capsule, oral solution
Partial Agonist-Antagonist	
Buprenorphine	Buccal film, IM, IV, SL tablet
Kratom, an herbal supplement	Various
LONG-ACTING	
Agonists	
Fentanyl ER	TD patch
Hydromorphone ER	Oral tablet
Methadone	IM, IV, IT, oral solution, oral tablet, SQ
Morphine sulfate CR, ER	Oral capsule, epidural
Oxycodone CR, ER	Oral tablets
Partial Agonist	
Tramadol ER	Oral capsule
Partial Agonist-Antagonist	
Buprenorphine TD	TD patch
Buprenorphine XR	SQ

CR, controlled release; ER, extended release; IM, intramuscular; IN, intranasal; IR, immediate release; IV, intravenous; IT, intrathecal; SL, sublingual; SQ, subcutaneous; TD, transdermal; TM, transmucosal; XR, extended release.

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Potency

Potency is defined as the dose required to produce a given effect. Potency differs widely among opioids and among individuals under varying conditions. Among opioid agonists, potencies may vary from micrograms to milligrams. Approximate potency of different opioids relative to morphine is presented in the **Table** below.

Potency of Opioids Relative to Morphine

	Potency Relative to Morphine[a]
Agonists	
Codeine	1/10
Fentanyl	TD: 100 (150)[b]
Hydrocodone	2/3
Hydromorphone	4-5 (5-7.5)[b]
Oxycodone	1.5 (2)[b]
Meperidine	1/8
Methadone	5-10[c]
Partial Agonist	
Tramadol	1/10
Partial Agonist-Antagonist	
Buprenorphine	SL: 80 TD: 100 (75-115)[b]
Kratom, an herbal supplement[d]	Mitragynine: 1/4 7-HMG: 10

7-HMG: 7-hydroxymitragynine; SL, sublingual; TD, transdermal.

[a]Data apply to oral and immediate-release formulations unless stated otherwise; [b]The numbers in parenthesis are the manufacturers' preferred relative potencies; [c]A single 5 mg dose of methadone is equivalent to morphine 7.5 mg, but a variable long plasma half-life and broad-spectrum receptor affinity result in a much higher-than-expected relative potency when administered regularly - sometimes much higher than the range given above. Therefore, guidance from a specialist is recommended for conversions to regularly administered methadone; [d]Mitragynine and 7-HMG are believed to be the primary active alkaloids in the plant that are responsible for the opioid activity of kratom.

Knotkova H et al. *J Pain Symptom Manage*. 2009;38(3):426-439; WHO. WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain. 2018; Green M et al. *Front Public Health*. 2024:12:1416689; Prozialeck WC et al. *J Am Osteopath Assoc*. 2012;112(12):792-799; DrugBank. Tramadol. DrugBank website; Knox C et al. DrugBank 6.0. Nucleic Acids Res. 2024 Jan 5;52(D1):D1265-D1275.

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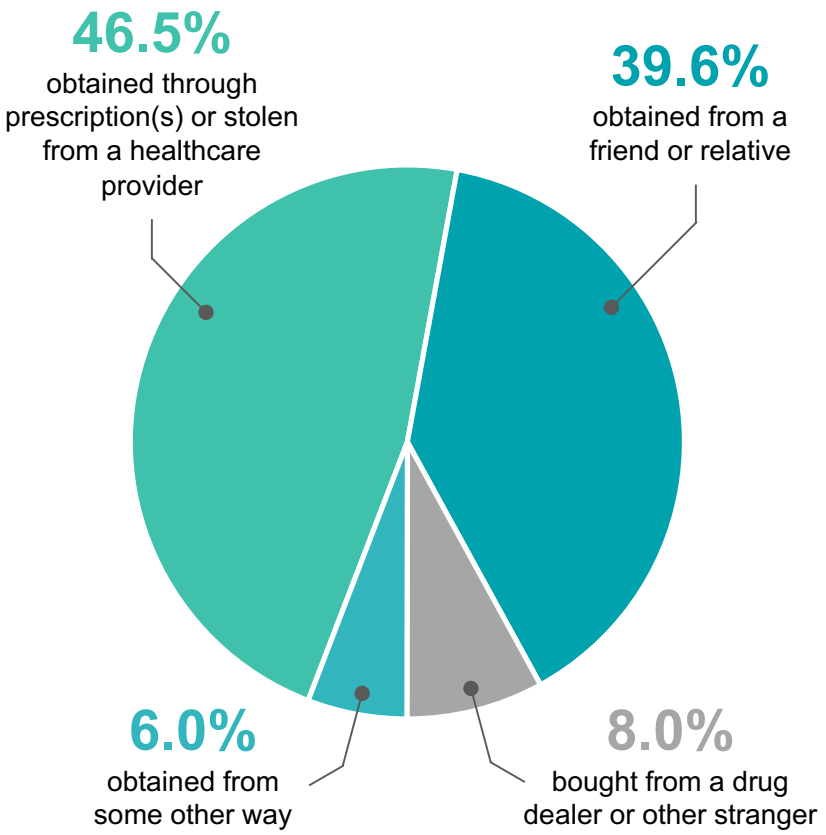
Source: Illicit vs Prescription

Opioids include both prescription medications used to treat pain and illegal drugs such as heroin and fentanyl analogs. The nonmedical use of prescription opioids is considered illicit.

According to the 2023 National Survey on Drug Use and Health, over 8 million adults aged 18 or older misused opioids in the past year. See the **Figure** for a breakdown of sources where prescription pain relievers were obtained for the most recent misuse.

A total of 779,000 adults aged 18 or older misused fentanyl in 2023 (includes use of illegally made or prescription fentanyl); 591,000 used illegally made fentanyl.

Ways in Which Prescription Pain Relievers Were Obtained for Most Recent Misuse Among Adults in 2023[a,b,c]



[a]Prescription pain relievers may include some nonopioids because respondents could occasionally specify the misuse of other prescription pain relievers that are not opioids [b]Respondents with unknown data for the source or who did not specify a valid way in the "some other way" category were excluded; [c]The percentages may not add to 100 percent due to rounding.

NIDA. Opioids; SAMHSA. 2023 NSDUH Detailed Tables; SAMHSA. Results from the 2023 National Survey on Drug Use and Health (NSDUH).

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Mixtures/Hidden Ingredients/Potentiation

Most overdose deaths in recent years involved illicitly manufactured fentanyl and other potent synthetic opioids. Combination with other drugs of abuse brings up the potential for drug-drug interactions: opioids, including fentanyl, may be added to illicit drugs including heroin, cocaine, and methamphetamine, possibly unbeknownst to the user.

Amphetamines are psychostimulants and are known to potentiate the analgesic effects of opioids. Xylazine, also known as “tranq”, is a non-opiate sedative, analgesic, and muscle relaxant. It is approved by the FDA only for veterinary use and is a known common adulterant of illicit drugs. Xylazine and opioids have similar pharmacological effects, and thus illicit opioids, including fentanyl, are often adulterated with xylazine to enhance and prolong their effects.

FDA, Food and Drug Administration.

NIDA. Opioids; CFR. Temporary Placement of Fentanyl-Related Substances in Schedule 1. 2018; Suzuki J et al. *Drug Alc Depend*. 2017;171:107-116; Comer SD, Cahill CM. *Neurosci Biobehav Rev*. 2019;106:49-57; DOJ DEA. National Drug Threat Assessment. 2019; Dalal S et al. *J Pain Symptom Manage*. 1998;16(4):245-253; DOJ DEA The growing threat of xylazine and its mixture with illicit drugs. 2022..

Reversal of Opioid Overdose

Naloxone and nalmefene are used to revert opioid overdose and respiratory depression associated with opioid use when the potential benefits are expected to outweigh the risks, such as precipitated withdrawal. These drugs should be administered as quickly as possible, and repeated as clinically indicated, after known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. Opioid antagonists that are indicated for reversal of opioid overdose are not indicated for the reversal of overdose with nonopioids such as amphetamines or “tranq” (xylazine).

Refer to the **Table** for specific properties of opioid antagonists indicated for reversal of opioid overdose.

Properties of Opioid Antagonists for Reversal of Opioid Overdose

	Formulations	Half-life	Duration of Action, m
Naloxone	IN	1.13-2.7[a] h	30-90[b]
	IM, IV, SQ	64±12[c] m	
Nalmefene	IN	11.4 h	30-60+[c]
	IM, IV, SQ	9.07 h	

h, hour; IM, intramuscular; IN, intranasal; IV, intravenous; m, minute; SQ, subcutaneous.

[a]Varies based on specific product and dose; [b]Varies based on route of administration, dose, and properties of opioid being reversed; [c]Mean.

NARCAN OTC Drug Facts Label; RIVIVE OTC Drug Facts Label; KLOXXADO Prescribing Information; REXTOVY Prescribing Information; REZENOPY Prescribing Information; ZIMHI Prescribing Information; Naloxone HCl Prescribing Information; Nalmefene HCl Prescribing Information; OPVEE Prescribing Information; ZURNAI Prescribing Information; DOJ DEA. The growing threat of xylazine and its mixture with illicit drugs. 2022; CDC. Stimulant Guide. CDC website; NIDA. Naloxone drug facts.

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Evaluating for Presence of Opioids

Clinical Opiate Withdrawal Scale (COWS)

The COWS is an 11-item scale used to rate common symptoms of opioid withdrawal. The total score of the 11 items is used to assess a patient's level of opioid withdrawal and physical dependence on opioids.

Resting Pulse Rate

Measured after patient is sitting or lying for 1 minute

- **0**: ≤ 80 bpm
- **1**: 81-100 bpm
- **2**: 101-120 bpm
- **4**: ≥ 120 bpm

Sweating

Over past ½ hour not accounted for by room temperature or patient activity

- **0**: No report of chills/flushing
- **1**: Subjective report of chills/flushing
- **2**: Flushed/ observable moistness on face
- **3**: Beads of sweat on brow/face
- **4**: Sweat streaming off face

Restlessness

Observation during assessment

- **0**: Able to sit still
- **1**: Reports difficulty sitting still, but is able to do so
- **3**: Frequent shifting or extraneous movements of legs/arms
- **5**: Unable to sit still for more than a few seconds

Pupil Size

- **0**: Pinned or normal size for room light
- **1**: Possibly larger than normal for room light
- **2**: Moderately dilated
- **5**: So dilated that only the rim of the iris is visible

Bone or Joint Aches

If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored

- **0**: Not present
- **1**: Mild diffuse discomfort
- **2**: Patient reports severe diffuse aching of joints/muscles
- **4**: Patient is rubbing joints/muscles and is unable to sit still because of discomfort

Runny Nose or Tearing

Not accounted for by cold symptoms or allergies

- **0**: Not present
- **1**: Nasal stuffiness or unusually moist eyes
- **2**: Nose running or tearing
- **4**: Nose constantly running or tears streaming down cheeks

GI Upset

Over last ½ hour

- **0**: No GI symptoms
- **1**: Stomach cramps
- **2**: Nausea or loose stool
- **3**: Vomiting or diarrhea
- **5**: Multiple episodes of vomiting or diarrhea

Tremor

Observation of outstretched hands

- **0**: No tremor
- **1**: Tremor can be felt, but not observed
- **2**: Slight tremor observable
- **4**: Gross tremor or muscle twitching

Yawning

Observation during assessment

- **0**: No yawning
- **1**: Yawning 1-2x
- **2**: Yawning ≥ 3x
- **4**: Yawning several times/minute

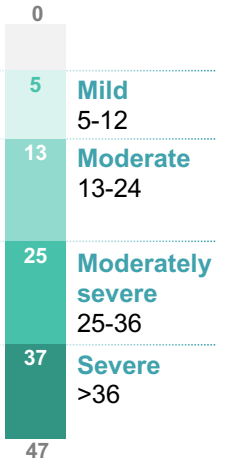
Anxiety or Irritability

- **0**: None
- **1**: Patient reports increasing irritability or anxiousness
- **2**: Patient obviously irritable/anxious
- **4**: Patient so irritable/ anxious that participation in the assessment is difficult

Gooseflesh Skin

- **0**: Skin is smooth
- **3**: Piloerection of skin can be felt or hairs standing up on arms
- **5**: Prominent piloerection

Total Score (0-47)



Evaluating for Presence of Opioids continues on next page

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Urine Drug Screening

Urine drug screening is a useful tool to evaluate recent drug use. Consideration of timing of testing and possible drug use is important when measuring drug urine levels, as the window that will read positive results varies. Both very recent use and less recent use of substances may not appear positive on the urine drug screen. Refer to specific urine test kits for specifications.

Evaluating for Presence of Opioids continues on next page

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Naloxone Challenges + Protocols

Naloxone Challenge

According to the 2020 American Society of Addiction Medicine (ASAM) Guidelines for the Treatment of Opioid Use Disorder, a naloxone challenge can be used if it is uncertain whether the patient is no longer physically dependent on opioids. In the naloxone challenge, naloxone hydrochloride (a short-acting injectable opioid antagonist) is administered, and the patient is monitored for signs and symptoms of withdrawal.

Examples of Naloxone Challenge Protocols

The patient is administered a dose of naloxone to evaluate their level of opioid dependence prior to the initiation of an opioid antagonist pharmacotherapy. See the **Table** below.

Naloxone Challenge: Interpretation of Results

Abrupt reversal of opioid effects in persons who are physically dependent on opioids may precipitate an acute withdrawal syndrome which may include, but is not limited to the following signs and symptoms: 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.

Example Naloxone Challenge Protocols

Source	XR-Naltrexone: A Step-by-Step Guide (2021)[a]	WHO guidelines for psychosocially assisted pharmacological treatment of persons dependent on opioids (2007)[b]		Naltrexone HCl Prescribing Information (2023)		Opioid Detoxification and Naltrexone Induction Strategies: Recommendations for Clinical Practice[c]	
Dose	0.4 mg	0.4 mg	0.2 mg	0.2 mg	0.8 mg	0.8-1.6 mg	6 mg to ⅛ of a 50 mg tablet
Route	IM to deltoid	IM	IV	IV	SQ	IM/IV	PO
Observe for signs or symptoms of withdrawal	20 minutes; if no change in COWS, follow up dose	10 minutes; if no signs or symptoms of withdrawal, follow up dose	1 minute; if no signs or symptoms of withdrawal, follow up dose	30 seconds; if no signs or symptoms of withdrawal, follow up dose	20 minutes	N/A	
Follow up dose	0.8 mg to opposite deltoid and monitor for additional 20 minutes	0.4 mg IM	0.6 mg IV	0.6 mg IV; observe for additional 20 minutes	N/A	N/A	

[a]Adapted from Providers' Clinical Support System Medications for Opioid Use Disorders Training.
[b]World Health Organization (WHO). Background document prepared for Third Meeting of Technical Development Group (TDG) for the WHO "Guidelines for Psychosocially Assisted Pharmacological Treatment of Persons Dependent on Opioids". Geneva, Switzerland. 2007. WHO website. Accessed March 17, 2026.
[c]Adapted from Sigmon SC, et al. *Am J Drug Alcohol Abuse*. 2012.

COWS, Clinical Opiate Withdrawal Scale; IM, intramuscular; IV, intravenous; N/A, not available; PO, oral; SQ, subcutaneous; WHO, World Health Organization; XR, extended-release.

Evaluating for Presence of Opioids continues on next page

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Naltrexone Challenges + Protocols

Oral naltrexone Challenge

According to the 2020 ASAM Guidelines, a low-dose oral naltrexone challenge has been used as an alternative to a naloxone challenge.

Naltrexone HCl (oral tablet), an opioid antagonist, is a synthetic congener of oxymorphone with no opioid agonist properties. Naltrexone HCl is a pure opioid antagonist.

- It markedly attenuates or completely blocks, reversibly, the subjective effects of intravenously administered opioids.
- Naltrexone HCl has few, if any, intrinsic actions besides its opioid blocking properties.
- In individuals physically dependent on opioids, naltrexone HCl will precipitate withdrawal symptomatology.
- Clinical studies indicate that 50 mg of naltrexone HCl will block the pharmacologic effects of 25 mg of intravenously administered heroin for periods as long as 24 hours.
- Other data suggest that doubling the dose of naltrexone HCl provides blockade for 48 hours and tripling the dose of naltrexone HCl provides blockade for about 72 hours.

Wesson DR et al. *J Psychoactive Drugs*. 2003;35(2):253-259; ASAM. Appropriate use of drug testing. 2017; ASAM. *J Addict Med*. 2020;14(2S):1-91; NALOXONE HYDROCHLORIDE Prescribing Information; PCSS. XR-Naltrexone: A step-by-step guide; WHO. Guidelines for psychosocially assisted pharmacological treatment of persons dependent on opioids. 2007; Bell J et al. Clinical guidelines and procedures for the use of naltrexone in the management of opioid dependence. 2009; NALTREXONE HYDROCHLORIDE Prescribing Information; Sigmon SC et al. *Am J Drug Alcohol Abuse*. 2012;38(3):187-99.

Examples of an Oral Naltrexone Challenge Protocol

An example of a possible oral naltrexone challenge is provided in the **Table** below.

Naltrexone Challenge: Interpretation of Results

According to the Naltrexone HCl Prescribing Information, when withdrawal is precipitated abruptly by the administration of an opioid antagonist to an opioid-dependent patient, the resulting withdrawal syndrome can be severe enough to require hospitalization.

- Symptoms of withdrawal have usually appeared within five minutes of ingestion of naltrexone HCl and have lasted for up to 48 hours.
- Mental status changes including confusion, somnolence and visual hallucinations have occurred.
- Significant fluid losses from vomiting and diarrhea have required IV fluid administration.

Review of post-marketing cases of precipitated opioid withdrawal in association with naltrexone treatment has identified cases with symptoms of withdrawal severe enough to require hospital admission, and in some cases, management in the intensive care unit.

Example of an Oral Naltrexone Challenge Protocol[a]

Source	XR-Naltrexone: A Step-by-Step Guide (2021)	
Prior to giving naltrexone challenge	Obtain baseline COWS	COWS >4 Treat withdrawal with adjunctive medication and reevaluate in 1-2 days.
		COWS ≤4 and opioid-negative toxicology proceed with the challenge
Naltrexone challenge dose	Administer naltrexone 25 mg PO	
Observe for signs or symptoms of withdrawal	Observe for 90 minutes	

COWS, Clinical Opiate Withdrawal Scale; PO, oral; XR, extended-release.

[a]Adapted from Providers' Clinical Support System Medications for Opioid Use Disorders Training.

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Comorbidities

Comorbidity refers to when two or more medical conditions occur in the same person, at the same time or one after the other. Comorbid medical conditions impact each other, affecting the course of both conditions. For example co-occurring opioid and non-opioid substance use disorders can contribute to negative outcomes, including overdose and mortality. The existence of comorbidities needs to be considered when developing a treatment approach for the individual. Common comorbidities among people with OUD include:

Psychiatric disorders

- Anxiety
- Depression
- Bipolar disorder
- Schizophrenia
- Suicidal behavior

Pain

Infectious diseases

- Hepatitis C
- Human immunodeficiency virus

Non-opioid substance use disorders

- Cocaine
- Alcohol
- Cannabis
- Sedatives
- Methamphetamine

Thyroid disease

- Hyperthyroidism
- Hypothyroidism

Diabetes mellitus type 2

OUD, opioid use disorder.

NIDA. Common Comorbidities with Substance Use Disorders Research Report; Santo TJ et al. *Int J Drug Policy*. 2024;128:104434; NICE. Multimorbidity: Clinical Assessment and Management; Jennings MV et al. *Complex Psychiatry*. 2022;8(1-2):47-55; Pan Y et al. *BMC Med Inform Decis Mak*. 2022;22(Suppl 2):155.

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Demographic and Environmental Factors

Risk factors for OUD may be modifiable or fixed, including:

Criminal behavior

Parental divorce or death

Poor school performance

Current community deprivation

Divorce

Male sex

Exposure to opioids following trauma, as early as 3 months after initial exposure

Multiple surgical interventions and intensive care unit treatment

Pain management and treatment using opioids only, compared to multimodal therapy

Multimorbidity, long-term alcohol misuse, depression, or chronic pain disorder in the elderly population (> 65 years of age)

OUD, opioid use disorder.

Kendler KS et al. *Psychol Med.* 2023;53(13):6223-6231; Baumann L et al. *Curr Pain Headache Rep.* 2023;27:437–444.

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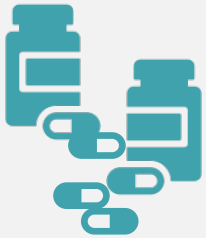
Medical History

Major risk factors for OUD include:

Duration of patients' misuse following initial therapy



Higher opioid doses and duration than initially prescribed

Patients using their own prescriptions

History of mental illness, such as anxiety disorders or depression

Preexisting use of antidepressants, benzodiazepines, or recreational drugs, such as tobacco, alcohol, or cocaine

OUD, opioid use disorder.

Baumann L et al. *Curr Pain Headache Rep.* 2023;27:437–444.

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Body Composition

Increasing BMI was associated with an increase in the use of prescription opioids. Patients with higher BMI had higher odds of reporting chronic prescription opioid use. The reported association between high BMI and prescription opioid use was significantly stronger for chronic use than for use with a duration of <90 days. Patients with obesity had higher odds of receiving prescribed opioids for management of pain due to osteoarthritis and other joint disorders than patients with normal weight.

A high lipophilicity of a drug plays a critical role in its ability to cross the blood-brain barrier. Opioids such as methadone and fentanyl are highly lipophilic and after the absorption by highly perfused tissues, including the brain, these drugs tend to redistribute to peripheral tissues, such as muscle and fat. Prolonged administration of these drugs may result in accumulation in the peripheral tissues, contributing to prolonged exposure and clearance, and secondary plasma peaks. Secondary peaking in patients receiving fentanyl has been associated with recurrence of respiratory depression.

BMI, body mass index.

Stokes A et al. *Pain.* 2019;160(10):2255–2262; Stokes A et al. *JAMA Netw Open.* 2020;3(4):e202012; Bird HE et al. *J Addict Med.* 2023;17(5):503-508; Trescot AM et al. *Pain Physician.* 2008;11:S133-S153.

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Duration of Use and Tolerance

Patients who regularly receive opioid drugs develop predictable tolerance and physical dependence. Tolerance is characterized by a reduced responsiveness to the drug, leading to a need for increasing doses to maintain the initial effects. Physical dependence is characterized by the need for opioid use to maintain normal physiological function. Opioid withdrawal symptoms occur when someone abruptly stops the drug or has a rapid dose reduction, and result from physical dependence.

Pain relief or illicit use are often the main reason for starting opioid use. However, after development of dependence, avoidance of opioid withdrawal symptoms often becomes the main reason for continued use. Common opioid withdrawal signs and symptoms can be both physical and emotional, and include:

Opioid Withdrawal Signs and Symptoms

Physical

- Bone pain and muscle aches, spasms, or tension
- Weakness

- Changes in body temperature
- Chills and goosebumps

- Enhanced pain sensitivity

- Insomnia

- Tearing/watery eyes
- Drooping eyelids and pupil dilation

- Stomach cramps
- Nausea/vomiting
- Diarrhea

- Rapid heart rate
- Irregular heartbeat
- High blood pressure

- Teeth chattering
- Yawning

Emotional

- Inability to recognize or describe own emotions
- Anxiety
- Severe unhappiness
- Emotional pain
- Irritability
- Loss of motivation for natural rewards
- Malaise
- Stress
- Opioid craving

Pergolizzi JV et al. *J Clin Pharm Ther*. 2020;45(5):892-903; Kosten TR et al. *Am J Addict*. 2019;28(2):55-62; Englander H et al. *JAMA Intern Med*. 2024;184(6):691-701.

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Disclosure

Patients tend to deny or underreport the use of opioids, especially illicit opioids. Omitting information about opioid use history from a healthcare provider can increase the risk of precipitated withdrawal, particularly when initiating treatment for opioid use disorders. For example, a buprenorphine administration too close to the last use of an opioid agonist may trigger a precipitated withdrawal.

Macias Konstantopoulos WL et al. *Ann Emerg Med*. 2014;64(5):516-525; Soares WE et al. *JAMA Netw Open*. 2024;7(9):e2435857.

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Stigma

Stigma happens when someone is mistreated, diminished or neglected by another person because of a behavior, disease, or condition. Stigma is harmful, and can be a result of bias, purposeful exclusion, or ignorance about the causes of a personal struggle.

Although millions are affected by substance use disorders, such as OUD, these people are still commonly stigmatized. OUD is treatable, and people with this condition need support like those with any other disease.

Stigma and fear of stigma can have an impact on OUD treatment and prevention, as it can prevent a person from getting help because:

- People seeking treatment may have to deal with healthcare providers that refuse to prescribe medications to treat OUD;
- People may avoid sharing their condition with friends or family;
- People may avoid seeking help from medical or behavioral services.

Stigma may come from an individual person, from the community, or from within the person, as a result of feelings of personal shame or failure.

Examples of stigma include:

Assuming a person chooses not to change their behavior

Considering OUD to be a moral instead of a medical issue

Withholding instead of offering support or treatment, including medications for OUD, by assuming that offering support, whether social or financial, enables a person to continue using drugs

Social rejection related to drug use or relapse

Not understanding the reasons behind OUD, including a greater risk of developing a substance use disorder based on a person's genetic background and their personal environment, adverse childhood experiences, or mental health conditions

A person's own negative feelings about their use

Stereotyping

OUD, opioid use disorder.

CDC. Stop overdose: stigma reduction. CDC website.

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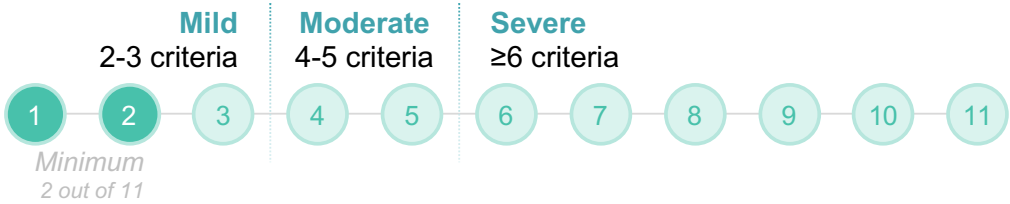
Diagnosis of Opioid Use Disorder

To make the diagnosis of OUD, the patient must meet the diagnostic criteria per the DSM-5. Per the DSM-5, OUD is demonstrated by at least 2 out of the 11 criteria below occurring within a year. Severity of OUD is determined based on the number of criteria met.

Severity of OUD



Diagnostic Criteria

- ☐ Taking opioids in larger amounts or over a longer period of time than intended
- ☐ Having a persistent desire or unsuccessful attempts to reduce or control opioid use
- ☐ Spending excess time obtaining, using, or recovering from opioids
- ☐ Craving opioids
- ☐ Continued opioid use causing inability to fulfill work, home, or school responsibilities
- ☐ Continuing opioid use despite having persistent social or interpersonal problems
- ☐ Lack of involvement in social, occupational, or recreational activities
- ☐ Using opioids in physically hazardous situations
- ☐ Continuing opioid use in spite of awareness of persistent physical or psychological problems
- ☐ Tolerance, as defined by either of the following:*
  - A need for markedly increased amounts of opioids to achieve intoxication or desired effect, or
  - Markedly diminished effect with continued use of the same amount of an opioid
- ☐ Exhibiting withdrawal symptoms, as manifested by either of the following:*
  - The characteristic opioid withdrawal syndrome, or
  - Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; OUD, opioid use disorder.

*Tolerance and withdrawal are not considered to be met for those taking opioids solely under appropriate medical supervision

CDC Opioid Use Disorder: Diagnosis 2024.

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