

Treatment of Opioid Withdrawal

Opioid withdrawal symptoms include musculoskeletal, gastrointestinal, and autonomic symptoms; anxiety; agitation; and insomnia. Withdrawal severity can be assessed using the Clinical Opiate Withdrawal Scale (COWS; www.ncbi.nlm.nih.gov/books/NBK143183/bin/annex10-fm3.pdf) or Clinical Institute Withdrawal Assessment (CIWA).¹⁴ The chart below lists medications used to treat opioid withdrawal symptoms, dosing examples, and other considerations. Much of this information is based on expert experience as opposed to high-level evidence. Buprenorphine and methadone are the preferred agents; other pharmacotherapy is best used adjunctively.¹⁷ Opioid antagonist (e.g., naloxone)-induced withdrawal with sedation or anesthesia is not recommended due to risk of serious harm without benefit.^{16,17}

| Drug | Target Symptom(s) | Dosing EXAMPLES for Adults (oral unless otherwise specified) | Comments |
|-----------|---|--|---|
| Clonidine | Anxiety, irritability; ²² chills, ¹ goosebumps, ¹ yawning, ⁸ lacrimation, ⁸ runny nose, ⁸ sweating, ²² pupil dilation, ⁸ fever, ⁸ increased heart rate and blood pressure, ¹ myoclonus ²⁵ More effective for objective/nor-adrenergic vs subjective/psychological symptoms. ^{8,30} | Oral clonidine (can also be given sublingually) <ul style="list-style-type: none"> • A test dose of 0.1 mg is recommended.¹⁹ Consider 0.2 mg for patients >91 kg or with severe withdrawal.¹⁹ Check BP 30 to 60 minutes post-dose.^{24,25} • Usual outpatient dose is 0.1 to 0.2 mg two to four times daily.²⁵ Some patients may need 0.3 mg every 6 hrs or 0.2 mg every 4 hrs).^{1,17,22} Can be given as needed or scheduled.¹⁹ Start to taper by day two to five (e.g., by 0.1 to 0.2 mg/day) and stop by day seven to ten.^{1,30,26} Transdermal clonidine (US only)(information limited) <ul style="list-style-type: none"> • Do not start if BP <110/70 mmHg.²³ • Sublingual test dose 0.1 mg. If systolic BP drops to <90 mmHg within one hour, do not proceed.²³ • Start with one (<45 kg), two (45 to 91 kg), or three 0.2 mg patches (>91 kg).²³ • Monitor BP four times daily.¹⁹ • Because the patches do not work right away, patients will need oral clonidine for the first 24 hrs. Cautious use can be considered for the second 24 hrs.²³ • Reduce dose by 50% at patch change (one week after initial application).²³ Stop after the second week of treatment, or sooner.²³ | <ul style="list-style-type: none"> • Hold oral clonidine if pre-dose BP <90/60 mmHg, HR <50 bpm, or dizziness or orthostasis occurs.^{19,24} (The BP cut-off could be reduced to <80/50 mmHg for patient with continued withdrawal symptoms, but without orthostasis.¹⁹) • Stop patch if BP <80/50 mmHg or pulse pressure is <20 mmHg, or per clinical judgement.²³ • Advise patients given clonidine for home use about sedation, hypotension, and bradycardia.^{20,21} • It is recommended that patients be given no more than a three-day supply of oral clonidine for home use due to need for titration, monitoring, and risk of overdose.^{21,23} • May cause excessive sedation if used with buprenorphine or methadone.^{10,13} |

| Drug | Target Symptom(s) | Dosing EXAMPLES for Adults (oral unless otherwise specified) | Comments |
|-----------------------------------|---|--|---|
| Lofexidine (<i>Lucemyra</i>) | See comments. | <ul style="list-style-type: none"> Start with three 0.18 mg tablets four times daily (every 5 to 6 hrs), then titrate dose based on efficacy and side effects. Max single dose is four tablets (0.72 mg), and max total daily dose is 16 tablets (2.88 mg). May continue for up to 14 days.¹⁸ Taper over two to four days when stopping.¹⁸ Patients using lofexidine at home should be told to hold their dose and contact prescriber if they experience low blood pressure, slow heart rate, faintness, dizziness, or lightheadedness.¹⁸ Dose must be reduced for kidney or liver impairment.¹⁸ <ul style="list-style-type: none"> Dose is three tablets four times daily for mild liver impairment, two tablets four times daily for moderate liver or kidney impairment, and one tablet four times daily for severe liver or kidney impairment.¹⁸ | <ul style="list-style-type: none"> A central alpha-2 agonist¹⁸ (like clonidine). FDA-approval based on patient rating of the following symptoms: feeling sick, stomach cramps, muscle spasms/twitching, feeling cold, pounding heart, muscle tension, aches/pains, yawning, lacrimation, insomnia.²⁵ Expect to use adjunctive medications to ameliorate insomnia and aches/pains.²⁶ Similar efficacy to clonidine. Causes less hypotension than clonidine at doses lower than the recommended starting dose.²⁶ Labeled starting dose has not been compared head-to-head with clonidine. |
| NSAID or Acetaminophen | Headache, musculoskeletal pain, other pain ^{17,19,22,30} | <ul style="list-style-type: none"> Acetaminophen (e.g., 650 mg every 6 hrs prn).^{17,19,22,25} Naproxen (e.g., 375 to 500 mg twice daily prn, with food)^{1,30} Ibuprofen (e.g., 400 to 600 mg every 4 to 6 hrs [max 2,400 mg/day] prn, with food)^{10,25,30} | None |
| Loperamide | Diarrhea ²² | <ul style="list-style-type: none"> 4 mg x 1, then 2 mg after every loose stool. Max daily dose 16 mg.¹⁰ | None |
| Dicyclomine | Abdominal cramps ³ | <ul style="list-style-type: none"> 10 to 20 mg four times daily as needed^{3,10,45} | None |
| Ondansetron | Nausea ^{1,17,22,30} | <ul style="list-style-type: none"> 4 mg every 6 hrs prn²⁵ 8 mg every 8 hrs prn¹ | None |
| Trazodone | Insomnia ^{3,22} | <ul style="list-style-type: none"> 50 to 150 mg at bedtime prn^{3,30} | None |

| Drug | Target Symptom(s) | Dosing EXAMPLES for Adults (oral unless otherwise specified) | Comments |
|---|---|---|--|
| Hydroxyzine | Anxiety, dysphoria, ²⁵ insomnia, ¹⁹ lacrimation, rhinorrhea ²⁵ | <ul style="list-style-type: none"> • 25 to 50 mg three times daily prn (anxiety, dysphoria, lacrimation, rhinorrhea).²⁵ • Insomnia: 25 to 50 mg at bedtime¹⁹ | None |
| Zolpidem | Insomnia ^{21,30} | <ul style="list-style-type: none"> • Up to 10 mg at bedtime prn.³⁰ See our chart, <i>Comparison of Insomnia Treatments</i>, for dosing details. | <ul style="list-style-type: none"> • Not preferred due to abuse potential.²¹ |
| Benzodiazepine | Agitation, anxiety, ^{1,3,12,17} | <ul style="list-style-type: none"> • Anxiety: clonazepam 0.5 to 2 mg every 4 to 8 hrs as needed (max 6 mg/day).³⁰ • Agitation: lorazepam 0.5 mg every 4 hrs prn for three to five days.^{3,12} | <ul style="list-style-type: none"> • Not preferred due to abuse potential.²¹ • Time-limited use for specific indication in monitored setting lessens abuse concern.¹² • Use increases risk of respiratory depression with buprenorphine or methadone.¹⁷ |
| Percutaneous auricular nerve stimulation device (NSS-2 Bridge, Drug Relief, Sparrow Ascent) | See comments | <ul style="list-style-type: none"> • Patient wears prescription device behind ear during withdrawal (up to five days for <i>NNS-2 Bridge</i> or <i>Drug Relief</i>).^{11,28,29} | <ul style="list-style-type: none"> • <i>NSS-2 Bridge</i> reduced COWS score >60% within 30 min in open trial.²⁷ • <i>Drug Relief</i> claims to reduce symptoms within 30 to 60 minutes.²⁹ • <i>Sparrow Ascent</i> claims to reduce symptoms within 30 minutes.⁷ |
| Opioid substitution, oral methadone (hospital) <i>Continued...</i> | Moderate to severe opioid withdrawal symptoms ⁴ | <p>Methadone (oral, hospital):</p> <ul style="list-style-type: none"> • Start with 10 to 20 mg daily (5 to 10 mg for patients who have not taken an opioid for ≥5 days, don't use daily, use weak opioids like codeine, or are at risk of respiratory depression).^{5,22} • Observe for 2 to 4 hours to assess withdrawal symptoms and sedation (sedation peaks 2 to 4 hours post-dose).²² • If the patient shows neither sedation nor reduction in objective signs of withdrawal, an additional 5 mg dose can be given (with adjuvant medications [see above]).^{5,22} Assess again in 2 to 4-hrs and give another 5 mg if appropriate.²² First day max total dose is 30 mg (rarely 40 mg).²² | <ul style="list-style-type: none"> • US: Methadone can be started in the hospital (see footnote b). However, its continued use for opioid use disorder requires seamless transition to an outpatient maintenance program.^{4,22} • Canada: Check with your provincial licensing body for methadone prescribing requirements. • Weaning may be easier if patients are not told their dose.⁹ |

| Drug | Target Symptom(s) | Dosing EXAMPLES for Adults (oral unless otherwise specified) | Comments |
|--|---|--|--|
| Oral methadone (hospital), continued | | <ul style="list-style-type: none"> If needed, adjust dose by 5 to 10 mg every three days to minimize withdrawal symptoms, and sedation 2 to 4 hrs post-dose.^{5,22} If patient does not desire long-term methadone maintenance, taper by 5 to 10 mg daily until discontinued.⁵ | |
| Opioid substitution, parenteral opioids (hospital) | Moderate to severe opioid withdrawal symptoms ¹⁵ | <p>Parenteral use of short-acting opioid (hospital) (morphine, hydromorphone, fentanyl) in closely monitored setting (e.g., ICU):¹⁵</p> <ul style="list-style-type: none"> Calculate opioid withdrawal score: one point for each of the following; two if severe: pupil dilation; lacrimation; rhinorrhea; goose bumps; nausea or vomiting; diarrhea or cramping; chills or hot flashes; muscle symptoms; yawning; restlessness, irritability, or insomnia. Goal is symptoms score of five or less. May give up to 1 mg morphine (or equivalent) intravenously every five minutes. Once the patient is stabilized, reduce the dose by 10% every day. May convert to oral opioid. | <ul style="list-style-type: none"> Opioids other than methadone have shorter durations of action (meaning more frequent dosing and risk of end-of-interval withdrawal symptoms) but might be preferred in unstable patients (e.g., ICU).^{9,15} |
| Opioid substitution, buprenorphine/naloxone | Cravings and withdrawal symptoms ² | <p>Buprenorphine/naloxone: see our chart, <i>Management of Opioid Dependence</i>, for information on outpatient use as opioid replacement therapy. See footnote a for information on inpatient use.</p> <ul style="list-style-type: none"> US: Opioid replacement therapy can be started in the hospital. However, its use requires seamless transition to an outpatient prescriber.²² Canada: Check with your provincial licensing body for buprenorphine/naloxone (<i>Suboxone</i>) prescribing requirements. | <ul style="list-style-type: none"> Buprenorphine may precipitate withdrawal in patients with opioids still on board.²² The COWS score should be >10 before starting.² Not a good choice for patients requiring pure opioid agonists for pain.² Weaning may be easier if patients are not told their dose.⁹ |

Abbreviations: BP = blood pressure; bpm = beats per minute; hrs = hours; HR = heart rate; prn = as needed

- a. In one study, buprenorphine/naloxone sublingual was administered in the hospital as a total daily dose of up to 8 mg/2 mg on day 1, then either:⁶
- tapered over five days (8 mg/2 mg on day two, 6 mg/1.5 mg on day three, 4 mg/1 mg on day four, 2 mg/0.5 mg on day five)
- OR
- buprenorphine/naloxone 12 mg/3 mg on day two, then 16 mg/4 mg on day three and for the remainder of the hospitalization, with follow-up by a buprenorphine prescriber.

In the US, the Controlled Substances Act contains some exceptions from the requirement to provide methadone through an opioid treatment program. **These exceptions include:** administering (not prescribing) an opioid for no more than three days to a patient in acute opioid withdrawal while arrangements are made for ongoing care; and administering opioid medications in a hospital to maintain or detoxify a patient as an adjunct to treatment of medical or surgical conditions.²²

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

| Level | Definition | Study Quality |
|----------|---|---|
| A | Good-quality patient-oriented evidence.* | <ol style="list-style-type: none"> High-quality randomized controlled trial (RCT) Systematic review (SR)/Meta-analysis of RCTs with consistent findings All-or-none study |
| B | Inconsistent or limited-quality patient-oriented evidence.* | <ol style="list-style-type: none"> Lower-quality RCT SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings Cohort study Case control study |
| C | Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening. | |

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).

[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician*. 2004 Feb 1;69(3):548-56.

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Cite this document as follows: Clinical Resource, Treatment of Opioid Withdrawal. Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. January 2024. [400160]

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Meds for Opioid Overdose

modified November 2025

To reverse an opioid overdose in the community setting, opioid receptor blockers can be administered by nasal spray or injection (subcutaneous [nalmeferene only] or IM. In the hospital setting naloxone or nalmeferene are usually administered parenterally. The FAQ below addresses common questions regarding these opioid receptor blockers. See our *Naloxone Quick Start Guide* for a simplified resource about identifying patients for whom naloxone may be beneficial and getting them started.

| Question | Answer/Pertinent Information/Suggested Resources |
|---|---|
| Who should an opioid receptor blocker be considered for? | <ul style="list-style-type: none"> • Consider for people: <ul style="list-style-type: none"> ○ with a history of opioid intoxication or overdose.^{1,9,27} ○ with a suspected history of substance abuse or nonmedical opioid use (e.g., opioid use disorder).^{1,9,27} ○ on treatment (buprenorphine, etc) for opioid use disorder.^{1,9,27} ○ taking high opioid doses (e.g., 50 mg or more of oral morphine or its equivalent) daily.^{18,27} <ul style="list-style-type: none"> ▪ Tools to calculate daily morphine equivalents can be found at: <ul style="list-style-type: none"> • https://stacks.cdc.gov/view/cdc/38481. • http://www.agencymeddirectors.wa.gov/Calculator/DoseCalculator. ○ being rotated from one opioid to another (due to risk of incomplete cross-tolerance).⁹ ○ taking an opioid who:^{1,9,27} <ul style="list-style-type: none"> ▪ smoke or have a respiratory illness (e.g., COPD, sleep apnea, asthma). ▪ have kidney, liver, or heart disease; or human immunodeficiency virus (HIV). ▪ use alcohol or a benzodiazepine, sedative, or antidepressant. ○ who live in a remote location (consider providing more than one kit or dose due to potential for delays with emergency response personnel in remote areas).⁹ ○ who live with people at risk for accidental opioid overdose (e.g., children).¹ ○ who request it.⁹ ○ who may be in a position to help some at risk of an opioid overdose.²⁷ • The FDA is requiring that recommendations for co-prescription of naloxone be added to the prescribing information of opioid pain medicine, as well as medicines used to treat opioid use disorder.¹ • In some states, naloxone co-prescription is required for certain high-risk patients.¹⁵ |

| Question | Answer/Pertinent Information/Suggested Resources |
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| What should you tell patients, caregivers, and families about naloxone and nalmefene? | <ul style="list-style-type: none">• Help patients, caregivers, and families get on board with naloxone and nalmefene by covering these talking points:<ul style="list-style-type: none">○ Anyone on an opioid can be at risk of respiratory depression. Naloxone or nalmefene is like a seatbelt: most people don't need it, but it's there just in case they need it.○ Reinforce that naloxone or nalmefene can save a life.○ Naloxone or nalmefene are easy to use, have low risk of adverse effects, and are not harmful if the person didn't really need it.○ Note that the vast majority of patients are not offended by an offer of naloxone or nalmefene.¹²• Help patients, caregivers, and families get naloxone or nalmefene. Consider keeping an updated list of free naloxone/nalmefene sources in your community, what insurance might cover, and manufacturer programs to cover costs.• Help patients, caregivers, and families get trained to administer naloxone or nalmefene.<ul style="list-style-type: none">○ US: https://prescribtoprevent.org/patient-education/materials/.○ Video from the Canadian Pharmacists Association (Naloxone Made Easy): https://www.youtube.com/watch?v=0Z-y7CoeDMc.○ Training will cover the essential steps to take if an opioid overdose is suspected: check for signs of opioid overdose (reduced level of consciousness with breathing difficulty or blue/purple lips or nails), try to get person to respond (e.g., shout the person's name, sternal rub), call 911, provide rescue breathing if needed, and give naloxone or nalmefene.^{6,17}○ Patient instruction sheets from the College of Pharmacists of British Columbia are available at https://www.bcpharmacists.org/naloxone.• Explain to family and caregivers what to expect after naloxone or nalmefene administration.<ul style="list-style-type: none">○ Most patients respond to naloxone or nalmefene and return to spontaneous breathing with only mild withdrawal symptoms.⁶○ Opioid withdrawal is not typically life-threatening in adults.^{6,34}○ Opioid withdrawal symptoms can include sweating, goose bumps, achiness, shivering, gastrointestinal symptoms, tachycardia, irritability, increased blood pressure, fever, runny nose, sneezing, trembling, and yawning.^{6,34}<ul style="list-style-type: none">▪ Patients may become agitated or confused, or vomit after naloxone or nalmefene is given.^{6,34}○ To prevent aspiration, the patient should be positioned on their side after naloxone or nalmefene is given.^{6,34}<ul style="list-style-type: none">▪ This "recovery position" is illustrated in the <i>Narcan</i>, <i>Kloxxado</i>, and <i>Opvee</i> nasal sprays, <i>Zimhi</i>, <i>Zurnai</i>, and <i>S.O.S Naloxone</i> patient labeling, and in the patient instruction sheets available at http://www.bcpharmacists.org/naloxone. |

| Question | Answer/Pertinent Information/Suggested Resources |
|---|---|
| <p>When should an opioid receptor blocker be administered?</p> | <ul style="list-style-type: none"> ● Naloxone or nalmefene should be given if a person has respiratory and/or CNS depression in a situation where opioids may be present.^{3,16,25,26,32,34} <ul style="list-style-type: none"> ○ Give if the patient is excessively sleepy and cannot be aroused with a loud voice or sternal rub.^{3,25,26,32} ○ Other indications include slow, shallow, or no respirations, or pinpoint pupils in a patient who is difficult to arouse.^{3,25,26,32} ○ Other signs of overdose include blue or purple fingernails or lips, death rattle (gurgling noise in the throat form build-up of saliva and mucus), slow heartbeat, or low blood pressure.^{3,6,16} |
| <p>What is the role of nalmefene (US only, <i>Opvee, Zurnai</i>) in opioid overdose?</p> | <ul style="list-style-type: none"> ● Nalmefene (available by prescription only) is an opioid antagonist that may be used as a naloxone alternative. ● It is indicated for the emergency treatment of known or suspected opioid overdose (respiratory and/or CNS depression) in patients 12 years and older.^{34,37} ● Nalmefene has a similar onset (three to five minutes) and a longer duration of action (six hours) compared to naloxone.^{7,24,31,37} ● There is no good evidence that nalmefene is more effective than naloxone for opioid overdose. Its longer duration of action theoretically could reduce the risk of relapse of opioid overdose symptoms, but could also prolong opioid withdrawal symptoms. ● Check your local state laws and procedures. Some states allow pharmacists to provide nalmefene (as they do with naloxone) by standing orders, protocols, etc.^{35,36} |
| <p>Is naloxone available without a prescription?</p> | <ul style="list-style-type: none"> ● US: Naloxone is available without a prescription.²⁹ <ul style="list-style-type: none"> ○ Narcan nasal spray 4 mg has been FDA-approved for Rx-to-OTC switch. It will be available in pharmacies, grocery stores, gas stations, and other retail and online stores.³³ ○ To understand specific laws about prescription naloxone in your state (e.g., protocol, standing order), consult your state pharmacy board, or go to one of these websites: <ul style="list-style-type: none"> ▪ SafeProject: https://www.safeproject.us/naloxone-awareness-project/state-rules/. ▪ National Alliance of State Pharmacy Associations: https://naspa.us/resource/naloxone-access-community-pharmacies/. ▪ Prescription Drug Abuse Policy System https://pdaps.org/datasets/laws-regulating-administration-of-naloxone-1501695139. ● Canada: Naloxone is available without a prescription (unscheduled in Alberta, British Columbia, Manitoba, and Saskatchewan; Schedule II elsewhere).^{19,28} <ul style="list-style-type: none"> ○ To find where to get naloxone in your province or territory go to https://www.canada.ca/en/health-canada/services/substance-use/problematic-prescription-drug-use/opioids/naloxone.html#5. |

| Question | Answer/Pertinent Information/Suggested Resources |
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| What is the availability of naloxone nasal spray? | <p>Naloxone nasal spray 4 mg (the 2 mg strength, found in product labeling, is not marketed in the US or Canada). Generics are available in the US.</p> <ul style="list-style-type: none">• <i>Narcan</i> 4 mg brand is available OTC (US only). <i>Narcan</i> (Canada) and generic 4 mg formulations (US only) are available without a prescription through various protocols (depending on the state/provincial/territorial laws).• Each carton contains TWO blister-packed, single-dose nasal sprays, each containing 4 mg of naloxone.^{3,26}• Be careful of mix-ups between the newer <i>Narcan</i> nasal spray and an older, no longer available <i>Narcan</i> brand injection. For some, “<i>Narcan</i>” has become synonymous with injectable naloxone. <p>Kloxxado nasal spray (US only) is available as an 8 mg strength.²⁵</p> <ul style="list-style-type: none">• Each carton contains TWO blister-packed, single-dose nasal sprays, each containing 8 mg of naloxone.²⁵ <p>Naloxone kits for intranasal administration using injectable solution; each kit should contain:^{2,5}</p> <ul style="list-style-type: none">• Two mucosal atomization devices (e.g., MAD Nasal device). Examples of sources for ordering include:<ul style="list-style-type: none">○ Common Cents EMS Supplies: https://www.savelives.com/ or 866-388-4599.○ Teleflex Medical: https://www.teleflex.com/usa/en/index.html (US) or https://www.teleflex.com/ca/en/index.html (Canada) or 866-246-6990 (US) or 800-387-9699 (Canada).• Two naloxone 2 mg/2 mL Luer lock prefilled syringes (e.g., IMS/Amphastar [NDC# 76329-3369-1], Dr. Reddy’s [NDC# 43598-750-11], Auromedics [NDC# 55150-345-01]).<ul style="list-style-type: none">○ Some atomizers contain needles allowing naloxone to be drawn up from vials instead of attaching to syringes. |
| How should commercially available naloxone or nalmefene nasal sprays be administered? | <ul style="list-style-type: none">• Keep the spray in the original packaging until use.^{3,25,26,34}• The person to receive the spray should be lying on their back.^{3,25,26,34}• Remove the spray from its packaging and hold it with the thumb on the bottom of the plunger and the first and middle fingers on either side of the nozzle.^{3,25,26,34}• Tilt the patient’s head back gently. Insert the tip of the nozzle into one nostril until the fingers holding the nozzle are touching the bottom of the person’s nose.^{3,25,26,34}<ul style="list-style-type: none">○ When administering naloxone in young children, if the nozzle does not fit completely in the nostril, make sure the nozzle seals the nostril before naloxone administration.²⁶• Press the plunger firmly, spraying the naloxone or nalmefene into the nostril.^{3,25,26,34}• Remove the nozzle from the nostril.^{3,25,26,34} |

| Question | Answer/Pertinent Information/Suggested Resources |
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| How should an intranasal naloxone kit (using prefilled injectable naloxone) be administered? | Follow these steps to administer prefilled naloxone injectable solution intranasally . ^{5,30} (There are three parts: the atomizer device, a plastic tube, and the naloxone Luer lock prefilled needleless syringes.) <ul style="list-style-type: none">• Remove the two yellow caps from the plastic tube AND remove the cap from the naloxone.• Hold the atomizer device by its plastic wings and attach it to the plastic tube by twisting it into place.• Screw the naloxone Luer lock container into the barrel of the tube.• Place atomizer into one of the patient’s nostrils.• Deliver the first half of the naloxone dose (1 mL [1 mg]) by giving a short, vigorous push on the naloxone container.• Move the atomizer into the patient’s other nostril.• Deliver the second half of the naloxone dose (1 mL [1 mg]) by giving a short, vigorous push on the naloxone container. |
| How should injectable naloxone be administered intramuscularly? | Follow these steps to administer naloxone IM . ^{4,16,30,32} <ul style="list-style-type: none">• Remove the cap from the naloxone vial or break the naloxone ampule neck.• Uncover the needle.• If using a naloxone ampule:<ul style="list-style-type: none">○ Insert the needle into the liquid within the ampule.○ Pull back the plunger to draw 1 mL (0.4 mg) into the syringe.• If using a naloxone vial:<ul style="list-style-type: none">○ Hold the vial upside down and insert the needle through the rubber plug.○ Pull back the plunger to draw 1 mL (0.4 mg) into the syringe.• Inject the naloxone into the muscle of the shoulder, thigh, or upper outer buttocks at a 90° angle.<ul style="list-style-type: none">○ Feel comfortable giving the injection through clothing, if it is not thick, such as a jacket or heavy sweater.• Repeat doses can be given every two to three minutes if there is no change in the patient’s status or if the patient gets sleepy again.• Naloxone needles used for IM injection should be disposed of in a sharps container.<ul style="list-style-type: none">○ Emergency medical personnel might do this.¹⁶ |

| Question | Answer/Pertinent Information/Suggested Resources |
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| How can injectable naloxone be used to prepare naloxone kits for administration via injection? | <p>US:</p> <ul style="list-style-type: none">• Naloxone for IM injection is available from single-dose or multidose naloxone vials. For IM use, it is recommended to give naloxone 0.4 mg (1 mL).⁴ Each kit should contain:^{2,4}<ul style="list-style-type: none">○ one multidose vial or two single-dose vials.○ one 3 mL syringe with an appropriately sized needle (22 to 25 gauge, 1 to 1.5 inches). Include two syringes if using the single-dose vials and ten syringes with a 10 mL vial.• Information on preparing and prescribing naloxone rescue kits is available at:<ul style="list-style-type: none">○ Harm Reduction Coalition: https://harmreduction.org/issues/overdose-prevention/naloxone-kits-materials/.○ Prescribe to Prevent: http://prescribetoprevent.org/. <p>Canada:</p> <ul style="list-style-type: none">• Injectable naloxone is available as 0.4 mg/mL in 1 mL single-dose ampoules or vials, and as 1 mg/mL in 2 mL multidose vials.¹⁶• The College of Pharmacists of British Columbia recommend dispensing at least two doses of 0.4 mg/mL naloxone plus at least two 3 mL safety syringes (e.g., <i>Vanish Point</i>, <i>BD Integra</i>) with 25 gauge, 1-inch needles.²⁰• Other supplies that might be helpful include a one-way barrier breathing mask for giving rescue breaths and an ampoule breaker.²⁰<ul style="list-style-type: none">○ Gloves and alcohol swabs could be included but are not necessary, as the injection can be given through lightweight clothing.^{16,20}• Kits are also available from community-based programs (often called “take-home naloxone” programs).<ul style="list-style-type: none">○ These programs provide kits and naloxone training.²¹○ Kits typically consist of two 1 mL single-dose ampoules, needles, syringes, alcohol swabs, one-way barrier mask, instructions, and case.²¹• For available programs throughout Canada, see:<ul style="list-style-type: none">○ https://www.canada.ca/en/health-canada/services/opioids/naloxone.html#5.○ https://www.pharmacists.ca/cpha-ca/assets/File/cpha-on-the-issues/Naloxone_Scan_Nov_2021.pdf. |
| What is the maximum recommended naloxone dose? | <ul style="list-style-type: none">• There is not a well-established maximum naloxone dose.¹⁸• Product labeling indicates initial doses of 0.4 mg to 8 mg (dose based on route of administration), with repeat doses, as necessary.^{10,18}• Typically, patients will respond to the first dose.¹⁸<ul style="list-style-type: none">○ Second doses are often supplied as a backup.¹⁸○ Additional doses may be needed, especially when emergency help is delayed, and initial naloxone doses wear off.¹⁸○ Higher doses or repeated administration may be required in patients having taken longer-acting opioids or partial opioid agonists (buprenorphine, pentazocine).¹¹• Healthy volunteers have received 24 mg without experiencing toxicity.¹⁸ |

| Question | Answer/Pertinent Information/Suggested Resources |
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| <p>What happens after a dose of naloxone or nalmefene is administered?</p> | <ul style="list-style-type: none"> • The duration of most opioids is longer than that of naloxone (30 to 120 minutes).^{6,23,24,30,32} The duration of nalmefene (about six hours) is as long as most opioids.³⁴ <ul style="list-style-type: none"> ○ Emergency medical help should be requested (call 911) immediately.^{6,13,16,26,34} • If symptoms return or if the patient doesn't respond or achieve the desired response (i.e., adequate spontaneous breathing), and emergency medical help has not yet arrived, repeat doses of naloxone can be given every two to three minutes (or nalmefene every two to five minutes).^{3,16,25,26,32,34,37} <ul style="list-style-type: none"> ○ When giving additional doses of <i>Narcan</i> (Rx), <i>Kloxxado</i>, or <i>Opvee</i> nasal spray, use alternate nostrils.^{3,25,26,34} • Rescue breathing may be required, and ideally, patients experiencing opioid overdose should be given oxygen.^{6,34} • Naloxone or nalmefene use may precipitate withdrawal in opioid-dependent patients. (See details above in section, "What should you tell patients, caregivers, and families about naloxone?") • If naloxone is given to a patient who is not opioid-dependent or is not opioid-intoxicated, it has no clinical effects.⁶ |
| <p>How should naloxone and nalmefene be stored?</p> | <ul style="list-style-type: none"> • Store naloxone and nalmefene at room temperature and protect from light.^{8,34} • Store all formulations in the original packaging. <ul style="list-style-type: none"> ○ <i>Narcan</i> nasal spray: Store below 77°F (25°C), but not below 5°F (-15°C), as it freezes and will not be usable if needed.^{3,26} Excursions up to 104°F (40°C) are allowed.^{3,26} ○ <i>Kloxxado</i> nasal spray: Store between 68°F and 77°F (20°C and 25°C). Excursions up to 104°F (40°C) and down to 41°F (5°C) are allowed. <i>Kloxxado</i> freezes below 5°F (-15°C) and will not spray; however, it can be thawed for 15 minutes at room temperature and then used. Seek emergency medical help right away if needed, and do NOT wait for <i>Kloxxado</i> to thaw.²⁵ ○ Store injectable naloxone between 15°C and 30°C (59°F and 86°F).¹⁶ ○ <i>Zimhi</i> and <i>Zurnai</i> injections: Store between 68°F and 77°F (20°C and 25°C).^{32,37} Excursions between 59°F and 86°F (15°C and 30°C) are allowed.^{32,37} ○ <i>Opvee</i> nasal spray: Store between 15°C and 25°C (59°F and 77°F). Short-term excursions between 4°C and 40°C (39°F and 104°F) are allowed.³⁴ • It is a good idea for patients to carry naloxone or nalmefene products with them, and to tell family and others who may need to administer naloxone or nalmefene where it is kept.^{3,25,32} <ul style="list-style-type: none"> ○ While counseling patients about storage, consider reminding them to keep their prescription opioid secure; divulging opioid use to others might invite theft. • Patients should periodically check the appearance of their injectable naloxone and nalmefene.^{16,32} <ul style="list-style-type: none"> ○ If the solution is discolored, cloudy, or contains particulates it should be replaced.^{16,32,37} • Naloxone and nalmefene products (and syringes, if applicable) should be replaced before the expiration date.⁸ <ul style="list-style-type: none"> ○ If stored properly, products should be effective at least until the manufacturer's expiration date. Typically, the shelf-life is 12 to 24 months.^{8,19} ○ It has been suggested that pharmacists dispense naloxone or nalmefene with at least a six-month shelf-life at time of sale, and ideally longer than one year.²⁰ |

| Question | Answer/Pertinent Information/Suggested Resources |
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| Can naloxone or nalmefene be provided to a third party? | <ul style="list-style-type: none"> • Providing naloxone or nalmefene to a third-party (e.g., to a caregiver or family member) as opposed to a patient may be permitted. <ul style="list-style-type: none"> ○ In the US, to find out about providing naloxone or nalmefene to a third-party, consult any of the following: <ul style="list-style-type: none"> ▪ http://pdaps.org/datasets/laws-regulating-administration-of-naloxone-1501695139. ▪ your state medical board. ▪ patient-specific insurance programs, including Medicaid and Medicare. ○ In Canada, naloxone is available to anyone without a prescription (unscheduled in Alberta, British Columbia, Manitoba, Saskatchewan; Schedule II elsewhere).^{19,28} |
| How much do naloxone and nalmefene cost in the US?^a | <ul style="list-style-type: none"> • OTC Narcan (naloxone) nasal spray 4 mg (includes two nasal sprays): \$45. • Naloxone nasal spray 4 mg (includes one or two nasal sprays): ~\$102/box containing two sprays (generic). <ul style="list-style-type: none"> ○ For first responders, governments, schools, and community programs, <i>Narcan</i> may be available at a reduced cost (844-4NARCAN). ○ Most major insurance plans cover naloxone nasal spray 4 mg.²⁹ • Kloxxado (naloxone) nasal spray 8 mg (includes two nasal sprays): \$125. • Opvee (nalmefene) nasal spray 2.7 mg (includes two nasal sprays): \$98 • Naloxone prefilled injectable syringe 2 mg/2 mL: \$31/2 mg syringe. • Zimhi (naloxone) prefilled injectable syringe 5 mg/0.5 mL: \$62.50 for one or \$125 for two syringes. • Zurnai (nalmefene) auto-injector 1.5 mg/0.5 mL: \$50 for one auto-injector. • Naloxone “kits” (US): <ul style="list-style-type: none"> ○ Intranasal (two naloxone 2 mg/2 mL prefilled syringes [~\$63] plus two nasal atomizers [~\$20]): ~\$84. ○ Intramuscular (two naloxone 0.4 mg/mL single-dose vials): ~\$20 plus cost of syringes. ○ Check with your local health department, as some may offer naloxone at no charge. ○ Some insurance plans, including Medicaid and Medicare in some states, will cover the kits or some components.¹⁰ |
| How much does naloxone cost in Canada?^a | <ul style="list-style-type: none"> • Narcan nasal spray: \$157/box containing two sprays. • S.O.S. Naloxone (Canada): <ul style="list-style-type: none"> ○ naloxone 0.4 mg/mL vial or ampoule: ~\$15/0.4 mg dose. ○ <i>BD Integra</i> syringe: ~\$0.80/syringe. • Do not expect naloxone to be covered on the patient’s provincial/territorial drug plan, or their extended healthcare plan. • If cost is an issue, consider referring patients to a community-based program, which might provide naloxone for free. In some provinces, publicly funded take-home kits with injectable naloxone or <i>Narcan</i> nasal spray may be available through pharmacies. See https://www.pharmacists.ca/cpha-ca/assets/File/cpha-on-the-issues/Naloxone_Scan_Nov_2021.pdf or https://www.canada.ca/en/health-canada/services/opioids/naloxone.html#5. |

| Question | Answer/Pertinent Information/Suggested Resources |
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| How do I bill for naloxone- or nalmefene-related counseling (US)? | Prescribers (US) <ul style="list-style-type: none">• Use the codes for Screening, Brief Intervention, and Referral to Treatment (SBIRT) to bill for counseling a patient about how to recognize overdose and how to administer naloxone or nalmefene.⁶<ul style="list-style-type: none">○ Use these billing codes for SBIRT:⁶<ul style="list-style-type: none">▪ CPT 99408 (commercial insurance, 15 to 30 minutes).▪ CPT 99409 (commercial insurance, longer than 30 minutes).▪ G0396 (Medicare, 15 to 30 minutes).▪ G0397 (Medicare, longer than 30 minutes).▪ H0049 (Medicaid, alcohol and/or drug screening).▪ H0050 (Medicaid, alcohol and/or drug services, brief intervention, per 15 minutes).○ For counseling and instruction on the safe use of opioids, including the use of naloxone or nalmefene, outside of the context of SBIRT services, the prescriber should document the time spent and use the E&M code that accurately captures the time and complexity. For example, in new patients deemed appropriate for opioid pharmacotherapy, when a substantial and appropriate amount of additional time is used to provide a separate service such as behavioral counseling (e.g., opioid overdose risk assessment and naloxone or nalmefene administration training), consider using modifier –25 in addition to the E&M code.⁶• When using an evidence-based opioid misuse/abuse screening tool, CPT Code 99420 (administration and interpretation of health risk assessment instrument) can be used for patients with commercial insurance.⁶ |
| Does the availability of opioid receptor blockers encourage opioid misuse? | <ul style="list-style-type: none">• In communities where naloxone distribution programs exist, opioid overdose deaths decrease.¹⁴ These programs have not been shown to increase drug use but do increase interest in treatment.⁶• Patients who are given a naloxone prescription have positive behavioral changes related to opioids, such as improved dosing (e.g., being more careful to take the right dose, and count the hours between doses), and improved knowledge of opioids and overdose.¹² |
| Are there liability issues related to opioid receptor blockers? | <ul style="list-style-type: none">• The medico-legal risks of prescribing naloxone to opioid users are low.^{6,10}• In the US, laws are being drafted and passed to protect prescribers, dispensers, and bystanders who administer naloxone.<ul style="list-style-type: none">○ See http://pdaps.org/datasets/laws-regulating-administration-of-naloxone-1501695139 for information by state.○ Good Samaritan Laws may require “good faith” and “reasonable care.”• In Canada, the “Good Samaritan Drug Overdose Act” became law in May of 2017.²²<ul style="list-style-type: none">○ Witnesses are protected and encouraged to carry and provide naloxone during suspected opioid overdoses.²² |

| Question | Answer/Pertinent Information/Suggested Resources |
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| How are nalmefene (US only) and naloxone used in hospitals and emergency departments? | <ul style="list-style-type: none">• IM and subcutaneous naloxone are the most likely methods of naloxone administration in hospitals and emergency departments.<ul style="list-style-type: none">○ Subcutaneous and IM doses have a similar onset of action and are less expensive than intranasal naloxone.¹⁸○ The onset of action for subcutaneous and IM naloxone is likely quicker than obtaining IV access.¹⁸• Nalmefene (US only) injection is for administration by healthcare professionals, with a similar cost^a (\$30/2 mg vial) compared to naloxone.^{7,24,31} There is no evidence that it is more effective than naloxone, and its longer duration of action may be a downside (e.g., longer duration of stay for monitoring and management of precipitated withdrawal).<ul style="list-style-type: none">○ Nalmefene can be given IV (fastest onset), IM, or subcutaneously.⁷ The IV dose is 0.5 mg/70 kg, with a second dose of 1 mg/70 kg two to five minutes later if needed.⁷ If precipitated withdrawal is a concern, consider a test dose of 0.1 mg/70 kg, followed in two minutes by the usual dose if there are no withdrawal symptoms.⁷• Follow your facility policies for providing naloxone or nalmefene at discharge. Options may include:<ul style="list-style-type: none">○ Providing naloxone, naloxone kits, or nalmefene directly to patients, families, or caregivers.○ Giving a written order for patients, families, or caregivers to obtain naloxone or nalmefene (e.g., pharmacy, health department). |

Abbreviations: CNS = central nervous system; IM = intramuscular; IV = intravenous; OTC = over-the-counter.

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Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

| Level | Definition | Study Quality |
|----------|---|---|
| A | Good-quality patient-oriented evidence.* | 1. High-quality randomized controlled trial (RCT) 2. Systematic review (SR)/Meta-analysis of RCTs with consistent findings 3. All-or-none study |
| B | Inconsistent or limited-quality patient-oriented evidence.* | 1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study |
| C | Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening. | |

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life). [Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician*. 2004 Feb 1;69(3):548-56. <https://www.aafp.org/pubs/afp/issues/2004/0201/p548.html>.]

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Cite this document as follows: Clinical Resource, *Meds for Opioid Overdose. Pharmacist’s Letter/Pharmacy Technician’s Letter/Prescriber Insights*. November 2023. [391108]

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