OPIOID ANTAGONIST

Naloxone

Narcan, Kloxxado, RiVive, Zimhi, Evzio (discontinued)

Short-acting opioid receptor antagonist that reverses opioid overdose within minutes and is now sold over the counter as a nasal spray.

USUAL ADULT DOSE	HALF-LIFE	METABOLISM	ONSET
4 mg IN or 0.4 mg IM/IV	30-90 min in adults	Hepatic glucuronidation	IV 1-2 min; IN or IM 2-5 min

No FDA boxed warning on the current US label.

INDICATIONS

- FDA-approved for emergency treatment of known or suspected opioid overdose with respiratory or central nervous system depression, at any age.
- The **4 mg** nasal spray moved to over-the-counter status in 2023, followed by a 3 mg over-the-counter product, so no prescription is required.
- Also approved for postoperative reversal of opioid depression and as a diagnostic aid when opioid overdose is suspected but unconfirmed.
- CDC and ASAM advise co-prescribing to patients on 50 morphine milligram equivalents daily or more, on concurrent benzodiazepines, or with any opioid use disorder history.
- Included in buprenorphine-naloxone products purely as an injection deterrent, not for any therapeutic antagonist effect when taken sublingually.
- Give it when overdose is suspected even if the substance is unknown, because naloxone is harmless when no opioid is present.

DOSING & TITRATION

- Intranasal: **4 mg** into one nostril (or 3 mg or 8 mg products), repeated every 2-3 min in alternating nostrils until breathing resumes.
- Intramuscular or subcutaneous: **0.4 mg** repeated every 2-3 min; the prefilled 5 mg/0.5 mL syringe is available for high-potency exposures.
- Intravenous in a hospital with a dependent patient: titrate **0.04-0.4 mg** to restore adequate respiration, not to restore full consciousness.
- Continuous infusion at roughly two-thirds of the effective bolus dose per hour is appropriate after overdose with methadone or extended-release opioids.
- Pediatric dosing is **0.1 mg/kg** IV or IM up to 2 mg; avoid routine use in neonates of opioid-dependent mothers because seizures may follow.
- Always activate emergency services, provide rescue breathing, place the patient on their side and observe for at least 2 h after the last dose.

MECHANISM OF ACTION

- Competitive antagonist at mu, kappa and delta opioid receptors with highest affinity for mu, displacing agonists from the receptor.
- Reverses opioid-induced respiratory depression, sedation, miosis and hypotension within minutes of reaching the central nervous system.
- Has no intrinsic agonist activity, so it produces no effect at all in a person who has not taken opioids.
- Precipitates acute withdrawal in opioid-dependent patients, which is intensely unpleasant and carries aspiration and agitation risk.
- Oral bioavailability is under **2%** because of near-total first-pass metabolism, which is why it must be given by injection or intranasally.

PHARMACOKINETICS

- Onset is 1-2 min intravenously and 2-5 min by intramuscular or intranasal route, with the 4 mg spray matching roughly 0.4 mg intramuscular exposure.
- Clinical duration is only **30-90 min**, far shorter than methadone, extended-release oxycodone or large fentanyl and fentanyl-analogue exposures.
- Elimination half-life is 30-90 min in adults but substantially longer in neonates, in whom it can approach 3 h.
- Metabolized in the liver by glucuronidation to naloxone-3-glucuronide with subsequent renal excretion of conjugated metabolites.
- The short duration relative to most opioids is the single most important pharmacokinetic fact: renarcotization is expected, not exceptional.

ADVERSE EFFECTS

- Precipitated withdrawal with nausea, vomiting, diaphoresis, agitation, tachycardia, hypertension and piloerection is the expected effect in dependent patients.
- Vomiting in an obtunded patient carries real aspiration risk, so recovery position and airway attention matter as much as the drug.
- Non-cardiogenic pulmonary edema and ventricular arrhythmias have followed abrupt complete reversal, particularly in postoperative patients.
- Severe uncontrolled pain returns immediately when naloxone is given to a patient receiving opioids for legitimate analgesia.
- Nasal formulations cause nasal dryness, congestion, headache and nasal discomfort, all minor relative to the indication.
- Return of overdose as naloxone wears off is the leading cause of death after apparently successful field reversal.

MONITORING

- Continuous respiratory rate, oxygen saturation and level of consciousness until the patient is reliably breathing on their own.
- Observe at least 2 h after the last dose, and considerably longer after methadone, extended-release opioids or massive fentanyl exposure.
- Anticipate the need for repeat doses or an infusion, and keep additional naloxone immediately available at the bedside.
- Assess and treat precipitated withdrawal symptomatically rather than by giving opioids, which risks a second overdose.
- Use the encounter to offer buprenorphine initiation and direct linkage to ongoing treatment, which reduces subsequent mortality.

INTERACTIONS & CAUTIONS

- Reverses every opioid analgesic and antitussive, so anticipate uncontrolled pain and sympathetic surge in surgical patients.
- Buprenorphine binds mu receptors so tightly that reversal may require larger repeated doses or a continuous naloxone infusion.
- Precipitates withdrawal in patients maintained on methadone or buprenorphine, sometimes lasting hours beyond the naloxone itself.
- Has no meaningful cytochrome P450 interactions and no dose adjustment for concurrent psychotropic medications.
- Does not reverse benzodiazepine, alcohol, stimulant, clonidine or gabapentinoid toxicity, though it is safe to give while sorting that out.

SPECIAL POPULATIONS

- Pregnancy: give it to save the mother, but titrate to restore respiration since abrupt reversal can precipitate fetal distress and preterm labor.
- Lactation: essentially no oral bioavailability in the infant, so naloxone is considered compatible with breastfeeding.
- Pediatric and neonatal use is established at **0.1 mg/kg**, with the caution that neonates of dependent mothers may seize on rapid reversal.
- Geriatric patients tolerate reversal less well because the catecholamine surge can provoke arrhythmia or pulmonary edema, so titrate slowly.
- Renal or hepatic impairment requires no dose change in emergency use, although clearance is slower and re-dosing may be needed less often.

PRESCRIBING PEARLS

- Naloxone lasts 30-90 min; fentanyl and methadone last far longer. Call 911 and stay.
- In a dependent patient titrate **0.04-0.4 mg** IV to breathing, not to full consciousness.
- The 4 mg nasal spray is over the counter; put it in the hands of everyone on opioids.

References

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Emergent Devices Inc. (2024). *NARCAN (naloxone hydrochloride) nasal spray [Prescribing information]*. U.S. Food and Drug Administration. https://dailymed.nlm.nih.gov/dailymed/

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U.S. Department of Veterans Affairs & U.S. Department of Defense. (2021). *VA/DoD clinical practice guideline for the management of substance use disorders*. https://www.healthquality.va.gov/guidelines/MH/sud/

NOTE

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.