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Naloxone

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Naloxone

Definition

Naloxone is a lifesaving drug for rapidly reversing opioid overdoses. It is available in the United States for the general public as prefilled auto-injected Evzio, and as Narcan nasal spray; there are generic injectables available for use by medical personnel. Naloxone is also combined with buprenorphine under the U.S. brand names Bunavail and Zubsolv to treat opioid addiction.

Purpose

Naloxone quickly restores normal respiration when breathing has slowed or stopped due to an overdose of heroin or other opiates, including prescription pain medications. An estimated 2.1 million Americans suffer from opioid-use disorder, and overdose deaths have skyrocketed from just over 21,000 in 2010 to more than 42,000 in 2016. In 2017, an estimated 145 Americans died from opioid overdoses every day. The largest increase in deaths has been caused by the illicit synthetic opioids fentanyl and its analogs. In addition to being highly potent, these drugs may be mixed with heroin, cocaine, or methamphetamine or disguised to look like prescription drugs, so that users are unaware of their strength and can easily overdose. Even patients taking higher doses of prescription opioids for chronic pain can overdose accidentally or by combining opioids with alcohol or sedatives such as benzodiazepines. In addition to saving lives, overdose "rescue" with naloxone can help connect opioid users with ongoing medical services and/or addiction treatment.

Naloxone can be administered by emergency medical personnel, first responders, family members, or bystanders. Many authorities recommend that people at risk for opioid overdose keep naloxone with them at all times, including those who:



(Kevin Link/Science Source)

- misuse prescription opioids such as oxycodone or use heroin or illicit synthetic opioids such as fentanyl or carfentanil
- have opioid-use disorder, especially those completing opioid detoxification or being discharged from treatment without ongoing methadone, buprenorphine, or naltrexone
- were recently discharged from emergency care following an overdose
- were recently discharged from incarceration with a history of opioid misuse
- take high opioid doses for long-term pain management

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- take certain extended-release or long-lasting opioid medications
- have rotating opioid medication regimens

Symptoms of opioid overdose include:

- excessive sleepiness
- not waking when spoken to loudly or rubbed firmly on the middle of the chest
- shallow or stopped breathing
- small pupils

Naloxone also may be:

- injected to reverse the effects of opiates used during surgery
- injected in newborns to decrease the effects of opioids transmitted from their mothers before birth
- administered as a “challenge” to estimate a patient's level of opioid dependence
- combined with buprenorphine to prevent opioid withdrawal symptoms and treat opioid dependence and addiction

Description

Naloxone—or *N*-allylnoroxymorphone hydrochloride—is a mu-opioid receptor antagonist, meaning that it binds to and inhibits opioid receptors, thereby blocking opioid binding, reversing opioid effects, and preventing fatalities. Naloxone was developed and patented in 1961 by Jack Fishman (1930–2013), who was searching for a treatment for constipation caused by chronic opioid use. It was approved as injectable Narcan in 1971 by the U.S. Food and Drug Administration (FDA) and has been used in hospitals for decades. Auto-injected and nasal spray naloxones were approved in 2014 and 2015, respectively, for use by laypeople.

In 2014, the U.S. Attorney General and the National Governors Association recommended increased availability of naloxone to address the opioid overdose epidemic. In 2018, the U.S. Surgeon General released a public health advisory recommending that, in addition to first responders, individuals at risk for opioid overdose and their families and friends keep naloxone auto-injectors or nasal sprays on hand. Administration of naloxone in the early stages of opioid overdose, before the arrival of professional responders, greatly increases the likelihood of survival. In many states and in Canada naloxone is available from pharmacies without a

prescription. Some states require a prescription, and some medical centers may prescribe it along with opioid prescriptions. “Good Samaritan” laws provide immunity to persons administering naloxone in overdose situations. Increased access to naloxone has been associated with a decrease in fatal overdoses with no corresponding increase in opioid use. The American Society of Addiction Medicine recommends co-prescribing of naloxone for people at risk of overdose, including those being treated for opioid-use disorder or prescribed opioids for chronic pain, and that naloxone be available to:

- people who use or are prescribed opioids and their family members or companions
- emergency medical personnel and early responders
- clinicians and others who provide services to people with substance-use disorders
- corrections staff
- law-enforcement officers
- organizations that serve populations at high risk for opioid overdose

U.S. brand names

The FDA-approved forms of naloxone are:

- various generic brands of injectable naloxone used by paramedics, emergency-department physicians, and other trained first responders
- prefilled, single-use Evzio autoinjectors
- prefilled Narcan nasal spray
- Bunavail, Zubsolv, and generic buprenorphine/naloxone combinations

Canadian brand names

In addition to generic naloxone, Canadian brand names include Suboxone (buprenorphine/naloxone).

International brand names

International naloxone brand names include:

- Naloxon
- Naloxona
- Naloxoni
- Naloxonum
- Nalokson
- Narcon
- Naxan
- Naxolan
- Nexodal
- Nokoba
- Mapin
- Prenoxad

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International brand names of combination products include:

- Suboxone, Addnok-N (naloxone and buprenorphine)
- Targin, Targinact (naloxone and oxycodone)
- Tilicomp, Tilidin, Tilidura, Tinalox, Valoron N, Valtran (naloxone and tilidine)

Recommended dosage

Initial doses of intravenous naloxone are 0.4–2 mg, repeated as necessary at 2–3-minute intervals up to 10 mg total. Naloxone can also be administered intramuscularly (IM) or under the skin (subcutaneously).

Prefilled, single-dose Evzio and Narcan are packaged in two-dose cartons, since high-potency opioids may require multiple doses. Emergency help should be summoned immediately after administration, and the patient should be watched closely until help arrives. If symptoms return, doses can be repeated every 2–3 minutes. Patients should be observed by medical personnel for at least two hours after the last dose. An Evzio dose is 0.4 mg, preferably injected IM into the outer thigh, although it can also be injected subcutaneously and through clothing if necessary. Once activated, the device provides verbal instructions for administration. A Narcan dose is 4 mg administered as follows:

- The patient is laid on their back.
- The inhaler is opened by peeling back the tab.
- With a thumb on the bottom of the plunger, and the first and middle fingers on either side of the nozzle, the nozzle tip is gently inserted into one nostril until the fingers are against the bottom of the nose.
- The plunger is pressed while supporting the back of the patient's neck to tilt their head back.
- The nozzle is removed, and the patient is turned on their side in the recovery position.
- Any additional doses are administered into alternate nostrils.

Buprenorphine/naloxone combinations are supplied as sublingual tablets (Zubsolv and generic) that melt under the tongue or buccal films (Bunavail) that dissolve between the gum and wetted cheek. They are usually taken once a day. Depending on the type of opioid use, treatment may start with a low dose of buprenorphine that is increased for one or two days before switching to the combination drug. Dosages may be increased or decreased based on response.

Precautions

Opioid users should ensure that family members, caregivers, and friends know how to recognize and respond to an overdose. If the red safety guard on Evzio is removed, the device should be discarded even if it was not used. There has been widespread use of improvised emergency kits with injectable naloxone in an atomizer for intranasal use. Such devices require training for proper assembly and administration and may not deliver appropriate doses.

Naloxone is effective for opioids used in combination with other sedatives or stimulants. However, it is not effective for treating benzodiazepine, cocaine, or amphetamine overdoses. Reversing the effects of opioid agonists such as buprenorphine and pentazocine may require additional naloxone doses.

Not all experts support widespread availability of naloxone—such as stocking it in schools and libraries—because of the risk of moral hazard or unintended consequences: as the risk of fatal overdoses decreases, some users may use more often, use higher doses, or turn to stronger drugs, such as switching from heroin to fentanyl. There have been media reports of naloxone parties where people use heroin or prescription opioids because of the availability of naloxone. There also have been reports of increased drug thefts and emergency-department visits and higher overall drug mortality in the midwestern United States.

Because buprenorphine is a partial agonist that activates opioid receptors, there are additional precautions for buprenorphine/naloxone combination drugs:

- The medication can cause drowsiness; people should not drive or operate machinery until they know how it affects them.
- Alcohol—including prescription and nonprescription medications containing alcohol—should be avoided.
- Dizziness, lightheadedness, or fainting can occur when rising too quickly from a lying position, especially when first starting the combination drug.
- Lab tests are required to measure drug response.
- Doctors, laboratory personnel, and dentists should be told about this drug use prior to any surgery or lab tests.
- Stopping the drug too abruptly can cause withdrawal symptoms.
- This drug combination may decrease fertility.

Pediatric

As buprenorphine/naloxone prescriptions increased in 2010–2011, they became the most common cause of hospitalizations for medication ingestion in young children. Although unintended ingestions substantially decreased with the introduction and widespread adoption of unit-dose, child-resistant packaging, emergency-department visits for pediatric ingestion have not been eliminated.

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Pregnant or breastfeeding

Limited naloxone under medical supervision for opioid overdoses saves the lives of pregnant women, but their fetuses may require monitoring. Regular use of a buprenorphine/naloxone combination during pregnancy may cause life-threatening withdrawal symptoms in newborns. If breastfeeding while taking the combination medication, the doctor should be notified immediately if the baby becomes unusually sleepy or has trouble breathing.

Other conditions and allergies

The doctor should be told of allergies to naloxone, naloxone ingredients, or any other medications and whether the patient has or has ever had heart, kidney, or liver disease. Before taking a buprenorphine/naloxone combination, the doctor should be informed if the patient has ever consumed large amounts of alcohol or has or has ever had adrenal problems, benign prostatic hypertrophy, trouble urinating, head injury, hallucinations, curvature of the spine that interferes with breathing, gallbladder disease, or thyroid or lung disease.

Side effects

At normal low doses, naloxone is very safe and effective with only mild side effects. Injection may cause pain, burning, or redness at the injection site or hot flashes or flushing. The nasal spray may cause nasal dryness or swelling, congestion, or muscle pain. Naloxone begins wearing off after about 30 minutes and is mostly gone after about 90 minutes—sufficient time for opioids to have been metabolized so that overdose symptoms should not recur. However, naloxone sometimes precipitates symptoms of opioid withdrawal that may include:

- nervousness, restlessness, or irritability
- body aches
- headache
- blood pressure changes
- rapid heartrate
- sweating
- dizziness or weakness

- stomach pain, diarrhea, nausea, or vomiting
- fever, chills, or goose bumps
- tremors
- sneezing or runny nose
- yawning

Rare but serious naloxone side effects that require emergency medical treatment include:

- rapid, pounding, or irregular heartbeat
- hallucinations
- seizures
- loss of consciousness

Buprenorphine/naloxone

Possible side effects of the combination drug include:

- tongue pain
- mouth numbness or redness
- headache
- stomach pain
- constipation
- difficulty falling asleep or staying asleep
- blurred vision
- back pain

Serious side effects of the combination drug that require immediate medical consultation include:

- hives, rash, or itching
- difficulty breathing or swallowing
- swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs
- agitation, hallucinations, fever, sweating, confusion, fast heartbeat, shivering, severe muscle stiffness or twitching, loss of coordination, nausea, vomiting, or diarrhea
- weakness
- inability to get or keep an erection
- irregular menstruation
- decreased sexual desire
- upset stomach
- extreme tiredness
- slurred speech
- unusual bleeding or bruising
- lack of energy
- pain in the upper right of the stomach
- yellowing of the skin or eyes
- dark-colored urine
- light-colored stools
- symptoms of overdose such as pinpoint pupils, extreme drowsiness, dizziness, blurred vision, or slowed breathing

Pediatric

Babies treated with naloxone injection may cry excessively or have stronger than normal reflexes.

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Agonist—

A drug that binds to a receptor causing activity similar to the binding of the endogenous substance, such as buprenorphine binding to opioid receptors.

Antagonist—

A chemical that blocks the action of a chemical by binding to its receptor, such as naloxone binding to opioid receptors.

Benzodiazepines—

A class of anti-anxiety drugs.

Buprenorphine—

A partial opioid agonist that is often combined with naloxone for treating opioid dependence and addiction.

Fentanyl—

A synthetic opioid pain reliever with effects similar to morphine but many times stronger.

Heroin—

An illegal, highly addictive narcotic that is made from morphine and widely abused for its euphoric effects.

Opiate—

A narcotic containing or derived from opium—such as codeine, morphine, or heroin—that alleviates pain and induces sleep; however, the terms “opiate” and “opioid” are generally used interchangeably.

Opioid—

A synthetic drug, such as methadone, that has narcotic properties similar to opiates but is not derived from opium.

Oxycodone—

A narcotic painkiller that is widely abused.

Withdrawal—

Unpleasant, sometimes life-threatening, physiological effects of discontinuing some drugs, such as opioids, following prolonged regular use.

Interactions

The doctor and pharmacist should be told of all prescription and nonprescription medications, vitamins, nutritional supplements, and herbal products the patient is taking or plans to take. Many different heart and blood pressure medications can increase the risk of serious side effects from naloxone injection.

Many different drugs can interact with buprenorphine/naloxone combinations. The doctor and pharmacist should be told if the patient is taking:

- antidepressants including selective serotonin- or serotonin and norepinephrine-reuptake inhibitors or tricyclic antidepressants
- antihistamines
- antipsychotics
- benzodiazepines
- diuretics
- erythromycin
- HIV medications
- ipratropium
- ketoconazole
- medications for irritable bowel disease, motion sickness, Parkinson disease, ulcers, or urinary problems
- certain migraine medications
- mirtazapine
- monoamine oxidase inhibitors within the past two weeks
- muscle relaxants
- opiates
- rifampin
- seizure medications
- 5HT₃ serotonin blockers
- sleeping pills
- St. John's wort
- tramadol
- trazodone
- tryptophan

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ORGANIZATIONS

American Society of Addiction Medicine, 11400 Rockville Pike, Ste. 200, Rockville, MD 20852, (301) 656-3920, Fax: (301) 656-3815, email@ASAM.org, <https://www.asam.org>

Coalition to Stop Opioid Overdose, c/o Capitol Decisions Inc., 800 Maine Ave. SW, Ste. 800, Washington, D.C. 20024, (202) 638-0326, Fax: (202) 638-0358, <http://www.stopopioidoverdose.org>

National Institute on Drug Abuse, Office of Science Policy and Communications, Public Information and Liaison Branch, 6001 Executive Blvd., Rm. 5213, MSC 9561, Bethesda, MD 20892, (301) 443-1124, <https://www.drugabuse.gov>

Substance Abuse and Mental Health Services Administration, 5600 Fishers Ln., Rockville, MD 20857, (877) SAMHSA-7, <https://www.samhsa.gov>.

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