Naloxone for Opioid Overdose: FAQs

Background

Opioid prescribing doubled from the late 1990s to 2012, when pain treatment became the subject of several quality initiatives and practice guidelines. Prescription opioid overdose deaths quadrupled between 1999 and 2010, while heroin overdoses increased by <50%. Now, opioid prescribing seems to be plateauing or even decreasing based on data from 2011 to 2013. This may be due to prescribing restrictions and education, state prescription monitoring programs, and availability of abuse-deterrent formulations such as OxyContin. Although prescription opioids are still the main source of illegal opioids, these trends have been associated with an increase in heroin use and heroin overdose. Heroin is relatively inexpensive and easier to get in some areas than prescription opioids. Based on data from 28 states, from 2010 to 2012, the death rate from heroin overdose increased from 1 to 2.1 per 100,000 people. During this same timeframe, the death rate due to prescription opioid overdose decreased slightly from 6 per 100,000 to 5.6 per 100,000. In April 2014, the FDA approved Evzio, a naloxone auto-injector that can be administered by a lay person to treat a person known or suspected to have overdosed on opioids. This article answers common questions that arise in clinical practice related to naloxone for opioid overdose, including Evzio.

How is naloxone supplied?

Each Evzio carton contains two active auto-injectors, each containing naloxone 0.4 mg, and one trainer. The trainer is in a black and white outer case, while the active Evzio auto-injector is in a purple and yellow outer case. The trainer can be used over 1000 times. The trainer is exactly like Evzio, except that it does not contain a needle or naloxone, and has no expiration date. Unlike Evzio, the red safety guard on the trainer can be removed and replaced.

Alternatively, naloxone can be supplied in vials for intramuscular injection, or in prefilled syringes for intranasal use. For intramuscular use, it is recommended that naloxone be provided as 0.4 mg/mL in two 1 mL single-dose vials or one 10 mL multidose vial. For each injection, a 23 gauge, 3 cc syringe with a 1-inch needle will be needed. Intranasal use will require two naloxone 2 mg/2 mL luer-lock prefilled syringes made by IMS/Amphastar (NDC# 76329-3369-1), along with two mucosal atomization devices (MAD 300), which pharmacists can order by calling 800-788-7999. This device fits into the luer-lock of the IMS/Amphastar naloxone.

When should naloxone be administered?

Respiratory and/or central nervous system depression in a situation where opioids may be present is an indication to use naloxone. Naloxone should be given if the patient is excessively sleepy and cannot be aroused with a loud voice or sternal rub. Other indications include slow, shallow, or no respirations, or pinpoint pupils in a patient who is difficult to arouse. Other signs of overdose include blue or purple fingernails or lips. The patient may emit a death rattle, which may be mistaken for snoring. The patient may also have a slow heartbeat and/or low blood pressure.

How is naloxone administered?

As mentioned previously, each Evzio carton contains a trainer. Patients and anyone who may need to help the patient in the event of an overdose should practice with the trainer. Evzio product labeling recommends that the patient and caregivers practice daily for the first week, then weekly.

Evzio has a speaker that provides voice instructions. If the voice instructions don’t work for some reason, Evzio will still work. Users should follow the written instructions on the label.
To use, Evzio must first be removed from its case. When the user is ready to give the injection, the red safety guard is removed, and the black end of the injector is placed against the outer thigh. (Evzio can be injected through pants.) To administer the dose, the injector is pressed firmly and held for five seconds. If the patient is an infant, the injection should be given into a pinched-up area of the middle of the outer thigh muscle. The injector makes a click and hiss noise during injection.

For naloxone supplied via vial and syringe for intramuscular injection, the caregiver should first remove the cap from the naloxone and uncover the needle. They should then insert the needle through the rubber plug with the bottle upside down, and pull back the plunger to draw 1 mL into the syringe. The naloxone can then be injected into the muscle of the shoulder or thigh.

For intranasal use, the caregiver must attach the atomizer device to the naloxone. They will see three parts: the atomizer device, a plastic tube, and the naloxone vial. First, they remove the two yellow caps from the plastic tube and the red cap from the naloxone. They should then hold the atomizer device by its plastic wings and twist it onto the plastic tube. They then screw the naloxone into the barrel of the tube. After inserting the atomizer into the patient’s nostril, the naloxone is delivered by giving a short, vigorous push on the naloxone vial, delivering half of the naloxone into each nostril. A second dose is repeated in three minutes if there is no response.

What happens after a dose is administered?
The duration of most opioids is longer than that of naloxone, so emergency medical help must be summoned immediately after use, even if the patient wakes up. In fact, deaths have occurred when naloxone was administered in an outpatient setting and the ambulance left. Rescue breathing may be required, and ideally, patients experiencing opioid overdose should be given 100% oxygen. Patients who have overdosed on partial agonists and mixed agonist-antagonists (e.g., buprenorphine) may not respond well. Naloxone can be given every two to three minutes to achieve the desired response (i.e., adequate spontaneous breathing).

Naloxone use may precipitate withdrawal in opioid-dependent patients. Opioid withdrawal symptoms include sweating, goose bumps, achiness, shivering, GI symptoms, tachycardia, irritability, and increased blood pressure. Fever, runny nose, sneezing, and yawning are other signs and symptoms of opioid withdrawal. The patient may even become agitated or combative. Fortunately, most patients respond to naloxone with a return to spontaneous breathing with only mild withdrawal symptoms. Opioid withdrawal is not typically life-threatening in adults. If naloxone is given to a patient who is not opioid-dependent or is not opioid-intoxicated, it has no clinical effects.

Once the Evzio injector has been used, the needle will retract into the base, the base will lock, the voice instruction will state that the injector has been used, a red light will blink, and a red indicator will show in the viewing window. The used injector should be placed in its case and disposed of in a sharps container, following any state or local laws about disposal of auto-injectors or perchlorate-containing batteries (California). Naloxone needles used for intramuscular injection should also be disposed of in a sharps container.

How should naloxone be stored?
Naloxone should be stored at room temperature and protected from light. Evzio should be stored in the provided case at 59°F to 77°F, although excursions to 39°F and 104°F are allowed. Product labeling advises that patients carry Evzio with them, and tell family, friends, co-workers, and others who may need to administer Evzio where it is kept. While counseling patients about Evzio 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 Evzio through the window in the auto-injector. If the solution is discolored, cloudy, or contains particulates it should be replaced. Evzio should be replaced before the expiration date. The manufacturer intends to ship Evzio with a 24-month shelf-life. If stored properly, other naloxone products should be effective until the manufacturer’s expiration date. Typically, the shelf-life is 12 to 18 months.

For whom should naloxone be prescribed?
Consider a naloxone prescription for patients on chronic opioids and others at risk of overdose.
These include patients prescribed high doses.\textsuperscript{12} Twenty percent of opioid overdoses occur in patients prescribed less than 100 mg of morphine or its equivalent per day, while 40% occur in patients prescribed higher doses.\textsuperscript{13} Other patients at risk are those rotating (switching) from one opioid to another (risk of incomplete cross-tolerance), patients with a history of opioid overdose, and patients with a history of substance abuse.\textsuperscript{12}

Most states currently prohibit third-party prescribing, such as to a caregiver or family member as opposed to a patient. Consult www.prescribetoprevent.org or your state medical board to find out if third-party prescribing of naloxone is allowed in your state.\textsuperscript{12}

**How much does naloxone cost?**

*Evzio* costs about $600 for two auto-injectors and a trainer, but *Evzio* is covered by most insurance plans, including government plans. Medicaid in some states (e.g., California, New York, North Carolina, Washington, New Mexico), will cover naloxone.\textsuperscript{16-18} Insurance does not cover the nasal atomizer device.\textsuperscript{15}

Patients with private insurance may be eligible to have *Evzio* mailed directly to their home without a copay. A patient assistance program is also available at www.evzio.com. Naloxone “kits” may cost <$100. If cost is still an issue, consider referring patients to a community-based program that offers generic naloxone kits. See www.prescribetoprevent.org for programs in your area. This site also has information on prescribing naloxone in a vial or intranasal naloxone (off-label) for bystander use, with patient instructions.

**How do I bill for naloxone-related counseling?**

Prescribers can 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.\textsuperscript{12} Complete the DAST-10 drug use questionnaire (available at http://www.emcdda.europa.eu/attachements.cfm/a tt_61480_EN_DAST%2020008.pdf) and refer to a substance abuse treatment program if applicable.\textsuperscript{15} Billing codes for SBIRT are CPT 99408 (commercial insurance, 15 to 30 minutes), G0396 (Medicare, 15 to 30 minutes), and Medicaid H0050 (Medicaid, per 15 minutes). For counseling and instruction on the safe use of opioids, including the use of naloxone, 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 administration training), consider using modifier –25 in addition to the E&M code. When using an evidence-based opioid misuse/abuse screening tool (see http://www.painedu.org/soapp.asp), CPT Code 99420 (administration and interpretation of health risk assessment instrument) can be used for patients with commercial insurance.\textsuperscript{12}

**Does naloxone availability encourage opioid misuse?**

Surveys of heroin users in the late 1990s suggest they do not use more heroin if naloxone is available. This may be because they do not want to experience withdrawal precipitated by naloxone.\textsuperscript{19} In one naloxone program for heroin users, the frequency of heroin injection (p=0.003) and number of overdoses (p=0.83) actually decreased.\textsuperscript{20} Furthermore, in communities where naloxone distribution programs exist, opioid overdose deaths decrease.\textsuperscript{21,22} Monitor patients for opioid dose escalation, and discuss the risks with patients.\textsuperscript{19}

**Are there liability issues related to naloxone?**

The medico-legal risks of prescribing naloxone to opioid users appear low.\textsuperscript{15,19} Laws are being drafted and passed to protect bystanders who administer naloxone and prescribers who prescribe it. This is a rapidly evolving area. See lawatlas.org or www.prescribetoprevent.org for information by state.

**Commentary**

Even though *Evzio* is new, use of naloxone by bystanders and first responders is not new, and has been used across the country with reported success. This includes off-label use of intranasal naloxone.\textsuperscript{11,21,22} Although intranasal use has some
advantages over intramuscular injection (e.g., easier disposal, no needle stick risk, no "needle anxiety"), assembly is more difficult.  

The American Medical Association has long supported the availability of naloxone for patients, bystanders, and first responders. Pharmacists can advocate for laws allowing pharmacists to furnish or administer naloxone without a prescription, perhaps through a collaborative practice agreement, such as in Washington, Rhode Island, San Francisco, New Mexico, and Allegheny County, Pennsylvania. The FDA views Evzio approval as another tool to combat opioid abuse, along with actions such as labeling revisions and Risk Evaluation and Mitigation Strategies (REMS) for long-acting opioids, and moving hydrocodone to Schedule II.

Another consideration in the growing heroin problem is dirty needles. Syringe-sharing was recently linked to an HIV outbreak in rural Indiana. Access to clean syringes reduces the spread of HIV without increasing drug use or crime. A list of needle exchange programs in each state is available at https://nasen.org/news/2015/apr/13/new-nasen-sep-directory-page/. In most states, it is permissible for syringes to be dispensed without a prescription. On January 1, 2015, a law went into effect allowing California pharmacies to choose to provide this service, which must include safe needle disposal, and information on accessing drug treatment and HIV and hepatitis C testing. Many states also allow prescribers to prescribe, and pharmacists to dispense, needles for injection drug users to prevent the spread of infectious disease. Consult with your medical and pharmacy boards to find out what is allowed in your state, or check lawatlas.org. Prescription of syringes is best done within the framework of a comprehensive prescriber/patient relationship. Prescribers can discuss the dangers of continued injection drug use, with encouragement to stop or reduce use, and offer to refer patients to appropriate programs. Also consider whether the patient may be self-medicating legitimate pain with street drugs.

Naloxone is not a magic bullet for opioid overdose. Think of it as an adjunct to other measures to keep patients and their families safe. These measures include limiting opioid quantities, and use of opioid treatment agreements, abuse-deterrent opioids, and your state prescription drug monitoring programs.

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References

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