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# The naloxone option

This quick guide provides you with naloxone dosing information and steps you'll want to take once the crisis has passed.

**M**ore than 64,000 people in the United States died of drug overdoses in 2016.<sup>1</sup> Of those overdose deaths, more than 34,000 were related to the use of natural (eg, codeine, morphine); synthetic (eg, fentanyl); and semisynthetic (eg, oxycodone, hydrocodone) opioids.<sup>1</sup> The number of drug-overdose fatalities (driven largely by opioids) has increased so dramatically in recent years that drug overdose is now the leading cause of intentional and unintentional injury-related death in the United States.<sup>2</sup> Furthermore, opioid use is increasing among college students, with many injecting these agents.<sup>3</sup> Those injecting (as opposed to other routes of delivery) have the highest death rate.<sup>4</sup>

■ **The Department of Health and Human Services** has identified 3 important issues to address with regard to the opioid epidemic: prescriber education, community naloxone access, and better interventions (such as naloxone overdose-reversal take-home kits) for people with opioid use disorders and/or a history of overdoses.<sup>5</sup> (For more on overdose reversal kits, see "What FPs need to know about naloxone kits," a 3-in-3 video available at: <http://bit.ly/2GPqApP>.) With these goals in mind, we provide the following review of naloxone dosing and postoverdose treatment.

## Steps FPs can take to reverse the overdose

Opioids act on delta, kappa, and mu receptors in the brain to produce analgesic effects,<sup>6</sup> but, in large quantities, their mu receptor ac-

tivity can cause fatal respiratory depression.<sup>7</sup> Some of the most commonly abused opioids are heroin and the prescription opioids fentanyl, oxycodone, and hydrocodone.<sup>8</sup>

People who have overdosed on opioids generally present with evidence of obtundation, miosis, and difficulty breathing. Respiratory failure is the most common cause of death.<sup>9</sup> Hypothermia, compartment syndrome, rhabdomyolysis, renal failure, and acute pulmonary edema are less common complications. Overdoses and these medical issues can potentially be reversed and/or mitigated by naloxone administration.<sup>10,11</sup>

■ **Naloxone and its routes of administration.** Naloxone is the agent of choice in overdose situations.<sup>12</sup> It works as an antagonist of the delta, kappa, and mu receptors,<sup>6,13</sup> has a rapid onset of action, and is associated with minimal adverse effects.<sup>14</sup>

Naloxone can be administered via the intravenous (IV), intranasal, intramuscular, subcutaneous, intraosseous, or endotracheal routes.<sup>6</sup> Although IV administration has been the most common and is still generally preferred in the hospital setting, the intranasal route has gained favor, partly because it can be difficult to establish an IV in IV drug users and partly because it is easier for nonmedical people to administer.<sup>6</sup>

In addition, the nasal mucosa has an abundant blood supply resulting in rapid absorption. The drug reaches the systemic circulation quickly and avoids first-pass hepatic metabolism.<sup>6</sup> Intranasal route absorption is enhanced by deep inhalation and patient cooperation, but it can still be effective in an unconscious patient. Response time is nearly

the same as that with IV administration (both act within 1-2 mins).<sup>6</sup>

■ **Naloxone has a short duration of action** (shorter than that of some opiates), and its duration of action is influenced by the pharmacology and toxicity of the overdose drug.<sup>15</sup> The serum half-life in adults ranges from 30 to 81 mins, and clinical impact varies from minutes to an hour.<sup>15</sup> Thus, even if a patient initially improves after administration, close observation is mandatory due to the frequent need for repeat naloxone dosing.

■ **Adverse effects.** Naloxone is considered safe, with relatively few adverse effects and doesn't have any effects on someone who isn't experiencing an opioid overdose or currently on opioids.<sup>15</sup> The only downside is that naloxone administration to an opioid-dependent person often precipitates an acute withdrawal event, characterized by global pain, agitation, generalized distress, and gastrointestinal complaints, including vomiting and diarrhea. Although withdrawal is not life-threatening, it can cause great discomfort.

### Getting a handle on naloxone dosing

The starting dose of naloxone used to be 0.04 mg, but this was later increased to 0.4 mg. The advent and high overdose lethality of more potent drugs like fentanyl and carfentanil has made low-dose naloxone less effective.<sup>12</sup>

Currently, 1 mg is often the initial recommendation, but doses of 2 to 4 mg are not uncommon, and multiple administrations or continuous IV administration are frequently needed to reverse severe toxicities, such as those involving fentanyl or longer-action opioids like methadone. Anyone exhibiting difficulty breathing mandates a starting naloxone dose of at least 1 to 2 mg.<sup>12,16</sup> In addition to breathing, additional doses are indicated clinically by medical parameters such as vital signs, ocular pupil diameter, and/or alertness.<sup>6</sup>

Intranasal administration often utilizes up to 4 mg of naloxone in one nostril, followed by a titrated additional administration in the other nostril. In life-threatening circumstances, especially those in which a patient is exhibiting respiratory depression, a much larger quantity of naloxone—up to 10 mg—may be administered by trained

medical personnel.<sup>12,16</sup> In the end, all dosing varies and must be individualized to the patient's signs and symptoms. Those who have overdosed require prolonged monitoring to treat potential complications.

■ **Emergency assistance and transport.** Because of the dangers that can result from opioid toxicities, any hint or evidence of physiologic compromise merits a 911 call for emergency medical assistance and transport to a hospital emergency department (ED). Hospitalization is at the physician's discretion.

### Expanding the availability of naloxone in the community

The availability of naloxone overdose-reversal kits is growing among hospitals, other types of health care facilities, first responders, medical offices, and the general public. Distributing the kits to opioid users and their families has wide support but remains controversial (more on this in a bit).

Support even includes that from the current US Surgeon General, Jerome Adams, MD, MPH, who noted in a statement on April 5, 2018, the lifesaving success of opioid-overdose reversal naloxone kits by medical personnel, first responders, and other people. As a result, he formally recommended that more Americans keep such kits available in order to be able to quickly diminish opioid toxicities.<sup>17,18</sup> His advice was especially directed toward people at risk for an opioid overdose or anyone associated with opioid drug users.

Prehospital management of overdoses is ideally managed by emergency medical service (EMS) personnel,<sup>10</sup> but even nonmedical people can safely administer naloxone. About 10,000 overdose cases were documented to have been reversed by nonmedical providers between 1996 and 2010.<sup>10</sup> Many states have laws limiting the civil and criminal liability for naloxone administrators. New Mexico was the first state to legally allow naloxone administration by individuals without a prescription.<sup>7</sup> Pharmacists often participate in efforts to counter opioid drug overdose deaths by offering naloxone administration kits, along with training about techniques of use, to people



**Opioids are responsible for 61% of drug-overdose deaths.**

IMAGE: © SHUTTERSTOCK

➤ **About 10,000 overdose cases were documented to have been reversed by nonmedical providers between 1996 and 2010.**

filling opioid prescriptions and to household members and/or other individuals in the social support network of an opioid user.<sup>6</sup>

Some physicians co-prescribe naloxone to patients along with opioid therapies during long-term pain management. Such dual prescribing is encouraged by many clinics.<sup>19</sup> This method has decreased opioid overdose deaths in North Carolina,<sup>20</sup> in its army base at Fort Bragg,<sup>19</sup> and in California.<sup>21</sup>

### The issue of "risk compensation"

To those who say that having naloxone available to users of opioids or those in their social network promotes even riskier behavior resulting in increased overdoses, research points to just the opposite. A nonrandomized study that examined co-prescribing naloxone to patients on chronic opioid therapy for non-cancer-related pain, documented fewer opioid-related ED visits following use by prescribers and patients at community health centers.<sup>22</sup> Other research has demonstrated a reduced number of community-level opioid overdose deaths once opioid overdose education and community naloxone distribution were implemented.<sup>23,24</sup>

### After the overdose: Getting patients into treatment

After reversing initial toxicities, a protracted period of assessment is required to assure pa-

tient safety. Beyond prolonged observation after an overdose, it is critical to recommend and provide long-term substance abuse therapies. Simply reversing the overdose is not medically sufficient, even if postoverdose patients refuse such treatment referrals. The fact that many of these people subsequently die is evidence of the importance of adhering to a formal, long-term chemical dependence intervention program.

Persistent diligence is usually needed to convince a patient who has recovered from an acute drug overdose event to accept a treatment referral. Some EDs institute special teams to facilitate such referrals, using a multidisciplinary approach, including substance abuse counselors and social workers. Referral agencies are also sometimes included to aid patient acceptance and retention in drug abuse treatment interventions. (See "Resources" below for more information.)

**JFP**

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