Washington State Department of HEALTH

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Issue Brief: The Risks of High-Dose Naloxone Products and Nalmefene for Community Opioid Overdose Response

Key Points

- Washington State Department of Health **supports the practice of using standard-dose naloxone products to reverse the effects of an opioid overdose in community settings.** A standard dose is 0.4 mg/mL intramuscular (IM) injection or 3-4 mg/0.1mL intranasal (IN) spray.
- Standard-dose naloxone is appropriate for all opioid overdoses, including fentanyl overdoses.
- According to current data, newly released high-dose naloxone products or nalmefene don't offer more benefits than standard-dose naloxone products, and they come with greater risks.
- Using high-dose naloxone and nalmefene to reverse an overdose may increase the likelihood of precipitated withdrawal in people who are opioid dependent, which can be dangerous to them and those caring for them.

Purpose of this issue brief

This issue brief provides a summary of the current data and the Washington State Department of Health's recommendations on opioid overdose reversal medication types and dosages. Organizations can consider these recommendations when purchasing or acquiring these medications for community-based distribution.

What are opioids? What is an opioid overdose?

Opioids are a class of drugs that either come from natural substances found in the opium poppy plant or are lab-created to mimic these substances. Opioids include the drugs fentanyl, oxycodone, hydrocodone, codeine, morphine, and heroin, among others. In the United States, some of these drugs are legal prescription pain medications, and others are illegal. Opioids work in the body to produce a variety of physiologic effects. These effects include:

- Pain relief
- Slowed breathing (respiratory depression)
- Constipation
- Slowed heart rate (bradycardia)

An opioid overdose occurs when a person has more opioids in their body than the body can handle. An overdose can cause breathing to slow or stop completely, which can lead to cardiac arrest.

What is naloxone?

Naloxone is a medication that can rapidly reverse an opioid overdose, usually in 3-5 minutes. Naloxone is an opioid antagonist. It attaches to opioid receptors in the brain and reverses and blocks the effects of opioids. Naloxone can restore a person's normal breathing if their breathing has slowed or stopped due to an opioid overdose. Generally, naloxone is injected into a large muscle like the thigh or upper arm or sprayed into a nostril. Naloxone has a short half-life and generally wears off after 30-90 minutes. A person treated with naloxone may continue to experience the effects of overdose and need an additional dose after the first dose wears off. People with opioid dependence may experience precipitated withdrawal or other symptoms of opioid withdrawal when taking any opioid antagonist.

What is nalmefene?

Nalmefene is a long-acting, high-potency opioid antagonist. Using this medication during an opioid overdose increases the risk of prolonged opioid withdrawal. Research on the use of nalmefene in community-based settings and with overdoses involving synthetic opioids like fentanyl remains limited. The American College of Medical Toxicologists and the American Association of Clinical Toxicologists have released a position statement that nalmefene should not replace naloxone as the primary opioid antidote at this time.

What does the Washington State Department of Health recommend?

Washington State Department of Health supports using standard-dose naloxone in community settings to reverse the effects of opioid overdose. A standard dose is 0.4 mg intramuscular (IM) injection or 3-4 mg intranasal (IN) spray.

Some examples of current standard-dose products include:

- 0.4mg/1mL generic naloxone for intramuscular use
- 3mg/0.1mL naloxone for nasal use (brand name RiVive®)
- 4 mg/0.1mL naloxone (available as a generic and under the brand name NARCAN®)

Are current standard-dose naloxone products enough to reverse a fentanyl overdose? How many doses may be needed?

- Standard-dose naloxone can treat all opioid overdose events, including fentanyl-involved overdoses. It is safe for people of all ages, including infants.
- Most of the time, 1 dose of standard-dose naloxone will reverse an opioid overdose. In some cases, a person may need 2 doses. Very rarely, a person experiencing an overdose may need more than 2 standard doses of naloxone.

Giving more naloxone by using a high-dose product or multiple standard doses does not reverse an opioid overdose more quickly or effectively. Giving multiple doses or using high-dose products may lead to serious health effects, like precipitated withdrawal, for people with opioid dependence.

"An overdose may appear to need additional doses if other sedating drugs are present in the person's body, such as alcohol, benzodiazepines, or xylazine; however, rapidly giving more naloxone or using a stronger, more concentrated [opioid overdose reversal medication] will not necessarily speed up the reversal process. Multiple studies have found that despite the presence of fentanyl, more doses were not associated with improved outcomes. Administering a second dose… too quickly after the first dose may make it appear that multiple doses were needed. However, in some cases**, waiting 2-3 minutes before administering a second dose** and ensuring that effective rescue breaths [or CPR] are being provided would have been sufficient to reverse the overdose. Taking time to consider the effects of putting someone into withdrawal is compassionate and potentially lifesaving." *U.S. Substance Abuse & Mental Health Services Administration*

Why are high-dose naloxone and nalmefene not included in Washington State Department of Health recommendations?

Currently, the Washington State Department of Health doesn't recommend the use of higher-dose or long-acting opioid antagonists like high-dose naloxone products or nalmefene.

Examples of these products include:

- ZIMHI® (a 5 mg/0.5 mL naloxone prefilled syringe)
- KLOXXADO® (an 8mg/0.1mL naloxone nasal spray)
- OPVEE® (a 2.7mg/0.1mL nalmefene nasal spray)
- ZURNAI® (a 1.5mg/0.5mL nalmefene autoinjector)

These products may have serious unintended health consequences for people with opioid dependence.

The Washington State Department of Health only includes standard-dose naloxone in the Statewide Standing Order to Dispense Naloxone for these reasons:

- Opioid antagonists can trigger acute withdrawal symptoms in people with opioid dependence. This can cause symptoms like body aches, cramping, diarrhea, agitation, nausea, and vomiting. High-dose or longer-acting products can worsen these issues. As the federal Substance Abuse & Mental Health Services Administration (SAMHSA) explains, "Extreme experiences of withdrawal can be painful, dangerous, and traumatizing, leading to negative feelings towards naloxone and people who use it."

People in severe withdrawal may seek opioids to ease the withdrawal symptoms. After the medication wears off, they could experience another overdose that may be worse. Higher doses of naloxone and nalmefene pose a higher risk of precipitated withdrawal. As a result, some people who use opioids may avoid carrying or using naloxone. Using drugs alone is a major risk for fatal overdose since no one can respond and provide aid during an overdose. However, the fear of withdrawal may prevent people from seeking needed care, according to SAMHSA. They might also hide their drug use to avoid treatment with naloxone.

How can I access standard-dose naloxone products?

People in Washington can get naloxone from various community-based organizations at no cost. To find naloxone near you, visit stopoverdose.org. You can get several different naloxone products without a prescription or at pharmacies using health coverage.

Where can I get training on overdose prevention and response, including how to use naloxone?

Washington State Department of Health has written instructions and a video available online. DOH also provides free training for agencies in Washington. For more information, please contact naloxoneprogram@doh.wa.gov.

Information, research evidence, and clinical views informing this statement are on the following page.

For more information, research evidence, and clinical views informing this statement, please see:

Bell A, Bennett AS, Jones TS, Doe-Simkins M, Williams LD. Amount of naloxone used to reverse opioid overdoses outside of medical practice in a city with increasing illicitly manufactured fentanyl in illicit drug supply. Substance Abuse, 40 (1) (2019), pp. 52-55.

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Hill LG, Zagorski CM, Loera LJ. Increasingly powerful opioid antagonists are not necessary. *Int J Drug Policy*. 2022;99:103457.

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Klebacher R, et al. Incidence of naloxone redosing in the age of the new opioid epidemic. Prehospital Emergency Care, 21 (6) (2017), pp. 682-687.

Moustaqim-Barrette A, Papamihali K, Williams S, Ferguson M, Moe J, Purssell R, Buxton JA. Adverse events related to bystander naloxone administration in cases of suspected opioid overdose in British Columbia: An observational study. PLoS One. 2021 Oct 29;16(10):e0259126.

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Rock P, Slavova S, Westgate PM, Nakamura A, Walsh SL. Examination of naloxone dosing patterns for opioid overdose by emergency medical services in Kentucky during increased fentanyl use from 2018 to 2021. Drug and Alcohol Dependence, 255 (2024), Article 111062.

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SAMHSA Overdose Prevention and Response Toolkit. Publication No. PEP23-03-00-001. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2023.

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