

## Opioid Reversal Agents

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Drug overdoses have become a national epidemic in the United States (US).<sup>1</sup> In a 12-month period, ending in October 2022, there were more than 101,750 reported fatal opioid overdoses in the US.<sup>2</sup> Deaths from opioids occur most often in those 18 to 65 years of age and is the leading cause of death in individuals between 25 and 34 years of age.<sup>3,4</sup> In Oregon, unintentional opioid overdose deaths have risen annually since 2019.<sup>1</sup> Opioid reversal agents are a valuable treatment antidote for accidental or intentional overdose with opioid products. This newsletter will discuss opioid reversal agents, prescription status, and their role in reversal of potent synthetic opioids.

### Background

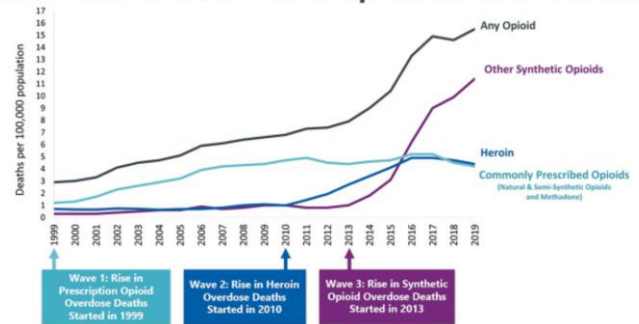
Dangerous opioid overdoses result from respiratory and central nervous system depression. Additionally, brain injuries can occur from hypoxia and anoxia.<sup>4</sup> Symptoms of overdose may present as seizures, temporary motor paralysis, coma, gait disturbances, and diminished motor skills.<sup>4</sup> The degree and duration of respiratory depression associated with the overdose is related to physiologic issues (e.g., preexisting conditions that affect pulmonary function), pharmacokinetics of ingested opioid (e.g., half-life) and pharmacodynamics (e.g., number and potency of opioid taken).<sup>4</sup>

In October 2017, the US federal government declared the opioid epidemic a public health emergency.<sup>5</sup> The World Health Organization (WHO) and the American Society of Addiction Medicine (ASAM) recommend that people with opioid use disorder (OUD), and those likely to witness an opioid overdose, should have naloxone accessible.<sup>6</sup> All 50 states have policies, called naloxone access laws, which are designed to expand access of naloxone for layperson use.<sup>3</sup> Despite efforts to increase distribution and use of opioid reversal agents, barriers still exist that prevent access.

The shift in causation of opioid deaths over the past 20 years is outlined in **Figure 1**. Fentanyl and fentanyl analogs account for the most recent wave of overdoses.<sup>4</sup> There has been a large increase in the deaths of teens contributing to these statistics, which is thought to be due in part to the availability of illegal synthetic opioids, such as fentanyl.

**Figure 1. Mortality Based on Opioid Type**

### Three Waves of the Rise in Opioid Overdose Deaths



The National Vital Statistics System Mortality File

<https://www.cdc.gov/opioids/data/analysis-resources.html>

In addition to the recent surge in synthetic opioid use, additional contributors to opioid overdoses are outlined in **Figure 2**. Adding complexity to the issue is that multiple opioids are often associated with overdoses, such as adulteration of heroin with the addition of synthetic opioids.<sup>4</sup>

**Figure 2. Potential Contributors to Opioid Overdose:**

- Initiating medication that may compete for the same metabolic pathway
- Addition of a medication that may also effect the central nervous system
- Concomitant alcohol use
- Inadvertently taking a higher dose than prescribed to better manage pain
- Increased availability of illegal synthetic opioids

### Opioid Reversal Agents

Opioid reversal agents are antagonists at the opioid receptor which cause reversal of the effects of opioids (e.g., sedation, hypotension, and respiratory depression) and prevent hypoxia-associated injury and death.<sup>3</sup> Naloxone and nalmefene are the two opioid reversal agents approved by the Food and Drug Administration (FDA). Common adverse events associated with high-dose naloxone include: nausea, dizziness, and lightheadedness.

Naloxone and nalmefene are available in several formulations that can be given by intramuscular (IM), intranasal (IN), intravenous (IV) and subcutaneous (SC) routes of

administration (**Table 1**). Absorption differs across different tissue types, and therefore, doses are not interchangeable and depend on the route of administration. Time to onset is approximately 2-5 minutes for naloxone and nalmefene. Evidence for naloxone suggests that the IM formulation has an onset of action about 2 minutes faster than the IN route of administration, which is considered a clinically meaningful difference.<sup>7</sup> However, the nasal formulations are preferred due to ease of administration. Naloxone remains effective for 20-90 minutes after administration. There is some evidence that higher doses of naloxone may be needed to adequately reverse an overdose, as more commonly experienced with potent synthetic opioids.<sup>8</sup> Nalmefene has a longer half-life (8-10 hours) than naloxone, which may be advantageous when overdoses occur in people who have taken opioids that have a longer half-life.<sup>5</sup> Current recommendations are to re-dose naloxone or nalmefene within 2-5 minutes if there is no response.<sup>8</sup> Emergency personnel should be called after administering opioid reversal agents.

In 2023, the FDA approved two over-the-counter (OTC) IN naloxone products, NARCAN and REVIVE (**Table 1**). The switch was prompted by FDA soliciting safety and effectiveness data for naloxone products from manufacturers in order to increase availability and access to naloxone. Increased availability of naloxone for layperson use was associated with decreased mortality due to reductions in fatal overdoses.<sup>9</sup> Due to the limitations of studying opioid reversal agents, many of the newer products have been approved based on pharmacokinetic data comparisons to existing formulations. Preferred opioid reversal agents for OHP fee-for-service (FFS) patients are displayed in **Figure 2**.

**Table 1. FDA Approved Opioid Reversal Products**

Drug	Route of Administration	Layperson Use
<b>OTC Products</b>		
Naloxone (Narcan®) <sup>10</sup>	4 mg IN	Yes
Naloxone (ReVive™) <sup>11</sup>	3 mg IN	Yes
<b>Prescription Products</b>		
Naloxone <sup>12</sup>	Injectable 0.02 mg, 0.4 mg or 1 mg per vial (IM, IV, SC)	No
Naloxone <sup>12</sup>	2 mg and 4 mg IN	Yes
Naloxone (Kloxxado®) <sup>13</sup>	8 mg IN	Yes
Naloxone (Zimhi®) <sup>14</sup>	5 mg per syringe (IM, SC)	Yes
Naloxone (Rextovy™) <sup>15</sup>	4 mg IN	Yes
Nalmefene <sup>16</sup>	2 mg (IM, IV, SC)	No
Nalmefene (Opvee®) <sup>17</sup>	2.7 mg IN	Yes
Abbreviations: IM = intramuscular; IN = intranasal; IV = intravenous; OTC = over-the-counter; SC = subcutaneous		

**Figure 2. Preferred Opioid Reversal Products for Oregon Fee-for-service Patients:**

- **Naloxone (IN, IM, SC, IV, cartridge)**
- **Narcan®**
- **Kloxxado®**
- **Opvee®**

### Synthetic Opioids

The use of synthetic opioids has risen steadily in the last 7-8 years and is thought to account for over 80% of the fatal opioid overdoses.<sup>4</sup> Synthetic opioids are easy to manufacture and the increase in use of synthetic opioids observed recently is driven by their low cost. Potent synthetic opioids like fentanyl are often added to illicit opioid products which increases the risk of overdose and death. The most commonly abused synthetics are fentanyl and other piperidine-based analogs as well as benzimidazoles such as etonitazene, metonitazene, isotonitazene (“iso”) which are available in illicit drug markets.

The high affinity of synthetic opioids for the opioid receptor contributes to increased incidence of overdoses. Potent synthetic opioids require higher doses of competitive antagonists at the opioid receptor, so it is suggested that higher doses of opioid reversal agents are required to reverse an overdose.<sup>8</sup> Additionally, the plasma concentrations of synthetic opioids remain higher longer, so repeat dosing of the opioid reversal agent may be required.

### Oregon Health Plan Coverage of OTC Naloxone

Effective January 2024, the Oregon Health Plan (OHP) will pay for OTC naloxone formulations dispensed to an OHP member at a pharmacy. The following are required for OTC coverage:

- The transaction must take place at the pharmacy counter and not at the retail counter.
- The prescriber is an enrolled provider for OHP.

Oregon pharmacists are already licensed to prescribe any FDA-approved short-acting opioid reversal agent (e.g., naloxone, nalmefene) and the necessary medical supplies to administer the agent:

- To an individual seeking a short-acting opioid reversal agent;
- To an entity seeking a short-acting opioid reversal agent; or
- When dispensing an opioid prescription in excess of 50 morphine mg equivalents.<sup>18</sup>

### Standing Order for Short-acting Opioid Reversal Agents

Effective January 2024 and pursuant to 2023 HB 2395<sup>19</sup>, the Oregon Health Authority will issue a statewide standing order

that permits Oregon licensed Pharmacists in the State of Oregon to dispense short-acting opioid reversal agents and necessary supplies to certain people:

- Anyone at risk of overdosing;
- People who might come across someone who has overdosed;
- Owners or any staff members of a building or facility with public access where an overdose may occur.

The standing order will help pharmacies who do not have prescribing pharmacists to bill OHP for the short-acting opioid reversal agent.<sup>19</sup> When the standing order is available, please refer to the Board of Pharmacy's website for specific details.

Naloxone resources for providers and patients are provided in **Figure 3**.

### Figure 3. Opioid Reversal Resources for Providers and Patients

- Obtaining and using naloxone in Oregon:  
<https://www.reverseoverdose.org/>
- <https://staysafeoregon.com/>
- OHA Guidance on Using Naloxone:  
<https://www.oregon.gov/pharmacy/pages/naloxone-prescribing.aspx>
- Oregon Board of Pharmacy:  
<https://www.oregon.gov/pharmacy/pages/index.aspx>

### Civil and Criminal Immunity (Good Samaritan Laws)

Oregon has a Good Samaritan law that protects individuals from civil prosecution if they give someone an opioid reversal agent like naloxone in a good faith effort to reverse opioid overdose.<sup>20</sup> It is always important to learn how to use naloxone safely through online training resources.<sup>20</sup>

Oregon's Good Samaritan law also provides immunity from arrest, charge or prosecution for drug possession to anyone who seeks medical assistance in the event of a drug overdose.<sup>21</sup>

### Conclusion

New opioid reversal therapies offer advances in fighting the opioid epidemic by offering treatments that can be used in the community setting to quickly reverse the effects of an opioid overdose and potentially save a life. Additional outcome data on the risks and benefits between naloxone and nalmefene, as well as the higher dose naloxone products, in reversing the

effects of potent synthetic opioids would help to inform optimal treatment.

*Peer Reviewer: Andrew Gibler, Pharm.D., RPh, Clinical Pharmacy Policy and Programs Manager, Oregon Health Authority, Health Policy and Analytics Division.*

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