



Opioid overdose, interventions, and challenges

Samaneh Alaei^{ID}, Hossein Omidian^{ID}*

College of Pharmacy, Nova Southeastern University, Fort Lauderdale, FL, United States

Article Info



Article Type:
Editorial

Article History:

Received: 20 Sep. 2021
Accepted: 28 Sep. 2021
ePublished: 8 Mar. 2022

Keywords:

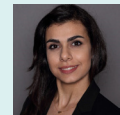
Opioid
Overdose
Naloxone

Summary

This short letter briefly reviews the significance of opioid overdose as well as the existing approaches to combat the epidemic. It also signifies the importance of naloxone, its commercially available dosage forms, and the unmet need for developing safe and effective naloxone dosage forms that can easily be administered in emergency settings.

Authors' Biosketch

Samaneh Alaei is a pharmacist currently pursuing her Ph.D. in Pharmaceutical Sciences at Nova Southeastern University (NSU). Her research interests include oral retentive drug carriers and controlled drug delivery through the buccal and sublingual routes, novel delivery systems to bypass first-pass metabolism and to enhance drug bioavailability, as well as abuse-deterrent formulations and opioid overdose solutions to tackle the current opioid epidemic.



Hossein Omidian is a professor of pharmaceutical sciences at Nova Southeastern University (NSU). His specific research interests are abuse deterrent formulations to combat opioid abuse, gastro-retentive oral delivery to enhance bioavailability of drugs with narrow absorption window, oral-retentive drug carriers to enhance drug bioavailability in oral cavity, and reduce alcohol absorption into the systemic circulation to combat alcohol overdose and toxicity.



Since the beginning of the new millennium, there has been an ongoing opioid epidemic in the United States and many other countries. The harmful outcomes of the medicinal and non-medicinal opioids' use, misuse and abuse include not only opioid dependence and its related adverse effects but also opioid-related intentional and unintentional overdose (OD) and death.¹ According to the Center for Disease Control and Prevention, nearly half a million people have died of opioid-related OD during 1999-2019. Prescription and illicit opioids resulted in 33,000 deaths in 2015² and over 47,000 deaths in 2017.³ In 2019, OD was the leading cause of death in the United States in people under 45⁴ and opioid OD accounted for 70.6% of 70,630 overdose-related deaths.⁵ Additionally, the rise in opioid-related ODs in the 1990s started due to the increased use of prescription opioids; however, synthetic opioids and particularly those involving illicitly manufactured fentanyl have been responsible for a significant rise in opioid-related OD deaths since 2013.⁶ This further complicates the opioid OD treatment and prevention as fentanyl has much greater potency compared to morphine and heroin (100 and 50 times more potent, respectively). This in turn increases the OD risks, requiring greater doses of antidote to reverse the

respiratory depression they cause.^{7,8}

According to their chemical structures, opioid pharmaceuticals and substances are analogous to the three endogenous opioid peptides (endorphins, dynorphin, and enkephalins). Opioid agonists (full or partial) and antagonists manifest themselves by acting on one or more of three major opioid receptors. They are present in the central and peripheral nervous system and exert their effect by modulating the release of various neurotransmitters. The μ or MOP receptors are responsible for the euphoric effect as well as respiratory depression related to the opioid OD. There is a wide variation in opioids' half-lives, leading to significant differences in their dependence and overdose (OD) management. For instance, methadone has a half-life of about 27 hours (with high variation among individuals) making it a good candidate for the treatment of opioid use disorder, while morphine and fentanyl's half-lives are 1.9 and 3.7 hours, respectively. Therefore, withdrawal syndrome pertinent to the abrupt discontinuation of methadone is usually milder and longer compared to that of morphine and fentanyl.⁷ There are also differences in their lipophilicity, which can affect the risk of OD and the required interventions following an OD. For instance, methadone exhibits relatively high



*Corresponding author: Hossein Omidian, Email: omidian@nova.edu



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protein binding and significant tissue distribution due to its lipophilic properties.^{9,10} This can further complicate the management of methadone toxicity compared to other opioids since it increases the chances of re-narcotization after the usual opioid antidote dosing.⁸ Therefore, hospital admission and continuous monitoring as well as repeated-dose or continuous infusion of naloxone, have been recommended for patients suffering from methadone or other long-acting/extended-release opioids' OD.¹¹

The most prominent complication of opioid overdose is respiratory depression, which can result in respiratory arrest and death if not treated. Along with respiratory depression, other complications, including hypothermia, aspiration pneumonia, seizure, rhabdomyolysis, head trauma, and coma may also be present. Certain opioid drugs can cause specific complications like QRS and QT interval prolongation and wide-complex tachycardia pertinent to loperamide overdose or QT interval prolongation and Torsade de Pointes in the case of methadone toxicity. Moreover, coingestants such as alcohol or other drugs (e.g., benzodiazepines, acetaminophen) can further complicate opioid OD symptoms and management.¹²

Currently, naloxone is the gold standard pharmacotherapy to counter acute opioid overdose.¹³ Although it has adequate permeability and water solubility, naloxone suffers from high hepatic metabolism leading to its extremely low oral bioavailability (0.9-2%¹⁴) and short half-life. It is available as 0.4 mg/mL solution for injection, prefilled 2 mg/2 mL Syringe (LifEMS), and 4 mg/0.1 mL (Narcan[®]) and 8 mg/0.1 mL (Kloxado[®]) intranasal sprays. Evizo[®], 0.4 mg/0.4 mL and 2 mg/0.4 mL naloxone auto-injector has recently been discontinued by the manufacturer, Kaleo.¹⁵ The FDA approved Evizo[®] as an intramuscular and subcutaneous injection in opioid OD emergencies, however, no reason was stated regarding its discontinuation by the manufacturer. The intranasal spray of naloxone is currently the only FDA-approved form of naloxone to be used by layperson during opioid OD emergencies. Moreover, similar products including Nyxoid[®], Nalscue[®], and Ventizolve[®] using the same intranasal spray device and with similar dosage have been approved in European Medicines Agency, France, and twelve European countries, respectively.¹¹ Narcan[®] is supplied as two packs of 4 mg/0.1mL naloxone hydrochloride each. Additionally, a higher dose naloxone injection product candidate (Zimhi[™]) by Adamis is currently reviewed by the FDA for the treatment of OD caused by opioids.¹⁶

Along with overdose education, take-home naloxone is one of the most important preventive measures for people who are at risk of overdose. Unlike regular naloxone dosage forms (i.e., solution for injection), community-based naloxone products are designed to be administered by laypersons (e.g., patients themselves, their family members, friends, or caregivers). Only naloxone intranasal spray and auto-injector were recommended by

the FDA in such settings. However, given that the latter has been discontinued by the manufacturer, the naloxone intranasal spray will remain the only available dosage form approved by the FDA for layperson administration in the United States. Furthermore, although not approved by the FDA due to unpublished pharmacokinetic data including bioavailability and the formulation effects, improvised naloxone nasal kit containing 2 mg/2 mL naloxone hydrochloride injection vial and a mucosal atomizer device has been used for many years in the community settings. Similarly, 0.4 mg/mL intramuscular injection of naloxone has also been dispensed in many communities for opioid OD emergencies, however, there is an increased risk of needle-stick injury, especially for non-medically trained individuals administering such dosage forms.¹⁷

In addition to the take-home naloxone and OD education, introducing abuse-deterrent formulations (ADFs) has also, to some extent, helped reducing the number of ODs due to prescription opioids.¹⁸ Opioid products like Hysingla ER, Nucynta[®] ER, Oxaydo[®] IR, Oxycontin[®] ER, Xtampza ER, and Zohydro[®] ER have been designed to deter drug product manipulation and abuse by routes of administrations other than the ones intended. However, in general, they cannot prevent overdose by oral route where multiple doses are taken at once.

Another challenge in overcoming opioid OD is determining the dose of naloxone to reverse the respiratory depression caused by the opioid as low doses cannot reverse the depression completely and high doses may induce precipitated withdrawal.² In the clinical setting, health care providers start by administering naloxone at low doses through the intravenous route and then titrate upward till respiratory rates reach a certain threshold. Depending on the half-life of the agent taken, they might continue with naloxone infusion or other approaches to prevent re-narcotization. Such an approach is not feasible in the community settings as determining the amount and the type of substance taken by the patient is challenging even for the health care providers. Moreover, currently available community-based naloxone products have limited dosing and their effective administration is highly challenging with many limitations affecting the efficacy of the administered dose. For example, there are limitations attributed to intranasal naloxone including the slower onset of action than intramuscular injection,¹⁹ the limited surface area of the nasal mucosa which limits the administered volume to less than 200 μ L, and variable systemic absorption due to recent use of vasoconstrictors such as cocaine or nasal decongestants.²⁰⁻²² Furthermore, the ease and safety of administering injectable naloxone by non-medically trained individuals is of concern as parenteral products pose a high risk of needle-stick and blood borne pathogen exposure. Therefore, developing non-invasive dosage forms of naloxone that can easily, effectively, and safely be administered by non-professionals in out-of-hospital emergencies is very much needed.

Ethical statement

Not applicable.

Competing interests

None.

Authors' contribution

SA: Writing and Draft Preparation; HO: Reviewing and Editing.

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