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Naloxone

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Abstract

Introduction and Definition: Naloxone is a "fast-acting medication used to temporarily reverse the effects of opioid overdoses […]." It was approved for use by the Food and Drug Administration (FDA) in 1971; however, its mainstream use as a critical overdose antidote emerged between the 1990s and 2010s in response to the opioid crisis. It is most commonly available in the nasal spray form under the brand name Narcan.

Body: Naloxone is an opioid receptor antagonist, meaning it attaches to opioid receptor sites in the brain, displacing other opioid drugs (such as heroin, fentanyl and morphine) and stopping their effects (e.g. restoring slowed or stopped breathing). It can begin to take effect within two minutes, but is only active in the body for 30 to 120 minutes, which may be shorter than most opioids' effects. As such, subsequent doses may be required. Naloxone may induce withdrawal symptoms in opioid-dependent individuals, but is safe for use in people of all ages, does not create dependence, and has no effect if no opioids are present. Naloxone will not reverse the effects of overdoses from non-opioid drugs.

Methods of Use: The FDA has approved two forms of naloxone delivery: injectable and nasal spray. If injected, naloxone is delivered intramuscularly, intravenously or subcutaneously. Injectable naloxone requires some needle training, making it less user-friendly than the nasal spray form. Prepackaged naloxone nasal spray is administered into one nostril. It is a needle-free alternative to the injectable naloxone medications, making it easier for bystanders or loved ones to administer without any training. Both forms are highly effective at reversing opioid overdoses and are often used by first responders in such cases.

Availability and Implications for Public Health: In Canada, take-home naloxone kits are now available without prescription at most pharmacies or harm reduction centers, and similar programs are in place worldwide. Studies have shown that the implementation of take-home naloxone programs has been cost-effective at reducing opioid overdose deaths and related morbidity. Such layperson interventions increase public awareness and knowledge, reducing stigma around naloxone as well as increasing overdose identification and recovery.

Keywords: naloxone; opioid; overdose; overdose reversal; Narcan; opioid crisis; public health

Introduction and Definition

Naloxone is a "fast-acting medication used to temporarily reverse the effects of opioid overdoses […]" [1]. It is an opioid receptor antagonist, meaning it attaches to opioid receptors in the brain, displacing other opioid drugs and blocking their effect [2]. Naloxone can begin to take effect within two minutes of administration and should be given to anyone showing signs of an opioid overdose [1, 2]. It is safe, non-addictive, and has no effect on non-opioid drugs [1]. First synthesized by Dr. Jack Fishman and Dr. Mozes J. Lewenstein in 1960, naloxone was approved by the U.S. Food and Drug Administration (FDA) in 1971 as a prescription-only medication [3]. Gradually, its use expanded from hospitals to first responders to the general public thanks to developments in user-friendly administration devices and techniques [4]. Between the late 1990s and the late 2010s, community-based interventions and "take-home" naloxone (THN) programs emerged in response to the opioid crisis, rendering the medication widely accessible to first responders and laypeople alike [5, 6]. Today, naloxone nasal spray – most commonly known under the brand name Narcan – remains the most widely available form of the medication due to its ease of use, safety and effectiveness [2]. Naloxone is now a crucial tool in the effort to reduce opioid-related mortality and is endorsed by various health authorities worldwide [1, 7]. The following sections will provide an overview of naloxone's mechanism of action, methods of use, availability, and broader implications for public health.

Body

Function

Naloxone hydrochloride is a synthetic derivative of oxymorphone similar in structure to morphine [8, 9, 10]. It thus preferentially occupies morphine or mu-opioid receptors in the brain, though it is also active at other kappa- and delta-opioid receptor sites [8, 9, 10]. These receptors are usually stimulated endogenously by molecules like endorphins, and are responsible for feelings of euphoria, sedation, and respiratory depression, among other things [9]. As such, when opioid drugs are introduced into the body, they bind to these receptors, causing analgesia and euphoria, but also leading to irregular, slow breathing and, eventually, hypoxia [11]. Naloxone, however, is a competitive opioid receptor antagonist: it has high affinity for mu-opioid receptors, effectively displacing other opioid drugs and taking their place at receptor sites without stimulating them [7]. In this way, the effects of an opioid overdose can be stopped and reversed by naloxone: by binding to opioid receptors in brainstem areas responsible for breathing control, naloxone stops opioid drugs from causing potentially fatal respiratory depression [12].

Naloxone begins to take effect in about two minutes, and subsequent doses can safely be administered if no response is seen to an initial dose [1]. However, naloxone is only active in the body for 30 to 120 minutes, and many opioids last in the body for much longer [1, 2]. Thus, in some cases, symptoms of overdose resume after naloxone wears off [1, 2]. As such, it is crucial to monitor the individual following naloxone administration and to contact emergency medical services immediately [2]. Naloxone is not a treatment for opioid use disorder, and may cause withdrawal symptoms in opioid-dependent individuals [2]. Furthermore, some people may experience allergic reactions to naloxone, though such cases are extremely rare [2]. The medication is safe for use in people of all ages, and has no effect on the body if opioids are not present in the individual's system [1, 2]. It thus does not reverse non-opioid overdoses [1, 2].

Methods of Use

There are two FDA-approved forms of naloxone: injectable and nasal spray [2]. Naloxone was originally injected intravenously, mostly by trained medical staff in hospital settings [4]. Intravenous delivery is still the gold standard in clinical settings as it provides the fastest onset and allows for precise dosing [13]. However, this method requires venous access and medical training, making it unsuitable for layperson use and limiting its accessibility [13, 14].

Intramuscular and subcutaneous injections are now used by first responders outside of hospital settings, as they offer rapid onset and reliable absorption without requiring as much training or venous access [2, 15]. Injectable naloxone delivery was further simplified in 2014 with the introduction of FDA-approved auto-injector devices, which enabled use by laypersons with minimal training, further expanding the accessibility of the medication [2]. Importantly, all injectable forms of naloxone pose a risk of needle-stick injuries and exposure to blood-borne pathogens, and thus require safe needle handling [14, 16].

An intranasal form of naloxone delivery was approved in 2015, further increasing accessibility [4]. These nasal spray kits consist of a pre-filled device which delivers a fixed dose of naloxone into one nostril, requiring no assembly or prior training [2]. It is a needle-free alternative to injection methods, making it optimal for use by bystanders and non-medical personnel [2, 16]. While naloxone nasal sprays are effective at reversing overdose symptoms, they generally have a slower onset than injectable routes [14, 15, 17]. They may require repeat dosing, and their effectiveness can be reduced by nasal congestion or damage [14, 15, 17].

Both forms (injectable and intranasal) are effective at delivering the stated dose of naloxone and are used by first responders regularly [1, 15, 16]. Research has shown that FDA-approved naloxone products are more effective and safer than improvised nasal spray devices (a combination of injectable naloxone and a mucosal atomizer, an attachment designed to allow for intranasal delivery), suggesting that approved forms may be preferable [2, 4]. Critically, administration of naloxone does not replace the need for emergency medical intervention in the event of an opioid overdose [1, 2].

Table 1. Summarizes Advantages and Disadvantages of Naloxone Administration Methods

Method	Form	Advantages	Disadvantages
Injection	Intravenous/subcutaneous	Fastest onset Precise dosing	Requires medical expertise and venous access
	Intramuscular/subcutaneous (Including auto-injector)	Rapid onset	Some training required Risk of needle-stick injuries and exposure to blood-borne pathogens
Nasal spray	Pre-filled kit	Needle-free Requires no training Suitable for public distribution	Reduced effectiveness if person has nasal congestion, injury or excessive mucus Higher cost per dose

Availability and Implications for Public Health

In the early 1990s, the idea of "take-home" naloxone (THN) kits was first proposed in Italy, Australia and the United Kingdom in response to an increase in preventable opioid overdose deaths [6]. These kits would provide individuals outside the medical field access to the medication [6]. Public health advocates and community activists pioneered the distribution of naloxone to opioid users and their loved ones, effectively leading a broader harm reduction movement [5]. By the early 2000s, these efforts resulted in the implementation of many naloxone distribution programs organized by public health agencies worldwide [5]. Despite initial pushback by some institutions arguing that THN might enable or encourage drug use, community-based interventions such as THN are now recognized as an integral part of overdose prevention [5]. This is reflected in the endorsement of THN programs by organizations such as the Centers for Disease Control and Prevention and the Substance Abuse and Mental Health Services Administration [5]. The development of non-injectable forms of naloxone, such as nasal sprays, has further broadened access to the medication, as these user-friendly administration methods are more suited for layperson use [3]. Access to THN continues to grow, with Australia, Canada, Italy, and other countries having it available without prescription at most pharmacies [1, 18]. In March of 2023, Narcan was approved for over-the-counter sale in all U.S. states, making it available in pharmacies nationwide [19]. As of 2024, THN is available in 34 countries, but remains unavailable in many low- and middle-income regions [20].

Studies have shown that peers and family members of people who use opioids are highly willing and able to provide interim emergency care by administering naloxone while awaiting emergency medical treatment [3]. Research also confirms that THN programs lead to improved overdose survival rates among opioid users [3]. Meta-analyses indicate that 93-98% of overdoses are successfully reversed when naloxone is delivered by trained bystanders, including other opioid users, loved ones and first-responders [21]. Additionally, substantial reductions in overdose mortality have been found in a number of pre- and post-implementation studies of overdose education and naloxone distribution programs [21]. The adoption of good Samaritan laws, such as Canada's Good Samaritan Drug Overdose Act, protects anyone seeking emergency support during an overdose, including laypersons administering naloxone, from charges for possession of a controlled substance, encouraging opioid users and bystanders to seek emergency medical help and provide naloxone when they can [22].

Although there is much evidence for the effectiveness of THN programs, several barriers continue to limit their implementation. These include the lack of a unified model for the implementation of these programs and the absence of a consistent framework for the evaluation of their outcomes [3]. A study involving first responders and opioid users found that some responders believe that the distribution of naloxone enables or exacerbates opioid use [23]. Responders also describe safety concerns, explaining that users receiving naloxone often become "unintentionally violent" due to the acute withdrawal symptoms the medication induces [23]. Users, however, report uncertainty about naloxone's availability or find it difficult to obtain [23]. Some mention misunderstanding how the medication is used or being influenced by strained relationships with first responders or previous negative experiences witnessing overdoses [23]. Such findings highlight the importance of expanding awareness, availability and acceptability of naloxone to reduce overdose deaths most effectively [23].

Conclusion

In summary, naloxone is a critical lifesaving tool in opioid overdose prevention and treatment, and its development from a hospital-only medication to an accessible layperson intervention has reshaped public health. Its proven effectiveness in these roles highlights not only its importance in the fight against the opioid crisis but also its potential in becoming a mainstream over-the-counter overdose remedy. Moving forward, efforts must be made to continue to expand accessibility and education regarding naloxone, and to further develop a framework within which community-based programs and scientific research alike can progress in a meaningful fashion.

List of Abbreviations

FDA: Food and Drug Administration
THN: take-home naloxone

Conflicts of Interest

The author declares that they have no conflict of interest.

Authors' Contributions

KC: assumes the sole responsibility for the research, writing, and editing of the work, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgements

The author acknowledges the use of Perplexity AI v4.0.0 (perplexity.ai) to assist in researching and editing this article. The author critically evaluated and edited all information generated by the model. The author assumes sole responsibility for the final version of this text.
The author also acknowledges the use of Grammarly AI v.8.932.0 to help correct and edit this text.

Funding

The development of this encyclopedia entry was not funded.

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Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Shaina Smith, Jeremy Y. Ng
Article Dates: Received Jul 27 25; Accepted Sep 05 25; Published Nov 17 25

Citation
Please cite this article as follows:
Cavallo K. Naloxone. URNCST Journal. 2025 Nov 17: 9(10). https://urncst.com/index.php/urncst/article/view/935
DOI Link: https://doi.org/10.26685/urncst.935