# Alcohol Deterrents—Narcotic Antagonists

## Narcotic Antagonists Overview

- Drug overdose accounts for the leading cause of death in adults in the United States; since 1999, the number of deaths due to drug overdose has doubled. In 2013, there were approximately 44,000 deaths due to overdoses, of which 16,234 (37%) were attributed to prescription opioids and 8,257 (19%) due to heroin.[1]
- Due to the high visibility of the risks with heroin and prescription opioid use and abuse, numerous programs are underway, ranging from the executive and federal level down to the individual state level. The majority of programs focus on expanding access to treatment, preventing overdose deaths, and increasing community prevention strategies by expanding public health safety partnerships. The Substance Abuse and Mental Health Services Administration (SAMHSA) is releasing a new $11 million funding opportunity to states to purchase and distribute the opioid overdose reversal drug, naloxone, and to train first responders and others on its use, along with other overdose prevention strategies.[2, 3]
- Naloxone is the treatment of choice to reverse the adverse effects of opioids, including respiratory depression and sedation, but its administration is time dependent, as death typically occurs within one to three hours after an overdose. Repeat doses are often necessary, as naloxone does not remove opioids from the blood. As naloxone wears off, opioids still circulating in the blood may again bind to the mu receptors.

## Executive Summary

### Current Uniform Formulary (UF) Status

The Alcohol Deterrents—Narcotic Antagonist Drug Class has not been previously reviewed. However, in July 2016, generic vial and syringe formulations of naloxone were added to the UF and the self-injectable administration list. The naloxone nasal spray formulation (Narcan Nasal Spray) was reviewed as an innovator drug at the February 2016 DoD P&T Committee meeting and also added to the UF.

### Drugs in the Class (Table 1)

The naloxone formulations include generic syringes and vials and two new bystander-administration products, an autoinjector (Evzio) and nasal spray (Narcan Nasal Spray). The brand name Narcan, which previously applied to the original vials and syringes has been withdrawn, and now is the trademark name for the nasal spray.

**Table 1: Naloxone Formulations in the Drug Class**

| Brand Name | | | | | |
|---|---|---|---|---|---|
| Narcan (brand D/C) | • 1 mL vials/ampules<br>• 10 mL vials<br>• IV/IM/SQ | • 0.4 mg/mL<br>• 4 mg/10 mL | Hospira<br>Mylan<br>Amphastar | 1971 | Expired generics available |
| Narcan (brand D/C) | • Prefilled syringe<br>• IV/IM/SC<br>• Nasal (with mucosal atomization device) | 1mg/mL (2mg/2mL) | Amphastar syringe<br>Teleflex (nasal adapter) | 1971 | Expired generics available |
| **Bystander Administration** | | | | | |
| Evzio | autoinjector | 0.4 mg/0.4 mL | Kaleo | 4/3/2014 505(b)(2) | Nov 2024 |
| Narcan Nasal Spray | nasal spray | 4 mg/0.1 mL | Adapt Pharma | 11/18/2015 505(b)(2) | Mar 2025 |

The 505(b)(2) application for FDA approval includes data from the original 1971 new drug application for naloxone.

## Naloxone Formulations[4-9]

- Naloxone is an opioid antagonist used to reverse opioid overdose. It was first marketed in 1971 in syringe and vial formulations under the brand name Narcan. These products are now available in generic formulations, and are labeled for intravenous (IV), intramuscular (IM), or subcutaneous (SQ) use. The initial doses for opioid overdose range from 0.4 mg to 2 mg, with repeat doses given at 2- to 3-minute intervals, as needed.

- Generic formulations of naloxone are available in the following concentrations:

- 0.4 mg/ml single-dose (1 ml) prefilled cartridges, ampules, and vials, and multi-dose (10 ml) vials (from the manufacturers Hospira, Mylan, and Amphastar)
- 1 mg/ml: single-dose syringes (2 ml) (Amphastar)

- Historically, naloxone was used in the community setting to reverse the effects of opioids, including heroin, by two methods: administering naloxone via the IM or SQ routes, or using parenteral formulations via the off-label intranasal administration route. Naloxone was reportedly first administered nasally in 1992. Assembled naloxone "kits" are frequently used by first responders or distributed to heroin abusers in the community, and contain the following:
  - IM/SQ kits: The 0.4 mg/mL vials are recommended for the IM/SQ kits. The contents typically include two of the 1 mL single-dose vials or one 10 mL multi-dose vial, plus two 23 gauge, 3 cc syringes with a 1-inch needle. A dosage of 1 mL (0.4 mg naloxone) is injected into the shoulder, thigh, or upper buttocks. Doses can be repeated after 2-3 minutes if there is no or minimal response.
  - Intranasal Kits (See Figure 1): The intranasal kits include two 2 mg/2mL luer lock prefilled glass syringes (from the manufacturer Amphastar, NDC# 76329-3369-1), along with two mucosal atomization devices (MAD) that fit into the luer lock (from the manufacturer Teleflex, NDC#60842-030-01; call 1-800-788-7999 to order). The dosing instructions are to spray 1 mL (1/2 of syringe) into each nostril, and then spray the remainder of the syringe into the other nostril, which provides a total dose of 2 mg. The dose can be repeated after 2-3 minutes if there is no or minimal response.

### Naloxone Autoinjector (Evzio) – See Figure 2

- In April 2014, the FDA approved the first naloxone product specifically for use in the community. This product is a naloxone autoinjector, available under the brand name Evzio (Kaleo Pharma), is labeled for IM or SQ use, and delivers a naloxone dose of 0.4 mg.
- Evzio was developed for administration with little to no training by family members of opioid overdose victims during an opioid emergency outside of a medical setting. The autoinjector provides voice instructions to the user. The device contains a retractable needle system that conceals the needle before, during, and after administration.
- Evzio is packaged in a carton containing two single-use autoinjectors containing naloxone 0.4 mg/0.4 mL, and a training device that does not contain active drug. The voice prompts guide the user to administer the dosage and also remind the user to call 911.
- To administer the dose, place the black side of the autoinjector firmly on the patient's outer thigh and depress and hold for 5 seconds. Repeat dosing with the second device after 2-3 minutes if there is no or minimal response. After dosing, the needle will retract into the base, the base will lock, and the voice instruction will state the injector has been used. Activation, needle penetration, drug injection, and needle retraction occur in less than 5 seconds. Dispose of the injector in a sharps container

### Naloxone Nasal Spray (Narcan Nasal Spray) – See Figure 2

- FDA approval of the Narcan Nasal Spray formulation occurred in November 2015. Intranasal naloxone works by diffusing across the nasal mucosa and entering the central nervous system through the circulatory system transportation.
- Each carton contains 2 single-use spray devices containing 4 mg/0.1 mL naloxone. For dosing, one spray is instilled into one nostril (dose of 4 mg). A new nasal spray device is used in the alternate nostril after 2-3 minutes if there is no or minimal response.
- Patients must be placed in the supine position prior to dosing. There is no assembly or priming required for the device. The tip of the nozzle is inserted in the nostril until the finger touches the bottom of the patient's nose. The plunger is then pressed firmly to release the dose. No inhalation is required. Following administration, the patient should be placed on their side ("recovery position") in case of vomiting.

### FDA Indications

- The two new naloxone formulations are distinguished from the original naloxone syringes and vials by their labeling. Evzio and Narcan Nasal Spray are both labeled for the "emergency treatment of known or suspected opioid overdose as manifested by respiratory and/or CNS depression." They are intended for immediate administration as emergency therapy in settings where opioids may be present. Both package inserts state that the products are not a substitute for emergency medical care.

- In contrast, the generic naloxone syringes and vials are labeled for the complete or partial reversal of narcotic depression, including respiratory depression, induced by opioid (natural and synthetic narcotics, propoxyphene, methadone, etc.). The label also states the generic formulations are indicated for the diagnosis of suspected acute opioid overdose.

## FDA Approval Process/Clinical Efficacy

### FDA Approval Pathways for New Naloxone Formulations[11]

The FDA has recognized the vast clinical experience of naloxone in reversing opioid effects, and acknowledged it is ethically infeasible to conduct a clinical efficacy study in the overdose setting. FDA approval was allowed with submission of a single bioequivalence study demonstrating comparable pharmacokinetics between generic naloxone products and the novel formulation in healthy volunteers.

### Bioequivalence Studies

The package inserts for Evzio and Narcan contain details of the respective pharmacokinetic studies used to show bioequivalence of the products to naloxone 0.4 mg administered by IM or SQ injection. Both pharmacokinetic studies showed that the new formulations had the same time-to-peak concentration to generic naloxone, and thus met the standards to prove bioequivalence.

### Narcan Nasal Spray[11]

Unpublished material provided to the FDA state that the manufacturer (Adapt) conducted three studies with a total of 175 subjects to determine the comprehension and ease of administration of the nasal spray device. Participants included adults, juveniles, and those with low literacy. No device training was provided. The primary endpoint was the administration of placebo dose, and secondary endpoints included ability of the participant to call 911 and to place the patient in the recovery position. The results showed that over 90% of participants successfully simulated administering Narcan Nasal Spray without training. There are no additional details provided for these studies.

### Evzio[12]

The manufacturer of Evzio also submitted an evaluation of the safety and efficacy of device and conducted a human factors validation study, which has been published. The objective of the study was to compare the usability of the Evzio autoinjector versus a naloxone intranasal (IN) kit using the mucosal atomizer device (MAD) in a simulated opioid overdose emergency. The study included 42 participants and evaluated their ability to successfully administer simulated naloxone before and after receiving training. The simulated environment was meant to induce stress, and included mannequins placed in a living room setting with a TV on and observers. The observers rated the participants' ability to administer naloxone to the mannequin. Prior to training, the proportion of participants who could successfully administer simulated naloxone was 90.5% with Evzio versus 0.0% with the IN kit ($p< 0.0001$). The study was repeated one week after training and the results showed 100% of the participants successfully administered Evzio versus 57.1% of participants using the IN kit ($p< 0.0001$). The authors concluded the success of bystander administration of simulated naloxone was significantly greater with Evzio versus the naloxone IN kits. No participants correctly used the IN naloxone without training.

### Clinical Efficacy of Evzio and Narcan Nasal Spray in an Opioid Emergency

There are no outcomes studies or real world experience valuating the efficacy of the new bystander-naloxone formulations in an actual opioid overdose emergency. Data was requested from both manufacturers. Kaleo pharmaceuticals mentioned they have a donation program to several local police and emergency medical services (EMS), but there are no reporting requirements. Kaleo stated recipients have voluntarily reported to them that Evzio has helped save more than 1,000 lives in the first responder setting, but there is no way to validate the data. Due to FDA's recent approval of Narcan Nasal Spray (in November 2015), Adapt Pharmaceuticals was unable to provide any data.

### Naloxone Efficacy with Bystander Administration

- One meta-analysis evaluated the effectiveness of naloxone administered by bystanders in a non-medical setting. Only four studies met the criteria for inclusion in the meta-analysis. The studies were all conducted using the naloxone kits. Bystander-naloxone administration was associated with a significantly increased odds of recovery compared with no naloxone administration (OR = 8.58, 95% CI = 3.90 to 13.25); the results were statistically significant, but highly heterogeneous.[10]
- Three published studies are available that describe use of the naloxone kits given by bystanders and/or police and EMS in actual opioid overdose emergencies in heroin users.[13-15] Two of the studies compared the ability of IM versus IN naloxone to improve respiratory rate in heroin overdose and found that there was comparable efficacy, based on return to spontaneous respirations.[13,14] The third study evaluated the use of IN naloxone given by a mix of bystanders and EMS personnel and found the IN kit formulation was successful in reversing heroin overdoses, and that only a small percentage (5%) of participants could not correctly attach the nasal MAD device.[15] These studies are limited by the observational

study design, but do provide some evidence that use of IM or IN kits in the outpatient emergency setting can successfully reverse heroin overdose.

### Naloxone Administration in the Primary Care Setting[16]

A recently published intervention study of naloxone co-prescription for primary care patients receiving long-term opioid therapy for pain is available. This was a non-randomized two-year trial in primary care patients. An naloxone intranasal kit was provided. The decision to co-prescribe naloxone was left to the primary care provider; 38.2% of 1,985 patients receiving long-term opioids were prescribed naloxone. The results showed patients prescribed higher doses of opioids and with opioid-related emergence department (ED) visits in the past 12 months were independently more likely to be prescribed naloxone. Patients prescribed naloxone versus patients not prescribed naloxone had 47% fewer opioid-related ED visits/month (incidence rate ratio (IRR) 0.54 [95% CI 0.34 – 0.83] p=0.005). There were 64% fewer ED visits after one year in the patients prescribed naloxone (IRR 0.37 [95% CI 0.22-0.64] p<0.001). The authors concluded co-prescribing naloxone with opiates may lead to fewer pain medication-related visits to the ED. This observational study has several limitations, including that it was not clear whether the naloxone itself prevented hospitalizations or that the "shock effect" of being given naloxone resulted in patients taking the risks of opioids more seriously.

## Safety[4-9]

**Contraindications:** The products are contraindicated in patients with known hypersensitivity to naloxone or any of the ingredients in the formulations.

### Warnings/ Precautions

- Overall, the safety profile of naloxone is well known and serious adverse effects are rare. Due to the duration of action, patients require continued surveillance and naloxone may be repeated as necessary while waiting for emergency medical assistance.
- Opioid Withdrawal: Abrupt reversal of opioid effects in patients physically dependent on opioids has precipitated signs and symptoms of opioid withdrawal including body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, and tachycardia. In neonates, convulsions, excessive crying, and hyperactive reflexes may occur.
- Reversal of respiratory depression by partial agonists or mixed agonists/antagonists, such as buprenorphine and pentazocine, may be incomplete.
- Use in patients who are opioid-dependent may precipitate acute abstinence syndrome. Patients with pre-existing cardiac disease or receiving concomitant medications with potential adverse cardiovascular effects should be monitored in the appropriate health care setting.

**Evzio:** Adverse effects unique to Evzio include potential injection-site reactions. The autoinjector device was used in another marketed product, epinephrine (Auvi-Q), which was the subject of a recall in October 2015 due to inaccurate dosage delivery.[17] However, Kaleo pharmaceuticals stated the manufacturing problems with Auvi-Q are not an issue with Evzio, since Evzio is produced in the United States.

**Narcan Nasal Spray:** Adverse effects unique to Narcan Nasal Spray include nasal inflammation, nasal edema, and nasal congestion. Adapt pharmaceuticals was not able to provide any information on use of the drug in patients with nasal polyps or other obstructions (e.g., deviated septum).

## Product Niches/Place in Therapy

**Evzio:** Advantages of the autoinjector include that it provides audio and visual cues for administration. The device is easy to use, with non-English speaking adults averaging only 60 seconds to administer. The device reminds the bystander to call 911. The retractable needle decreases the risk of accidental exposure. The product can be injected through pants, including denim jeans. Disadvantages to the device include the long needle, which for children under one year requires the skin to be pinched on the thigh. There is no data in patients/bystanders with an aversion to needles. The device is under FDA recall with another product (epinephrine Auvi-Q), but there have been no reports of malfunction with Evzio.

**Narcan Nasal Spray:** Advantages of Narcan Nasal Spray is that it provides for a smaller; more portable device than Evzio. Additionally, it is a needle-free alternative to injectable formulations. The volume of liquid (0.1 mL) is lower than that provided in intranasal kits. The product appears easy for bystander/first responder/family member administration; however, there is only

unpublished data showing the usability of this product. Disadvantages include the need for the patient to be in supine position then turned to the side ("recovery position"). It is unknown whether drug efficacy will adversely be affected by nasal malformations or blockage.

## Conclusion

- The FDA has now approved two formulations of naloxone specifically labeled for bystander use in the outpatient, non-medical setting.
- Evzio autoinjector and Narcan Nasal Spray were approved by showing bioequivalence to generic IM/SQ naloxone formulations. The manufacturer of Evzio also conducted a human factors validation study to the FDA, which has been published. Narcan Nasal Spray appears easy to use, based on unpublished data that the manufacturer submitted to the FDA.
- Data from studies using naloxone intramuscular or intranasal kits in the community setting to reverse heroin overdose has shown that these products can successfully reverse opioid-induced respiratory depression.
- The FDA approval of Evzio and Narcan Nasal Spray provide new easy-to-administer formulations to reverse opioid adverse effects, but neither product has data showing outcomes in the real word setting or data in patients receiving prescriptions for opioids.

**Figure 1. Intranasal naloxone kit with mucosal atomization device**

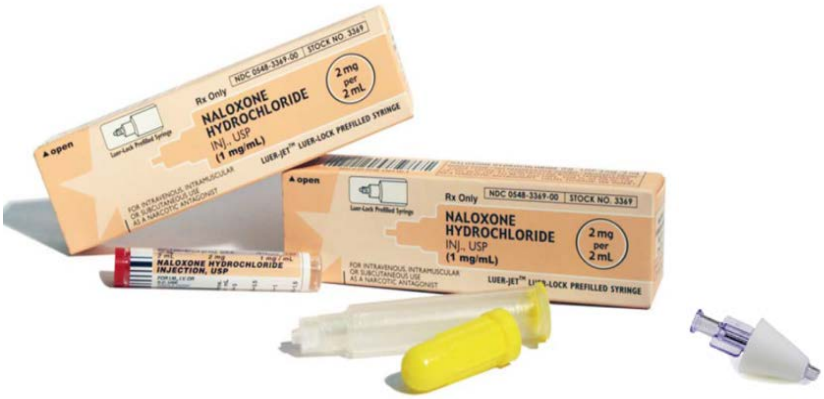


**Figure 2. Naloxone autoinjector (Evzio) and nasal spray (Narcan Nasal Spray)**

## References


1. Wheeler E, Jones TS, Gilbert MK, et al. Opioid overdose prevention programs providing naloxone to laypersons – United States, 2014. MMWR 2015;64(23):631-35.
2. Fact Sheet: Obama Administration Announces Additional Actions to Address the Prescription Opioid Abuse and Heroin Epidemic. 29 March 2016. https://www.whitehouse.gov/the-press-office/2016/03/29/fact-sheet-obama-administration-announces-additional-actions-address.
3. Joint Fact Sheet: DoD and VA Take New Steps to Support the Mental Health Needs of Service Members and Veterans. 26 August 2014. http://www.va.gov/opa/docs/26-AUG-JOINT-FACT-SHEET-FINAL.pdf.
4. Naloxone for opioid overdose (FAQs). Pharmacist's Letter/Prescriber's Letter. May 2016.
5. Lloyd J. The clinical use of naloxone. Exploring Naloxone Uptake and Use – A Public Meeting. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM454748.pdf.
6. Product information for Narcan. Endo Pharmaceuticals. Chadds Ford, PA 19317. April 2004.
7. Product information for Evzio. Kaleo. Richmond, VA 23219. April 2014.
8. Product information for Narcan Nasal Spray. Adapt Pharma. Radnor, PA 19087. November 2015.
9. Naloxone Product Comparison. Prescribe to Prevent. 21 January 2016. http://prescribetoprevent.org/wp2015/wp-content/uploads/Naloxone-product-chart.16_01_21.pdf.
10. Giglio RE, Guohua L, DiMaggio CJ. Effectiveness of bystander naloxone administration and overdose education programs: a meta-analysis. Injury Epidemiology (2015) 2:10.
11. Exploring Naloxone Uptake and Use – A Public Meeting July 2015. http://www.fda.gov/downloads/Drugs/NewsEvents/UMC469456.pdf
12. Edwards ET, Edwards ES, Mulcare M, et al. Comparative usability study of a novel auto-injector and an intranasal system for naloxone delivery. Pain Ther 2015;4:89-105.
13. Kelly AM, Kerr, D, Dietze P, et al. Randomized trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. Med J Australia 2005;182(1):24-7.
14. Kerr D, Kelly AM, Dietze P, et al. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction 2009;104:2067-74.
15. Doe-Simkins M, Walley AY, Epstein A, et al. Saved by the NOSE: bystander-administered intranasal naloxone hydrochloride for opioid overdose. Am J Public Health 2009;99(5):788-91.
16. Coffin PO, Behar E, Rowe C, et al. Nonrandomized intervention study of naloxone coprescription for primary care patients receiving long-term opioid therapy for pain. Ann Inter Med. DOI: 10.7326/M15-2771. Published ahead of print June 28, 2016.
17. FDA MEdwatch: Auvi-Q (epinephrine injection, USP): Recall - Potential Inaccurate Dosage Delivery. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm470010.htm.