



Naloxone: Guideline-Based Recommendations for Opioid Patients in Outpatient Community Settings

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Background and Purpose

A Surgeon General's Advisory released on April 5, 2018, recommends more widespread availability of naloxone for emergency treatment of opioid overdose.¹ The Advisory was based in part on concern over what is now recognized as a nationwide opioid epidemic, with a 2016 age-adjusted rate of drug overdose deaths in the United States that is more than triple the 1999 rate.² Surgeon General Jerome Adams, MD, acknowledges that while much of the recent mortality increase can be attributed to criminal drug-lacing of heroin with illicit fentanyl, this effect only compounds the already accelerating fatal overdose rate due to increased numbers of pain management patients receiving higher doses of prescription opioids.

The wide-reaching naloxone recommendations suggest availability for: (a) patients taking high doses of opioids legitimately prescribed for pain; (b) patients misusing prescription opioids; and (c) individuals using illicit opioids like heroin or fentanyl.¹ Evidence-based research to guide who should be targeted to receive naloxone in an outpatient medically prescribed setting remains limited and focuses mostly on overdose risk factors.^{3, 4, 5}

The purpose of this document is to thoroughly describe the use of naloxone for opioid overdose reversal, including how it works, contemporary formulations and dosing (including approximate average cost range), and current efforts to increase drug availability in outpatient community settings. This is followed by a detailed discussion of targeted prescribing of naloxone in a community clinical setting, particularly to those patients prescribed opioids for legitimate pain control (both acute and chronic).

Naloxone Overview

Naloxone is a competitive "mu" opioid-receptor antagonist that has no abuse potential. It is recommended for complete or partial reversal of opioid depression, including that of the respiratory and/or central nervous systems, that is induced by both natural and synthetic

opioids. Dosing is empirical, with effectiveness depending on the specific analgesic, the relative affinity for the mu receptor, the opioid being displaced, and other patient variables.⁶ Reversal may be transient, sometimes necessitating repeat dosing. When administered in a pre-hospital setting, the patient usually requires subsequent emergency and possible longer-term care; however, this does not always occur since some naloxone-treated individuals have proven to be resistant to this type of “after-treatment.” Naloxone is ineffective for treating overdose of benzodiazepines, barbiturates, stimulants, and alcohol, although naloxone may still be effective when opioids are taken in combination with other sedatives or stimulants.

Adverse effects depend on naloxone dosage and route of administration, with intravenous and higher doses producing more opioid withdrawal events and symptoms. Adverse effects following opioid depression reversal include cardiac abnormalities (e.g., cardiac arrest, rapid heartbeat, hypertension, ventricular dysrhythmias), nausea and vomiting, seizures and tremor, and pulmonary edema. Overt withdrawal symptoms may also occur, with acute withdrawal generally subsiding over the first 2 hours. Naloxone recipients should therefore be carefully observed for a minimum of 2 hours following the last dose, to monitor for recurrence of respiratory depression, withdrawal, and other rapid-reversal narcotic effects.^{7, 8}

Community Uses

Naloxone treatment in an outpatient setting was initially proposed to address the needs of individuals overdosing from heroin in programs referred to as Overdose Education and Naloxone Distribution (OEND). Initially developed by community-based and public health organizations, these efforts targeted prevention of overdose fatalities by educating laypersons to recognize opioid overdose and to properly administer naloxone. These programs have gradually expanded to include individuals who use prescription opioids illicitly, with additional research into the prevention of overdose deaths in medical settings. The latter includes education in risk factors for overdose (e.g., mixing opioids with sedatives or using prescription opioids in high doses).^{3, 5}

Until recently, obtaining naloxone and learning how to administer it was difficult, as it was generally only available in Syringe Exchange Programs and from harm reduction organizations. The Surgeon General now encourages increased availability, including making naloxone available through community programs and “third-party prescriptions.” Prescriptions for potential

administration to overdosed individuals can now be issued to a third-party who is not at risk of overdose, such as friends, family members, and professionals working with at-risk individuals. Additional training requirements may be required in some states before a third-party can obtain naloxone.⁹ Non-patient-specific prescriptions, which can be dispensed without interacting with a prescriber, are also available in most states.^{3, 9, 15} Prescription requirements vary by state, including use of standing orders that allow pharmacies to dispense naloxone to patients without a specific prescription from a provider.¹⁵ Other variations include protocol orders, which allow any pharmacist who follows the order requirements to dispense naloxone without a patient-specific prescription.¹⁰ Such non-patient-specific programs show promise for broad expansion of access to naloxone, and were already permitted in some variation in 49 states and Washington D.C. as of January 2018.¹⁵

Recommendations for Naloxone Prescribing/Dispensing in Non-Pain Management Settings

Individuals considered at high risk for an overdose event in non-pain management settings are recommended to receive naloxone, as indicated by the following risk factors:

- Active abuse of scheduled drugs, including opioids, or a history of substance abuse
- A history of known dependence or non-medical use of prescription or illicit drugs
- Current use of methadone or buprenorphine maintenance for treatment of opioid use disorder
- Recent discharge from emergency medical care following opioid intoxication and/or overdose
- A history of recent completion or discharge from treatment for opioid detoxification, with or without use of methadone, buprenorphine, or naltrexone
- Release from incarceration with a history of opioid misuse or disorder, due to reduced opioid tolerance and high risk of relapse

Recommendations for Naloxone Prescribing/Dispensing in Pain Management Settings

Regarding the question of who should receive naloxone in a pain management setting, current recommendations mirror the CDC Guideline for Prescribing Opioids for Chronic Pain.¹⁰

Characteristics of patients who are at greatest risk for overdose events in pain management settings include the following:

- Recent opioid rotation, particularly to methadone, and/or at risk for incomplete tolerance

- Prescribed high opioid doses of ≥ 90 mg oral morphine equivalents, where tapering below this value is not practical or is contraindicated
- Current use of an opioid dose of ≥ 50 mg oral morphine equivalents with any of the following additional history: (a) using concomitant benzodiazepines, sedative hypnotics (sleep aids), antidepressants, or muscle relaxants; (b) pulmonary disorders, including chronic obstructive pulmonary disease, emphysema, asthma, and/or sleep apnea; (c) liver and/or kidney disease; or (d) any diagnosis of mental illness
- Residence located far from emergency care and on high-dose opioids
- Voluntary request for naloxone

A complete history is recommended to evaluate for risk of overdose, including questions about prior drug and alcohol use, previous overdose, and recent detoxification or abstinence from drugs for any reason. It is also recommended that providers obtain a complete list of chronic medical illnesses and medications along with results of screening tools for potential prescription drug abuse (e.g., The Screener and Opioid Assessment for Patients with Pain–Revised, or SOAPP-R).

Dosing and Formulations

Current FDA-approved formulations of naloxone include the following:

- Naloxone (generic) 0.4 mg/ml or 2 mg/ml for injection (IV or IM). Injectable naloxone is no longer sold under the Narcan brand and should not be confused with the newer intranasal Narcan® product. Two doses should be provided (2 single-use 1 ml vials plus two 3 ml syringes with 23-25 gauge 1-1.5 inch IM needles). The average retail price for 2 doses ranges from \$35 to \$85 (GoodRx, 10/2018).
- Narcan® (naloxone) 4 mg/0.1 ml nasal spray. A 2 mg/ml dose is FDA-approved specifically for patients who are opioid-dependent and at risk for severe opioid overdose, where there is low risk for accidental or intentional opioid exposure by other household contacts. Narcan® nasal spray does not require assembly. A box of Narcan® contains 2 doses, with an average retail price of approximately \$145 (GoodRx, 10/2018).
- Evzio® 2-Pack Auto-Injector 0.4 mg/0.4 ml or 2 mg/0.4 ml solution for injection. The average retail price is \$4000 (GoodRx, 10/2018).

All 3 of these formulations demonstrate bioequivalence in pharmacokinetic studies, indicating that naloxone exposure is adequate to reverse opioid overdose.^{11, 12, 13} Choosing among the formulations can be influenced by cost and ease of delivery, with some patients preferring a non-injection formulation.

Prior to the introduction of Narcan® nasal spray, injectable naloxone has sometimes been converted into an off-label intranasal applicator; this method may or may not deliver naloxone levels equivalent to FDA-approved products. Even so, an unapproved formulation has been shown to be reasonably effective in reversing opioid overdose in a randomized controlled trial when compared to intramuscular naloxone.^{9, 14, 15, 16}

Recommended Education

Patient education is highly recommended, and family members and/or friends should encourage participation. Suggested training and review should include information on how to administer naloxone and practice with a training device, if available. Additionally, training should include education on opioid overdose prevention, overdose recognition, and appropriate response to an event necessitating naloxone administration. Information on how to quickly seek help from emergency medical services should also be provided, with an emphasis on remaining with the patient until arrival of qualified medical help.

Legal Issues

Before prescribing naloxone, it is recommended that clinicians become knowledgeable regarding their individual state laws, particularly related to third-party and non-patient prescription programs and applicable “Good Samaritan” laws. This is important because family members, friends, or other members of the community may be involved in the administration of the rescue drug. Useful information is available at the Prescription Drug Abuse Policy System website (<http://www.pdaps.org/>) and the National Institute on Drug Abuse, Opioid Overdose Reversal with Naloxone (Narcan, Evzio) website (<https://www.drugabuse.gov/related-topics/opioid-overdose-reversal-naloxone-narcan-evzio>).¹⁷

Conclusions

The current opioid epidemic continues to tragically affect individuals, families, and communities. Naloxone is considered to be one of several essential tools for the prevention of opioid overdose deaths, with increased availability now being strongly encouraged by the Surgeon General in an effort to reduce unacceptable mortality. The Surgeon General's Advisory additionally suggests that naloxone should be used in conjunction with other evidence-based treatments for opioid-related disorders. It is particularly important to identify patients who are at higher risk for opioid overdose, applying appropriate guideline criteria based on several common medical scenarios. Training should be expanded for all healthcare providers with regard to various state laws and policies for efficient and effective implementation of naloxone programs. An increase in the availability of cost-effective and easily administered naloxone formulations can also increase prescription rates and result in more widespread availability of community-based emergency treatment options. Naloxone is no longer indicated only for administration in healthcare facilities or during emergency medical services, but now has a specific role in outpatient community settings where laypersons can potentially save lives through more timely and effective rescue drug administration.

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