

Prescribing Naloxone: Managing and Preventing Opioid-Related Overdoses

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Abstract

Purpose of Review Rising opioid overdoses are a nationwide problem. This review aims to educate health care professionals on the various naloxone nasal formulations that are available.

Recent Findings National data confirms a significant increase in opioid overdoses and a need for all health care professionals to recognize the importance of dispensing naloxone when indicated. With four options available (two intranasal and two intramuscular), naloxone may be dispensed with or without a prescription in many states.

Summary Being aware of the current formulations and offering naloxone prescriptions to patients at risk are among the current recommendations for providers to impact addictive behaviors, thus, reducing the risk of overdose.

Keywords Naloxone · Emergency medicine · Opioid overdose · Opioid reversal

Introduction

The rising incidence of opioid overdose is a nationwide problem. It is estimated that 100 Americans die every day from an opioid overdose [1]. In 2014, more people died from drug overdoses than in any year. Most of drug overdose deaths involved an opioid (Fig. 1) [2, 3]. The most recent report from the Drug Abuse Warning Network, a public surveillance system, estimates that over 1.2 million emergency department visits involved the nonmedical use of prescription medications in 2011 [4]. The Substance Abuse and Mental Health Services Administration estimates there are approximately 0.5 million heroin users, aged 12 years and older. The problem is especially striking among US adolescents [5•].

Significant increases in opioid drug overdose death rates were seen in the northeast and southern regions of the United States (US) [6]. Massachusetts was a state reporting statistically significant increases in drug overdose death rates from 2014 to 2015. The Massachusetts Department of Public Health reported 488 confirmed unintentional opioid overdose-related deaths over a 6-month period but estimated an additional 500 suspected deaths. In 2015, the estimated rate of unintentional opioid-related overdose deaths was 24.6 deaths per 100,000 Massachusetts residents. This rate is the highest in their history and represents almost a 25% increase in the event rate from 2014. The rate of unintentional opioid-related overdose deaths in Massachusetts continues to rise with current data collection suggesting 2016 is higher than that of the comparable period in 2015.

Opioid intoxications are associated with high rates of morbidity and mortality as well as multiple emergency department visits and inpatient admissions [5•, 7]. A patient may experience several overdose incidents before a fatal one occurs [8]. The classic toxidrome of opioid intoxication is composed of apnea (specifically a respiratory rate of 12 breath per minute or less), miosis, and stupor [9••].

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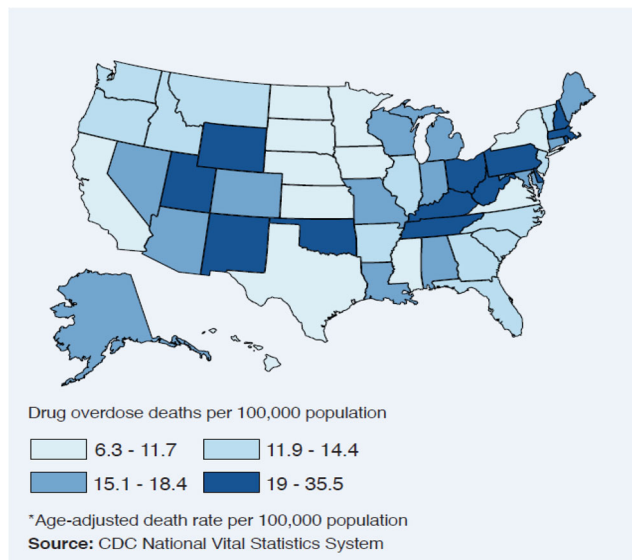


Fig. 1 Drug overdose death rates, United States, 2014 (sourced and adapted from the CDC)

The increase in the misuse of opioid pain relievers calls for efforts to provide clinicians and patients with tools and guidance in responding to an overdose [5•, 7]. We review the recent introduction of nasal naloxone formulations for rescue treatment of opioid overdose.

Naloxone as a Treatment Option

Naloxone is a pure opioid antagonist at mu, kappa, and delta opioid receptors and reverses the effects of opioid medications [9••]. Naloxone is available to the public in two different

formulations: intranasal (IN) and intramuscular (IM) administration (Table 1, Table 2) [10–13].

Due to the difficulties and challenges with obtaining an intravenous line (IV), the IN route appears to be a safe alternative despite having a longer administration time compared to IV [14]. IM route is clinically comparable to IN, as both routes achieve respiratory rate goals of over 10 breaths per minutes within 6–8 min [15]. IN administration allows for administration by the lay person in the prehospital setting, can be accomplished with minimal training and reduces time to treatment for the arrival of emergency medical support (EMS) or first responders (i.e., firefighters and police).

Naloxone Distribution

Naloxone may be dispensed with or without a prescription depending on state law to patients at risk of an opioid overdose or a family member, friend, or someone in a position to assist a person at risk of experiencing an opioid-related overdose [10]. In Massachusetts, a pharmacist can dispense naloxone kits without a prescription under a standing order to patients at risk of an opioid overdose or those witnessing an opioid overdose. The indications for dispensing naloxone are listed in (Table 3) [11–13]. The FDA currently requires that new naloxone formulations are equivalent to that of a 0.4 mg IM dose of naloxone [16]. Products available in the community usually come in packages of two to allow for repeated administration every 2 min. There is indeed a debate over the optimal naloxone dose and frequency of administration and, it is highly likely that more dosage forms and delivery systems will be introduced to the marketplace.

Table 1 Comparisons of naloxone rescue kits

Product	Naloxone with nasal adaptor rescue kit	Naloxone nasal spray rescue kits: Narcan	Naloxone muscle rescue kits	Naloxone muscle auto-injector kit: Evzio
Route	Intranasal	Intranasal	Intramuscular	Intramuscular
Strength	2 mg/2 ml	4 mg/0.1 ml	0.4 mg/mL	0.4 mg/mL
Kit	A nasal adaptor, an applicator, and two 2-ml Luer-Jet Luer-Lock naloxone-prefilled syringes	Two blister packed ready to use single-use spray devices	Either one multi-dose vial (10 mL) or as two single dose vials (1 mL) With two 1-in., 3-mL, 25-gauge needles	Two single use auto-injectors accompanied by one training device
Price	\$39.60 per vial \$3.68 for adaptor	\$75.00 each \$50.00 per two	\$140.36 per kit	\$4500 per kit \$4920 per two
Comments	Must be dispensed with two mucosal automation devices, as these are not included	Requires no measuring, assembly, or priming.	Requires preparation	Provides visual and voice instructions for ease of administration

Table 2 Naloxone rescue kit pictures

Product	Naloxone with nasal adaptor rescue kit	Naloxone nasal spray rescue kits: Narcan	Naloxone muscle rescue kit	Naloxone muscle auto-injector kit: Evzio
Product				

Table 3 Indications for dispensing naloxone

- I. FDA approved indications
 - a. Opioid overdose:
 - i. Complete or partial reversal of opioid depression (including respiratory depression)
 - ii. Diagnosis of suspected or known acute opioid overdosage
 - b. Septic shock: adjuvant agent to increase blood pressure
- II. Off-label use
 - a. Opioid-induced pruritus

Experience with Intranasally Administered Naloxone

In a randomized prospective, unblinded trial of 2 mg naloxone administered either intranasally or intramuscularly by paramedics as a response to suspected heroin overdose, the response time to regain a respiratory rate greater than 10 per minute was shorter in the IM compared to IN naloxone (6 vs. 8 min, respectively) [15]. However, both routes were

similar in terms of side effects and the proportion of patients requiring rescue naloxone.

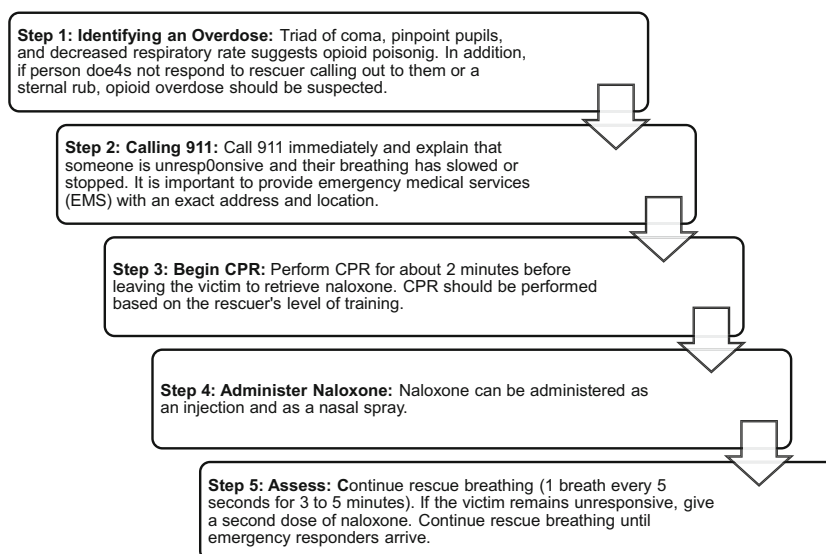
In another a prospective nonrandomized trial among all patients who presented with potential opiate drug intoxication, paramedics administered 2 mg of IN naloxone upon patient contact [17]. Of the 52 patients treated, 83% responded to IN naloxone alone and 16% were unresponsive to IN naloxone and required further doses of IV naloxone. Time from initial contact or drug administration to clinical response was around 3 minutes and was not statistically significant different between the two routes.

A retrospective chart review of adult patients admitted to the emergency room after receiving a 2 mg of IN naloxone found that IN naloxone had a clinical effect in 95.2% patients. An additional dose was given to only 8.8% patients [18].

Retrospective review before and after the implementation of an IN naloxone protocol evaluated the time from dose administration to clinical response and found a longer time for IN naloxone compared to IV (12.9 vs. 8.1 min, $P = 0.02$) [14]. However, the time from patient contact to response was similar between both groups (20.3 vs. 20.7 min, respectively).

In 2012, the Massachusetts Department of Public Health (MDPH) started an Overdose Education and Naloxone

Fig. 2 The five steps in responding to an opioid overdose



Distribution (OEND) pilot program that equips nonparamedic first responders with IN naloxone [19]. Starting 2012, the Office of Emergency Medical Services (OEMS) in MDPH allowed emergency medical services (EMS) directors to issue standing orders for IN naloxone. As a result, the communities in which those nonparamedic first responders have participated had been associated with reduced overdose deaths.

A study to assess the feasibility of an ED-based overdose prevention program surveyed by telephone a total of 415 patients who received overdose education (OE) or overdose education and naloxone rescue kits (OEN) after the ED visit [20•]. Approximately 1/3 of OEN and OE reported a 30-day past opioid use. In the study population, 53% of participants reported witnessing another individual experiencing an overdose in the past 30 days, of which, 32% used a naloxone kit to reverse the overdose.

Patient Education

When naloxone is dispensed, it is important that individuals at risk of experiencing or witnessing an opioid-related overdose are counseled on the five essential steps in responding to an opioid overdose (Fig. 2) as well as how to assemble and administer the dosage form they are receiving (Table 3) [11–13, 21]. In addition, patient information pamphlets with material on overdose prevention information, stepwise instructions for overdose responses, and naloxone administration should be dispensed along with naloxone.

Friends, family members, and caregivers should be made aware of the Good Samaritan law in states in which this may apply [22]. This drug immunity law provides protection from supervision violations or low-level drug possession to encourage people to seek medical attention in the event of an overdose. Versions of this law and its violations vary by state; however, with this growing epidemic, 37 states and the District of Columbia have enacted their own versions of the Good Samaritan law.

Conclusion

Naloxone is a safe and effective antidote for opioid overdose. It is available to the public in four easy to use formulations. Recent evidence shows that the time from IN administration to clinical response may be longer compared to other routes; however, the time from patient contact to clinical response is comparable. A small percentage of patients may require further doses of naloxone by an alternative route. There are several limitations for studies on IN naloxone; they are often retrospective and single-centered with a relatively small sample size. Since naloxone may be dispensed without a prescription in most states, health care providers should educate

patients about how to respond in the incident of an opioid overdose and how to utilize naloxone kits. Strategies to control the opioid epidemic should focus on controlling and monitoring opioid overprescribing and educating the public on how to respond to an opioid overdose.

Compliance with Ethical Standards

Conflict of Interest Dr. Alosaimy, Dr. Santos, and Dr. Fanikos declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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