Comparative Effectiveness Review
Number 193

Effective Health Care Program

Management of Suspected Opioid Overdose With Naloxone by Emergency Medical Services Personnel

Executive Summary

Background

Nature and Burden of Opioid Overdose

Addiction and overdoses associated with prescription and illicit opioids have been characterized by the U.S. Department of Health and Human Services as a national crisis.[1] Since 2000, the rate of overdose deaths involving opioids has increased four-fold.[2,3] Drug overdose deaths are now the leading cause of injury-related death in the United States.[4] Overdoses due to opioids cause respiratory depression that can progress to cardiac arrest if untreated. In 2015, the number of drug overdose deaths involving prescription or illicit opioids exceeded 33,000, the highest number on record.[3] Of recent concern is whether dosing guidelines are sufficient for reversing overdose related to highly potent synthetic opioids (e.g., fentanyl and fentanyl analogues).[3,5-9]

Field Treatment of Suspected Opioid Overdose With Naloxone

Naloxone can be administered by the intravenous (IV), intramuscular (IM), subcutaneous (SC), intranasal (IN), endotracheal (ET), nebulized/inhalational, buccal, or sublingual routes.[10] The U.S. Food and Drug Administration (FDA)

Purpose of Review

To determine optimal doses, routes of administration, and dosing strategies of naloxone for suspected opioid overdose in out-of-hospital settings, and whether transport to a hospital following successful opioid overdose reversal with naloxone is necessary.

Key Messages

- Higher concentration intranasal naloxone may be similarly effective and safe compared with intramuscular naloxone, but the available studies did not evaluate formulations approved by the Food and Drug Administration.
- While field administration of naloxone is generally effective in reversing opioid overdose, there is not strong evidence concerning differences in effectiveness between doses or routes of administration.
- More research is needed to determine optimal doses of naloxone, appropriate timing of repeat dosing, and whether it is necessary to dose patients to full consciousness.
- More research is needed to determine whether transporting patients to a hospital after successful reversal of overdose is necessary.

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approved a handheld naloxone IM or SC auto-injector in 2014[11] and a new IN formulation and delivery device in 2015;[12] both administer a preset dose. With IN administration of highly concentrated naloxone using a preloaded single dose device, there is no risk of needle stick injury. Both the auto-injector and IN formulation are designed for ease of administration even by individuals with limited or no health care training. Off-label administration of IN naloxone in a less concentrated formulation using an improvised intranasal device is also common. Naloxone has been shown to be effective for reversal of opioid overdose across various routes of administration and doses.[13,14] Naloxone may precipitate withdrawal symptoms.[15] While uncomfortable, withdrawal symptoms are generally not serious or life-threatening and generally short-lived; the half-life of naloxone is about 30 minutes. Post-withdrawal agitation following naloxone administration may put the person administering the naloxone at increased risk for injury.[16,17]

When responding to opioid overdoses, early intervention is critical to prevent death and other complications.[18] Emergency medical services (EMS) personnel are often involved in management of potential opioid overdoses. Management of opioid overdoses by EMS personnel includes airway management and continuous assessment of oxygenation and ventilation, along with administration of naloxone.[19] According to the National EMS Information System database, the number of EMS encounters for suspected opioid overdose has increased,[20] with nearly 160,000 doses of naloxone administered by EMS personnel in 2014.[21] Regulations vary, however, with regard to whether EMS personnel with different levels of training are permitted to administer naloxone. Naloxone administration is not currently within the National EMS Scope of Practice Model for EMTs and EMRs, which was last updated in 2007,[22] prior to the introduction of newer naloxone formulations and availability of newer evidence on the benefits of field use of naloxone.

Although a number of recommendations, guidelines, and protocols are available to inform out-of-hospital management of opioid overdose patients, including naloxone use, guidance varies across these documents, and there are uncertainties in a number of areas.[23-25] These include the optimal route of administration, the optimal dose for different routes of administration, optimal dosing strategies, and appropriate training levels for EMS personnel who are permitted to administer naloxone.

The purpose of this systematic review is to synthesize the evidence on naloxone route of administration and dosing for suspected opioid overdose in out-of-hospital settings, and on the need for transport to a hospital following successful opioid overdose reversal with naloxone; the review is intended to inform development of evidence-based guidelines on EMS management of suspected opioid overdose with naloxone and potentially inform an update to the National EMS Scope of Practice Model regarding naloxone use across EMS training levels.

Scope and Key Questions

The report addresses the following Key Questions.

Key Question 1: For patients with confirmed or suspected opioid overdose, what are the comparative benefits and harms of out-of-hospital administration of naloxone by EMS personnel using intravenous, intramuscular, subcutaneous, and intranasal routes of administration?

1a. For patients with confirmed or suspected opioid overdose who receive naloxone in the out-of-hospital setting from EMS personnel, what are the comparative benefits and harms of different intravenous, intramuscular, subcutaneous, or intranasal doses of naloxone?

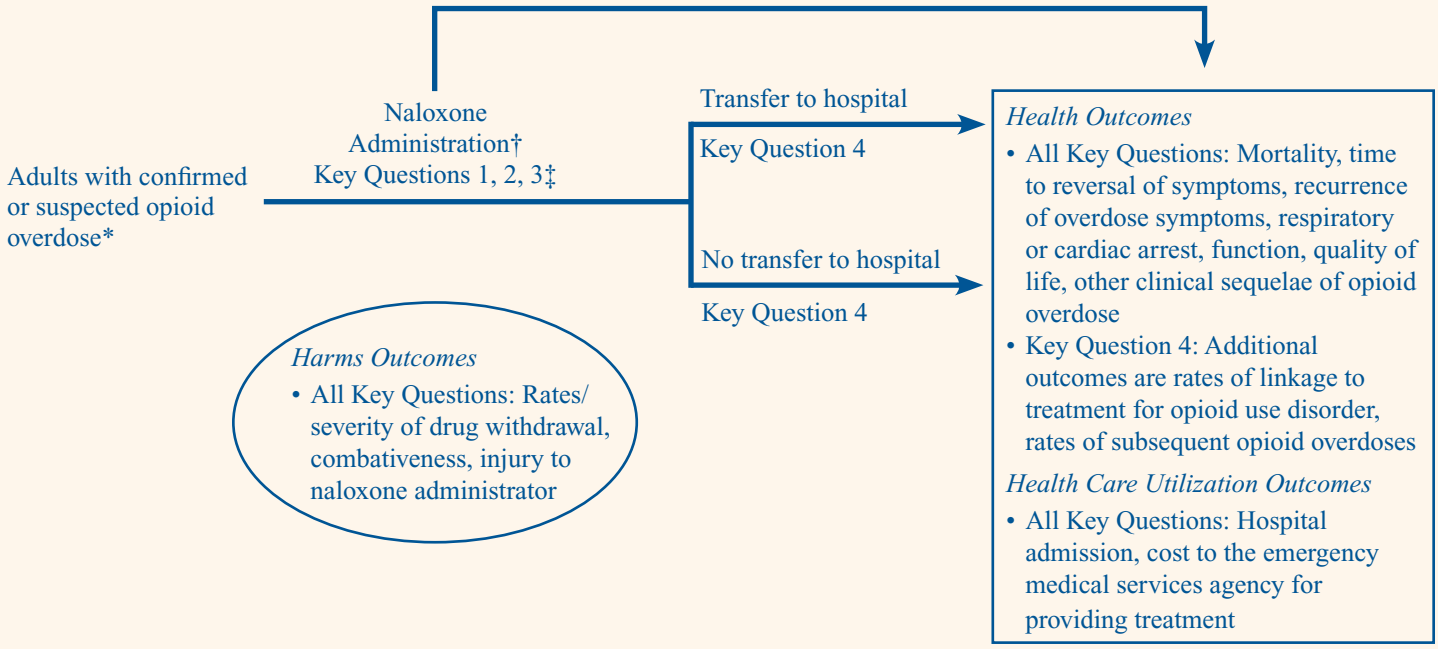
Key Question 2: For patients with confirmed or suspected opioid overdose in out-of-hospital settings, what are the comparative benefits and harms of titration of naloxone administered by EMS personnel until the patient resumes sufficient spontaneous respiratory effort versus until the patient regains consciousness?

Key Question 3: For patients with confirmed or suspected opioid overdose in out-of-hospital settings treated with multiple doses of naloxone (including patients who do not improve after an initial dose of intranasal naloxone), what are the effects on benefits and harms of differences in timing of repeat dosing?

Key Question 4: For patients with confirmed or suspected opioid overdose in out-of-hospital settings who regain sufficient spontaneous respiratory effort and are alert and oriented after naloxone administration by EMS personnel, what are the benefits and harms of transporting patients to a health care facility versus nontransport?

The analytic framework (Figure A) shows the target population, interventions, and health outcomes examined; the Key Questions are numbered and indicated in the framework. We focused on use of IN, IM, and IV naloxone; these are the formulations of naloxone most commonly used for reversal of suspected opioid overdose in the field.

Figure A. Analytic framework



* Patients with confirmed or suspected opioid overdose who exhibit altered mental status, miosis, or respiratory distress and who are treated in the out-of-hospital setting by emergency medical services personnel

†Administration of naloxone hydrochloride via the nasal, intravenous, intramuscular, or subcutaneous injection (including the naloxone auto-injector)

‡ Key Question 1 addresses comparisons involving route of administration and dose; Key Question 2 addresses comparisons involving dose titration to varying degrees of return of consciousness (intermediate outcome)

Methods

The final protocol was posted on the AHRQ Web site on November 30, 2016, at: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2360 and registered in PROSPERO (CRD42016053891).

Literature Search Strategy

A research librarian conducted searches in Ovid MEDLINE (1946-August Week 2 2016, PsycINFO), the Cochrane Central Register of Controlled Trials (CCRCT), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). We did not apply search date restrictions and updated searches were conducted through September 2017. The Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) Scientific Resource Center (SRC) sent email notification to relevant stakeholders about the opportunity to submit Scientific Information Packets (SIPs) via the Effective Health Care (EHC) Web site for naloxone.

We also hand-searched reference lists of relevant studies, searched for unpublished or ongoing studies in ClinicalTrials.gov, contacted representatives of federal agencies involved in naloxone or opioid overdose research (CDC, NIDA, SAMHSA), and reviewed materials presented at a recent FDA meeting[26] on naloxone dosing.[27-32]

Inclusion and Exclusion Criteria

We developed pre-established criteria for inclusion and exclusion of studies based on the Key Questions and the populations, interventions, comparators, outcomes, timing, types of studies, and setting (PICOTS) approach, in accordance with the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[33] Inclusion and exclusion criteria are described below.

Population(s)

- *Include*: Patients with confirmed or suspected opioid overdose who exhibit altered mental status, miosis, or respiratory depression and who are treated in the out-of-hospital setting by EMS personnel

- Also include studies of naloxone administration in out-of-hospital settings by non-EMS personnel (e.g., police, other first responders, laypeople), which may inform optimal dosing strategies in EMS personnel
- For Key Questions 1 and 1a, also include studies of patients treated in emergency department (ED) settings by ED personnel.

Interventions

- For Key Questions 1-3: See Table A for included naloxone formulations.

Table A. Naloxone: Dose and route of administration

Included Drug	Dose and Route of Administration
Naloxone	• Auto-injector, intramuscular (IM) – 0.4mg/0.4mL,* 2 mg/0.4 mL • Nasal spray, intranasal (IN) – Single dose intranasal device: 4 mg/0.1 mL, 2 mg/0.1 mL – Improvised intranasal device: 2mg/2mL† • Injection, intravenous, intramuscular or subcutaneous – 0.4 mg/mL, 1 mg/mL, 2 mg/mL

* Manufacturer has stopped production of 0.4mg/0.4mL IM
† Formulation not currently approved by the FDA for intranasal administration

- Potential modifiers of interventions: Based on training and background of the person administering naloxone
- For Key Question 4: Transport to health care facility
- *Exclude*: Naloxone in combination with other medications (e.g., buprenorphine/ naloxone)

Comparators

- *Key Question 1:* Injection (intramuscular, subcutaneous or intravenous) versus intranasal route of administration
- *Key Question 1a:* Comparisons of different doses of intranasal, intramuscular, and intravenous naloxone
- *Key Question 2:* Titration of patients until they resume spontaneous respiration but have some residual sedation/altered mental status versus dosing of patient until they resume spontaneous respiration and are awake and alert
- *Key Question 3:* Comparison of differences in timing of repeat dosing
- *Key Question 4:* Transport of patients following treatment of opioid overdose with naloxone to a health care facility versus nontransport

Outcomes

- *All Key Questions:* Mortality, time to reversal of symptoms, recurrence of overdose symptoms, respiratory or cardiac arrest, function, quality of life, other clinical sequelae of opioid overdose; health care utilization indicators (e.g., hospital admission, cost to the EMS agency for providing treatment); and adverse effects and other harms (such as rates/severity of drug withdrawal, combativeness, injury to administrator of naloxone)
- *Key Question 4:* Additional outcomes are rates of linkage to treatment for opioid use disorder and rates of subsequent opioid overdoses

Timing

- No restrictions on timing of followup

Settings

- *Include:* Out-of-hospital setting and ED setting (for Key Questions 1 and 1a). The addition of studies conducted in ED settings was a protocol modification for Key Questions 1 and 1a, due to few randomized controlled trials (RCTs) conducted in field settings.
- *Exclude:* Inpatient, clinic, or ED setting (for Key Questions other than 1 and 1a)

Study Designs

- Randomized controlled trials
- Cohort and case-control studies
- For comparisons related to different doses, a preliminary search indicated that there are few head-to-head studies directly comparing different doses; therefore, we also included placebo-controlled studies that evaluated single doses for the purpose of potentially informing indirect comparisons related to dosing.

- For Key Question 4, we included uncontrolled longitudinal studies of patients who were successfully treated for opioid overdose with naloxone in the field and not transported to a health care facility (protocol modification due to no controlled studies being available).

Study Selection and Data Extraction

Abstracts were reviewed by two investigators to identify studies for full-text review. Two investigators then independently reviewed all full-text articles for final inclusion. Inclusion was restricted to English-language articles. Discrepancies were resolved by discussion and consensus.

For each study that was determined to meet inclusion criteria, a single investigator abstracted information on study design, year, setting, country, sample size, eligibility criteria, population and clinical characteristics, intervention characteristics (route of administration, dose/concentration, time to initial and repeat dosing, training/background of personnel administering drug), source of funding, and results relevant to each Key Question. All data abstractions were reviewed by a second investigator for accuracy.

Risk of Bias Assessment of Individual Studies

We assessed risk of bias of included studies using predefined criteria. Two investigators independently assessed risk of bias. Disagreements were resolved by consensus. Our approach for assessing risk of bias is based on the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[34] We adapted criteria for assessing risk of bias from the U.S. Preventive Services Task Force.[35] For RCTs, risk of bias assessment criteria included randomization and allocation concealment methods, comparability of groups at baseline, blinding, attrition, use of intention-to-treat analysis, and prespecification of outcomes. For cohort studies, assessment criteria were based on patient selection methods; comparability of groups at baseline; methods used to ascertain exposures, confounders, and outcomes; blinding of outcomes assessors; attrition and missing data; and statistical analysis of potential confounders. For uncontrolled longitudinal studies, we used the same criteria as for cohort studies, but did not assess comparability of groups at baseline or statistical adjustment for confounders. Studies were rated as "low risk of bias," "medium risk of bias," or "high risk of bias" based on the presence and seriousness of methodological shortcomings; uncontrolled studies were rated high risk of bias since they can only address the comparative effectiveness questions addressed in this review indirectly.

Assessing Research Applicability

Factors important for understanding the applicability of studies were recorded, such as population characteristics (e.g., age, type and dose of opioid involved in overdose, or involvement of other drugs or substances), setting (United States vs. other country, out-of-hospital vs. ED administration of naloxone), and type and level of training of people administering naloxone were recorded and assessed in subgroup and sensitivity analyses to the extent possible.[36] We also recorded the funding source for studies.

Data Synthesis

We constructed evidence tables with study characteristics, results, and risk of bias ratings for all included studies, and summary tables to highlight the main findings. Given the small number of studies for each Key Question and clinical and methodological heterogeneity among the studies, we determined that meta-analysis was not indicated. Rather, we synthesized studies qualitatively.

Strength of the Body of Evidence

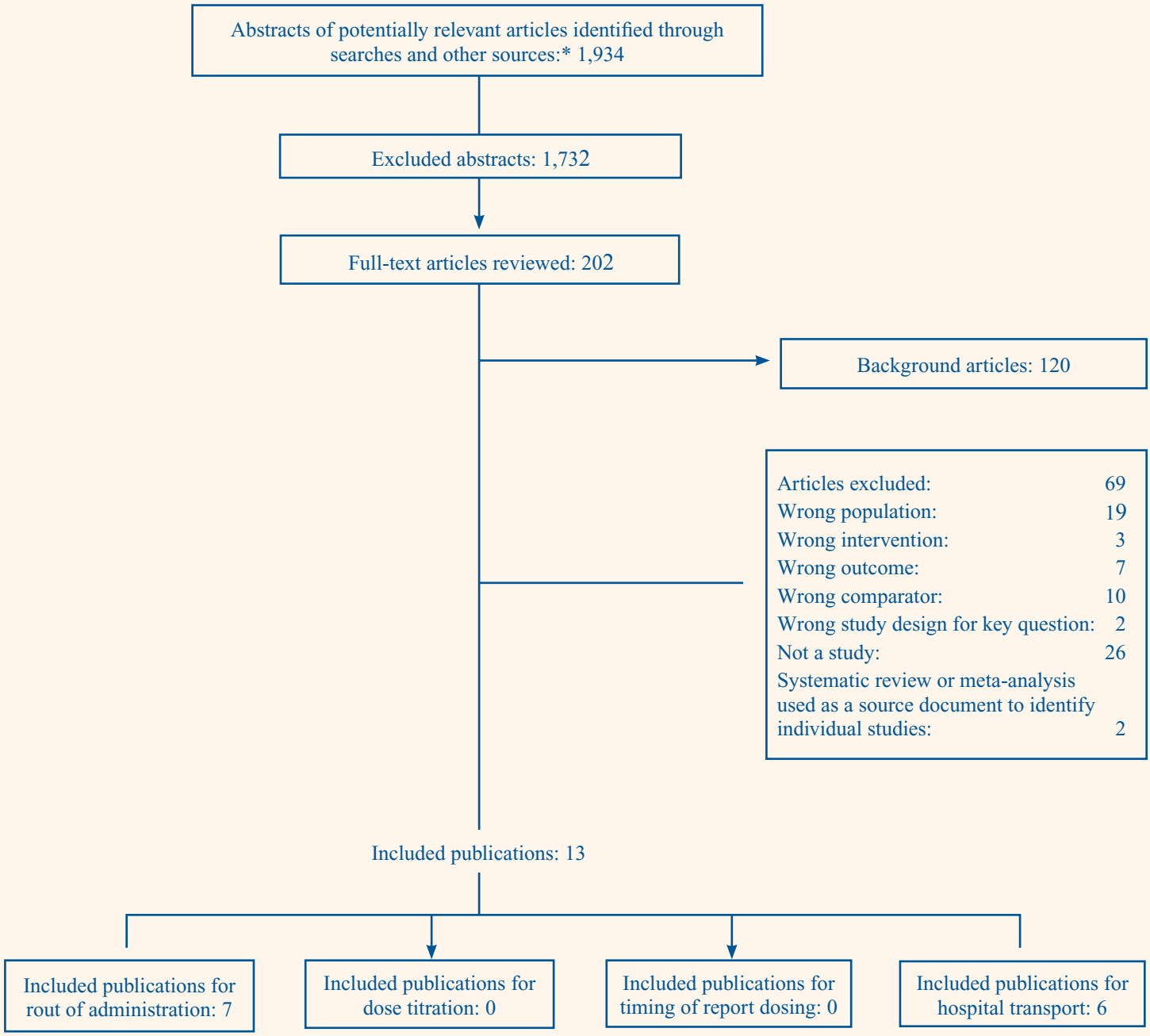
We graded the strength of evidence for each Key Question and comparison for prioritized clinical outcomes (mortality, time to reversal of symptoms, recurrence of overdose symptoms, respiratory or cardiac arrest, rates/severity of drug withdrawal, and combativeness) by using the approach described in the AHRQ Methods Guide.[34] One investigator performed the initial strength of evidence assessment and discussed with the entire team to reach consensus.

Results

Results of Literature Searches

The search and selection of articles are summarized in the literature flow diagram (Figure B). Database searches resulted in 1,934 potentially relevant articles. After dual review of abstracts and titles, 202 articles were selected for full-text dual review, and 13 studies were determined to meet inclusion criteria and were included in this review.

Figure B. Literature flow diagram



*Other sources include prior reports, references lists, referrals from experts, and grey literature

Key Question 1: For patients with confirmed or suspected opioid overdose, what are the comparative benefits and harms of out-of-hospital administration of naloxone by EMS personnel using intravenous, intramuscular, subcutaneous, and intranasal routes of administration?

We identified three RCTs (n=100 to 182)[37-39] and four cohort studies (n=93 to 609)[40-43] that compared different routes of naloxone administration.

- **IN versus IM naloxone:**
  - One trial found no difference between IN naloxone (2 mg, administered as a 2 mg/1 mL formulation) versus IM naloxone (2 mg) in the likelihood of adequate response within 10 minutes (72% vs. 78%, adjusted odds ratio [OR] 0.7, 95% confidence interval [CI] 0.3 to 1.5), mean response time (8.0 vs. 7.9 minutes), or agitation/violence (6.0% vs. 7.9%, relative risk [RR] 0.77, 95% CI 0.25 to 2.3). IN naloxone was associated with increased likelihood of rescue naloxone use (18% vs. 4.5%, adjusted OR 4.8, 95% CI 1.4 to 16).
  - Another trial found lower concentration IN naloxone (2 mg administered as a 2 mg/5 mL formulation) associated with lower likelihood of spontaneous respirations within 8 minutes (63% vs. 82%, OR 0.38, 95% CI 0.18 to 0.81), higher likelihood of rescue naloxone use (26% vs. 13%, OR 2.4, 95% CI 1.0 to 5.7), longer time to respirations >10/minutes (8 vs. 6 minutes, p=0.006), and trend towards decreased likelihood of Glasgow Coma Scale score >11 at 8 minutes (57% vs. 72%, OR 0.52, 95% CI 0.27 to 1.0) than IM naloxone (2 mg). IN naloxone was associated with decreased risk of agitation and/or irritation (2.4% vs. 14%, RR 0.19, 95% CI 0.04 to 0.83).
  - The strength of evidence (SOE) for this comparison was low, due to moderate study limitations and inconsistency.
- **IN versus IV naloxone:**
  - One trial conducted in an Iranian ED setting found that IN naloxone (0.4 mg, administered as a 0.4 mg/2 mL formulation) was associated with a greater likelihood than IV naloxone (0.4 mg) of an adequate response (defined as level of consciousness following naloxone of lethargic or conscious, 100% vs. 60%, RR 1.7, 95% CI 1.3 to 2.1) and lower likelihood of agitation than IV naloxone (0% vs. 24%, RR 0.04, 95% CI 0.002 to 0.66). The SOE was insufficient, due to moderate study limitations, inability to assess consistency, and indirectness (poor applicability to U.S. field settings due to high proportion of overdoses related to use of opium and ED setting).
  - Two cohort studies reported few clear differences between IN and IV naloxone, but had serious methodological shortcomings, including failure to adjust for confounders (SOE: insufficient).

Key Question 1a: For patients with confirmed or suspected opioid overdose who receive naloxone in the out-of-hospital setting, what are the comparative benefits and harms of administration of different intravenous, intramuscular, subcutaneous, and intranasal doses of naloxone?

- No study compared different doses of naloxone administered via the same route; there was too much clinical heterogeneity to determine effects of dose from indirect comparisons (SOE: insufficient).

Key Question 2: For patients with confirmed or suspected opioid overdose in out-of-hospital settings, what are the comparative benefits and harms of titration of naloxone administered by EMS personnel until the patient resumes sufficient spontaneous respiratory effort versus until the patient regains consciousness?

- No study compared benefits and harms of titration of naloxone until the patient resumes sufficient spontaneous respiratory effort versus until the patient regains consciousness (SOE: insufficient).

Key Question 3: For patients with confirmed or suspected opioid overdose in out-of-hospital settings treated with multiple doses of naloxone (including patients who do not improve after an initial dose of intranasal naloxone), what are the effects on benefits and harms of differences in timing of repeat dosing?

- No study compared benefits and harms of differences in timing of repeat dosing of naloxone (SOE: insufficient).

Key Question 4. For patients with confirmed or suspected opioid overdose in out-of-hospital settings who regain sufficient spontaneous respiratory effort and are alert and oriented after naloxone administration by EMS personnel, what are the benefits and harms of transporting patients to a health care facility versus nontransport?

No study compared outcomes among patients with confirmed or suspected opioid overdose who responded to

naloxone administration and were transported to a health care facility versus not transported. Six studies (n=84 to 2241) reported on outcomes in patients who received naloxone for opioid overdose and were not transported to a health care facility.[44-49]

- Among patients who were successfully treated for opioid overdose by naloxone in the field and not transported to a hospital, uncontrolled studies reported rates of deaths within 0 to 2 days were 0 percent in three studies (total N=1867), 0.6 percent in one study and 0.49 percent (1/205) in another study; one study reported one case of a life-threatening adverse event (1.25% [1/84]) (SOE: insufficient).
- No study evaluated outcomes such as linkage to treatment for opioid use disorder or subsequent repeat opioid overdose episodes.

Discussion

Key Findings and Strength of Evidence

While field administration of naloxone is generally effective in reversing opioid overdose, evidence to inform optimal management of suspected opioid overdose with naloxone by EMS personnel in terms of forms of administration or dosage is limited. We identified no previously published systematic review addressing the Key Questions in our report. Our findings are generally consistent with the conclusions of a recent FDA meeting that focused on naloxone dosing for devices intended for use by laypeople.[26] The committee convened by the FDA generally found a lack of evidence to determine optimal dosing of naloxone.[50]

Three RCTs directly compared different routes of naloxone administration, but all had methodological shortcomings, including use of unblinded design.[37-39] Among the three trials, two compared IN versus IM naloxone[37,38] and one trial evaluated IN versus IV naloxone.[39] No trial evaluated the recently FDA-approved naloxone auto-injector for IM administration or highly concentrated (4 mg/0.1 mL or 2 mg/0.1 mL) IN formulations of naloxone.

For IN compared with IM naloxone, results suggest that a higher concentration formulation of IN naloxone (2 mg/1 mL) is similar in efficacy to IM naloxone (SOE: low).[38] Although another trial found the same dose of IN naloxone using a lower concentration formulation (2 mg/5 mL) to be less effective than IM naloxone,[37] these findings are of limited applicability to the United States, where off-label IN naloxone is typically given at a concentration of 2 mg/2 mL and FDA-approved concentrations are 4 or 2 mg/0.1 mL. Evidence regarding other route of administration comparisons is even more limited, with one trial of IN compared with IV naloxone conducted in an Iranian ED setting (SOE: insufficient). Observational studies were of very limited usefulness for informing route of administration comparisons, due to serious methodological shortcomings, including failure to adjust for potential confounders.[40-43] In addition, the route of administration comparisons varied across the studies.

Evidence was insufficient to determine how comparative benefits and harms of different routes of naloxone administration differed according to demographics or clinical factors, such as the type and dose of opioid involved in overdose (including whether fentanyl or a fentanyl analogue was involved), presence of other drugs or substances, estimated time since overdose, concomitant psychiatric comorbidities, or prior overdose episodes. There was also insufficient evidence to determine how the type or training of EMS personnel administering naloxone impacted comparisons involving different routes of administration or doses of naloxone.

There was insufficient evidence to determine the optimal dose of naloxone by route of administration. No study directly compared different doses of naloxone administered via the same route. It was not possible to determine effects of dose via indirect comparisons based on the studies of route of administration comparisons, given the small number of studies and differences in factors other than dose.

Evidence to determine effects of hospital transport versus nontransport following successful treatment of opioid overdose was too limited to reach reliable conclusions. No study compared outcomes in patients transported to a hospital versus those not transported following successful reversal of opioid overdose with naloxone. Although six studies reported low rates (0 to 1.2%) of death or serious adverse events among patients who received naloxone for opioid overdose and refused transport to a health care facility,[44-49] there was no comparison group of patients who were transported, which makes findings difficult to interpret, as patients who refuse transport or are assessed as not requiring transport are likely to differ substantially from patients who are transported.

No study compared titration of naloxone administered by EMS personnel until the patient resumes sufficient spontaneous respiratory effort versus until the patient regains consciousness or differences in timing of repeat naloxone dosing.

Applicability

Several factors limited the applicability of our findings. A key applicability limitation is that all studies meeting inclusion criteria evaluated older formulations of naloxone. No study evaluated the FDA-approved naloxone auto-injector for IM administration, at either a dose of 0.4 mg or the very recently approved 2 mg dose. Similarly, no study evaluated the recently FDA-approved formulations of highly-concentrated IN naloxone. One trial evaluated IN naloxone at a concentration lower (2 mg/5 mL) than used off-label in the United States (2 mg/2 mL)[37] and another trial evaluated IN naloxone at a concentration (2 mg/1 mL) that appears to have been formulated specifically for that study, and is not available in any product otherwise.[38] Studies indicate very high usability rates (>90%) with the auto-injector and FDA-approved IN naloxone, even without prior training, compared with older/off-label devices.[51,52]

The settings of some studies may also limit applicability to use of naloxone in U.S. field settings by EMS personnel. All of the RCTs that compared naloxone routes of administration were conducted in non-U.S. settings (Australia and Iran). In the Iranian trial, a high proportion of opioid overdoses were related to ingestion of opium; it was also conducted in an ED setting.[39]

Applicability was also limited by the populations evaluated in the studies. In almost all studies, characteristics of the opioid overdose were not reported. In addition, almost all studies were conducted before the recent increase in availability of high potency synthetic opioids. In studies regarding patients who received naloxone for opioid overdose who were not transported to a health care facility, details regarding the characteristics of patients were limited. This poses a challenge for interpreting the results of these studies, because patients who refuse transport are likely to differ substantially from patients who are transported. One study reported that 100 percent of patients who were not transported to an ED had a Glasgow Coma Scale score of 14 or 15, compared with about 50 percent of patients who were transported, but the study did not compare outcomes in patients transported versus those not transported.[44]

Research Recommendations

Additional research is urgently needed to optimize administration of naloxone by EMS personnel. Randomized controlled trials in U.S. field settings that compare the FDA-approved IN formulations of naloxone versus IM auto-injectors (0.4 or 2 mg doses), compare effects of the FDA-approved formulations versus non-FDA approved versions, and compare different doses for a given route of administration (e.g., 0.4 vs. 2 mg doses of the IM auto-injector) are needed. Randomized controlled trials could pose ethical and logistical challenges in field settings, such as requiring an exception to informed consent or the need to obtain consent prior to an overdose event occurring, which would pose a challenge in identifying and engaging at-risk populations.

In addition to studies of naloxone administration by EMS personnel, studies of naloxone administration by non-EMS first responders and laypersons with limited medical training could also be informative for understanding optimal use of naloxone by Basic Life Support personnel. Ideally, studies would include (to the extent possible) information regarding the opioids involved in the overdoses and other patient factors. Studies should evaluate benefits as well as important harms, including withdrawal, agitation, aspiration, and injury.

Future research could leverage existing EMS registries with naloxone administration data, which are available from a number of local and state agencies. In addition, the National Highway Traffic Safety Administration (NHTSA)-funded National Emergency Medical Services Information System (NEMSIS) contains data from EMS agencies across the United States.[53] Ideally, registry studies should include information about the dose, formulation, and route of administration of naloxone; opioid involved in exposure; training of EMS personnel administering naloxone; clinical response to initial and repeat dosing; protocol for initial and repeat naloxone dosing; and clinical outcomes, including response rates using predefined criteria, risk for recurrence of opioid overdose symptoms, and adverse outcomes. Importantly, observational studies should be designed to reduce risk of confounding and bias, including statistical adjustment.

Research is also needed to determine optimal timing and strength of dose(s) of repeat dosing as well as whether to dose until fully conscious or until patients have adequate respirations (e.g., in situations in which adequate ventilatory support is not available). For studies addressing either of these questions, the protocols used for naloxone dosing will need to be clearly defined, including indications for additional "rescue" dosing. Registry and pilot studies would be helpful for informing appropriate naloxone dosing protocols, to aid in the design of future clinical trials.

For comparing effects of nontransport following successful treatment of opioid overdose with naloxone, RCTs may not be logistically or ethically feasible. However,

comparative observational studies would better inform this question than the noncomparative studies currently available. For example, studies could identify patients who are not transported to a hospital and match them with patients who are transported, based on factors such as age, sex, suspected opioid involved in overdose, response to naloxone (e.g., based on Glasgow Coma Scale score), other substances and drugs involved in overdose, or other factors. Studies should supplement use of medical examiner and hospital records to identify outcomes with formal followup assessments, and evaluate outcomes such as linkage to treatment for opioid use disorder and risk of future overdose episodes, in addition to serious adverse outcomes such as death.

Conclusions

Low-strength evidence suggests that IN naloxone at a dose of 2 mg and concentration of 2 mg/1 mL is similar in efficacy to IM naloxone at a dose of 2 mg, with no difference in adverse events. Research is needed on the comparative effectiveness of the FDA-approved naloxone auto-injectors and highly concentrated IN naloxone formulations, different doses, and dosing strategies. Uncontrolled studies suggest that nontransport of patients following successful naloxone reversal of overdose might be associated with a low rate of serious harms, but patients were probably at low risk for such events, and there is insufficient evidence to determine risk of adverse effects for transported versus nontransported patients after opioid reversal in the field setting.

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Full Report

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