Management of Suspected Opioid Overdose With Naloxone by EMS Personnel

DATE: January 10, 2018 PRESENTED BY: Roger Chou, M.D., Director, Pacific Northwest Evidence-based Practice Center

Purpose of Report

- To synthesize evidence on optimal doses, routes of administration, and dosing strategies of naloxone in out-of-hospital settings, and on need for hospital transport following successful opioid overdose

Systematic Review Process

- Topic nominated and initial research questions developed by NHTSA, questions revised with input from Technical Expert Panel
- Overseen and methods guidance by AHRQ
- Review conducted by Pacific Northwest EPC
- Draft underwent peer review and was posted for public comment

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Background

- In 2015, over 33,000 drug overdose deaths involving prescription or illicit opioids
- Naloxone is an opioid antagonist that rapidly reverses CNS and respiratory depressant effects of opioid
  - IM autoinjector (FDA-approved)
  - IN spray
    - FDA-approved, highly concentrated (4 mg or 2 mg/0.1 mL)
    - Non-FDA-approved administration of injectable, less concentrated naloxone (2 mg/2 mL) with an atomizer
      - Maximum amount absorbed by nasal mucosa <0.5 mL
  - Main adverse event is precipitated withdrawal/agitation; little effect in persons not exposed to opioids
- Variability in route of administration, formulation, dosing protocols, mandatory transport to hospital
  - Overdoses related to highly potent fentanyl may require higher doses

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Key Questions

For patients with confirmed or suspected opioid overdose:

Key Question 1. What are the comparative benefits and harms of out-of-hospital administration of naloxone using intravenous, intramuscular, subcutaneous, and **routes of administration**?

Key Question 1a. What are the comparative benefits and harms of different intramuscular, subcutaneous, or intranasal **doses** of naloxone?

Key Question 2. What are the comparative benefits and harms of **titration of** administered by EMS personnel until the patient resumes sufficient spontaneous effort versus until the patient regains consciousness?

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Key Questions

Key Question 3. For patients who require repeat dosing, what are the effects on benefits and harms of differences in **timing of repeat dosing**?

Key Question 4. For patients who regain sufficient spontaneous respiratory effort and alert and oriented after naloxone administration by EMS personnel, what are the and harms of **transporting patients to a health care facility versus nontransport**?

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Inclusion Criteria

Included Naloxone Formulations

- Auto-injector, intramuscular (IM)
  - 0.4mg/0.4mL (no longer manufactured) (2016 price ~$4500, compared to $690 in 2014)
  - 2 mg/0.4 mL
- Nasal spray, intranasal (IN)
  - Single dose intranasal device: 4 mg/0.1 mL (2016 price $150.00 for 2-pack), 2 mg/0.1 mL
  - Improvised intranasal device: 2mg/2mL injectable naloxone with atomizer (not FDA approved) (2016 price ~$40.00)
- Injection, intravenous, intramuscular or subcutaneous
  - 0.4 mg/mL, 1 mg/mL, 2 mg/mL (2016 price $14 to $24)

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Inclusion Criteria

Key Question 1-3: Randomized controlled trials, cohort studies and case-control studies conducted in out-of-hospital or ED (KQ1 and 1a) settings that reported:

Comparisons

- Injection (intramuscular, subcutaneous or intravenous) vs. intranasal route of administration [KQ1]
- Different doses of intranasal, intramuscular and intravenous naloxone [KQ1a]
- Titration of patients until they resume spontaneous respirations but have residual sedation vs. dosing of patients until they are awake and alert [KQ2]
- Differences in timing of repeat dosing [KQ3]

Outcomes

- 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)
- Adverse effects and other harms (such as rates/severity of drug withdrawal, combativeness, injury to administrator of naloxone)

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Inclusion Criteria

Key Question 4:

- Randomized controlled trials, cohort studies and case-control studies conducted in out-of-hospital settings of patients transported vs. not transported
- 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.

Additional Outcomes

- Rates of linkage to treatment for opioid use disorder [KQ4 only]
- Rates of subsequent opioid overdoses [KQ4 only]

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Literature Searches

Sources:

- MEDLINE and Cochrane Libraries through September 2017
- Reviewed materials presented at the October 5, 2016 FDA meeting on naloxone dosing
- Pharmaceutical companies invited to send unpublished data/studies
- Hand-searched reference lists of relevant studies
- Searched for unpublished or ongoing studies on ClinicalTrials.gov
- Contacted representatives of federal agencies involved in naloxone or opioid overdose research (CDC, NIDA, SAMHSA)

Process:

- Abstracts reviewed by two investigators to identify studies for full-text review
- Two investigators independently reviewed all full-text articles for final inclusion
- Studies assessed for risk of bias using predefined, study design-specific criteria
- Pooling not attempted due to small numbers of studies, heterogeneity, few RCT's
- Strength of evidence for each KQ graded as high, moderate, low, or insufficient, based on:
    - Risk of bias
    - Consistency of results across studies
    - Directness of evidence linking the intervention and health outcomes
    - Precision of estimates of effects

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Data Synthesis and Strength of Evidence Ratings

Data Synthesis

- For each study that was determined to meet inclusion criteria, a single investigator abstracted study characteristics, results relevant to each Key Question, risk of bias ratings and study funder
- Pooling of studies was not performed due to small numbers of studies for most key questions, heterogeneity between studies in populations and outcomes addressed, and methodological shortcomings in the studies, with few randomized trials

Strength of the Body of Evidence

- One investigator performed the initial strength of evidence assessment and discussed with the entire team to reach consensus.
- Graded each Key Question and comparison for prioritized clinical outcomes as ‘high,’ ‘moderate,’ ‘low,’ or ‘insufficient’
- SOE determined by:
    - Risk of bias of individual studies
    - Consistency of results across studies
    - Directness of the evidence linking the intervention and health outcomes
    - Precision of the estimate of effect

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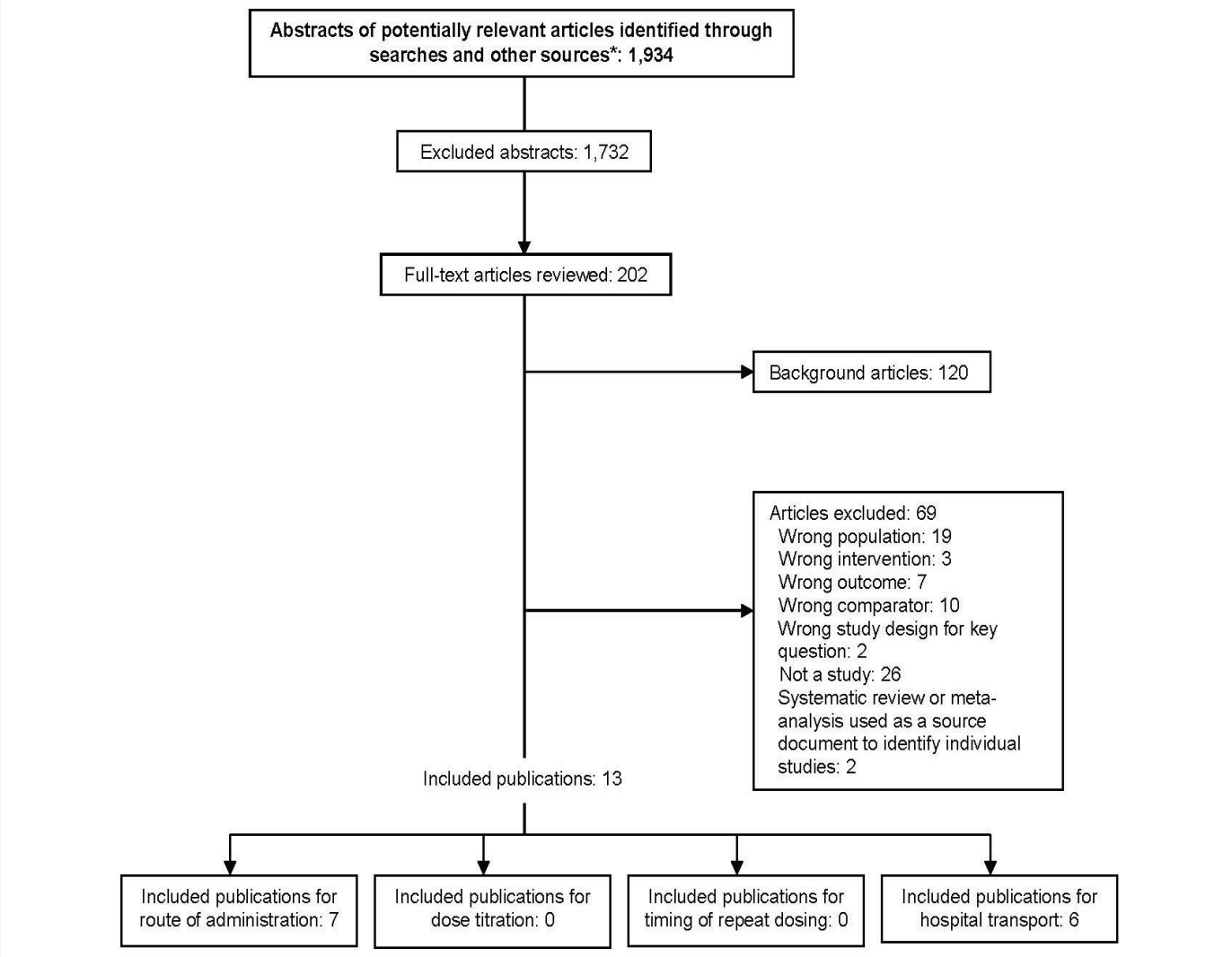
Results of Literature Searches



Results Key Question 1

Three RCTs and four cohort studies compared routes of naloxone administration

Comparison Number of Studies N	Strength of Evidence	Conclusion

IN vs. IM Naloxone
 	
2 RCTs
 	
Total N = 327 (155 and 172)
	Low	• Two Australian RCTs compared 2 mg IM vs. 2 mg IN naloxone, concentrations of IN naloxone differed from FDA-approved formulation
		• IM vs. IN (2 mg/1 mL) naloxone
		  • No difference 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 associated with increased likelihood of rescue naloxone use (18% vs. 4.5%, adjusted OR 4.8, 95% CI 1.4 to 16).
		• IM vs. IN (2 mg/5 mL) naloxone
		  • IN naloxone 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).
		  • IN naloxone associated with decreased risk of agitation and/or irritation (2.4% vs. 14%, RR 0.19, 95% CI 0.04 to 0.83).

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Results Key Question 1

Three RCTs and four cohort studies compared routes of naloxone administration

Comparison Number of Studies N	Strength of Evidence	Conclusion
IN vs. IV Naloxone 1 RCT, n=100 2 cohort studies, n=247 (93 and 154)	Insufficient	• One open-label RCT conducted in an Iranian ED setting found IN naloxone (0.4 mg, administered as a 0.4 mg/2 mL formulation) 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 (0% vs. 24%, RR 0.04, 95% CI 0.002 to 0.66). • Opium was cause of overdose in almost half of patients • Two cohort studies reported few clear differences between IN and IV naloxone, but had serious methodological shortcomings, including failure to adjust for confounders
IM vs. IV Naloxone 1 cohort, n=556	Insufficient	• No difference in likelihood of a positive response (GCS ≥14 and respiratory rate ≥10/minute within 5 minutes of naloxone administration) (94% vs. 95%; RR 1.0, 95% CI 0.94 to 1.1)
SC vs. IV Naloxone 1 cohort, n=222	Insufficient	• SC naloxone associated with longer time from administration to respiratory rate ≥10/minute (5.5 vs. 3.8 minutes, p=0.001) • No difference in time from arrival at patient's side to respiratory rate ≥10/minute (9.6 vs. 9.3 minutes, p=0.67) • SC naloxone was associated with lower likelihood than IV naloxone of requiring multiple doses (15% vs. 35%, RR 0.42, 95% CI 0.25 to 0.71)

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Results Key Questions 1a, 2 and 3

Comparison Number of Studies N	Strength of Evidence	Conclusion
Key Question 1a	Insufficient	• No study compared different doses of naloxone administered via the same route.
Key Question 2	Insufficient	• No study compared benefits and harms of titration of naloxone until the patient resumes sufficient spontaneous respiratory effort versus until the patient regains consciousness.
Key Question 3	Insufficient	• No study compared benefits and harms of differences in timing of repeat dosing of naloxone.

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Results Key Question 4

Six uncontrolled studies reported outcomes in patients who were not transported to a health care facility.

Comparison Number of Studies N	Strength of Evidence	Conclusion
Transported vs. nontransported to health care facility	Insufficient	• 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.
Not transported to health care facility 6 uncontrolled studies, n= 4,397 (552, 998, 317, 2241, 205 and 84)	Insufficient	• 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 (14/2241) 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]) • No study evaluated outcomes such as linkage to treatment for opioid use disorder or subsequent repeat opioid overdose episodes

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Conclusions

Key Findings

- 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 and effects of transport on longer-term outcomes (e.g., treatment for opioid use disorder and subsequent overdose episodes)

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Conclusions

Applicability

- All studies meeting inclusion criteria evaluated older formulations of naloxone or formulations not used in the U.S.
- No study evaluated the recently FDA-approved formulations of highly-concentrated IN naloxone
- Studies indicate very high usability rates (>90%) with the auto-injector and FDA-approved IN naloxone, even without prior training; data on usability of off-label intranasal administration of injectable naloxone not available
- All of the RCTs that compared naloxone routes of administration were conducted in non-U.S. settings (Australia and Iran)
- 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 fentanyl and fentanyl analogues

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Conclusions

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
- Future research could leverage existing EMS registries with naloxone administration data, which are available from a number of local and state agencies.
- 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 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 help inform this question

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Pacific Northwest Evidence-based Practice Center Research Team

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- Full report: https://www.effectivehealthcare.ahrq.gov/topics/emt-naloxon/systematic-review
- Journal publication: Ann Intern Med 2017;167:867-75

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Thank You