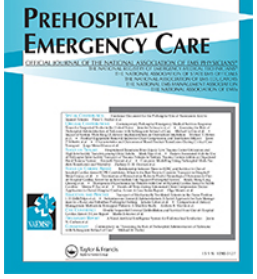

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Evidence-Based Guidelines for EMS Administration of Naloxone

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ABSTRACT

The opioid crisis is a growing concern for Americans, and it has become the leading cause of injury-related death in the United States. An adjunct to respiratory support that can reduce this high mortality rate is the administration of naloxone by Emergency Medical Services (EMS) practitioners for patients with suspected opioid overdose. However, clear evidence-based guidelines to direct EMS use of naloxone for opioid overdose have not been developed. Leveraging the recent Agency for Healthcare Research and Quality (AHRQ) systematic review on the EMS administration of naloxone for opioid poisonings, federal partners determined the need for a clinical practice guideline for EMS practitioners faced with suspected opioid poisoning. Project funding was provided by the National Highway Traffic Safety Administration, Office of EMS, (NHTSA OEMS), and the Health Resources and Services Administration, Maternal and Child Health Bureau's EMS for Children Program (EMSC). The objectives of this project were to develop and disseminate an evidence-based guideline and model protocol for administration of naloxone by EMS practitioners to persons with suspected opioid overdose. We have four recommendations relating to route of administration, all conditional, and all supported by low or very low certainty of evidence. We recommend the intravenous route of administration to facilitate titration of dose, and disfavor the intramuscular route due to difficulty with titration, slower time to clinical effect, and potential exposure to needles. We equally recommend the intranasal and intravenous routes of administration, while noting there are variables which will determine which route is best for each patient. Where we are unable to make recommendations due to evidence limitations (dosing, titration, timing, and transport) we offer technical remarks. Limitations of our work include the introduction of novel synthetic opioids after many of the reviewed papers were produced, which may affect the dose of naloxone required for effect, high risk of bias and imprecision in the reviewed papers, and the introduction of new naloxone administration devices since many of the reviewed papers were published. Future

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While this manuscript was reviewed and shaped by many members of the Technical Expert Panel (TEP or Panel), only those meeting the criteria for authorship by the International Committee of Medical Journal Editors (ICMJE) have been listed as authors. We wish to acknowledge the work of other contributors, including Project Coordinator Zoe Renfro, whose technical editing skills made this document possible, and Mary Hedges, Program Manager, whose coordination and organizational skills facilitated the work of the TEP. The members of the TEP, their expertise and affiliations, are available in Table 1.

The contents of this report are solely the responsibility of the authors and do not necessarily represent the official views of NHTSA.

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James Gasper, Ashish Panchal, John Gouda, Peter Taillac, and Mary Hedges report no conflict of interest. Eddy Lang reports receiving an honorarium from NASEMSO for the support he provided this project as a GRADE methodologist. Kenneth A Williams reports receiving an honorarium from NASEMSO for his leadership of the project.

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research should be conducted to evaluate new devices and address the introduction of synthetic opioids. **Key words:** naloxone; opioid-related disorders; narcotic antagonists; drug overdose; emergency medical services; evidence-based emergency medicine

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BACKGROUND

Impact of the Opioid Crisis

Rates of opioid overdose (OD) in the United States have increased fourfold since 2000, with data for 2016 indicating that over 42,000 died from opioid overdose that year alone (1). In 2016, opioid overdose deaths (2) overtook traffic crashes (3) as the leading cause of death by traumatic injury in the United States. In recent years, synthetic opioids, predominantly illicitly-manufactured fentanyl and its analogs, have overtaken prescription opioids and heroin as the leading cause of overdose deaths (1). In 2017, the sharpest increase in drug overdose fatalities was related to fentanyl and fentanyl analogs, representing nearly 30,000 overdose deaths (1). As many opioid overdose patients are discovered by family and close friends (4), the US Surgeon General issued an advisory urging more Americans to carry naloxone to combat the opioid crisis (5). The opioid epidemic has widespread impact on the population at large, affecting family and friends, employers and coworkers, and others who know overdose patients. Factors which contribute to the crisis include substance use disorders, mental health disorders such as depression and bipolar disorder, chronic pain, relapse after a period of abstinence during drug treatment or incarceration and polypharmacy (6, 7).

A drastic burden is placed on society as more resources and personnel are allocated to combat this epidemic. Between 2012 and 2016, the rate of naloxone administration by EMS increased 75.1%, from 573.6 to 1004.4 per 100,000 EMS events (8). The increased rate of administration of naloxone mirrors the overdose mortality rate (8). A retrospective study which analyzed data from Northern New England revealed that basic life support (BLS) practitioners were as effective as advanced life support (ALS) practitioners in naloxone administration (9). The role of first responders has expanded to include identification and management of the effects of opioid toxicity through supportive management as well as reversal through the administration of naloxone (10).

Management of Opioid Overdose

For EMS practitioners who suspect an opioid overdose, the first step is to evaluate the extent of the patient's respiratory depression. Overdoses of opioids are associated with both central nervous system (CNS) and respiratory depression, making the primary risk of death inadequate oxygenation and ventilation, which can decompensate to cardiac arrest. In many situations, it may not be readily apparent if a patient is suffering an opioid overdose versus respiratory depression due to other etiologies or co-ingestions. Due to these concerns, the patient's airway and respiratory mechanics must be assessed immediately upon patient contact and supported with airway maneuvers and ventilation (e.g., bag-valve-mask) as indicated. Even when naloxone is clinically indicated, respiratory support should be given first or at least contemporaneously. Bag-valve-mask ventilation, incorporating oropharyngeal or nasopharyngeal airways to promote a patent airway, should be used to provide adequate oxygenation and ventilation until the patient is able to breathe adequately without support. In cases where the response to naloxone is inadequate, further airway management may be required, such as a supraglottic airway device or endotracheal tube placement (if within applicable scopes of practice). In other cases, respiratory support may result in recovery as accumulated carbon dioxide is purged, and naloxone may not be necessary.

Naloxone. Naloxone is a mu-opioid receptor antagonist effective at reversing the symptoms of opioid toxicity and associated life-threatening respiratory depression. First synthesized in 1961, naloxone was approved for use in 1971 as an opioid reversal agent, and EMS practitioners began administering naloxone shortly thereafter (11). The need for rapid access to naloxone in the community has expanded naloxone use to include both first responders and laypersons in the out of hospital setting (12). Common routes of naloxone administration include intravenous (IV), intramuscular (IM), subcutaneous (SQ), and intranasal (IN). Two Food and Drug Administration (FDA) approved products for layperson use have been developed: an autoinjector for IM administration and a commercial nasal spray with a bioavailability of approximately 50% relative to IM (13).

Naloxone has a rapid onset of action, reaching maximal serum concentration within 2 minutes after IV administration, 10 minutes after IM, and 15–30 minutes after IN (14). Naloxone distributes to the central nervous system and equilibrates with the plasma within minutes (15). Naloxone is extensively metabolized in the liver to inactive metabolites with

a serum half-life of 30–90 minutes (15). Naloxone is an extremely safe medication but can precipitate opioid withdrawal symptoms including agitation or irritability, anxiety, body aches, nausea or vomiting, diarrhea, piloerection, rhinorrhea, and sweating. More severe reactions are extremely rare but may include acute respiratory distress syndrome (ARDS), hypertensive emergency, ventricular tachycardia and fibrillation, and sudden death (16). Dosing of naloxone is based on the goal of restoring adequate respiratory function while minimizing the risk of opioid withdrawal symptoms, which is best accomplished with dose titration and careful monitoring when conditions permit.

Presence of Other Substances and Opioids. An apparently inadequate response to initial dosing of naloxone could be the result of co-ingestants, such as ethanol or benzodiazepines. Additionally, some extremely powerful fentanyl analogs, such as carfentanil or acetyl fentanyl, as well as the opioid partial agonist buprenorphine, may require larger than usual or repeat doses of naloxone to achieve adequate respiratory function and are increasingly involved in opioid overdoses.

Occupational Exposure. The potential for occupational exposure to fentanyl and its analogs has created distinct concern among public safety and EMS practitioners. Therefore, it is important that practitioners utilize appropriate practices and personal protective equipment (PPE) when potentially in the presence of opioids in a form that could pose toxicity. In responding to most suspected opioid overdoses, standard PPE medical gloves are sufficient protection. Credible resources exist to advise public safety and EMS professionals and include the American College of Medical Toxicology's *Statement on Fentanyl Exposure* (17).

Project Objectives

The objectives of this project were to develop and disseminate an evidence-based guideline and model protocol for administration of naloxone by Emergency Medical Services (EMS) practitioners to persons with suspected opioid overdose. Also included in the objectives were the development of training materials for EMS practitioners in implementing the guideline, the creation of performance measures by which adherence to the clinical practice guideline and its impact could be assessed, and the development of a manuscript for publication in a peer-reviewed scientific journal. This paper describes the process by which the evidence-based guideline was developed.

Methods

The Institute of Medicine report on trustworthy clinical practice guidelines has made clear that the development of recommendations intended to improve care are to be based on a systematic review of the scientific literature (18). While systematic reviews are the optimal means of evaluating and synthesizing the existing scientific evidence to inform clinical questions, this information alone is insufficient. This clinical practice guideline was developed as a follow-up to the Agency for Healthcare Research and Quality (AHRQ) systematic review on the prehospital administration of naloxone for opioid poisonings that occur in the field (10). This evidence was given in-depth consideration by a panel of relevant stakeholders to develop concise recommendations based on GRADE methodology.

In August 2016, the National EMS Advisory Council (NEMSAC) recommended that the National Highway Traffic Safety Administration develop an evidence-based guideline regarding administration of naloxone by EMS clinicians. The advisory was approved and published after the September 2016 National EMS Advisory Council meeting (19). The current project was developed in the fall of 2017 by the Medical Directors Council of the National Association of State EMS Officials (NASEMSO) in collaboration with the National Association of EMS Physicians (NAEMSP) and the EMS Committee of the American College of Emergency Physicians (ACEP). A Technical Expert Panel (TEP or Panel) was assembled, which included experienced EMS field practitioners, EMS physician medical directors, experts in addiction medicine, pain medicine, toxicology/pharmacology, and GRADE methodologies, as well as a patient advocate (see Table 1: Members of Expert Panel). Funding was provided by the National Highway Traffic Safety Administration, Office of EMS, and the Health Resources and Services Administration, Maternal and Child Health Bureau's EMS for Children Program.

The project scope of work focused on translating the systematic review published by the Agency for Healthcare Research and Quality (AHRQ) in November 2017 into an evidence-based guideline and model protocol for administration of naloxone by EMS practitioners to persons suspected of an opioid overdose (10). This was done through review of the Population Intervention Comparison Outcome (PICO) questions addressed in the

TABLE 1. Members of Technical Expert Panel

Name	Area(s) of Expertise	Institution
James Gasper, PharmD, BCPP	Pharmacology	Pharmacy Benefits Division, California Department of Health Care Services
Jeffrey Goodloe, MD *Co-Investigator (ACEP)*	EMS Medical Direction Emergency Medicine	American College of Emergency Physicians (ACEP) Emergency Medical Services System for Metropolitan Oklahoma City & Tulsa Oklahoma Center for Prehospital & Disaster Medicine
Richard Hale	Performance Measure Development	ESO Solutions
Vicki L. Hildreth, BA, EMT-B	Patient Advocate EMS Clinician Pediatrics	WV Department of Health & Human Resources
Eddy Lang, MDCM, CCFP (EM)	EBG Development Emergency Medicine GRADE Methodology	Emergency Medicine Department, Cumming School of Medicine, University of Calgary, Alberta Health Services
John W. Lyng, MD, EMT-P *Co-Investigator (NAEMSP)*	EMS Medical Direction Emergency Medicine	North Memorial Health Ambulance & Air Care (Minneapolis, MN) National Association of EMS Physicians (NAEMSP)
Anne Montera, RN, BSN*	Patient Advocate	Caring Anne Consulting, LLC
Ashish R. Panchal, MD, PhD	Emergency Medicine EMS Medical Direction Research	National Registry of EMTs (NREMT) Department of Emergency Medicine, The Ohio State University Wexner Medical Center
Tim Seplaki, NRP*	EMS Clinician	NJ Department of Health, Office of EMS
Sharon Stancliff, MD	Addiction Medicine	Harm Reduction Coalition
Nate Sullivan, EMT-P*	EMS Clinician	Cherokee County Fire & Emergency Services
Peter Taillac, MD	EMS Medical Direction Prehospital Guidelines Consortium EBG Development Performance Measure Development	Bureau of EMS and Preparedness, Utah Department of Health
Debbie Vass, RN, EMT-P	EMS Administration Clinician Performance Measure Development	Sunstar Paramedics Paramedics Plus
Kenneth A Williams, MD *Principal Investigator (NASEMSO)*	EMS Medical Direction Emergency Medicine	Brown Department of Emergency Medicine Rhode Island Dept. of Health National Association of State EMS Officials (NASEMSO)

Staff and Federal Partner Support: Mary Hedges, Project Manager; Zoe Renfro, Project Coordinator; Dia Gainor, NASEMSO Executive Director; Dave Bryson, NHTSA Office of EMS; Jeremy Kinsman*, NHTSA Office of EMS; Cathy Gotschall, NHTSA Office of EMS
*New members added in April 2018. Most members were added in November 2017.

systematic review and the evidence identified by the searches. The PICO questions addressed by the AHRQ systematic review are listed in Table 2. Following PICO question and evidence review, the TEP used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to summarize the evidence and assess the strength of the literature and develop treatment recommendations. GRADE is emerging as the most widely used system for clinical practice guideline development (20). It has been endorsed as an optimal method for guideline development in the EMS environment (21). The advantages of the GRADE approach include an outcome-centric analysis of the certainty of evidence as well as a transparent and explicit means of conveying judgements and recommendations through evidence profile tables and evidence to decision (EtD) tables. GRADE also establishes clear and reproducible approaches to the assessment of certainty in evidence, and the direction and strength of recommendations.

Evidence Review

This work leverages the published AHRQ systematic review on the *Management of Suspected Opioid Overdose with Naloxone by Emergency Medical Services Personnel* (10). The review synthesized the data from inception of databases to September 2017 on four key areas: (question 1) route of administration of naloxone; (question 2) titration of naloxone dosing to specific therapeutic endpoints (e.g. spontaneous ventilation); (question 3) timing of repeat dosing of naloxone; and (question 4) transportation or non-

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