Pulmonary Complications of Opioid Overdose Treated With Naloxone

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Study objective: We aim to determine whether administration of higher doses of naloxone for the treatment of opioid overdose is associated with increased pulmonary complications.

Methods: This was a retrospective, observational, cross-sectional study of 1,831 patients treated with naloxone by the City of Pittsburgh Bureau of Emergency Medical Services. Emergency medical services and hospital records were abstracted for data in regard to naloxone dosing, route of administration, and clinical outcomes, including the development of complications such as pulmonary edema, aspiration pneumonia, and aspiration pneumonitis. For the purposes of this investigation, we defined high-dose naloxone as total administration exceeding 4.4 mg. Multivariable analysis was used to attempt to account for confounders such as route of administration and pretreatment morbidity.

Results: Patients receiving out-of-hospital naloxone in doses exceeding 4.4 mg were 62% more likely to have a pulmonary complication after opioid overdose (42% versus 26% absolute risk; odds ratio 2.14; 95% confidence interval 1.44 to 3.18). This association remained statistically significant after multivariable analysis with logistic regression (odds ratio 1.85; 95% confidence interval 1.12 to 3.04). A secondary analysis showed an increased risk of 27% versus 13% (odds ratio 2.57; 95% confidence interval 1.45 to 4.54) when initial naloxone dosing exceeded 0.4 mg. Pulmonary edema occurred in 1.1% of patients.

Conclusion: Higher doses of naloxone in the out-of-hospital treatment of opioid overdose are associated with a higher rate of pulmonary complications. Furthermore, prospective study is needed to determine the causality of this relationship. [Ann Emerg Med. 2019;■:1-10.]

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INTRODUCTION

Background

Pulmonary complications are among the most frequently reported adverse events after opioid overdose and include a wide array of conditions.[1] One of these is permeability pulmonary edema, also referred to as noncardiogenic pulmonary edema, defined as the accumulation of alveolar fluid caused by increased capillary permeability. Pulmonary edema has been described after the use of naloxone to reverse sedation with opioids.[2,3] It has also been described as a complication of heroin and fentanyl intoxication without the use of naloxone.[4-6] Reversal of opioid intoxication with naloxone has been implicated in intrinsically causing pulmonary edema through several theorized mechanisms. One hypothesized physiologic cause is negative pressure resulting from inspiration against a closed glottis.[7] Alternatively, increased capillary permeability or pulmonary arterial pressure caused by a catecholamine surge from precipitated withdrawal or sudden cerebral recognition of hypoxia has been proposed to link naloxone administration to pulmonary edema.[8]

In addition to pulmonary edema, aspiration is commonly encountered under these circumstances. In fact, aspiration events are among the most frequent complications of heroin overdose requiring ICU admission, with the potential to cause pneumonitis, pneumonia, or acute respiratory distress syndrome.[9-11] Acute respiratory distress syndrome is the most severe complication and, as established by the Berlin Criteria, is defined as respiratory failure (Pa_{O_2}/Fi_{O_2} ratio <300 while the patient is receiving assisted ventilation with >5 cm H_2O of positive end expiratory pressure) occurring within 7 days of an inciting event because of pulmonary edema, with the respiratory failure not fully explained by heart failure or fluid overload. Naloxone reversal has been proposed to place patients at risk for aspiration pneumonia caused by vomiting from precipitated withdrawal.[12]

There is considerable diagnostic and clinical overlap between the pulmonary complications of opioid overdose

Editor's Capsule Summary

What is already known on this topic

Naloxone is increasingly used by bystanders, law enforcement, and out-of-hospital providers for patients with suspected opioid overdose.

What question this study addressed

This retrospective review of 1,831 patients who received out-of-hospital naloxone from emergency medical services, bystanders, or law enforcement evaluated the risk for pulmonary complications.

What this study adds to our knowledge

Although pulmonary edema after naloxone is unusual, there seems to be a dose-response relationship between naloxone and pulmonary aspiration.

How this is relevant to clinical practice

Although this association may not be causal, whether it is a more cautious approach to out-of-hospital naloxone administration with attentiveness to airway protection should be evaluated.

and reversal, increasing the challenge of defining, preventing, and treating these disease entities. It is plausible that some or all of these mechanisms are exaggerated by higher doses of naloxone.

Importance

Deaths from drug overdose in the United States continue to increase, having reached a rate of 19.8 per 100,000 in 2017, driven primarily by fentanyl and its analogues.[13] Simultaneously, the hospitalization rate for complications of opioid overdose has increased, reaching 295.6 hospitalizations per 100,000 people per year as of 2012.[14] These trends establish a clear need to identify risk factors for complications of opioid overdose, as well as optimize strategies for preventing and diagnosing these complications.

Goals of This Investigation

We aimed to evaluate whether higher doses of out-of-hospital naloxone are associated with an increased risk of pulmonary complications, including pulmonary edema and aspiration events. Our secondary objective was to assess for associations between pulmonary complications and other clinical factors, such as the involved opioid or vital sign abnormalities.

MATERIALS AND METHODS

Study Design and Setting

This was a retrospective, observational, cross-sectional study of patients provided naloxone in the out-of-hospital setting and subsequently transported to emergency departments (EDs) within an urban, academic medical system. This study was approved by the institutional review board of the University of Pittsburgh. Patients were treated and transported by the City of Pittsburgh Bureau of Emergency Medical Services. During the study period, this was an all–advanced life support agency, with each ambulance staffed by 2 paramedics. Additionally, the Pittsburgh Bureau of Fire provides first-responder services. Both first responders and emergency medical services (EMS) providers can administer naloxone, first responders by the intranasal route and EMS providers by intranasal, intramuscular, or intravenous routes. Intranasal naloxone was administered by 2 mg/2 mL syringe. Statewide EMS protocols from the Pennsylvania Department of Health guide care in this EMS system and currently include standing orders for the administration of up to 4.4 mg of naloxone in titrated doses (0.4 mg by the intravenous/intraosseous route or 2 mg by the intramuscular/intranasal route), although during the study period the maximum total dose was only 2 mg. Under either protocol, additional doses may be administered under a medical command physician order. Medical command orders for the City of Pittsburgh EMS are provided through a centralized medical communications center at the University of Pittsburgh Medical Center.

Selection of Participants

From April 1, 2013, through December 31, 2016, the City of Pittsburgh EMS patient care records (emsCharts, Warrendale, PA) were selected for inclusion by a text word search in the history of present illness field for the words "naloxone" or "Narcan," or a coded entry of naloxone administration either before arrival or by EMS. The date range was based on availability of records after a transition to using emsCharts. The search was limited to patients transported to 1 of 3 large EDs within the University of Pittsburgh Medical Center health system, where there was access to inpatient records. During 2014 to 2016, these 3 hospitals were the destination facility for 63% of all adult patients transported by the City of Pittsburgh EMS. These EMS patient care reports were then manually reviewed and included if any naloxone administration was provided by bystanders, first responders, or EMS. Out-of-hospital records were manually linked with inhospital records by use of any

available identifiers, including name, date of birth, age, sex, date of service, and receiving hospital. Patient records were excluded if a corresponding hospital chart could not be located or naloxone was not actually given. During the study period, heroin and fentanyl (and its analogues) were the drugs most commonly found in reported overdose decedents, having been found in 58.1% (962/1,656) and 38.1% (631/1,656), respectively, according to Allegheny County Medical Examiner data. During the study period, the presence of fentanyl and its derivatives in decedents increased markedly, from less than 1% in 2013 to 65.4% in 2016.[15]

Methods of Measurement

Patient data were abstracted from EMS records by 3 research assistants and an emergency physician (C.M.-G.). The data abstracted included patient demographic information (Table 1) and data about their clinical course (Tables 2 and 3). Hospital data were abstracted by 3 emergency physicians (A.F., R.W., and J.G.), who directly reviewed the hospital records and were blinded to the EMS records. The physician abstractors determined whether the ultimate diagnosis was likely to have been opioid overdose, considering the history from the patient or paramedics (eg, admitted use of heroin or patient found near drug paraphernalia), degree of response to naloxone, and presence of an alternative diagnosis to explain the patient presentation, such as hypoglycemia, seizure, or intoxication with a nonopioid. In ambiguous cases, urine drug testing results were occasionally used to assist in determining whether the patient overdosed on an opioid but were not relied on. A κ score was calculated to assess interreviewer agreement in regard to the determination of opioid overdose versus nonopioid overdose. If available, the likely identity of the opioid involved was collected as well. All data were abstracted into Excel (version 1808; Microsoft, Redmond, WA).

Outcome Measures

The primary outcome was a composite one for the presence of any of the following pulmonary findings: pulmonary edema, aspiration pneumonia, and aspiration pneumonitis. The secondary outcome was a subset of the above, examining pulmonary edema only. Both outcomes were based on chest radiograph or computed tomography scan results per official radiologist interpretation, or the clinical diagnosis documented by the treating physician(s). In some cases, radiologists provided a differential diagnosis rather than a single one. In these ambiguous cases, classification as pulmonary edema or other pulmonary complication was made by consensus of A.F. and C.M.-G after review of the clinical course, bronchoscopy results, or repeated imaging.

Primary Data Analysis

The primary analysis was intended to identify an association between out-of-hospital naloxone dosage and pulmonary complications. We performed a univariate analysis for the association of candidate variables with the outcomes of interest. Because our objective was to evaluate the safety of the current protocol, the primary exposure of interest was defined as out-of-hospital naloxone administration in excess of the current state EMS protocol dose, which allows a maximum dose of 4.4 mg without medical control authorization (titrated doses of 0.4 mg intravenously/intraosseously or 2 mg intramuscularly/intranasally in succession) (Appendix E1, available online at http://www.annemergmed.com). During the study period, the state treatment protocol differed, specifying that the above naloxone doses could be administered to a maximum of 2 mg (Appendix E2, available online at http://www.annemergmed.com). Neither protocol, however, accounts for administration of naloxone by first responders or bystanders toward the maximum total dose, and both allow additional naloxone to be given with authorization from medical command. Given the difference between the current and previous treatment protocols, as well as to provide greater generalizability, we performed a sensitivity analysis wherein a high total dose of naloxone was defined as greater than 2 mg. We also performed a secondary analysis with patients receiving an initial dose of naloxone, by any route, of greater than or equal to 0.4 mg. We then conducted a multivariable analysis using a logistic regression model to assess the association between total and initial naloxone dose and the composite outcome of pulmonary complications, accounting for potential confounders such as pretreatment Glasgow Coma Scale (GCS) score and vital signs, but not hospital vital signs, identified in the univariate analysis. Data were analyzed with Stata (version 15.1; StataCorp, College Station, TX). Statistical significance was assessed with the Mann-Whitney test for quantitative variables and Fischer's exact test for parametric variables. Two additional sensitivity analyses were performed: one excluded patients who were ultimately deemed to have received naloxone for a condition other than opioid overdose, such as alcohol intoxication, and another excluded any records with incomplete data.

RESULTS

Characteristics of Study Subjects

A total of 1,980 EMS patient records were identified. We excluded 79 cases for incomplete or missing hospital records and 70 cases in which naloxone was not administered (Figure). The study cohort comprised 1,831 cases, including 1,456 likely opioid overdoses and 375 unlikely opioid overdoses. The κ score was 0.59, indicating significant agreement between reviewers about whether patients had overdosed on an opioid. The mean total dose of naloxone was 2.5 mg (SD 1.5 mg). The demographic data and clinical characteristics for these patients are presented in Table 1. The intubation rate for the study population was high (8.8%), but a majority of intubations (90) were performed on patients who received naloxone for mental status change caused by something other than opioid overdose, such as severe sepsis or intracranial hemorrhage. Excluding these, the overall intubation rate was much lower (4.9%).

Main Results

A total of 485 cases (26.5%) met criteria for the composite outcome of pulmonary complications. Most cases (461/485) were diagnosed as aspiration pneumonitis or pneumonia. In univariate analysis, patients receiving more than 4.4 mg naloxone experienced pulmonary complications 42% of the time compared with 26% for those receiving smaller doses (odds ratio [OR] 2.14; 95% confidence interval [CI] 1.44 to 3.18), a relative difference of 62%. Patients receiving an initial naloxone dose of greater than 0.4 mg also had a higher rate of pulmonary complications compared with those who received less (27% versus 13%; OR 2.57; 95% CI 1.45 to 4.54). Other factors associated with pulmonary complications included intranasal naloxone administration (at least one dose), emesis after naloxone administration, decreased GCS score before naloxone, heroin as the suspected overdose agent, decreased pulse oximetry before naloxone, and increased pulse rate or decreased oxygen saturation on hospital arrival (Table 2). We found no association between pulmonary complications and patient age, sex, race, ethnicity, out-of-hospital cardiopulmonary resuscitation (CPR), temperature on ED arrival, and out-of-hospital or ED blood pressure.

A sensitivity analysis excluding the patients who did not overdose on an opioid did not significantly alter the association between total naloxone dosage greater than 4.4 mg and the composite outcome of pulmonary complications (OR 2.08; 95% CI 1.38 to 3.14). After removal of cases of nonopioid overdose, heroin was no longer statistically significantly associated with pulmonary complications (OR 1.19; 95% CI 0.90 to 1.59), suggesting that the effect observed before the sensitivity analysis may have been identifying the risk of opioid exposure that was not specific to heroin. Using a cutoff of 2 mg for high naloxone dosing rather than 4.4 mg still showed a statistically significant association with pulmonary complications (34% versus 15%; OR 1.66; 95% CI 1.33 to 2.06).

In the multivariable analysis accounting for potential confounders (Table 4), the association between naloxone dosage exceeding 4.4 mg and pulmonary complications persisted (OR 1.85; 95% CI 1.12 to 3.04), as did the association with an initial dose greater than 0.4 mg (OR 2.02; 95% CI 1.07 to 3.80).

There were 24 cases of pulmonary edema, representing 1.1% of the study cohort who received naloxone. Six of these cases were among the 375 cases in which naloxone was likely administered for a condition other than opioid overdose, an incidence of 1.6%. In each of these 6 cases, an explanation for pulmonary edema not related to opioid exposure was identified, such as cocaine toxicity, preexisting congestive heart failure, or a cardiac arrest ultimately deemed unrelated to an opioid overdose. The rate of pulmonary edema in patients with suspected opioid overdose was 1.2%. Among the 18 patients treated for opioid overdose who developed pulmonary edema, 8 (44%) were treated with positive-pressure ventilation by bilevel positive airway pressure, intubation, or both and met Berlin Criteria for acute respiratory distress syndrome. Ten patients (56%) received supplemental oxygen by nasal cannula or nonrebreather mask. One patient (5%) had radiographic evidence of pulmonary edema, but no hypoxia requiring supplemental oxygen.

The risk of pulmonary edema appeared higher in the group receiving greater than 4.4 mg of total naloxone (OR 2.23; 95% CI 0.65 to 7.60) or an initial dose greater than 0.4 mg (OR 1.51; 95% CI 0.20 to 11.30), but these results were not statistically significant. Results were similar when cases that were not opioid overdoses were excluded. There were several statistically significant associations identified with other clinical characteristics measured (Table 4). Because of the small number of patients with pulmonary edema, multivariable analysis was not performed.

LIMITATIONS

The primary limitation of this study is its retrospective nature, which constrains the ability to make conclusions in regard to the causality of the relationship between naloxone dosage and pulmonary complications; the use of a multivariate analysis to account for confounders mitigates but does not eliminate this limitation. Similarly, the

Table 1. Demographics and clinical characteristics.

Characteristic	All Patients (n=1,831)	Patients With Pulmonary Complications (n=485)	Patients Without Pulmonary Complications (n=1,346)	Patients With Pulmonary Edema (n=24)	Patients Without Pulmonary Edema (n=1,807)
Age, mean (SD), y	40 (15)	40 (15)	41 (15)	38 (15)	41 (15)
Men	1,224 (67)	338 (70)	886 (66)	17 (71)	1,207 (67)
Race					
White	1,350 (75)	342 (71)	1,008 (76)	20 (91)	1,329 (75)
Black	430 (24)	127 (27)	303 (23)	2 (9)	428 (24)
Other	26 (1)	10 (2)	16 (1)	0	26 (1)
Ethnicity					
Non-Hispanic	1,778 (99)	473 (99)	1,305 (99)	23 (100)	1,755 (99)
Hispanic	19 (1)	4 (1)	15 (1)	0	19 (1)
Total naloxone dose (SD), mg	2.5 (1.5)	2.9 (1.7)	2.4 (1.4)	3.4 (2.8)	2.5 (1.5)
Death before discharge	36 (2.0)	6 (1.2)	30 (2.2)	1 (4.2)	35 (1.9)
Intubation	162 (8.8)	44 (9.1)	118 (8.8)	6 (25)	156 (8.6)
Chest radiograph	312 (17)	162 (33)	437 (32)	24 (100)	577 (32)
Hospital admission	526 (29)	120 (25)	406 (30)	23 (96)	503 (28)

Data are presented as No. (%) unless otherwise indicated.

decisions to obtain imaging or perform other interventions such as intubation could represent additional independent variables affecting the observed rate of complications (eg, confounding by indication). The decision to obtain radiographic data is a prerequisite to identifying a radiographic outcome and is in turn influenced by the decision to intubate. Additionally, any study using historical records depends on the accuracy and fidelity of those records, which is not ensured. Because this study was performed with records from hospitals in one city, the generalizability of the results may be limited because of EMS practice variation, region-specific demographics, differences in the local drug supply, and other factors. Diagnosis of pulmonary complications depended on radiologist interpretation of imaging and the clinical impression of treating physicians, which can vary. This may have affected the reported rate of aspiration complications versus pulmonary edema. Finally, the study evaluated the presence of radiographic or initial clinical diagnosis of pulmonary complications; an increased rate of radiographic findings may or may not be clinically significant in the absence of more detailed outcomes data.

DISCUSSION

Previous research about empiric naloxone administration by EMS has demonstrated safety, with a low overall complication rate.[16] However, that study was performed before the advent of bystander- and first-responder-administered naloxone, and significantly lower doses of naloxone were used overall (0.9 mg [SD 0.6 mg]). In the setting of expanded nonmedical access to naloxone, as well as evolving and diversified illicit opioid availability, we identified an association between higher cumulative and initial naloxone dosing in out-of-hospital treatment of opioid overdose and pulmonary complications.

Our composite outcome of pulmonary complications included cases of pulmonary edema, aspiration pneumonitis, and aspiration pneumonia, with 8 (44%) of the pulmonary edema cases meeting Berlin Criteria for acute respiratory distress syndrome. We combined these in our analysis for several reasons. First, there is often diagnostic ambiguity between these clinical entities. Second, there is significant potential for overlap in the pathogenesis of pulmonary edema, aspiration pneumonia or pneumonitis, and acute respiratory distress syndrome because of effects of opioid overdose, and several of these effects could be modulated by naloxone reversal. Specifically, aspiration pneumonia could result from opioid overdose directly or from vomiting caused by precipitated withdrawal because of naloxone. Acute respiratory distress syndrome can be caused directly by aspiration of gastric contents, by pneumonia subsequent to aspiration events, or by catecholamine effects caused by the hypoxia of overdose

Table 2. Univariate analysis of out-of-hospital factors potentially associated with pulmonary complications of opioid overdose.

Characteristic	All Cases (n=1,831)	Pulmonary Complications (n=485)	No Pulmonary Complications (n=1,346)	OR (95% CI)
Age, mean (SD), y	41 (15)	40 (15)	41 (15)	0.996 (0.989 to 1.003)
Men	1,221 (67)	338 (70)	883 (66)	1.21 (0.96 to 1.51)
Race				
White	1,350 (75)	342 (71)	1,008 (76)	1 [Reference]
Black	430 (24)	127 (27)	303 (23)	1.24 (0.97 to 1.57)
Other	26 (1)	10 (2)	16 (1)	1.84 (0.83 to 4.10)
Ethnicity				
Non-Hispanic	1,778 (99)	473 (99)	1,305 (99)	1 [Reference]
Hispanic	19 (1)	4 (1)	15 (1)	0.74 (0.24 to 2.23)
Total naloxone dose >4.4 mg	109 (6.1)	46 (9.7)	63 (4.8)	2.14 (1.44 to 3.18)
Initial naloxone dose >0.4 mg	1,666 (94)	457 (97)	1,209 (93)	2.57 (1.45 to 4.54)
Route				
Any intramuscular	913 (50)	271 (56)	642 (48)	1.32 (1.14 to 1.53)
Any intranasal	1,190 (65)	357 (74)	833 (62)	1.52 (1.26 to 1.84)
Any intravenous/intraosseous	738 (40)	160 (33)	578 (43)	0.76 (0.65 to 0.89)
CPR	111 (6.1)	23 (4.7)	88 (6.5)	0.71 (0.44 to 1.14)
Emesis after naloxone administration	43 (2.3)	18 (3.7)	25 (1.9)	2.03 (1.10 to 3.76)
Initial hypertension (SBP >160 mm Hg)	196 (11)	52 (11)	144 (11)	1.00 (0.72 to 1.40)
Heroin use suspected	1,151 (63)	342 (71)	809 (60)	1.59 (1.27 to 1.99)
Initial oxygen saturation, mean (SD), %	90 (17)	88 (18)	91 (16)	2.80 (1.064 to 4.536)
Initial GCS score, mean (SD)	8 (5)	8 (5)	9 (5)	0.992 (0.972 to 1.012)
Temperature (hospital), mean (SD), °C	36.7 (0.6)	36.7 (0.6)	36.7 (0.6)	1.113 (0.910 to 1.362)

SBP, Systolic blood pressure.

potentially amplified by naloxone reversal.[17] Third, we suspect that an association between repeated naloxone administration and pulmonary complications may also result in part from delays in the management of a patient's compromised airway and ventilation in favor of giving antidotal therapy. Assisted ventilation or airway control might be more effective in treating the opioid-intoxicated patient by preventing aspiration or prolonged hypoxia.

The pathophysiology of pulmonary edema in the setting of opioid overdose treated with naloxone is controversial. Pulmonary edema has been described as an adverse effect of opioid intoxication without naloxone administration.[5,6] However, there is evidence to support either a direct or additive effect of naloxone in causing this outcome. An article by Mills et al[12] examined the additive cardiovascular effects of naloxone reversal in an animal model of opioid toxicity. In this study, catecholamine levels in intubated dogs increased when fentanyl was given to induce hypercarbia, but this effect was significantly exaggerated when naloxone reversal was also given. Catecholamine surges may be amplified by sudden autonomic recognition of elevated carbon dioxide levels, which then induce pulmonary arterial hypertension and increased capillary permeability. Opioid withdrawal precipitated by naloxone reversal could also abruptly increase catecholamine levels. There is precedent for pulmonary edema to be caused by sudden catecholamine excess in previously healthy patients, which is the suggested mechanism for neurogenic pulmonary edema, a potentially similar disease process.[18] Alternatively, sudden forced inspiration against an obstructed airway has been postulated to produce sufficient negative pressure to cause fluid accumulation within air spaces.[7]

There is both a theoretic basis and previous research to suggest that patients may be receiving unnecessarily high amounts of naloxone in the out-of-hospital setting. Smaller doses of naloxone (0.04 to 0.12 mg) can be effective in reversing opioid-induced respiratory depression, and naloxone administration results in rapid, but not immediate, improvement in toxicity.[19] This slight delay

Table 3. Univariate analysis of factors potentially associated with pulmonary edema.

Characteristic	All Cases (n=1,831)	Pulmonary Edema (n=24)	No Pulmonary Edema (n=1,807)	OR (95% CI)
Age, mean (SD), y	41 (15)	38 (15)	41 (15)	0.976 (0.956 to 1.014)
Men	1,221 (67)	17 (71)	1,207 (67)	1.21 (0.50 to 2.95)
Race				
White	1,350 (75)	21 (91)	1,329 (75)	1 [Reference]
Black	430 (24)	2 (9)	428 (24)	0.29 (0.07 to 1.27)
Other	26 (1)	0	26 (1)	1.17 (0.07 to 19.8)
Ethnicity				
Non-Hispanic	1,778 (99)	23 (99)	1,755 (99)	1 [Reference]
Hispanic	19 (1)	0	19 (1)	1.92 (0.11 to 32.7)
Total naloxone dose >4.4 mg	109 (6.1)	3 (13)	21 (1.2)	2.23 (0.66 to 7.60)
Initial naloxone dose >0.4 mg	1,666 (94)	23 (96)	1,643 (94)	1.51 (0.20 to 11.30)
Route of naloxone administration				
Any intramuscular	913 (50)	10 (42)	819 (45)	1.15 (0.66 to 2.01)
Any intranasal	1,190 (65)	15 (63)	1,175 (65)	1.52 (0.80 to 2.90)
Any intravenous/intraosseous	738 (40)	11 (46)	727 (40)	1.27 (0.81 to 1.99)
CPR	111 (6.1)	3 (13)	108 (6.0)	2.25 (0.66 to 7.65)
Emesis after naloxone administration	43 (2.3)	1 (4.2)	42 (2.3)	1.82 (0.24 to 13.8)
Initial hypertension (SBP >160 mm Hg)	196 (11)	3 (13)	193 (11)	1.19 (0.35 to 4.04)
Heroin use suspected	1,151 (63)	13 (54)	1,138 (63)	0.69 (0.31 to 1.56)
Initial oxygen saturation, mean (SD), %	90 (17)	76 (27)	91 (17)	0.976 (0.963 to 0.988)
Initial GCS score, mean (SD)	8.5 (5.2)	7.0 (5.4)	8.5 (5.2)	0.946 (0.872 to 1.027)
Temperature (hospital), mean (SD), °C	36.7 (0.6)	36.7 (0.8)	36.7 (0.6)	0.983 (0.476 to 2.029)

Data are presented as No. (%) unless otherwise indicated.

may result in unnecessary repeated dosing before full effectiveness of the initial dose and could contribute to the higher mean doses of naloxone identified in our cohort. Additionally, naloxone administration is ideally intended to reverse respiratory depression, but not necessarily fully reverse all opioid effects. This subtlety of treatment endpoint may not be understood or recognized by lay people or first responders, leading to excessive dosing to fully arouse an individual who may have experienced an opioid overdose. Many patients who are experiencing opioid toxicity with respiratory depression are also experiencing toxic effects of other central nervous system depressants, such as alcohol, benzodiazepines, or gabapentin, or have incurred an anoxic brain injury. Even if respiratory drive has been restored after naloxone administration, mental status depression may be misunderstood to represent ongoing opioid toxicity. Additional doses of naloxone may increase the risk of withdrawal, vomiting, aspiration, and pulmonary complications. Our experience has been that many cases initially thought to represent opioid intoxication are the result of an alternate process that would not benefit from naloxone administration, but instead leads to a delay in definitive treatment. Finally, widespread but unfounded concerns related to "naloxone-resistant" opioids may fuel responder motivation to provide higher-than-necessary naloxone doses, putting patients at risk of complications.

One unexpected finding of this analysis was an association between pulmonary complications and patients who had at least one intranasal dose of naloxone (OR 1.52; 95% CI 1.26 to 1.84). It is unclear why patients receiving intranasal naloxone would have more pulmonary complications. The intranasal bioavailability of naloxone is only 50% (making it less potent per unit dose compared with intramuscular or intravenous naloxone), but it is possible that patients receiving an intranasal dose are inherently different from those who received no intranasal doses. Alternatively, the intranasal route of administration for naloxone may intrinsically increase the risk of pulmonary complications for unknown reasons.

Our study was principally concerned with the safety of EMS dosing protocols. However, paramedic and

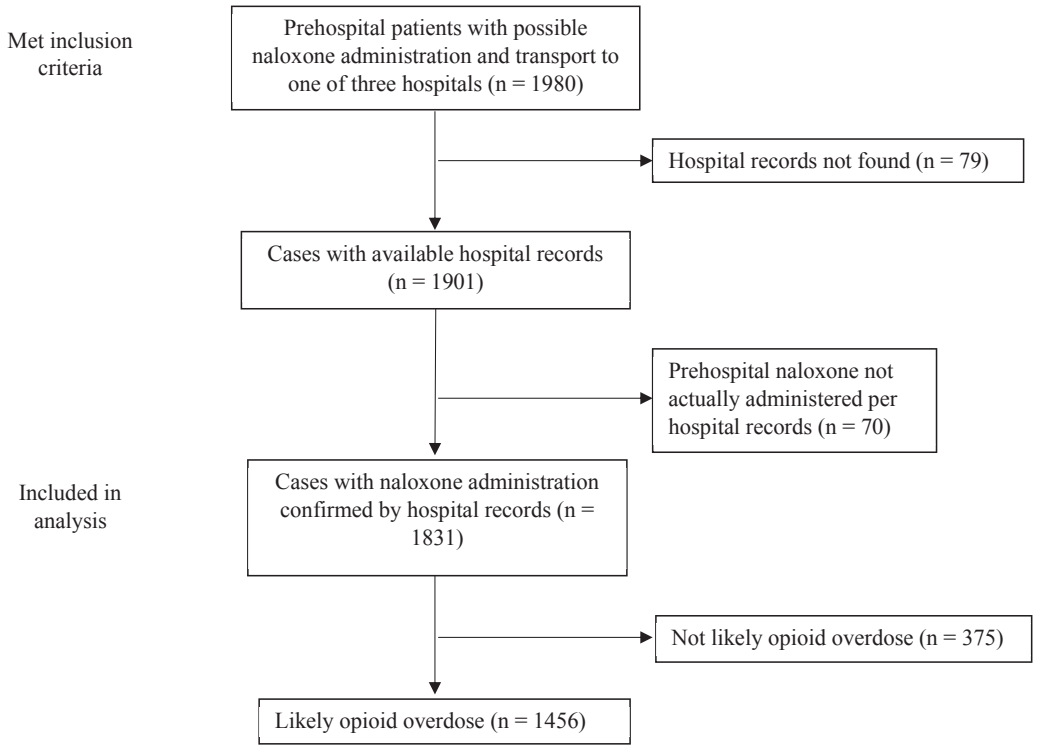

Figure. Strengthening the Reporting of Observational Studies in Epidemiology diagram.

emergency medical technician administration of naloxone now occurs in an out-of-hospital environment that includes lay-person naloxone administration. Protocols guiding EMS naloxone administration may benefit from accounting for bystander or first-responder dosing, when known. Community naloxone distribution programs have demonstrated significant reductions in overdose mortality, with low incidence of serious adverse effects,[20-23] although vomiting and other precipitated withdrawal effects have been commonly reported in literature assessing adverse effects of naloxone distribution programs. Public health campaigns have previously emphasized the role of naloxone in lay-person treatment of opioid overdose, with significant variability in the training that accompanies naloxone distribution programs.[22] A more uniform emphasis on education about nonpharmacologic treatment strategies such as rescue breathing or performing a sternal rub, combined with improved awareness of the endpoints of naloxone administration, may improve outcomes of opioid overdose. These strategies could potentially decrease unnecessary or excessive naloxone administration without discouraging its use when appropriate. Although our study has identified potential risks stemming from excessive administration of naloxone, there is potential for harm that could result from undertreatment in the form of possible incomplete reversal of respiratory depression. Therefore, our goal is not to discourage out-of-hospital naloxone use, but rather to investigate whether a more nuanced approach to out-of-hospital naloxone dosing by trained EMS providers may reduce complication rates.

Furthermore, although efforts were made to account for potential confounders in our statistical analysis, we cannot definitively conclude that the relationship between pulmonary complications and naloxone dosing identified herein is causal. It stands to reason that pretreatment morbidity could have a correlational effect with the decision to administer additional naloxone to patients, and if such an effect were strong enough, it could even mask positive effects of high-dose naloxone administration; for

Table 4. Multivariable analysis of patient factors associated with pulmonary complications.

Characteristic	OR (95% CI)
Total naloxone dose >4.4 mg	1.84 (1.12–3.04)
Initial naloxone dose >0.4 mg	2.02 (1.07–3.80)
Initial GCS score	0.98 (0.96–1.01)
Initial oxygen saturation	0.99 (0.98–1.0)
Route of naloxone administration	
Any intramuscular	1.21 (0.83–1.77)
Any intranasal	1.64 (1.15–2.35)
Any intravenous/intraosseous	0.72 (0.49–1.05)

example, if the number needed to treat were lower than the number needed to harm. Additionally, our study did not measure nonpulmonary adverse outcomes of naloxone administration, such as agitation, that could lead to other negative outcomes. Therefore, further study evaluating specific dosing guidelines is needed to establish the potential benefit of limiting the dose of administered naloxone with increased emphasis on rescue breathing. Prospective research could compare outcomes in patients treated with current guidelines versus naloxone dosing that was previously used (eg, 0.4 mg), or could alter guidelines to account for first-responder or lay-person naloxone administration. Alternatively, rates of adverse effects could be compared between different training programs for lay persons or first responders treating opioid overdoses according to emphasis on appropriate use of naloxone and nonpharmacologic management. Given the prevalence of opioid overdose and high rate of hospitalization for patients who develop pulmonary complications because of overdose, even a small reduction in the rate of aspiration and pulmonary edema has the potential for a large absolute reduction.

In summary, changing patterns of opioid usage, as well as the dissemination of naloxone to non-EMS personnel, have created a new paradigm for treating of opioid overdose in which increased dosage of naloxone has become the norm. In this study, we aimed to assess the effect of this evolution and found that pulmonary complications were more likely to occur in patients receiving a higher total dose of naloxone in the out-of-hospital arena. However, this relationship may or may not be causal. There is also an association between pulmonary complications and providing naloxone by the intranasal route, but the nature of this link is not known and requires further investigation and verification. Given the overall magnitude of opioid-overdose-related morbidity, and in particular pulmonary complications, there is significant potential for harm reduction from optimizing treatment strategies with an updated approach. Therefore, future studies should prospectively evaluate the effect of limiting naloxone dosing.

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