Published in final edited form as:

Addiction. 2018 January ; 113(1): 59–66. doi:10.1111/add.13925.

Risk Factors for Severe Respiratory Depression from Prescription Opioid Overdose

Lindsay M. Fox, MD¹, Robert S. Hoffman, MD¹, David Vlahov, RN, PhD², and Alex F. Manini, MD, MS³

¹Division of Medical Toxicology, Ronald O. Perelman Department of Emergency Medicine, New York University School of Medicine, 455 1st Ave, Room 123, New York, NY 10016

²Office of the Dean, School of Nursing, University of California San Francisco, Office of the Dean, UCSF School of Nursing, 2 Koret Way, #N-319Y, San Francisco CA 94143

³Division of Medical Toxicology, Department of Emergency Medicine, Icahn School of Medicine at Mount Sinai, Elmhurst Hospital Center, 1 Gustave L. Levy Place, New York, New York 10029

Abstract

Background and aims—Prescription opioid overdose is a leading cause of injury-related morbidity and mortality in the US. We aimed to identify characteristics associated with clinical severity in emergency department patients with prescription opioid overdose.

Design—This was a secondary data analysis of adult prescription opioid overdoses from a large prospective cohort of acute overdoses. We examined elements of a typical emergency department evaluation using a multivariable model to determine which characteristics were associated with clinical severity, specifically severe respiratory depression (SRD).

Setting—This study was conducted at two urban academic emergency departments in New York City, USA.

Participants—Adult patients who presented with acute prescription opioid overdose between 2009 and 2013 were included in the current study. We analysed 307 patients (mean age 44.7, 42% female, 2.0% mortality).

Measurements—Patient demographics, reported substances ingested, suspected intent for ingesting the substance, vital signs, laboratory data, treatments including antidotes and intubation, and outcome of death were recorded by trained research assistants. Intent was categorized into four mutually exclusive categories: suicide, misuse, therapeutic error, and undetermined. The primary outcome was SRD, defined as administration of either (a) naloxone or (b) endotracheal intubation (ETI).

Findings—109 patients suffered SRD with 90 patients receiving naloxone alone, 9 ETI alone, and 10 both naloxone and ETI. The most common opioids were oxycodone (n=124) and methadone (n=116). Mean age was higher in patients with SRD (51.1 vs. 41.1, $p<0.001$). Opioid

Corresponding author: Lindsay M. Fox, MD, 455 1st Ave, New York, NY 10016, Room 123, 212-447-4534, Lindsay.Fox@nyumc.org.

Conflicts of interests: none

misuse was associated with SRD in the multivariable analysis (OR 2.07, 95% CI 1.2–3.6). The unadjusted relative risk of SRD was high for fentanyl (83.3% SRD) and lowest for codeine (3.6% SRD).

Conclusion—In emergency department patients in the US with prescription opioid overdose, worse clinical severity was associated with opioid misuse, increased with age, and was widely variable depending on the specific opioid medication involved.

Keywords

Opioid-related disorders; Drug overdose; Emergency Medicine; Hypoventilation

1. INTRODUCTION

1.1. Prescription Opioid Abuse and Overdose

Opioid abuse, addiction and overdose have reached proportions never seen before in the United States, and the death toll continues to rise. In 2012, 2.1 million Americans were estimated to have dependence or abuse of prescription opioids, and 4.9 million, or 1.9% of the US population were estimated to be nonmedical users of prescription opioids.(1) Adverse events from prescription opioids were related to 855,348 ED visits in 2011 the US. (2) Opioids were involved in 28,647 overdose deaths in the United States in 2014, accounting for 61% of overdose deaths overall.(3) More than half of the those opioid-related deaths were due to prescription opioids, although it is increasingly difficult to determine exactly what proportion, as fentanyl-related deaths are increasing, and fentanyl may originate in pharmaceutical or non-pharmaceutical sources.(4)

1.2. Overdose Risk Factors

Research has identified patient characteristics and prescribing practices that increase the risk of prescription opioid-related overdose and death. Patients with psychiatric disorders, and those using benzodiazepines or illicit drugs have higher risk for opioid-related overdose and death.(5, 6) Recent release from prison increases the risk of prescription and non prescription opioid-related overdose death presumably from a loss of tolerance.(7) Higher doses of prescription opioids are also associated with more overdose deaths.(8, 9) Likewise, long-acting opioids are associated with increased risk for non-fatal overdose.(10) Among long-term opioid users on Medicaid, pharmacy shopping and overlapping prescriptions are associated with an increase risk for overdose.(11) Additionally, for patients on opioid substitution therapy in England and Wales, methadone had a relative risk of overdose death of 6.23 when compared with buprenorphine.(12) Among injection drug users in British Columbia, prescription opioid abuse was independently associated with overdose.(13) Recently, Zedler et al examined insurance claims to derive risk factors for overdose or opioid-induced respiratory depression.(14) They found that among various comorbidities examined, a history of a substance use disorder was closely associated with development of opioid-induced respiratory depression, with an odds ratio of 12.7. Additionally, of the different prescription opioids examined, fentanyl was the most closely associated with respiratory depression with an odds ratio of 3.7.(14)

1.3. Overdose Risk Reduction

In response to the aforementioned research, numerous pain societies have released guidelines to encourage safer opioid prescribing, recommending interventions such as careful screening of patients for high-risk characteristics or behaviors, use of prescription drug monitoring programs and urine drug testing to detect aberrant behavior, lower dosing and slower titration of opioids with careful monitoring, and use of non-opioid pain relievers preferentially over opioids when possible.(5) However, more research is needed to describe risk factors for adverse outcomes in patients who present to the emergency setting with prescription opioid overdose.

Naloxone is an important tool for harm-reduction in the midst of a nation-wide opioid epidemic. Naloxone is not only used in medical settings, but increasingly is utilized both by prehospital providers and in the community. Respiratory depression is the primary indication for naloxone.(15–17) In the pre-hospital setting in New York City, previous research suggests that EMS gives naloxone mostly when there is either respiratory depression or coma with miotic pupils, and less often when there is suspected drug-related CNS depression without clear hallmarks of an opioid toxidrome.(18) Data also show that EMS in New York City give naloxone less than half of the time when it would be indicated to treat opioid-poisoned patients.(18)

1.4. The Present Study

The objective of this study was to identify clinical characteristics associated with in-hospital morbidity and mortality among patients who presented to the emergency department following a prescription opioid overdose. Specifically, this study primarily aimed to identify predictors for in-hospital severe respiratory depression (SRD). We hypothesized that behaviors such as opioid misuse and demographics such as age would increase the risk for SRD. We also hypothesized that some prescription opioids would have greater risk for respiratory depression than others, particularly high-potency opioids such as fentanyl and opioids thought to have higher abuse potential such as methadone and oxycodone. An additional exploratory aim of the study was to identify predictors for mortality in ED patients with prescription opioid overdose.

2. METHODS

2.1. Study Design

This was a secondary data analysis of a subgroup of patients with prescription opioid overdose taken from a larger prospective cohort of acute drug overdose cases, which has previously been described in more detail.(19) Briefly, the parent study was a prospective observational cohort of patients that presented with acute drug overdose to two urban tertiary-care emergency departments, which used elements of the routine ED evaluation to develop a prognostic tool to identify patients at risk for adverse cardiovascular events. The original study included 1,562 individual patients for analysis. The current study examines the subgroup from the parent study that overdosed on prescription opioids. Sections 2.2–2.4 will describe both the characteristics of the parent study as well as the specifics of the

current subgroup analysis when they are distinct from the parent study. Section 2.5 and 2.6 will refer to the current subgroup analysis only.

2.2. Setting

This study was conducted between 2009 and 2013 at two urban, tertiary-care hospitals (Mount Sinai Hospital and Elmhurst Hospital Center, both in New York, NY) that had a combined annual ED visit volume of over 150,000 patients at the time the study was conducted. Neither study location was a regional referral center for toxicology patients, but a medical toxicology consult service was available at both hospitals.

2.3. Participants

In the parent study, patients with suspected drug overdose were screened by trained research assistants for inclusion. Patients were included who met both of the following criteria: 1) acute presentation (within 24 hours of exposure) and 2) suspected overdose (i.e., illicit drug dose sufficient to cause symptoms or any prescription drug exposure greater than its therapeutic dose). Exclusion criteria were the following: alternative diagnosis (e.g., trauma or infection), chronic presentation (i.e., not meeting acute criteria above), nondrug overdose (e.g., plant), age younger than 18 years, anaphylaxis, patients with incomplete data (i.e., left against medical advice, transferred to an outside institution, or otherwise eloped from the hospital), patients with prior do-not-attempt-resuscitation orders (i.e., prior to hospital admission), and prisoners. The current subgroup analysis examined those patients who had overdosed on prescription opioid medications, and included any patients from the parent study where a prescription opioid medication was involved. Patients who used illicit opioids (e.g. heroin) but not prescription opioids were not included. Patients who overdosed on prescription opioids plus other classes of drugs were included and were classified as multi-drug exposures. At the time of the study fentanyl was not reported present in the heroin or illicit supply so all reported fentanyl cases were included in the prescription opioid group. Testing blood or urine for fentanyl was not part of routine practice at the institutions; all fentanyl cases described in this study were based on self-report of persons that were exposed to fentanyl patches.

2.4. Measurements

In the parent study, patients were identified by a trained research assistant who rounded in the ED during business hours to find acute overdose cases, and by cases that were called in to the poison center. While poison control center data were used for screening and inclusion, all other data, including outcomes, were abstracted from hospital medical records. Data were collected from the charts by research assistants trained in medical abstraction and recorded using standardized data collection forms. Random sampling of 10 charts with 95% agreement was done prior to initiation of mass data extraction. Data were abstracted to a de-identified electronic database with password protection. Patients were prospectively followed during their hospital stay through to hospital discharge with data that included electronic medical records, paper medical records, consult records. Results (from electronic physician notes, laboratory records, radiology results, and discharge summaries) were prospectively available to the study investigators.

This data included demographics (sex, age, race), exposure information such as timing of exposure, number of exposures, toxin identification (detail from history and physical interview, serum drug concentrations if available), toxicology screens (urine ELISA panel and serum concentration, if any), initial vital signs, and initial venous blood gas including serum lactate concentration. Blood and urine toxicology screen results sent as routine part of clinical care (i.e., no confirmatory gas chromatographic method coupled with mass spectrometry) were recorded to confirm exposure.

Prior to the initiation of data collection in the parent study, intent was categorized into four mutually exclusive categories: suicide, misuse, therapeutic error, and undetermined. Patients were categorized into classes of intent based on chart review by trained research assistants without knowledge of study hypotheses. "Suicide" was determined if history revealed that the patient was taking the medication in an attempt to end their life. Suicidal intent was defined according to the initial impression of the treating physician, and confirmed by psychiatry consultation, with disagreements settled by psychiatry consultation note. Intent was further classified as "misuse" if the patient was taking someone else's medication, was taking their own medication beyond the prescribed doses, or was taking the medication to get high. Finally, unintentional poisoning with the patient's own medication at the prescribed dose was categorized as "therapeutic error".

2.4. Outcomes

The primary outcome for the study was the incidence of severe respiratory depression (SRD), defined by either naloxone administration (either pre-hospital or in-hospital) or endotracheal intubation (ETI) performed either pre-hospital or in-hospital. The secondary outcome was in-hospital mortality, which was used for exploratory analysis.

2.5. Data Analysis

Associations between clinical factors and the primary outcome were calculated using univariate analysis. Additionally, a multivariable model incorporated the following variables: age, opioid misuse, multi-drug exposure, and hospital site. We calculated 95% confidence intervals using the estimated standard error method. Normality testing of demographic data (e.g., age) was confirmed using the Shapiro-Wilk test. Chi-squared tests of independence (with two-tailed Fisher's exact test when appropriate) and t-test were calculated for categorical and continuous variables, respectively, with 5% alpha (2-tailed). Software used for analysis was SPSS v 20.

3. FINDINGS

3.1. Demographics

Out of 354 prescription opioid overdose patients who were screened, 47 were excluded, leaving 307 patients for analysis. Mean age was 44.7 years, and 42% were female. Complete demographic data are presented in Table 1. Prescription opioid overdoses involved the following medications: oxycodone, 124; methadone, 116; hydrocodone, 31; codeine, 27; morphine, 12; tramadol, 12; hydromorphone, 9; buprenorphine, 7; fentanyl, 6; oxymorphone, 3; tapentadol, 2.

3.2.1. Severe Respiratory Depression (SRD)

109 patients (35.5%) met criteria for SRD. Ninety patients received naloxone alone, 9 underwent ETI alone, and 10 received both naloxone and ETI. Pre-hospital naloxone was provided in 41 patients. Mean age was higher in the SRD group (51.1 vs. 41.1, $p<0.001$). In the multivariable analysis, older age was associated with increased risk of SRD, with an OR of 1.05 (95% CI 1.03–1.07), respectively.

3.2.2. Intent of Overdose and SRD

Intent of overdose for the study patients is summarized in Table 2. Opioid misuse was significantly associated with SRD in multivariable model (OR 2.07, 95% CI 1.21–3.55). Opioid misuse was also associated with methadone overdose in the univariate analysis (OR 3.1, 1.9–5.1). Suicidality was associated with codeine in the univariate analysis (OR 2.7, CI 1.2–6.3). Suicidality was inversely correlated with SRD in the univariate analysis (OR 0.4, CI 0.2–0.7), as well as overdose of methadone (OR 0.4, CI 0.2–0.6).

3.2.3. Vital Signs and SRD

Initial ED vital signs for patients are summarized in Table 3. Mean temperature, pulse, blood pressure, respiratory rate, and saturation were similar between those with SRD and those without SRD. However, when using standard vital sign cut points, the following were associated with SRD: bradypnea (< 12 breaths per minute, OR 12.3, CI 2.7–55.8), decreased oxygen saturation ($< 90\%$, OR 5.4, CI 1.7–17.5), and hypotension (systolic blood pressure < 90 mmHg, OR 7.1, CI 2.3–22.3). Tachycardia (> 100 beats per minute, OR 1.3, CI 0.8–2.3) was not associated with SRD.

3.2.4 Multi-drug Exposure and SRD

Most patients reported ingesting more than one substance ($N=279$, 91%). Multi-drug exposures were not associated with SRD in either the univariate or multivariable analysis. Serum drug concentrations were positive for ethanol in 51 patients, salicylate in 3 patients, and acetaminophen in 52 patients. Serum drug concentrations were not done uniformly in all patients, and so these do not represent all patients that were exposed to these substances among this subgroup. Urine toxicology screening was done in 171 patients, and was positive for benzodiazepines in 85 patients, cocaine in 45 patients, methadone in 60 patients, barbiturates in 8 patients, amphetamines in 2 patients, PCP in 4 patients and cannabis in 10 patients.

3.2.5. Laboratory Data and SRD

In 233 (75%) patients, venous blood gas was sent as part of the initial ED workup, and results are summarized in Table 3. The following mean parameters were associated with SRD: pH, PCO₂, and lactate. Using a cutpoint of 3 mmol/L, lactate was significantly associated with SRD (OR 2.1, CI 1.0–4.4) and mortality (OR 32.6, CI 3.7–289). However, SRD was not associated with either PO₂ or calculated bicarbonate.

3.2.6. Type of Prescription Opioid and SRD

Risk for SRD was highly dependent on the type of prescription opioid (Table 4). Of the overdoses involving fentanyl, 83.3% experienced SRD. Only 3.6% of overdoses involving codeine experiences SRD. Buprenorphine (28.6% SRD) had similar clinical severity to oxycodone (32% SRD) and hydrocodone (29% SRD). The two most common opioids, methadone and oxycodone, experienced SRD commonly (50.9% and 32.3%, respectively).

3.3. In-hospital Mortality

Six patients (2%) died in-hospital, involving the following opioids (some had >1): oxycodone (n=4), methadone (n=2), hydromorphone (n=1), and fentanyl (n=1). There were no pre-hospital cardiac arrests, and 2 of 6 did not receive naloxone. Clinical factors associated with mortality compared with no mortality were initial tachycardia (>100 beats per minute, $p<0.001$), hyperlactatemia (>3 mmol/L, $p<0.05$), and initial hypotension (<90 mmHg, $p<0.01$).

4. DISCUSSION

4.1 Main Results and Implications

The main result of this study are that prescription opioid overdoses from misuse resulted in worse clinical severity than those from other intentions, such as suicidality. In addition, we found that clinical severity was correlated with age and the specific opioid medication. Given the scope of this problem, providers and policymakers should consider ways to reduce harm associated with prescription opioid misuse. The results of this study suggest that some opioid medications are much higher risk than others, which may lead providers to consider changing their prescribing practices to utilize opioid medication with lower risk.

4.2.1. Specific Prescription Opioids

It is notable that some prescription opioids had a much higher relative risk for SRD. Fentanyl for example had a relative risk of 22.5 compared to the lowest risk opioid, codeine. Buprenorphine had a higher risk than would have been expected for this medication, which in therapeutic dose produces minimal respiratory depression in adults. As would be expected from previous research, buprenorphine had a lower risk than methadone. Methadone and oxycodone had relative risks of 13.7 and 8.7 respectively, but were collectively responsible for most of the cases of respiratory depression given the higher prevalence of their use compared to the other opioid medications. The results from this study reflect CDC data on opioid related-deaths, which show that oxycodone, hydrocodone, methadone and fentanyl are particularly problematic among the available prescription opioids.(4, 20)

Urine drug screening was not able to confirm opioid exposure in most patients. This was in part because urine drug screening was only performed in 171/307 (56%) patients in this study. Additionally, commonly used assays test for opiates (i.e. natural or nonsynthetic opioids such as morphine and codeine), with limited cross-reactivity to detect semisynthetic opioids (buprenorphine, hydrocodone, hydromorphone, oxycodone) or synthetic opioids (tramadol, tapentadol, fentanyl, methadone). Only 12/307 (4%) reported morphine exposure,

and 27/307 (9%) reported codeine exposure, meaning the vast majority of patients in this study reported exposure to opioids that would not reliably test positive on an opiate screen.

4.2.2. Fentanyl

This study suggests that the risk of fentanyl to cause SRD appears to be particularly high when compared to other opioid medications, possibly due to the route of administration, the high potency, or both. Fentanyl is a high potency opioid often delivered in a patch form which may lend itself to tampering to deliver much higher doses than ingestion of pills, which may in part explain the high risk for SRD with this product. In 2012 the FDA released a warning to the public about the risks associated with transdermal fentanyl patches when altered or not properly disposed(21). Additionally, chest wall rigidity resulting from fentanyl exposure has been hypothesized to be a factor in fentanyl-related deaths.(22) Fentanyl-related deaths have grown dramatically since the completion of data collection in this study, due to both pharmaceutical and non-pharmaceutical fentanyl.(4) As testing for fentanyl was not part of routine clinical practice at the hospitals where this study was conducted, the cases of fentanyl overdose described in this study are based on self-report of fentanyl patches, and are almost certain to represent pharmaceutical fentanyl rather than non-pharmaceutical fentanyl that is sometimes surreptitiously added to the illicit drug supply.

4.2.3. Methadone and Buprenorphine

In this cohort of prescription opioid overdose patients, methadone had a much higher risk for SRD than did buprenorphine. This supports previous research suggesting that buprenorphine is safer than methadone.(12) Currently, more patients are prescribed methadone than buprenorphine for opioid substitution therapy, and there are regulatory limits that make it difficult for providers to increase the number of patients treated with buprenorphine. Given the growing literature on the safety of buprenorphine compared to methadone, we urge policymakers to make regulatory changes that facilitate starting opioid dependent patients on buprenorphine rather than methadone.

4.3 Pre-hospital Naloxone

This research also adds to the growing body of literature about pre-hospital naloxone to treat prescription opioid overdose. We found that 13.4% of our cohort received pre-hospital naloxone. Many individuals who overdose on prescription opioids are not fortunate enough to arrive to a hospital in time to prevent respiratory depression and subsequent arrest, and pre-hospital naloxone is life-saving in many cases.(23) Unfortunately, the pre-hospital availability of naloxone is variable. Basic life support first responders are not authorized to administer naloxone in some of the United States,(24), although the number of states with laws increasing access of naloxone to laypersons is growing.(25) Policy-makers should increase access of naloxone out of hospital, and develop protocols to ensure that pre-hospital providers are administering naloxone when appropriate. Naloxone programs should also be targeted to high-risk populations, such as those who were recently released from prison, a time when risk for opioid overdose is extremely high.(7) Additionally, policy-makers should expand the use Good-Samaritan laws, which help protect bystanders who call for help in case of a witnessed overdose, and are not on the books in a number of states.(25)

4.4 In-hospital Mortality

Mortality was associated with initial ED vital signs, as well as elevated lactate concentration. To our knowledge, these are novel predictors of mortality in prescription opioid overdose, however we were underpowered to evaluate robust predictors of fatality given the small number of fatal overdoses in our hospitalized patients. Although the mortality risk factors above are novel, they are not surprising given that abnormal vital signs and an elevated lactate concentration were previously derived as predictors of overdose fatality.(26)

4.5 Limitations

This study has several important limitations, including the use of surrogate markers of severe respiratory depression, namely naloxone administration and endotracheal intubation. It is possible that these interventions were sometimes given for other indications and not true respiratory depression. Additionally, this study did not examine other types of morbidity, such as acetaminophen-related liver toxicity. The present study excluded pediatric patients, and therefore it is not known if these results are relevant to pediatric patients. This study had 6 deaths, and therefore was not powered to give information about risk for mortality.

5. CONCLUSIONS

In this cohort of emergency department patients with prescription opioid overdose, clinical severity was associated with opioid misuse, increased with age and was widely variable depending on the specific opioid medication involved. Clinicians should be aware of these factors associated with risk for clinically severe prescription opioid overdose, and should consider adjusting prescription practices accordingly.

Acknowledgments

The project described was supported by award number K23DA026476 (PI:AFM) from the National Institute On Drug Abuse, as well as the Resident Research Grant from the Emergency Medicine Foundation and Medical Toxicology Foundation. Drs. Manini and Hoffman are currently supported by grant R01DA037317 from the National Institute On Drug Abuse.

References

1. Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD: 2013.
2. Substance Abuse and Mental Health Services Agency. DAWN 2011 Emergency Department Excel Files. 2014. [Available from: <http://www.samhsa.gov/>]
3. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in Drug and Opioid Overdose Deaths--United States, 2000--2014. MMWR Morbidity and mortality weekly report. 2016; 64(50-51):1378-82. [PubMed: 26720857]
4. Centers for Disease Control and Prevention. Fentanyl Overdose Data. 2016. [Available from: <https://www.cdc.gov/drugoverdose/data/fentanyl.html>]
5. Agarín T, Trescott AM, Agarín A, Lisanics D, Decastro C. Reducing opioid analgesic deaths in America: what health providers can do. Pain physician. 2015; 18(3):E307-22. [PubMed: 26000678]
6. Turner BJ, Liang Y. Drug Overdose in a Retrospective Cohort with Non-Cancer Pain Treated with Opioids, Antidepressants, and/or Sedative-Hypnotics: Interactions with Mental Health Disorders. J GEN INTERN MED. 2015; 30(8):1081-96. [PubMed: 25650263]

7. Binswanger IA. Mortality After Prison Release: Opioid Overdose and Other Causes of Death, Risk Factors, and Time Trends From 1999 to 2009. *Annals of Internal Medicine*. 2013; 159(9):592. [PubMed: 24189594]
8. Bohnert ASB. Association Between Opioid Prescribing Patterns and Opioid Overdose-Related Deaths. *JAMA*. 2011; 305(13):1315. [PubMed: 21467284]
9. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med*. 2010; 152(2):85–92. [PubMed: 20083827]
10. Miller M, Barber CW, Leatherman S, Fonda J, Hermos JA, Cho K, et al. Prescription Opioid Duration of Action and the Risk of Unintentional Overdose Among Patients Receiving Opioid Therapy. *JAMA Internal Medicine*. 2015; 175(4):608. [PubMed: 25686208]
11. Yang Z, Wilsey B, Bohm M, Weyrich M, Roy K, Ritley D, et al. Defining Risk of Prescription Opioid Overdose: Pharmacy Shopping and Overlapping Prescriptions Among Long-Term Opioid Users in Medicaid. *The Journal of Pain*. 2015; 16(5):445–53. [PubMed: 25681095]
12. Marteau D, McDonald R, Patel K. The relative risk of fatal poisoning by methadone or buprenorphine within the wider population of England and Wales. *BMJ open*. 2015; 5(5):e007629.
13. Lake S, Wood E, Buxton J, Dong H, Montaner J, Kerr T. Prescription opioid use and non-fatal overdose in a cohort of injection drug users. *The American Journal of Drug and Alcohol Abuse*. 2015; 41(3):257–63. [PubMed: 25699628]
14. Zedler BK, Saunders WB, Joyce AR, Vick CC, Murrelle EL. Validation of a Screening Risk Index for Serious Prescription Opioid-Induced Respiratory Depression or Overdose in a US Commercial Health Plan Claims Database. *Pain Med*. 2017
15. Bardsley, CH. Opioids. In: Marx, JA., editor. *Rosen's Emergency Medicine*. 8. 2014. p. 2052–6.
16. Nelson, LS., Dean, Olsen. Opioids. In: Hoffmane, Robert S., editor. *Goldfrank's Toxicologic Emergencies*. 10. McGraw-Hill; 2015.
17. Perrone, J. Drugs of Abuse. In: Cline ea, David M., editor. *Tintinalli's Emergency Medicine Manual*. 7. NY: McGraw-Hill; 2012.
18. Friedman MS, Manini AF. Validation of Criteria to Guide Prehospital Naloxone Administration for Drug-Related Altered Mental Status. *Journal of medical toxicology : official journal of the American College of Medical Toxicology*. 2016; 12(3):270–5. [PubMed: 27083903]
19. Manini AF, Hoffman RS, Stimmel B, Vlahov D. Clinical risk factors for in-hospital adverse cardiovascular events after acute drug overdose. *Acad Emerg Med*. 2015; 22(5):499–507. [PubMed: 25903997]
20. Centers for Disease Control and Prevention. Prescription Opioid Overdose Data. 2016. [Available from: <https://www.cdc.gov/drugoverdose/data/overdose.html>]
21. United States Food and Drug Administration. FDA Reminds the Public about the Potential for Life-Threatening Harm from Accidental Exposure to Fentanyl Trans-dermal Systems (“Patches”). 2015. [Available from: <http://www.fda.gov/Drugs/DrugSafety/ucm300747.htm>]
22. Burns G, DeRienz RT, Baker DD, Casavant M, Spiller HA. Could chest wall rigidity be a factor in rapid death from illicit fentanyl abuse? *Clin Toxicol (Phila)*. 2016; 54(5):420–3. [PubMed: 26999038]
23. Walley AY, Xuan Z, Hackman HH, Quinn E, Doe-Simkins M, Sorensen-Alawad A, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ*. 2013; 346:f174. [PubMed: 23372174]
24. Davis CS, Southwell JK, Niehaus VR, Walley AY, Dailey MW. Emergency Medical Services Naloxone Access: A National Systematic Legal Review. *Acad Emerg Med*. 2014; 21(10):1173–7. [PubMed: 25308142]
25. Davis, C. LEGAL INTERVENTIONS TO REDUCE OVERDOSE MORTALITY: NALOXONE ACCESS AND OVERDOSE GOOD SAMARITAN LAWS. Network for Public Health Law. 2016. [Available from: https://www.networkforphl.org/_asset/qz5pvn/legal-interventions-to-reduce-overdose.pdf]
26. Manini AF, Kumar A, Olsen D, Vlahov D, Hoffman RS. Utility of serum lactate to predict drug-overdose fatality. *Clinical Toxicology*. 2010; 48(7):730–6. [PubMed: 20704455]

Table 1

Demographics of ED Prescription Opioid Overdose Patients, 2009–13, n=307

Demographic	No SRD (n=198)	SRD (n=109)
Age (years, mean)	41.1	51.1
Female	84 (42%)	47 (43%)
Race		
Black	34 (31%)	10 (9%)
White	137 (69%)	82 (75%)
Asian	6 (3%)	1 (1%)
Other race	12 (6%)	7 (6%)
Not specified	9 (5%)	9 (8%)
Ethnicity		
Hispanic	49 (25%)	45 (41%)

Abbreviations: SRD = severe respiratory depression.

Table 2

Intent of ED Prescription Opioid Overdose Patients, 2009–13, n=307

Overdose Intent:	All	SRD (%)	No SRD (%)	OR (95% CI)
Intentional	259	90 (35)	169 (65)	0.8 (0.4–1.6)
Misuse *	177	72 (41)	105 (59)	1.8 (1.1–2.9)
Suicidal *	82	18 (22)	64 (78)	0.4 (0.2–0.7)
Therapeutic Error	40	13 (33)	27 (68)	0.9 (0.4–1.7)
Undetermined	8	6 (75)	2 (25)	8.8 (1.8–45)
TOTAL	307	109 (36)	198 (64)	-

* p < 0.05 using chi-squared

Abbreviations: 95% CI = 95% confidence intervals; OR = odds ratios; SRD = severe respiratory depression.

Table 3

Initial Vital Signs and Venous Blood Gas of ED Prescription Opioid Overdose Patients, 2009–13, n=307

Vital Sign	No SRD (n=198)	SRD (n=109)	Mortality (n=6)
	Mean $\pm$ SE		
Temperature ($^{\circ}$ F)	95.6 $\pm$ 0.8	93.9 $\pm$ 1.4	85.6 $\pm$ 12.7
Heart Rate (bpm)	87.3 $\pm$ 1.4	86.8 $\pm$ 2.0	116.8 $\pm$ 7.2
Systolic BP (mmHg)	128.4 $\pm$ 1.6	123.1 $\pm$ 2.8	90.3 $\pm$ 15.0
Diastolic BP (mmHg)	75.4 $\pm$ 1.2	75.4 $\pm$ 1.9	79.3 $\pm$ 21.1
Respiratory Rate (bpm)	18.7 $\pm$ 0.4	18.3 $\pm$ 0.4	18.7 $\pm$ 2.2
pH	7.36 $\pm$ 0.01	7.29 $\pm$ 0.01	7.17 $\pm$ 0.1
PCO ₂ (mmHg)	47.7 $\pm$ 0.9	54.9 $\pm$ 1.5	57.6 $\pm$ 16.2
PO ₂ (mmHg)	50.9 $\pm$ 2.3	54.1 $\pm$ 3.7	84.3 $\pm$ 31.7
HCO ₃ ⁻ (mmol/L)	25.9 $\pm$ 0.3	26.1 $\pm$ 0.6	18.3 $\pm$ 4.1
Lactate (mmol/L)	1.8 $\pm$ 0.1	2.5 $\pm$ 0.3	8.4 $\pm$ 1.9

Abbreviations: BP = blood pressure; bpm = beats/ breaths per minute; F = degrees Fahrenheit; SE = standard error; SRD = severe respiratory depression; CO₂ = carbon dioxide; HCO₃⁻ = calculated bicarbonate; O₂ = oxygen; P = partial pressure

Table 4

Severe Respiratory Depression from Prescription Opioid Overdose, in Descending Order of Risk, in ED Patients 2009–13, n=307

Prescription Opioid:	SRD Rate (%)	RR: (descending)	95% CI:
Tapentadol	2/2 (100)	27.0	3.9 – 185
Fentanyl	5/6 (83.3)	22.5	3.2 – 159
Oxymorphone	2/3 (66.7)	18.0	2.2 – 144
Methadone	59/116 (50.9)	13.7	2.0 – 95
Hydromorphone	4/9 (44.4)	12.0	1.5 – 94
Morphine	5/12 (41.7)	11.3	1.5 – 86
Oxycodone	40/124 (32.3)	8.7	1.3 – 60
Hydrocodone	9/31 (29.0)	7.8	1.0 – 58
Buprenorphine	2/7 (28.6)	7.7	0.8 – 73
Tramadol	3/12 (25.0)	6.8	0.8 – 58
Codeine	1/27 (3.7)	1.0 (<i>ref</i>)	-

Abbreviations: 95% CI = 95% confidence interval; RR = relative risk; SRD = severe respiratory depression (defined as naloxone or ETI)

* Some patients ingested more than one type of opioid, so cumulative total of patients described in this table is greater than the number of patients in the study.

Table 5

Multivariable Model for Clinical Predictors of Severe Respiratory Depression from Prescription Opioid Overdose, n=307

Factor	Univariate OR	Adjusted OR	Adjusted 95% CI
Age	1.05	1.05	1.03–1.07
Misuse	1.8	2.07	1.21–3.55
Multi-drug exposure	1.03	1.41	0.54–3.68
Hospital Site	0.63	0.99	0.56–1.78

Abbreviations: 95% CI = 95% confidence interval, OR = odds ratio