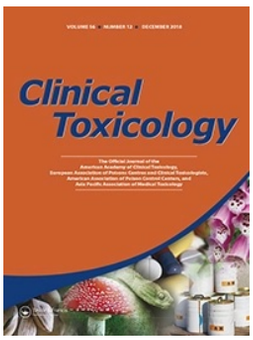

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CLINICAL RESEARCH

Comparison of rates of opioid withdrawal symptoms and reversal of opioid toxicity in patients treated with two naloxone dosing regimens: a retrospective cohort study

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ABSTRACT

Introduction: When managing opioid overdose (OD) patients, the optimal naloxone regimen should rapidly reverse respiratory depression while avoiding opioid withdrawal. Published naloxone administration guidelines have not been empirically validated and most were developed before fentanyl OD was common. In this study, rates of opioid withdrawal symptoms (OW) and reversal of opioid toxicity in patients treated with two naloxone dosing regimens were evaluated.

Methods: In this retrospective matched cohort study, health records of patients who experienced an opioid OD treated in two urban emergency departments (ED) during an ongoing fentanyl OD epidemic were reviewed. Definitions for OW and opioid reversal were developed *a priori*. Low dose naloxone (LDN; $\leq$0.15 mg) and high dose naloxone (HDN; >0.15 mg) patients were matched in a 1:4 ratio based upon initial respiratory rate (RR). The proportion of patients who developed OW and who met reversal criteria were compared between those treated initially with LDN or HDN. Odds ratios (OR) for OW and opioid reversal were obtained *via* logistic regression stratified by matched sets and adjusted for age, sex, pre-naloxone GCS, and presence of non-opioid drugs or alcohol.

Results: Eighty LDN patients were matched with 299 HDN patients. After adjustment, HDN patients were more likely than LDN patients to have OW after initial dose (OR = 8.43; 95%CI: 1.96, 36.3; $p = 0.004$) and after any dose (OR = 2.56; 95%CI: 1.17, 5.60; $p = 0.019$). HDN patients were more likely to meet reversal criteria after initial dose (OR = 2.73; 95%CI: 1.19, 6.26; $p = 0.018$) and after any dose (OR = 6.07; 95%CI: 1.81, 20.3; $p = 0.003$).

Conclusions: HDN patients were more likely to have OW but also more likely to meet reversal criteria versus LDN patients.

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Opioid; overdose; naloxone; reversal; withdrawal

Introduction

In 2015, an estimated 167,750 people worldwide died as a direct result of drug use, in most cases involving opioids [1]. In 2017, opioid overdose (OD) claimed the lives of 47,600 people in the USA [2]. In 2018, in Canada, 3394 of 4588 (73%) opioid-related deaths involved fentanyl [3].

Opioid OD causes decreased level of consciousness and potentially fatal respiratory depression. The competitive opioid antagonist naloxone reverses these effects. Increased availability of naloxone in take-home-naloxone programs saves lives [4–7]. However, naloxone can cause opioid withdrawal when given to opioid tolerant patients. Naloxone-precipitated opioid withdrawal syndrome is associated with adverse events including pulmonary edema [8–14], hypertensive emergencies [15–17], ventricular dysrhythmias [18], delirium [19], agitation and aggression [20,21], seizures [19], and death [22,23]. Patients with opioid withdrawal syndrome may also leave hospital against medical advice [24,25], and use opioids again to treat their symptoms, putting them at risk of another OD [26].

It is thus important to optimize naloxone administration so that life threatening opioid toxicity is rapidly reversed and opioid withdrawal syndrome is avoided. Low-dose naloxone regimens have been recommended to decrease the incidence of opioid withdrawal syndrome [19,27,28]. However, published naloxone administration guidelines-based on expert opinion prior to the epidemic of ultrapotent opioids exhibit great variability, with recommended initial naloxone doses ranging between 0.04 mg and 0.4 mg [29]. Although experts have recommended evaluation of naloxone dosing in clinical settings [30], the association between naloxone dose and occurrence of opioid withdrawal symptoms is not known

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and significant differences in the frequency of adverse events including opioid withdrawal symptoms were not found in two studies that compared different naloxone dosing regimens [31,32].

The primary objective of this study was to determine the proportion of patients who have OW after initial naloxone dose when first treated with low dose naloxone (LDN; ≤0.15 mg) compared to those treated with high dose naloxone (HDN; >0.15 mg) in a patient population in which fentanyl OD is common. Secondary objectives were to determine the proportion of patients who have OW after any dose, opioid reversal within 30 min of initial dose, and opioid reversal within 30 min of any dose, the total dose of naloxone used to reverse opioid toxicity, mean time to opioid reversal, and the incidence and mean time to naloxone redosing, if required.

Methods

Study setting

In this retrospective matched cohort study, emergency department (ED) and ambulance service (EMS) records of opioid OD patients treated in two urban EDs serviced by a single EMS from Jan 1, 2013 to Dec 31, 2017 were reviewed. Only ED and EMS records were available so patient outcome information after admission or discharge was not available. Naloxone administration was not based on a protocol. Each patient's attending physician directed the amount and timing of naloxone doses and infusions and naloxone could be administered to patients after study criteria for opioid reversal had been met. Drug testing was not routinely completed on patients.

Definitions

LDN was defined as an initial dose ≤0.15 mg naloxone and HDN as >0.15 mg naloxone. Presence of opioid withdrawal symptoms (OW) was defined as the presence of any of the following: new or worsening nausea requiring treatment, new or worsening agitation, aggressive behavior towards staff, restlessness, pulse >100, diarrhea, tremor, flushing, sweating, gooseflesh skin, piloerection, bone or joint aches, rhinorrhea, lacrimation, or yawning occurring any time after administration of naloxone. Criteria for reversal was defined as: Glasgow Coma Scale (GCS) >10 and either respiratory rate (RR) >11 or O_2 saturation >91% occurring within 30 min of naloxone administration before the administration of another dose of naloxone. Definitions were developed *a priori* based on criteria used in frequently cited manuscripts [29,33] and treatment guidelines [34,35].

Patient selection

Patients were identified by searching ED electronic records for consecutive patients with the presenting complaint of overdose ingestion, or substance misuse/intoxication, (Codes 751 and 752 in system of standardized triage presenting complaints [CEDIS] used in all Canadian EDs) [36] and automated ED medication dispensing records for patients who had been administered naloxone in the ED. Patients were included if they were treated for an opioid OD with naloxone administered by laypersons, paramedics or emergency personnel. Patients were excluded if they did not have an opioid OD, did not receive naloxone, or if there was incomplete or missing documentation of the initial naloxone dose or the vital signs prior to the initial naloxone dose.

Chart review

A preliminary chart review determined eligibility and exclusions, as well as naloxone dose and initial vital signs for matching. Rates of opioid reversal and OW were unknown at time of matching. Each LDN patient was matched with up to four HDN patients based on initial RR as a proxy for severity of OD. Matches were chosen randomly from exact matches, where available, and then from HDN patients within 1 unit of RR when no exact matches remained. Matching was repeated three more times until all LDN patients had up to four HDN matches. Full chart review including EMS records was performed for the subset of patients selected for the matched analysis. The proportion of patients who had (i) OW or (ii) reversal of opioid OD toxicity after receiving treatment with LDN or HDN was determined. If data was missing it was assumed that an event had not occurred. If post naloxone vital signs were missing, ODs were considered to be not reversed. Seven reviewers, blinded to study hypothesis and outcomes, collected demographics, patient vital signs and symptoms, as well as prehospital and ED treatments. Reviewers were trained on 20 health records and performance was evaluated at regular meetings. Each chart was assessed independently by two reviewers to determine if the patient had OW or opioid reversal. If a discrepancy occurred, the case was referred to an adjudication team consisting of two medical toxicologists and an emergency nurse.

Outcomes

Four binary outcomes were examined. The primary outcome was occurrence of OW after initial dose. Three secondary outcomes were occurrence of OW after any dose, meeting reversal criteria within 30 min of initial dose, and meeting reversal criteria within 30 min of any dose. For each outcome, conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95%CI) for outcome in LDN versus HDN matches. Adjusted ORs were then obtained from models that adjusted for age (years as a continuous variable), sex, initial GCS (categorized as 3–8, 9–10, or 11–15), and the documented presence of non-opioid drugs and/or alcohol (yes, no). Predictors were selected *a priori* based on clinical experience with factors that affect outcome following opioid OD in the ED. There was no evidence of predictor multicollinearity, as the GVIFs (generalized variance inflation factors) were all less than 1.5.

Survival analyses

Two post-hoc survival analyses using naloxone dosing times were also performed. The first examined time to opioid reversal, defined as the time between the initial dose and the first dose when opioid reversal of the opioid toxicity occurred within 30 min. When reversal did not occur, patients were right-censored at their final dose time. The second analysis examined time to re-dose following opioid reversal, defined as the time between the dose resulting in opioid reversal and a subsequent dose. Patients who did not receive a re-dose post-reversal were right-censored at last follow-up (discharge for 87% of censored patients, and time zero otherwise). Hazard ratios (HR) were obtained *via* Cox proportional hazards regression stratified by matched sets; adjusted HRs were also obtained using the same covariates as for the logistic regression models. The proportional hazards assumption was verified by examining correlation between Schoenfeld residuals and survival time, which was not statistically significant for any predictor. Crude Kaplan-Meier curves were constructed for LDN and HDN patients. Event probabilities at specific times and event time quantiles (25th, median, and 75th) were derived from these curves with 95% confidence intervals.

Subgroup analyses: Four post-hoc subgroup analyses were also performed with each model: i) excluding patients with initial RR $>$ 12; ii) including exact RR matches only; and, iii) excluding patients who met study criteria for opioid reversal before treatment with naloxone (pre-naloxone vitals consistent with study definition for opioid reversal); iv) including patients who received IV naloxone.

Statistical methods and ethics: *p*-values less than 0.05 are described as statistically significant, and no attempt was made to correct for multiple inference. All statistical tests were two-tailed. Analyses were conducted using R (version 3.5.1). The research was approved by the Clinical Research Ethics Board of the University of British Columbia: Certificate number: H18-00099. This study was supported the Michael Smith Foundation for Health Research under grant number 16794.

Results

A preliminary chart review to determine patient eligibility, initial RR and initial naloxone dose was performed on 5917 health records and identified 2352 opioid OD patients who were treated with naloxone and had full vital signs (Figure 1). Eighty patients who received LDN were matched to 299 patients who received HDN and the corresponding records were reviewed in depth. Of the LDN patients, 76% ($n = 61$) had four matches, 21% ($n = 17$) patients had three matches, and 3% ($n = 2$) patient had two matches.

Age ranges in LDN patients and HDN patients were similar, LDN mean age 44.9 (SD 15.2) and HDN mean age 41.8 (SD 14.8). There were fewer patients with initial GCS $\leq$8 in the LDN group (15.0%) vs the HDN group (39.5%) 33.8% of LDN patients and 36.5% of HDN patients were exposed to other drugs or alcohol. Patients reported exposure to the following co-ingestants: ethanol, cocaine, amphetamines, cannabis, gamma-hydroxybutyrate, gabapentin, benzodiazepines and other sedatives.

More patients in the LDN group received naloxone in the ED: (LDN 83.8%, HDN 33.4%) and by the intravenous (IV) route (LDN 91.2%, HDN 38.8%). More patients in the LDN group had opioid OD by IV injection (41.2%), vs the HDN group (31.4%) (Table 1).

OW occurred in 101 (26.6%) patients. OW occurred in 4 (5.0%) LDN patients and 59 (19.7%) HDN patients after a single dose of naloxone and 12 (15.0%) LDN patients and 89 (29.8%) HDN patients had OW after any dose of naloxone. The most common symptoms were agitation and nausea/vomiting (Table 2). In the adjusted analysis, OW was more common in HDN patients than in LDN patients after initial dose (OR = 8.43; 95%CI: 1.96, 36.3; $p = 0.004$) and after any dose (OR = 2.56; 95%CI: 1.17, 5.60; $p = 0.019$). In a subgroup analysis of 172 patients who received IV naloxone OW was more common in HDN patients than in LDN patients after initial dose (OR = 3.43; 95%CI: 1.17, 10.07; $p = 0.0251$). Results of primary analysis, subgroup analysis and information on exclusions due to missing data is reported (Table 3).

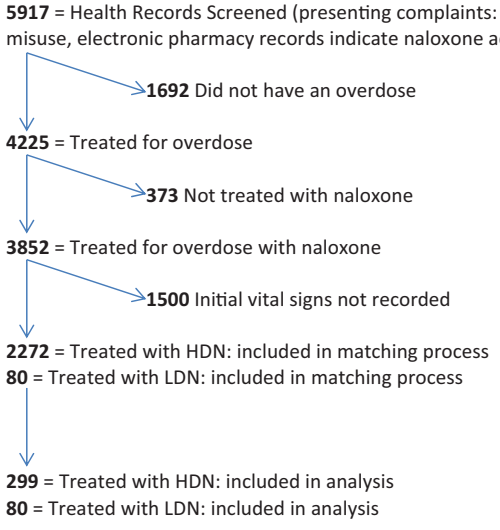

Figure 1. Study flow chart.

Table 1. Characteristics of matched cohort.

	All ($n = 379$)	Low dose ($n = 80$)	High dose ($n = 299$)
Demographics and initial vitals			
		Mean (SD)	
Age (years)	42.5 (14.7)	44.9 (15.2)	41.8 (14.6)
Respiratory rate	11.7 (5.0)	11.7 (5.1)	11.7 (5.0)
		Count (%)	
Male	$n = 255$ (67.3%)	$n = 57$ (71.2%)	$n = 198$ (66.2%)
Glasgow coma scale[a]			
3–8	$n = 130$ (34.3%)	$n = 12$ (15%)	$n = 118$ (39.5%)
9–10	$n = 52$ (13.7%)	$n = 13$ (16.2%)	$n = 39$ (13%)
11–15	$n = 157$ (41.4%)	$n = 40$ (50%)	$n = 117$ (39.1%)
Other drugs detected	$n = 136$ (35.9%)	$n = 27$ (33.8%)	$n = 109$ (36.5%)
Naloxone administration (Initial dose)			
		Count (%)	
Location administered			
ED	$n = 167$ (44.1%)	$n = 67$ (83.8%)	$n = 100$ (33.4%)
EHS	$n = 210$ (55.4%)	$n = 13$ (16.2%)	$n = 197$ (65.9%)
Pre-EHS (bystander)	$n = 2$ (0.5%)	$n = 0$	$n = 2$ (0.7%)
Route of administration			
IM	$n = 96$ (25.3%)	$n = 3$ (3.8%)	$n = 93$ (31.1%)
IV	$n = 189$ (49.9%)	$n = 73$ (91.2%)	$n = 116$ (38.8%)
SC	$n = 82$ (21.6%)	$n = 4$ (5.0%)	$n = 78$ (26.1%)
Unknown	$n = 12$ (3.2%)	$n = 0$	$n = 12$ (4.0%)
Opioid exposure			
		Count (%)	
Route of administration			
IH	$n = 11$ (2.9%)	$n = 3$ (3.8%)	$n = 8$ (2.7%)
IM	$n = 1$ (0.3%)	$n = 0$	$n = 1$ (0.3%)
IN	$n = 8$ (2.1%)	$n = 1$ (1.2%)	$n = 7$ (2.3%)
IV	$n = 127$ (33.5%)	$n = 33$ (41.2%)	$n = 94$ (31.4%)
PO	$n = 56$ (14.8%)	$n = 20$ (25.0%)	$n = 36$ (12.0%)
Unknown	$n = 176$ (46.4%)	$n = 23$ (28.7%)	$n = 153$ (51.2%)

[a]GCS was significantly different between groups (χ^2=13.5, $p = 0.001$). Other demographic factors were not significantly different.

Thirty-four (42.5%) LDN patients and 96 (32.1%) HDN patients met study criteria for reversal before they received treatment with naloxone (pre-naloxone vitals consistent with study definition for opioid reversal). Twelve (15.0%) LDN patients and 114 (38.1%) HDN patients who did not meet study criteria for reversal before treatment with naloxone but met study criteria for reversal after an initial single dose of naloxone. Overall, 46 (57.5%) of LDN and 210 (70.2%) of HDN patients required exactly one dose of naloxone before reversal (Table 2). After adjustment, HDN patients were more likely than LDN patients to have opioid reversal after initial dose (OR = 2.73; 95%CI: 1.19, 6.26; $p = 0.018$) and after any dose (OR = 6.07; 95%CI: 1.81, 20.3; $p = 0.003$) (Table 3).

At any given time after the initial dose of naloxone, HDN patients were more likely to have opioid reversal compared with LDN patients (HR = 1.43; 95%CI: 1.01, 2.03; $p = 0.046$). The probability of reversal after 1 h was 75% (95% CI: 60, 84) for LDN and 85% (95% CI: 80, 89) for HDN. Eight patients with missing reversal dose times were excluded (Table 4, Figure 2).

HDN patients were less likely than LDN patients to require re-dosing of naloxone at any given time post reversal (HR = 0.53; 95%CI: 0.30, 0.92; $p = 0.025$). The probability of re-dose after 30 min was 26% (95% CI: 13, 37) for LDN and 8% (95% CI: 5, 12) for HDN. Seventy-two patients whose opioid toxicity never reversed did not meet the inclusion criteria for this analysis, and two additional patients with missing dose times were excluded (Table 4, Figure 3).

LDN patients were treated with a mean total dose of 0.38 (SD 0.47) mg of naloxone: 0.22 (SD 0.41) mg before reversal and 0.19 (SD 0.33) mg after study criteria for reversal was met. HDN patients were treated with a mean total dose of 0.98 (SD 0.77) mg of naloxone: 0.66 (SD 0.43) mg before reversal and 0.27 (SD 0.46) mg after study criteria for reversal was met. LDN patients were treated with a mean of 1.5 doses of naloxone before reversal occurred and a mean of 1.0 doses of naloxone after study criteria for reversal was met. HDN patients were treated with a mean of 1.2 doses of naloxone before reversal occurred and 0.7 doses after study criteria for reversal was met (Table 5).

Discussion

In this retrospective matched cohort study, patients treated with initial HDN were more likely to have OW but also more likely to have opioid reversal versus patients treated with initial LDN. It is important to understand the association between naloxone dosing, OW and reversal of opioid toxicity in order to optimize naloxone administration. Although LDN has been recommended to prevent opioid withdrawal in patients who are tolerant to opioids [19,27,28], it has not been demonstrated in clinical studies that higher doses of naloxone are associated with a higher incidence of OW. This study demonstrates a strong association between naloxone dose and the frequency of OW: four times as many HDN

Table 2. Patient outcomes for matched cohort.

	All ($n = 379$)	Low dose ($n = 80$)	High dose ($n = 299$)
Adequate reversal within 30 min			
	Mean (SD)		
Time from first to reversal dose[a] (min)			
All patients	11.6 (67.0)	18.9 (71.5)	9.9 (66.0)
Patients who were not already reversed	20.4 (88)	48 (109.1)	16.3 (84.1)
Time from first to last dose (min)	84.5 (158.9)	86.5 (158.3)	83.9 (159.3)
Time from reversal to subsequent dose (min)	95.6 (84.5)	59.8 (60.2)	105.4 (87.8)
	Count (%)		
Appeared reversed prior to initial dose[b]	$n = 130$ (34.3%)	$n = 34$ (42.5%)	$n = 96$ (32.1%)
Cumulative number of patients who met reversal criteria[c] within 30 minutes of:			
1st dose	$n = 256$ (67.5%)	$n = 46$ (57.5%)	$n = 210$ (70.2%)
2nd dose	$n = 292$ (77.0%)	$n = 52$ (65.0%)	$n = 240$ (80.3%)
3rd dose	$n = 300$ (79.2%)	$n = 53$ (66.2%)	$n = 247$ (82.6%)
Any dose	$n = 307$ (81.0%)	$n = 57$ (71.2%)	$n = 250$ (83.6%)
Discharge disposition			
Discharged	$n = 262$ (69.1%)	$n = 45$ (56.2%)	$n = 217$ (72.6%)
Left against medical advice	$n = 44$ (11.6%)	$n = 15$ (18.8%)	$n = 29$ (9.7%)
Admitted	$n = 71$ (18.7%)	$n = 19$ (23.8%)	$n = 52$ (17.4%)
Died	$n = 2$ (0.5%)	$n = 1$ (1.2%)	$n = 1$ (0.3%)
Adequately reversed or discharged/left	$n = 363$ (95.8%)	$n = 71$ (88.8%)	$n = 292$ (97.7%)
Withdrawal and complications			
	Count (%)		
Any withdrawal symptom after 1st dose	$n = 63$ (16.6%)	$n = 4$ (5%)	$n = 59$ (19.7%)
Agitation	$n = 35$ (9.2%)	$n = 3$ (3.8%)	$n = 32$ (10.7%)
Nausea/Vomiting	$n = 19$ (5.0%)	$n = 2$ (2.5%)	$n = 17$ (5.7%)
Aggression	$n = 4$ (1.1%)	$n = 0$	$n = 4$ (1.3%)
Tachycardia	$n = 7$ (1.8%)	$n = 0$	$n = 7$ (2.3%)
Diaphoresis	$n = 7$ (1.8%)	$n = 0$	$n = 7$ (2.3%)
Restlessness	$n = 3$ (0.8%)	$n = 0$	$n = 3$ (1.0%)
Tremor	$n = 1$ (0.3%)	$n = 0$	$n = 1$ (0.3%)
Yawning	$n = 1$ (0.3%)	$n = 0$	$n = 1$ (0.3%)
Rhinorrhea	$n = 1$ (0.3%)	$n = 0$	$n = 1$ (0.3%)
Any withdrawal symptom after any dose	$n = 101$ (26.6%)	$n = 12$ (15%)	$n = 89$ (29.8%)
Agitation	$n = 57$ (15.0%)	$n = 9$ (11.2%)	$n = 48$ (16.1%)
Nausea/Vomiting	$n = 34$ (9.0%)	$n = 4$ (5.0%)	$n = 30$ (10.0%)
Aggression	$n = 13$ (3.4%)	$n = 0$	$n = 13$ (4.3%)
Tachycardia	$n = 11$ (2.9%)	$n = 0$	$n = 11$ (3.7%)
Diaphoresis	$n = 11$ (2.9%)	$n = 1$ (1.2%)	$n = 10$ (3.3%)
Restlessness	$n = 7$ (1.8%)	$n = 0$	$n = 7$ (2.3%)
Tremor	$n = 2$ (0.5%)	$n = 0$	$n = 2$ (0.7%)
Yawning	$n = 2$ (0.5%)	$n = 0$	$n = 2$ (0.7%)
Rhinorrhea	$n = 1$ (0.3%)	$n = 0$	$n = 1$ (0.3%)
Complications			
Pulmonary edema	$n = 4$ (1.1%)	$n = 0$	$n = 4$ (1.3%)
Intubation	$n = 6$ (1.6%)	$n = 0$	$n = 6$ (2.0%)

[a]Patients who appeared already reversed or met reversal criteria within 30 min of the initial dose have a value of 0 min.
[b]Based on pre-dose vitals: GCS > 10 and either respiratory rate > 11 or O2 saturation > 91%.
[c]Based on post-dose vitals within 30 min: GCS > 10 and either respiratory rate > 11 or O2 saturation > 91%. This also includes patients who appeared to meet reversal criteria prior to the initial dose.

patients (19.7%) as LDN patients (5.0%) had OW after a single dose of naloxone.

Other research has shown that adverse effects including OW are common in patients treated with naloxone for opioid OD. Incidence rates of OW varying from 3% to 40.6% have been reported [6,37–41]. However, in contrast to this study, significant differences in the frequency of adverse events including OW were not found in two studies that compared different naloxone dosing regimens by the same route of administration. Khosravi et al. compared patients with opioid OD receiving IV naloxone 0.1 mg in 2–3 min intervals versus 0.04 mg increasing to 0.4 mg, 2 mg, and 10 mg in 2–3 min intervals and found similar incidence of withdrawal syndrome [31]. Similarly, Wong et al. compared IV naloxone 0.4 mg versus 1–2 mg and found similar rates of adverse events including symptoms of withdrawal [32].

Our research also showed that, HDN patients were more likely than LDN patients to meet our criterion for reversal after the initial dose and after any dose of naloxone. In this study, 15.0% of LDN patients and 38.1% of HDN patients whose opioid OD toxicity was not reversed before receiving naloxone had opioid reversal after an initial single dose of naloxone, indicating HDN is more effective for reversing opioid OD than LDN. However, it should be noted that the adverse effects of opioid toxicity can be prevented by the provision of ventilation and supportive care. Patients can be ventilated while careful titration using small doses of naloxone is completed. When we analyzed the subgroup of 172 patients who received naloxone by the intravenous route,

Table 3. Odds ratios (ORs) and hazard ratios (HRs) for outcome in patients treated with high dose versus low dose naloxone.

	Conditional logistic regression[a] OR (95%CI) *p*-value				Cox proportional hazards regression[a] HR (95%CI) *p*-value	
	Withdrawal symptoms after initial dose	Withdrawal symptoms at any time	Met reversal criteria within 30 mins of initial dose	Met reversal criteria within 30 mins of any dose	Time to reversal[g]	Time to re-dose post reversal[h]
Primary analyses						
Unadjusted	OR = 4.38 (1.56, 12.35) $p = 0.0052$	OR = 2.34 (1.21, 4.52) $p = 0.0111$	OR = 1.70 (1.03, 2.83) $p = 0.0397$	OR = 2.01 (1.14, 3.55) $p = 0.0161$	HR = 1.33 (0.96, 1.84) $p = 0.0839$	HR = 0.54 (0.33, 0.88) $p = 0.0143$
Adjusted[b]	OR = 8.43 (1.96, 36.27) $p = 0.0042$	OR = 2.56 (1.17, 5.60) $p = 0.0187$	OR = 2.73 (1.19, 6.26) $p = 0.0181$	OR = 6.07 (1.81, 20.32) $p = 0.0034$	HR = 1.43 (1.01, 2.03) $p = 0.0458$	HR = 0.53 (0.30, 0.92) $p = 0.0251$
Subgroup analyses						
RR $\leq$ 12[c]	OR = 4.68 (1.08, 20.22) $p = 0.0390$	OR = 1.94 (0.85, 4.42) $p = 0.1143$	OR = 2.40 (1.26, 4.58) $p = 0.0077$	OR = 3.61 (1.70, 7.69) $p = 0.0008$	HR = 1.77 (1.34, 2.76) $p = 0.0115$	HR = 0.52 (0.28, 0.94) $p = 0.0317$
Exact match[d]	OR = 4.12 (1.46, 11.64) $p = 0.0075$	OR = 2.31 (1.20, 4.47) $p = 0.0127$	OR = 1.71 (1.03, 2.84) $p = 0.0386$	OR = 1.92 (1.08, 3.41) $p = 0.0259$	HR = 1.35 (0.97, 1.88) $p = 0.0740$	HR = 0.58 (0.34, 0.96) $p = 0.0346$
Not reversed before initial dose[e]	OR = 2.78 (0.78, 9.92) $p = 0.1141$	OR = 1.89 (0.79, 4.52) $p = 0.1505$	OR = 3.70 (1.67, 8.20) $p = 0.0013$	OR = 3.43 (1.55, 7.59) $p = 0.0024$	HR = 2.68 (1.44, 4.98) $p = 0.0018$	HR = 0.49 (0.22, 1.09) $p = 0.0815$
Naloxone administered by IV[f]	OR = 3.43 (1.17, 10.07) $p = 0.0251$	OR = 1.93 (0.85, 4.39) $p = 0.1143$	OR = 1.37 (0.69, 2.71) $p = 0.3621$	OR = 1.36 (0.66, 2.80) $p = 0.4068$	OR = 1.17 (0.73, 1.88) $p = 0.5199$	OR = 0.77 (0.37, 1.61) $p = 0.4877$

[a]Models are stratified by matched sets based on initial respiratory rate.
[b]Models include age in years, sex, pre-naloxone GCS (3–8, 9–10, and 11–15), and presence of other drugs; $n = 40$ (15 LDN, 25 HDN) patients with missing GCS were excluded.
[c]Models include $n = 239$ (49 LDN, 190 HDN) patients with a respiratory rate less than or equal to 12.
[d]Models include $n = 359$ (78 LDN, 281 HDN) patients with exact respiratory rate matches.
[e]Models include $n = 249$ (46 LDN, 203 HDN) patients who did not already meet reversal criteria prior to the initial dose.
[f]Models include $n = 172$ (57 LDN, 115 HDN) patients whose initial dose was administered by IV (excludes patients whose match did not receive IV naloxone).
[g]$n = 8$ (1 LDN, 7 HDN) patients with missing dosage times were excluded. Patients who never met reversal criteria were censored at their last known dose time.
[h]$n = 72$ (23 LDN, 47 HDN) patient who never met reversal criteria and an additional $n = 2$ (2 HDN) patients with missing dosage times were excluded. Patients who were never given a subsequent dose of naloxone were right-censored at last available follow-up (time of discharge or time 0 if unavailable).

we again found that OW and adequate reversal occurred more often in HDN patients than in LDN patients but these findings were not statistically significant. It should be noted, however, that HDN patients were much more likely than LDN patients to receive naloxone by the intramuscular or subcutaneous route. Since circulating naloxone levels after intravenous dosing would be at least as high as after intramuscular or subcutaneous dosing, it is reasonable to expect that if naloxone had been administered IV to all HDN patients that even higher rates of OW and adequate reversal would have occurred in the HDN group.

We found no other studies comparing rates of opioid reversal in patients treated with different dosing regimens of naloxone. However, Khosravi et al. evaluated another measure of naloxone effectiveness, time to reversal of opioid toxicity, and found more rapid time to reversal with HDN – (median 6 min; IRQ 5–8 min) versus (median 12.5 min; IRQ 7–18 min) for LDN [31].

Our study showed that LDN patients were more likely to receive re-dosing at any given time post reversal. In contrast, Wong et al. found similar time to re-dose in patients who were treated with 0.4 mg IV naloxone (median 72 min; IQR 46–139 min) compared to patients given 1–2 mg IV naloxone (median 70 min; IRQ 44–126 min), although the naloxone doses used were far higher than doses used on our study [32].

Most guidelines recommend an initial naloxone dose of 0.04 mg to 0.4 mg [29] but our LDN patients were treated with a mean total dose of 0.38 mg. This is less than the initial dose of naloxone recommended in some guidelines [29].

The findings of this study suggest that different approaches to naloxone dosing may be needed in different settings. With the rapid expansion of take-home-naloxone programs, an increasing number of opioid OD patients are being resuscitated by lay rescuers in the community. Although there is evidence that bystander resuscitation attempts improve outcomes [42], lay rescuers may not have the expertise to support ventilation until treatment with naloxone restores adequate ventilation. Several experts have stated that when patients are resuscitated by lay rescuers in community settings where fentanyl is common, rapid reversal of opioid toxicity using larger naloxone doses is the best approach because life-threatening respiratory depression can occur in 2–3 min with fentanyl OD [43,44]. Restoring ventilation must take precedence over avoidance of OW [45,46]. It should be noted that currently HDN is the standard community naloxone dosing regimen around the world, where either 0.4 mg injectable or 4.0 mg intranasal are generally used as an initial dose in take-home-naloxone kits.

However, the use of HDN may not be the best approach for patients treated by health care professionals in medical settings where patient monitoring and advanced respiratory support is possible. Health care professionals can support ventilation until opioid reversal is achieved, even if several doses of naloxone are required. Several experts have recommended that the best approach to naloxone dosing in

Table 4. Kaplan–Meier estimates and 95% confidence intervals for event probabilities and event time quantiles.

	Low dose			High dose		
Time to reversal (first dose to reversal dose)						
Event rate	70.1% (56/79)			83.2% (243/292)		
Event time quantiles (95%CI)[a]						
25th	0 (0, 0) min			0 (0, 0) min		
Median	0 (0, 10) min			0 (0, 0) min		
75th	230 (14, –) min			8 (1, 17) min		
Cumulative event probabilities						
Time (min)	At risk	Events	Prob. (95% CI)	At risk	Events	Prob. (95% CI)
0	79	45	0.57 (0.45, 0.67)	292	204	0.70 (0.64, 0.75)
15	14	5	0.67 (0.54, 0.77)	45	22	0.79 (0.74, 0.84)
30	13	1	0.70 (0.56, 0.79)	33	8	0.83 (0.78, 0.87)
60	8	2	0.75 (0.60, 0.84)	22	4	0.85 (0.80, 0.89)
120	7	0	0.75 (0.60, 0.84)	17	1	0.86 (0.81, 0.90)
240	4	1	0.80 (0.62, 0.89)	7	1	0.87 (0.82, 0.91)
420	2	1	0.85 (0.65, 0.94)	5	0	0.87 (0.82, 0.91)
Time to re-dose (reversal dose to subsequent dose)						
Event rate	49.1% (28/57)			41.5% (103/248)		
Event time quantiles (95%CI)[a]						
25th	30 (15, 87) min			86 (70, 127) min		
Median	162 (87, –) min			255 (207, –) min		
75th	–			–		
Cumulative event probabilities						
Time (min)	At risk	Events	Prob. (95% CI)	At risk	Events	Prob. (95% CI)
0	57	0	0.00 (0.00, 0.00)	248	0	0.00 (0.00, 0.00)
15	46	10	0.19 (0.08, 0.28)	222	11	0.05 (0.02, 0.08)
30	41	4	0.26 (0.13, 0.37)	211	8	0.08 (0.05, 0.12)
60	35	4	0.34 (0.20, 0.45)	185	23	0.19 (0.13, 0.23)
120	27	4	0.42 (0.27, 0.54)	135	27	0.31 (0.25, 0.37)
180	16	5	0.55 (0.38, 0.67)	104	13	0.38 (0.31, 0.45)
420	11	1	0.58 (0.40, 0.70)	30	20	0.54 (0.45, 0.61)
600	10	0	0.58 (0.40, 0.70)	18	1	0.55 (0.46, 0.63)

[a]Quantiles and confidence intervals are derived from the crude Kaplan-Meier curves. The median and its confidence limits, for example, are defined by drawing a horizontal line on the survival curve when survival is 50%. Some quantiles cannot be estimated because the survival function is not defined at that quantile. The upper confidence limit is not defined when the survival function is flat at that quantile.

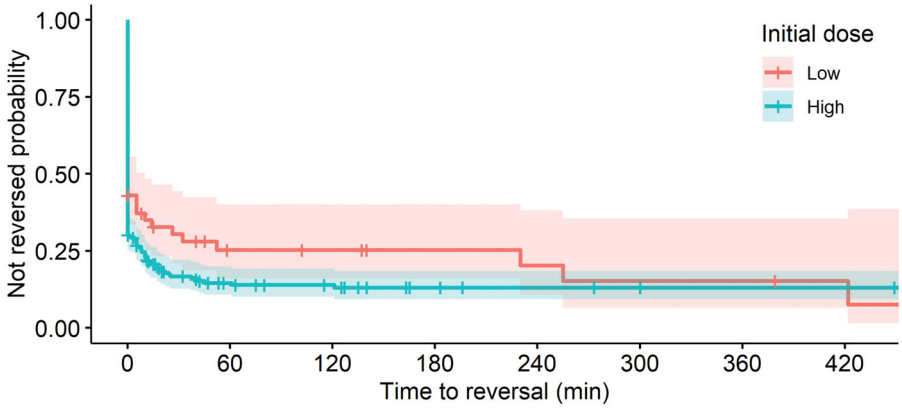

Figure 2. Crude Kaplan–Meier curves for time from first dose (0 min) until reversal dose among unmatched LDN ($n = 79$) and HDN ($n = 292$) patients whose dose times were recorded. Confidence intervals are shown as colored bands around the survival function.

medical settings is careful titration of naloxone using small doses [19,27,28,46–48]. Kim et al. recommends administration of IV naloxone in a dose of 0.04 mg administered every 2–3 min as needed to reverse respiratory depression [19]. The results of this study will provide guidance for emergency providers who must determine naloxone dosing when caring for patients with opioid ODs. However, high quality prospective studies are required to determine the best naloxone dosing regimens in different settings.

Limitations: Our urban setting has frequent opioid OD, often initially managed by lay rescuers with naloxone. A considerable proportion of patients decline transport when the ambulance arrives. A single EMS agency provides all prehospital care, and we collected data from two EDs where opioid OD patient are managed frequently; consequentially our results may not extend to all settings. Due to the retrospective nature of the study, it was not possible to control for all possible confounding between the two groups, including the severity of OD. Although we used RR in an attempt to match OD severity, there were fewer patients with GCS $\leq$8 in the LDN group. LDN patients were more likely to be managed in the ED and to receive naloxone by the IV route.

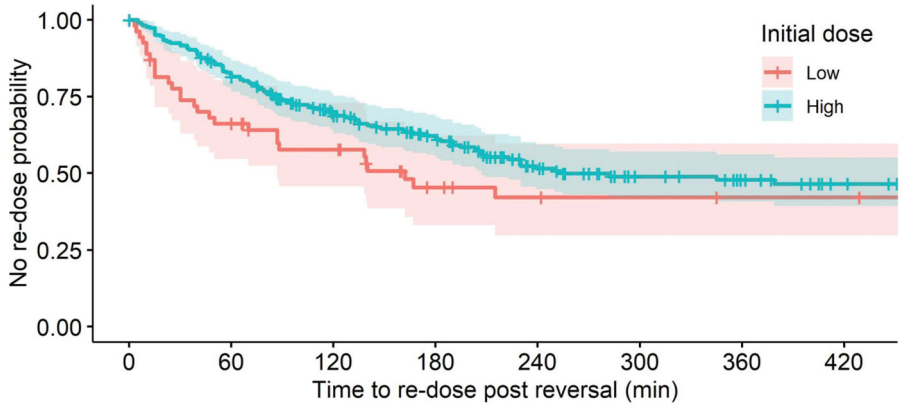

Figure 3. Crude Kaplan-Meier curves for time from reversal dose (0 min) to re-dose among unmatched LDN ($n = 57$) and HDN ($n = 248$) patients who met reversal criteria and whose dose times were recorded. Confidence intervals are shown as colored bands around the survival function.

Table 5. Naloxone doses and dosage amounts for matched cohort.

	All ($n = 379$)	Low dose ($n = 80$)	High dose ($n = 299$)
	Mean (SD)		
Number of doses given			
Until reversal	1.3 (0.8)	1.5 (1.4)	1.2 (0.6)
Post reversal	0.8 (1.2)	1.0 (1.4)	0.7 (1.2)
Total	2.1 (1.5)	2.5 (2)	2.0 (1.3)
Dosage given (mg)			
Until reversal	0.58 (0.46)	0.22 (0.41)	0.66 (0.43)
Post reversal	0.26 (0.44)	0.19 (0.33)	0.27 (0.46)
Total	0.85 (0.76)	0.38 (0.47)	0.98 (0.77)
Dosage given (mg)			
1st dose	0.45 (0.31)	0.10 (0.01)	0.55 (0.28)
2nd dose	0.37 (0.28)	0.17 (0.17)	0.43 (0.28)
3rd dose	0.40 (0.35)	0.18 (0.13)	0.47 (0.37)
4th dose	0.36 (0.34)	0.20 (0.16)	0.45 (0.38)
5th dose	0.33 (0.23)	0.25 (0.22)	0.38 (0.23)
	Count (%)		
Initial dosage			
<0.1 mg	$n = 6$ (1.6%)	$n = 6$ (7.5%)	$n = 0$
0.1 mg	$n = 74$ (19.5%)	$n = 74$ (92.5%)	$n = 0$
0.2 mg	$n = 50$ (13.2%)	$n = 0$	$n = 50$ (16.7%)
0.4 mg	$n = 129$ (34%)	$n = 0$	$n = 129$ (43.1%)
0.8 mg	$n = 108$ (28.5%)	$n = 0$	$n = 108$ (36.1%)
>0.8 mg	$n = 12$ (3.2%)	$n = 0$	$n = 12$ (4%)
Number of patients given			
1 dose	$n = 180$ (47.5%)	$n = 36$ (45.0%)	$n = 144$ (48.2%)
2 doses	$n = 91$ (24.0%)	$n = 18$ (22.5%)	$n = 73$ (24.4%)
3 doses	$n = 59$ (15.6%)	$n = 9$ (11.2%)	$n = 50$ (16.7%)
4 doses	$n = 22$ (5.8%)	$n = 6$ (7.5%)	$n = 16$ (5.4%)
5 or more doses	$n = 27$ (7.1%)	$n = 11$ (13.8%)	$n = 16$ (5.4%)
≥1 dose post reversal	$n = 133$ (35.1%)	$n = 28$ (35.0%)	$n = 105$ (35.1%)

Some health records had incomplete or missing data, and, in particular, some OW may not have been recorded, and the exact time of reversal may not have been accurately documented. Exclusion of patients because there was incomplete or missing documentation of the initial naloxone dose or vital signs prior to the initial naloxone dose was common in patients who received naloxone administration by laypersons. The use of specific definitions of adequate reversal because we did not have information on the physician's clinical judgement as to whether adequate reversal had occurred may have introduced bias, although the magnitude and direction of resulting bias are unclear. For some subgroup and survival analyses, the event rate may be low, with resulting wide confidence intervals, and potential model overfit. Drug testing was not routinely completed in EDs, so the proportion of patients with confirmed fentanyl OD cannot be confirmed, but in our jurisdiction fentanyl is implicated in the majority of cases of illicit opioid OD deaths [49].

Conclusions

HDN patients were more likely to have OW but also more likely to have opioid reversal versus LDN patients.

Disclosure statement

No potential conflict of interest was reported by the author(s).

References

[1] United Nations Office on Drugs and Crime: World Drug Report. 2018. (United Nations publication, Sales No. E.18.XI.9)

[2] Scholl L, Seth P, Kariisa M, et al. Drug and opioid-involved overdose deaths – United States, 2013–2017. Morb Mortal Wkly Rep. 2019;67:1419–1427.

[3] National report: Apparent opioid-related deaths in Canada. September 2019. [cited 2019 Oct 8]. https://health-infobase.canada.ca/datalab/national-surveillance-opioid-mortality.html

[4] McDonald R, Strang J. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. Addiction. 2016;111(7):1177–1187.

[5] Coffin PO, Sullivan SD. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. Ann Intern Med. 2013; 158(1):1–9.

[6] Dettmer K, Sauders B, Strang J. Take home naloxone and the prevention of deaths form opiate overdose: two pilot schemes. Brit Med J. 2001;322(7291):895–896.

[7] Irvine MA, Kuo M, Buxton JA, et al. Modelling the combined impact of interventions in averting deaths during a synthetic-opioid overdose epidemic. Addiction. 2019;114(9):1602–1613.

[8] Johnson C, Mayer P, Grosz D. Pulmonary edema following naloxone administration in a healthy orthopedic patient. J Clin Anesth. 1995;7(4):356–357.

[9] Nath SS, Tripathi M, Pandey C, et al. Naloxone-induced pulmonary edema: a potential cause of postoperative morbidity in laparoscopic donor nephrectomy. Indian J Med Sci. 2009;63(2): 72–75.

[10] Partridge BL, Ward CF. Pulmonary edema following low-dose naloxone administration. Anesthesiology. 1986;65(6):709–710.

[11] Flacke JW, Flacke WE, Williams GD. Acute pulmonary in healthy teenagers following naloxone reversal of high-dose morphine anesthesia. Anesthesiology. 1977;47:376–378.

[12] Prough DS, Roy R, Bumgarner J, et al. Acute pulmonary edema in healthy teenagers following conservative doses of intravenous naloxone. Anesthesiology. 1984;60(5):485–486.

[13] Taff RH. Pulmonary edema following naloxone administration in a patient without heart disease. Anesthesiology. 1983;59:576–577.

[14] Schwartz JA, Koenigsberg MD. Naloxone-induced pulmonary edema. Ann Emerg Med. 1987;16(11):1294–1296.

[15] Tanaka GY. Hypertensive reaction to naloxone. JAMA. 1974; 228(1):25–26.

[16] Estilo AE, Cottrell JE. Naloxone, hypertension and ruptured cerebral aneurysm. Anesthesiology. 1981;74:627–633.

[17] Azar I, Turndorf H. Severe hypertension and multiple atrial premature contractions following naloxone administration. Anesth Analg. 1979;58(6):524–525.

[18] Michaelis LL, Hickey PR, Clark TA, et al. Ventricular irritability associated with the use of naloxone hydrochloride. Two case reports and laboratory assessment of the effects of the drug on cardiac excitability. Ann Thorac Surg. 1974;18:608–614.

[19] Kim HK, Nelson LS. Reducing the harm of opioid overdose with safe use of naloxone: a pharmacologic review. Expert Opin Drug Saf. 2015;14(7):1137–1146.

[20] Popper C, Kelen GD, Cunningham G. Naloxone hazard in drug abuser. Lancet. 1989;334(8660):446.

[21] Gaddis GM, Watson WA. Naloxone-associated patient violence: an overlooked toxicity?. Ann Pharmacother. 1992;26:196–198.

[22] Cuss FM, Colaco CB, Baron JH. Cardiac arrest after reversal of effects of opiates with naloxone. Brit Med J. 1984;288(6414): 363–364.

[23] Andree RA. Sudden death following naloxone administration. Anesth Analg. 1980;59(10):782–784.

[24] Cook S, Moeschler O, Katarzyna M, Yersin B. Acute opiate overdose: characteristics of 190 consecutive cases. Addiction. 1998; 93(10):1559–1565.

[25] Seidler D, Stühlinger GH, Fischer G, et al. After antagonization of acute opiate overdose: a survey of hospitals in Vienna. Addiction. 1996;91:1479–1487.

[26] Caudarella A, Dong H, Milloy MJ, et al. Non-fatal overdose as a risk factor for subsequent fatal overdose among people who inject drugs. Drug Alcohol Depend. 2016;162:51–55.

[27] Nelson LS, Howland MA, et al. Opioid Antagonists. In: Nelson LS, editor. Goldfrank's toxicologic emergencies, 11th edn. New York: McGraw-Hil; 2019.

[28] Longnecker DE. Anesthesiology. 3rd edn. New York: McGraw-Hill Professional; 2017.

[29] Connors NJ, Nelson LS. The evolution of recommended naloxone dosing for opioid overdose by medical specialty. J Med Tox. 2016;12:1–6.

[30] Boyer EW. Management of opioid analgesic overdose. N Engl J Med. 2012;367(2):146–155.

[31] Khosravi N, Zamani N, Hassanian-Moghaddam H, et al. Comparison of two naloxone regimens in opioid-dependent methadone overdosed patients: a clinical trial study. CCP. 2018; 12(4):259–265.

[32] Wong F, Edwards CJ, Jarrell DH, et al. Comparison of lower-dose versus higher-dose intravenous naloxone on time to recurrence of opioid toxicity in the emergency department. Clin Toxicol. 2019;57(1):19–24.

[33] Hoffman JR, Schriger DL, Luo JS. The empiric use of naloxone in patients with altered mental status: a reappraisal. Ann Emerg Med. 1991;20(3):246–252.

[34] Thanacoody R, Winter W, Kelley A, et al. Opioid overdose. BMJ Best Practice. 2015; BMJ Publishing Group Ltd. Available from: https://bestpractice.bmj.com/topics/en-us/339

[35] Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs. 2003;35(2):253–259.

[36] Grafstein E, Bullard MJ, Warren D, et al. Revision of the Canadian Emergency Department Information System (CEDIS) presenting complaint list version 1.1. CJEM. 2008;10(02):151–161.

[37] Buajordet I, Næss A, Jacobsen D, et al. Adverse events after naloxone treatment of episodes of suspected acute opioid overdose. Eur J Emerg Med. 2004;11:19–23.

[38] Banjo O, Tzemis D, Al-Qutub D, et al. A quantitative and qualitative evaluation of the British Columbia Take Home Naloxone program. Can Med Assoc J Open. 2014;2(3):E153–E161.

[39] Doe-Simkins M, Walley AY, Epstein A, et al. Saved by the nose: bystander-administrated intranasal naloxone hydrochloride for opioid overdose. Am J Public Health. 2009;99(5):788–791.

[40] Enteen L, Bauer J, McLean R, et al. Overdose prevention and naloxone prescription for opioid users in San Francisco. J Urban Health. 2010;87(6):931–941.

[41] Watson WA, Steele MT, Muelleman RL, et al. Opioid toxicity recurrence after an initial response to naloxone. J Toxicol Clin Toxicol. 1998;36(1-2):11–17.

[42] Dietz P, Cantwell K, Burgess S. Bystander resuscitation attempts at heroin overdose: does it improve outcomes? Drug Alcohol Depend. 2002;67(2):213–218.

[43] Green TC, Gilbert M. Counterfeit medications and fentanyl. JAMA Intern Med. 2016;176(10):1555–1557.

[44] Yassen A, Olofsen E, Romberg R, et al. Mechanism-based PK/PD modeling of the respiratory depressant effect of buprenophine and fentanyl in healthy volunteers. Clin Pharmacol Ther. 2007; 81(1):50–58.

[45] Moss RB, Carlo DJ. Higher doses of naloxone are needed in the synthetic opiod era. Subst Abuse Treat Prev Policy. 2019;14(1): 6–6.

[46] Rzasa Lynn R, Galinkin JL. Naloxone dosage for opioid reversal: current evidence and clinical implications. Ther Adv Drug Saf. 2018;9(1):63–88.

[47] Sivilotti M. Flumazenil, naloxone and the 'coma cocktail'. Br J Clin Pharmacol. 2016;81(3):428–436.

[48] Hamel MG. Revisiting naloxone. a different take on overdose guidelines from Lee County, Fla. J Emerg Med Service. 2016;41: 46–48.

[49] BC Coroners Service Fentanyl-Detected Illicit Drug Overdose Deaths. [cited 2019 Oct]. Available from: https://www2.gov.bc.ca/assets/gov/public-safety-and-emergency-services/death-investigation/statistical/fentanyl-detected-overdose