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Outcomes associated with hospital admissions for accidental opioid overdose in British Columbia: a retrospective cohort study

Short title: Outcomes associated with opioid overdose hospitalizations

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ABSTRACT

Objectives: To study the association between accidental opioid overdose and neurological, respiratory, cardiac and other serious adverse events and whether risk of these adverse events was elevated during hospital readmissions compared to initial admissions.

Design: Retrospective cohort study.

Setting: Population-based study using linked administrative health data in British Columbia, Canada.

Participants: The primary analysis included 2,433 patients with 2,554 admissions for accidental opioid overdose between 2006 and 2015, including 121 readmissions within one year of initial admission. The secondary analysis included 538 patients discharged following a total of 552 accidental opioid overdose hospitalizations and 11,040 controls matched on sex and age +/- 2 years from a cohort of patients with >=180 days of prescription opioid use.

Outcome measures: The primary outcome was encephalopathy; secondary outcomes were adult respiratory distress syndrome, respiratory failure, pulmonary hemorrhage, aspiration pneumonia, cardiac arrest, ventricular arrhythmia, heart failure, rhabdomyolysis, paraplegia or tetraplegia, acute renal failure, death, a composite outcome of encephalopathy or any secondary outcome, and total serious adverse events (all-cause hospitalization or death).

Results: 3% of accidental opioid overdose admissions included encephalopathy and 25% included >=1 adverse events (composite outcome). We found no evidence of increased risk of encephalopathy (odds ratio 0.58; 95% CI 0.14 to 2.51) or other outcomes during readmissions versus initial admissions. In the secondary analysis, <5 patients in each cohort experienced encephalopathy. Risk of the composite outcome (OR 2.15; CI 1.48 to 3.12) and all-cause mortality (OR 2.13; CI 1.18 to 3.86) were higher for patients in the year following overdose relative to controls.

Conclusions: We found no evidence that risk of encephalopathy or other adverse events was higher in readmissions compared to initial admissions for accidental opioid overdose. Risk of serious morbidity and mortality may be elevated in the year following an accidental opioid overdose.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A strength is that adverse events associated with accidental opioid overdose were collected from population data rather than adverse event reports.
- This study provides new data to understand the risk of encephalopathy from a larger sample than previously studied.
- The study investigated a wide range of neurological, respiratory, cardiac and other adverse events over a 10-year period.
- Analysis of accidental opioid overdoses was limited to overdoses that led to a hospital admission.
- We controlled for prescription drug use but lacked information on the actual level of drug exposure including illicit drug use.

A rise in opioid-related deaths in British Columbia (BC) contributed to the declaration of a public health emergency in the province.[1] Serious morbidity related to opioid overdose, in contrast, has received relatively little attention. The rate of hospitalizations due to opioid overdose in Canada rose by more than 30% from 2007-08 to 2014-15.[2]

Opioid overdose may lead to a range of neurological, respiratory, cardiac or other adverse events, although the evidence linking most of these events to opioid poisoning has been limited to case reports. Neurological events include cerebral hypoxia[3-5], anoxic encephalopathy,[6] toxic encephalopathy,[7-9] delayed encephalopathy,[10-11] and leukoencephalopathy[9,12-14] or delayed leukoencephalopathy.[15-19] Respiratory adverse events include adult respiratory distress syndrome (ARDS),[4,6,20] respiratory failure,[20-22] pulmonary hemorrhage[21,23-25] and aspiration pneumonia.[6,26,27] Adverse cardiac outcomes may include cardiac arrest,[28,29] ventricular arrhythmia,[30-32] and heart failure.[22,33,34] Other adverse effects related to opioid overdose may include rhabdomyolysis,[4,35-39], paraplegia or tetraplegia due to spinal cord injury,[40-42] and acute renal failure.[4,26,37,39]

We investigated neurological, respiratory, cardiac or other adverse outcomes among patients who were admitted to hospital for accidental opioid poisoning from 2006 to 2015 in BC. Our study examined outcomes that occurred during hospital admissions for accidental opioid poisoning and in the 365 days following discharge from admissions for opioid poisoning. We provide the frequency of these adverse events, assess the influence of repeated overdose, and investigate whether risk of these outcomes increased over time. We hypothesized that repeated overdose would show a higher risk of adverse events than initial overdoses and that risk would increase over the period of our study due to use of more potent opioids.

METHODS

Study setting and design

We used a retrospective cohort study design to investigate the risk of neurological, respiratory, cardiac and other adverse events during hospital admissions for accidental opioid overdose or in the 1 year following discharge from overdose admissions. The source population for this study consisted of residents of BC who had been registered for provincial medical services for at least 1 year as of any time during 2006-2015.

In our primary analysis, we evaluated whether risk of the study outcomes was increased in repeat admissions for accidental opioid overdose in comparison to initial admissions. This analysis focused on patients who had been admitted to hospital during 2006-2015 for an accidental opioid overdose (diagnostic codes for accidental opioid overdose are found in Table S1 of the Supplementary Appendix). Only patients who had not experienced any of the study outcomes in the year prior to their overdose admission were included in the study, in order to focus on incident outcomes. Patients were excluded if they had received a diagnosis for non-accidental opioid poisoning in the year prior to their overdose admission or a diagnosis of self-harm in their overdose admission or in the previous year, or if they had previously entered long-term or palliative care (diagnostic codes for exclusions are found in Table S2).

We conducted a secondary analysis to evaluate whether risk of study outcomes was elevated in the year following an accidental opioid overdose. In contrast to our primary analysis, this analysis focused on patients with long-term prescription opioid use and included not only patients who had been hospitalized for an accidental opioid overdose but also controls who had not experienced an overdose hospitalization. While in theory we were interested in outcomes following any hospitalization for accidental opioid overdose within the general population, we

chose to focus on patients with long-term opioid use in order allow for greater similarity between overdose patients and controls and to better control for confounding. We included patients with 180 days or more of continuous use of prescription opioid pain medication during 2006-2014, where 'continuous use' was defined by a series of opioid dispensings with no more than 90 days between the end of the days' supply of one script and the beginning of another. Patients were eligible for selection into the "overdose cohort" or control group on or after the date of their first dispensing following 180 days of continuous use of opioid therapy.

In the secondary analysis, patients with long-term prescription opioid use as described above were selected to enter the overdose cohort, if they were admitted to hospital for an accidental opioid overdose and had been discharged from hospital during 2006-2014. We selected 20 controls for each member of the overdose cohort, matched on sex and age within 2 years. The date of each overdose patient's discharge from hospital following an overdose admission served as a "cohort entry date" for the overdose patient and that patient's matched controls. Patients were followed for up to 1 year starting the day after each patient's cohort entry date, and study outcomes were assessed during this follow-up period. Patients could enter the study more than once as a member of the overdose cohort and/or as a control, but it was only possible to enter the overdose cohort more than once if a readmission for accidental opioid overdose occurred at least 1 year from a patient's prior overdose hospitalization. Patients were excluded if they had received a diagnosis of opioid poisoning, self-harm or any of the study outcomes in the year prior to cohort entry, or if they had previously entered long-term or palliative care. Patients were followed from cohort entry date until the earliest of diagnosis with a relevant study outcome, hospital admission or readmission for opioid poisoning, a diagnosis of

self-harm, end of provincial health coverage, entry into long-term or palliative care, death, 365 days of follow-up, or 31 December 2015.

Data sources

We used de-identified, patient-level administrative health data from BC, which were linked with encrypted patient identifiers, to create the study cohorts and conduct analyses. Medical Services Plan (MSP) data included outpatient diagnoses, while the Canadian Institute for Health Information Discharge Abstract Database included hospital admissions and inpatient diagnoses and procedures. MSP registration data were used to determine study eligibility and to define patient demographics. BC PharmaNet data were used to identify a patient's prescription drug use and use of long-term or palliative care drug plans.

Outcome measures

The primary outcome in our study was encephalopathy, which was defined by an inpatient hospital diagnosis of anoxic brain damage, toxic encephalopathy or unspecified encephalopathy. Secondary outcomes included ARDS, respiratory failure, pulmonary hemorrhage, aspiration pneumonia, cardiac arrest, ventricular arrhythmia, heart failure, rhabdomyolysis, paraplegia or tetraplegia, acute renal failure, and death. We also included a composite outcome, which we defined as a diagnosis of encephalopathy and/or any of the secondary outcomes (diagnostic codes for outcomes are found in Table S3). In our secondary analysis, we added the unplanned outcome of "serious adverse events," which was defined as hospitalization or death from any cause, to provide a more comprehensive measure of potential harm. Inpatient hospital data were used to ascertain whether an outcome diagnosis had occurred. Deaths were ascertained with hospital data and MSP registration data.

Covariates

We adjusted our analyses for patient characteristics, including demographic variables, medical history and prescription history. Demographic variables included sex, age category, low-income status, and rural residence. Medical history included variables indicating mental or behavioural disorders due to opioid use, stimulant use, and other substance use, and variables for a history of psychiatric illness, pneumonia, other respiratory illness, Romano comorbidity score (0, 1-2, >=3), and cancer (diagnostic codes for medical covariates are found in Table S4). Prescription history included a variable indicating past use of high-dose opioid pain medication (>90 mg of "oral morphine equivalents" per day, calculated using conversion factors recommended in a recent review of opioid utilization studies)[43] and a variable for lack of any prescription opioid pain medication use (opioid medications are listed in Table S5), and a variable for past use of sedative/hypnotic medication (identified by Anatomical Therapeutic Chemical code N05C). In the secondary analysis, the variable for mental and behaviour disorders due to stimulant use was excluded (due to a low prevalence in the control group), and prescription history consisted of variables for high-dose opioid use (>90 mg of "oral morphine equivalents" per day), length of continuous opioid use (<1, 1 to <2, 2 to <3, 3 to <4, 4 to <5, or >=5 years) and prior sedative use.

Statistical analyses

In the primary analysis, we used logistic regression models to estimate whether the risk of each outcome was elevated during repeat hospital admissions for accidental opioid overdose in comparison to initial admissions. Repeat admissions or "readmissions" were any admissions for accidental opioid overdose that occurred within a year of a discharge for a previous admission. In the same models, we included a series of binary independent variables indicating

the year in which each opioid overdose admission occurred, using the first year of the study, 2006, as a reference year. We inferred the odds of each study outcome occurring in association with an opioid overdose in 2015 in comparison to 2006 (based on the variable indicating an overdose occurred in 2015 versus the reference year), as a test of our hypothesis that the risk of the adverse events we investigated may have increased in recent years due to the use of more potent opioids. In sensitivity analyses related to the outcome of acute kidney failure, we repeated our estimation for the outcome of acute kidney failure while excluding patients with a previous kidney transplant or use of dialysis and controlling for chronic kidney disease, and we examined trends in diagnosis of acute kidney failure among the general population.

In the secondary analysis, we similarly used logistic regression to evaluate whether risk was increased in the 1-year period following a hospital admission for accidental opioid overdose, as compared to controls. The model included a series of binary independent variables for the year in which patients entered the study (according to date of discharge from an overdose patient's overdose admission or corresponding cohort entry date for each control patient), using 2006 as a reference year, to control for time-varying confounding. In additional models, we included interaction terms representing interaction between these "cohort entry year" variables and a variable indicating whether a patient was in the overdose cohort (the "exposed" group), as a test for effect measure modification, to investigate whether risk of our study outcomes in the year following opioid overdose was elevated in more recent years.

All regression models used generalized estimating equations to adjust for "clustering effects" due to multiple observations from the same patients. We had planned to conduct analyses stratified on whether patients had a history of cancer, but due to a smaller than expected sample size we chose instead to control for cancer as a covariate.

Ethics approval

The study was approved by the University of British Columbia Clinical Research Ethics Board.

Patient characteristics

We identified 3,235 patients with a total of 3,519 hospital admissions involving accidental opioid overdose during 2006 to 2015. After excluding patients lacking 1 year of provincial medical services coverage prior to admission and applying other exclusion criteria (described above), the cohort for our primary analysis included 2,433 patients who had experienced 2,554 admissions for accidental opioid overdose, of which 121 were readmissions within a year of a previous admission (Table 1). The age of patients at time of overdose admission ranged from 1 to 99 years (median 48; interquartile range [IQR] 32 to 61 years). Patients who were readmitted tended to have a poorer health status and were more likely to have been diagnosed with opioid use disorder and have used a high-dose prescription opioid.

For the secondary analysis, we identified a cohort of 247,883 patients with at least one episode of long-term prescription opioid use during 2006 to 2014. Our secondary analysis included 538 patients discharged following a total of 552 accidental opioid overdose hospitalizations and 11,040 matched controls from the cohort (Table 2). Ages ranged from 19 to 100 years (median 58; IQR 49 to 67 years), as no younger patients met the entry criteria for overdose during long-term prescription opioid use. Patients in the overdose cohort had a poorer health status than controls, and notably many patients had a history of psychiatric illness, high-dose prescription opioid use for pain, continuous opioid use of 5 years or more, and/or sedative/hypnotic medication use.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. As the study used routinely collected administrative health data, there were no study participants to share results with. There are no plans to disseminate the results of the research to the relevant patient community.

RESULTS

The number of admissions for accidental opioid overdose more than doubled over the period from 2006 to 2015 (Table 3). We found that 3% of overdose admissions during this ten-year period included a diagnosis of encephalopathy and 25% of overdose admissions included at least one of the adverse outcomes included in our composite outcome.

In our primary analysis, we found no evidence of increased risk of encephalopathy during readmission in relation to initial admission for accidental opioid overdose (adjusted OR 0.58; 95% CI 0.14 to 2.51) (Table 4). Similarly, results for secondary outcomes did not indicate any increased risk during readmission. In analyses of the influence of year of overdose admission, the risk of encephalopathy was not elevated in 2015 in comparison to 2006 (OR 0.73; CI 0.28 to 1.89) (Table 4). In contrast, respiratory failure in association with opioid overdose was approximately three times higher in 2015 in relation to 2006 (OR 3.05; CI 1.15 to 8.08), although the estimate was imprecise. While no other outcomes showed a significantly higher risk in the last year of the study, the point estimate for risk of acute renal failure was elevated but non-significant (OR 1.86; CI 0.95 to 3.66). A sensitivity analysis excluding dialysis and kidney transplant patients and controlling for chronic kidney disease produced a similar estimate for increased risk of acute renal failure (OR 2.01; CI 0.99, 4.05). In an additional sensitivity

analysis, an examination of the secular trend in incidence of acute renal failure showed a similar elevation in risk of acute renal failure in the general population of BC (relative risk 2.38; CI 2.30 to 2.47).

In our secondary analysis, encephalopathy was diagnosed in fewer than five patients in each of the cohorts (the overdose cohort and the control cohort), so we could not estimate an odds ratio to compare overdose patients with controls for this outcome. Our analyses suggested a doubling of the odds of experiencing one of the events in our composite outcome (OR 2.15; CI 1.48 to 3.12) or a serious adverse event (OR 1.97; CI 1.62 to 2.39), or dying from any cause (OR 2.13; CI 1.18 to 3.86), for patients in the year following a hospital admission for accidental opioid overdose, compared to controls (Table 5). Analyses of effect measure modification (not shown) did not indicate that year of cohort entry was an effect modifier in relation to risk of our study outcomes among overdose patients in the year following an overdose relative to control patients.

DISCUSSION

In our study, we found that encephalopathy was diagnosed in about 3% of accidental opioid overdose admissions from 2006 to 2015, and at least one of the adverse events in our composite outcome occurred in 25% of accidental opioid overdose admissions. We found no evidence that risk of encephalopathy or other adverse outcomes was increased in readmissions in comparison to initial admissions for accidental opioid overdose. We found that risk of respiratory failure was elevated in 2015 in relation to 2006. Since reports suggest that more potent prescription and illicit opioids have been used in BC toward the end of our study period,[44,45] the apparent increase in risk of respiratory failure may reflect exposure to higher-dose opioids. While the risk of acute renal failure was non-significantly elevated in 2015 compared to 2006, a

sensitivity analysis indicated this may reflect a secular trend in diagnosis of acute kidney failure.[46] Our comparison of overdose patients to controls within a cohort of patients with long-term opioid use suggested that the risk of serious adverse events including respiratory failure and death may be elevated in the year following an accidental opioid overdose.

A potential link between opioid overdose and encephalopathy has been reported in case reports and case series.[3,5,7-19] Additionally, a prospective observational study reported that 1 of 573 patients visiting the emergency department for opioid overdose suffered from cerebral anoxia, ARDS and death,[4] and a retrospective chart review reported that 2 of 42 ICU patients with heroin overdose suffered form anoxemic encephalopathy and death.[6] Our finding that 77 (3%) of 2,554 admissions related to accidental overdose included a diagnosis of encephalopathy provides additional data on this association.

The association between respiratory failure and accidental opioid overdose in our study appears to be consistent with a recent U.S. study. While not directly reporting on respiratory failure, the US study found that 10.0% of emergency department visits for opioid overdose were associated with mechanical ventilation.[47] Our hospital admission data found that respiratory failure occurred in 9.4% of overdose admissions in 2015.

Our study provides new data on potential association between accidental opioid overdose and a range of serious adverse events. A strength of our study was that adverse events associated with overdose were collected from population data rather than adverse event reports. However, our study had some limitations. Our analysis of readmissions which occurred within one year of a previous admission excluded patients with adverse events in the year prior to readmission. However, this exclusion may have created selection bias by excluding patients who were more susceptible to these adverse events from the cohort of readmission patients. In addition, we

analyzed data on accidental opioid hospitalizations but lacked data about overdoses that did not result in a hospital admission and lacked complete information about drug exposure including illicit drug use.

CONCLUSIONS

We found no increased risk of encephalopathy or other adverse events in repeat hospital admissions compared to initial admission for accidental opioid overdose. Our analysis suggests that accidental opioid overdoses were associated with risk of respiratory failure and that risk of respiratory failure associated with opioid overdose was higher in 2015 compared to 2006. The risk of serious adverse events including respiratory failure and death may be elevated in the year following an accidental opioid overdose.

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Author contributions: RM, CD and KB contributed to the study design. RM conducted the data analysis and drafted the manuscript. All authors contributed to the interpretation of the data, revised the work for important intellectual content, provided final approval for the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests: The authors have no competing interests to declare.

Data sharing statement: The authors do not have permission to share data from this study. Study protocol is available on request from the corresponding author.

REFERENCES

1. Government of British Columbia. Provincial health officer declares public health emergency 2016 [updated April 14, 2016. News release]. Available from: https://news.gov.bc.ca/releases/2016HLTH0026-000568.
2. Canadian Centre for Health Information, Canadian Centre on Substance Abuse. Hospitalizations and emergency department visits due to opioid poisoning in Canada. Ottawa, ON: CIHI; 2016.
3. Voigt I. Fatal Overdose due to Confusion of an Transdermal Fentanyl Delivery System. case report. 2013;2013:154143.
4. Etherington J, Christenson J, Innes G, Grafstein E, Pennington S, Spinelli JJ, et al. Is early discharge safe after naloxone reversal of presumed opioid overdose? CJEM, Can. 2000;2(3):156-62.
5. Vila N, Chamorro A. Ballistic movements due to ischemic infarcts after intravenous heroin overdose: report of two cases. Clin Neurol Neurosurg. 1997;99(4):259-62.
6. Grigorakos L, Sakagianni K, Tsigou E, Apostolakos G, Nikolopoulos G, Veldekis D. Outcome of acute heroin overdose requiring intensive care unit admission. J Opioid Manag. 2010;6(3):227-31.
7. Morales Odia Y, Jinka M, Ziai WC. Severe leukoencephalopathy following acute oxycodone intoxication. Neurocrit Care. 2010;13(1):93-7.
8. Mills F, MacLennan SC, Devile CJ, Saunders DE. Severe cerebellitis following methadone poisoning. Pediatr Radiol. 2008;38(2):227-9.
9. Anselmo M, Campos Rainho A, do Carmo Vale M, Estrada J, Valente R, Correia M, et al. Methadone intoxication in a child: toxic encephalopathy? J Child Neurol. 2006;21(7):618-20.

10. Zanin A, Masiero S, Severino MS, Calderone M, Da Dalt L, Laverda AM. A delayed methadone encephalopathy: clinical and neuroradiological findings. J Child Neurol. 2010;25(6):748-51.
11. Shimizu F, Kawai M, Ogasawara J, Negoro K, Morimatsu M, Kanda T. [Delayed encephalopathy following acute fentanyl intoxication]. Rinsho Shinkeigaku. 2007;47(5):222-5.
12. Bellot B, Michel F, Thomachot L, Chaumoitre K, Battaglia F, Lagier P. Acute leukoencephalopathy after buprenorphine intoxication in a 2-year-old child. Europ J Paediatr Neurol. 2011;15(4):368-71.
13. Nanan R, von Stockhausen HB, Petersen B, Solymosi L, Warmuth-Metz M. Unusual pattern of leukoencephalopathy after morphine sulphate intoxication. Neuroradiology. 2000;42(11):845-8.
14. Foy L, Seeyave DM, Bradin SA. Toxic leukoencephalopathy due to transdermal fentanyl overdose. Pediatr Emerg Care. 2011;27(9):854-6.
15. Salazar R, Dubow J. Delayed posthypoxic leukoencephalopathy following a morphine overdose. J Clin Neurosci. 2012;19(7):1060-2.
16. Molloy S, Soh C, Williams TL. Reversible delayed posthypoxic leukoencephalopathy. AJNR Am J Neuroradiol. 2006;27(8):1763-5.
17. Shprecher DR, Flanigan KM, Smith AG, Smith SM, Schenkenberg T, Steffens J. Clinical and diagnostic features of delayed hypoxic leukoencephalopathy. J Neuropsychiatry Clin Neurosci. 2008;20(4):473-7.
18. Barnett MH, Miller LA, Reddel SW, Davies L. Reversible delayed leukoencephalopathy following intravenous heroin overdose. J Clin Neurosci. 2001;8(2):165-7.

19. Pirompanich P, Chankrachang S. Intravenous Heroin-Associated Delayed Spongiform Leukoencephalopathy: Case Report and Reviews of the Literature. J Med Assoc Thai. 2015;98(7):703-8.

20. Pichot C, Petitjeans F, Ghignone M, Quintin L. Swift recovery of severe acute hypoxemic respiratory failure under non-invasive ventilation. Anestezjol. 2015;47(2):138-42.

21. Cole JB, Dunbar JF, McIntire SA, Regelmann WE, Slusher TM. Butyrfentanyl overdose resulting in diffuse alveolar hemorrhage. Pediatrics. 2015;135(3):e740-3.

22. Liu SS, Kovell LC, Horne A, Jr., Chang D, Petronis JD, Zakaria S. A novel case of transient right ventricular failure in a patient with respiratory distress. J Intensive Care Med. 2013;28(3):185-8.

23. Ruzycki S, Yarema M, Dunham M, Sadrzadeh H, Tremblay A. Intranasal Fentanyl Intoxication Leading to Diffuse Alveolar Hemorrhage. J Med Toxicol. 2016;12(2):185-8.

24. Porter R, O'Reilly H. Pulmonary hemorrhage: a rare complication of opioid overdose. Pediatr Emerg Care. 2011;27(8):742-4.

25. Chaturvedi AK, Rao NG, Baird JR. A death due to self-administered fentanyl. J Anal Toxicol. 1990;14(6):385-7.

26. Eizadi-Mood N, Yaraghi A, Sharifian Z, Feizi A, Hedaiaty M, Sabzghabaee AM. Clinical Presentation and the Outcome of Therapy in a Cohort of Patients with Methadone Toxicity in Iran. Mater. 2015;27(4):276-9.

27. Shadnia S, Faiaz-Noori MR, Pajoumand A, Talaie H, Khoshkar A, Vosough-Ghanbari S, et al. A case report of opium body packer; review of the treatment protocols and mechanisms of poisoning. Toxicol. 2007;17(4):205-14.

28. Nielsen K, Nielsen SL, Siersma V, Rasmussen LS. Treatment of opioid overdose in a physician-based prehospital EMS: frequency and long-term prognosis. Resuscitation. 2011;82(11):1410-3.

29. Boyd JJ, Kuisma MJ, Alaspaa AO, Vuori E, Repo JV, Randell TT. Outcome after heroin overdose and cardiopulmonary resuscitation. Acta Anaesthesiol Scand. 2006;50(9):1120-4.

30. Ray WA, Chung CP, Murray KT, Cooper WO, Hall K, Stein CM. Out-of-hospital mortality among patients receiving methadone for noncancer pain. JAMA Intern Med. 2015;175(3):420-7.

31. Butler B, Rubin G, Lawrance A, Batey R, Bell J. Estimating the risk of fatal arrhythmia in patients in methadone maintenance treatment for heroin addiction. Drug Alcohol Rev. 2011;30(2):173-80.

32. Daubin C, Quentin C, Goulle JP, Guillotin D, Lehoux P, Lepage O, et al. Refractory shock and asystole related to tramadol overdose. Clin Toxicol (Phila). 2007;45(8):961-4.

33. Garrett PM. Tramadol overdose and serotonin syndrome manifesting as acute right heart dysfunction. Anaesth Intensive Care. 2004;32(4):575-7.

34. Mitchell Heggs L, Genee O, Fichet J. Bi-ventricular failure following methadone overdose. Intensive Care Med. 2008;34(8):1553-4.

35. Melandri R, Re G, Lanzarini C, Rapezzi C, Leone O, Zele I, et al. Myocardial damage and rhabdomyolysis associated with prolonged hypoxic coma following opiate overdose. J Toxicol Clin Toxicol. 1996;34(2):199-203.

36. Zele I, De Tommaso I, Melandri R, Barakat B, Pezzilli R, Re G, et al. [Rhabdomyolysis during acute poisoning with drugs and narcotics. Experience with 7 clinical cases]. Minerva Med. 1992;83(12):847-52.

37. Sahni V, Garg D, Garg S, Agarwal SK, Singh NP. Unusual complications of heroin abuse: transverse myelitis, rhabdomyolysis, compartment syndrome, and ARF. Clin Toxicol (Phila). 2008;46(2):153-5.

38. Pascual Calvet J, Pou A, Pedro-Botet J, Gutierrez Cebollada J. [Non-infective neurologic complications associated to heroin use]. Arch Neurobiol (Madr). 1989;52 Suppl 1:155-61.

39. Rice EK, Isbel NM, Becker GJ, Atkins RC, McMahon LP. Heroin overdose and myoglobinuric acute renal failure. Clin Nephrol. 2000;54(6):449-54.

40. Kumar R, West DM, Jingree M, Laurence AS. Unusual consequences of heroin overdose: rhabdomyolysis, acute renal failure, paraplegia and hypercalcaemia. Br J Anaesth. 1999;83(3):496-8.

41. Riva N, Morana P, Cerri F, Gerevini S, Amadio S, Formaglio F, et al. Acute myelopathy selectively involving lumbar anterior horns following intranasal insufflation of ecstasy and heroin. J Neurol Neurosurg Psychiatry. 2007;78(8):908-9.

42. Sahni V, Garg D, Garg S, Agarwal SK, Singh NP. Unusual complications of heroin abuse: transverse myelitis, rhabdomyolysis, compartment syndrome, and ARF. Clin Toxicol (Phila). 2008;46(2):153-5.

43. Nielsen S, Degenhardt L, Hoban B, Gisev N. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. Pharmacoepidemiol Drug Saf. 2016;25(6):733-7.

44. Smolina K, Gladstone E, Morgan SG. Determinants of trends in prescription opioid use in British Columbia, Canada, 2005-2013. Pharmacoepidemiol Drug Saf. 2016;25(5):553-9.

45. British Columbia Coroners Service. Illicit drug overdose deaths in BC: January 1, 2007 - Jun 30, 2017. Burnaby, BC; 2017 Aug 4, 2017.

46. Siew ED, Davenport A. The growth of acute kidney injury: a rising tide or just closer attention to detail? Kidney International. 2015;87(1):46-61.

47. Hasegawa K, Brown DF, Tsugawa Y, Camargo CA, Jr. Epidemiology of emergency department visits for opioid overdose: a population-based study. Mayo Clin Proc. 2014;89(4):462-71.

Table 1. Characteristics of patients admitted to hospital for accidental opioid overdose, 2006-2015

Characteristic		Admission n (%)	Readmission n (%)
Hospitalizations		2,433	121
Type of opioid overdose	Opium	8 (0.3)	0
	Heroin	419 (17.2)	15 (12.4)
	Methadone	401 (16.5)	26 (21.5)
	Synthetic opioids§	123 (5.1)	7 (5.8)
	Other opioids‖	1,101 (45.3)	46 (38.0)
	Unspecified/other opioids	515 (21.2)	34 (28.1)
Sex	Female	1,134 (46.6)	54 (44.6)
	Male	1,299 (53.4)	67 (55.4)
Age (years)	Under 10	36 (1.5)	0
	10 to 19	80 (3.3)	<5
	20 to 29	371 (15.2)	16 (13.2)
	30 to 39	411 (16.9)	19 (15.7)
	40 to 49	415 (17.1)	15 (12.4)
	50 to 59	477 (19.6)	21 (17.4)
	60 to 69	329 (13.5)	36 (29.8)
	70 to 79	186 (7.6)	10 (8.3)
	80 or over	128 (5.3)	<5
Low income		719 (29.6)	35 (28.9)
Rural residence		325 (13.4)	17 (14.1)
Substance use disorders*	Opioids	192 (7.9)	25 (20.7)
	Sedatives and hypnotics	22 (0.9)	<5
	Stimulants	112 (4.6)	9 (7.4)
	Other	395 (16.2)	35 (28.9)
Romano comorbidity score*	Zero	1,380 (56.7)	54 (44.6)
	1 to 2	723 (29.7)	40 (33.1)
	3 or more	330 (13.6)	27 (22.3)
Other medical history*	Psychiatric illness	931 (38.3)	58 (47.9)
	Pneumonia	224 (9.2)	27 (22.3)
	Other respiratory illness	473 (19.4)	35 (28.9)
	HIV	42 (1.7)	<5
	Hepatitis C	33 (1.4)	<5
	Cancer	172 (7.1)	11 (9.1)
Opioid prescription history‡	Methadone	29 (1.2)	<5
	Buprenorphine/naloxone	30 (1.2)	<5
	High dose opioid for pain	569 (23.4)	33 (27.3)
	No use of opioids for pain	1,097 (45.1)	50 (41.3)
Other prescription history‡	Sedatives and hypnotics	571 (23.5)	37 (30.6)
	Stimulants	63 (2.6)	<5

Types of opioid overdose correspond to ICD-10 T40.0-T40.4 and T40.6 (some overdoses appear in >1 category). Readmissions are defined as additional accidental opioid overdose admissions within 365 days of prior admission. *Based on diagnoses at a physician or hospital visit in the 365 days before opioid overdose. ‡Based on dispensings in the 180 days prior to opioid overdose. High dose opioid use is defined by a dispensing of opioid pain medication of >90 oral morphine equivalents per day. Small cell sizes are denoted as '<5' or 0 as applicable. §includes buprenorphine, fentanyl, pethidine and tramadol ‖includes codeine, hydromorphone, morphine and oxycodone

Table 2. Characteristics of patients discharged from hospital after accidental opioid overdose and matched controls among patients with long-term prescription opioid use (>=180 days), 2006-2014

Characteristic		Overdose patients n (%)	Controls n (%)
Number of patients		552	11,040
Type of opioid overdose	Heroin	14 (2.5)	n/a
	Methadone	43 (7.8)	n/a
	Synthetic opioids§	42 (7.6)	n/a
	Other opioids‖	337 (61.1)	n/a
	Unspecified/other opioids	143 (25.9)	n/a
Sex	Female	332 (60.1)	6,640 (60.1)
	Male	220 (39.9)	4,400 (39.9)
Age, years	19 to 29	14 (2.5)	269 (2.4)
	30 to 39	41 (7.4)	829 (7.5)
	40 to 49	89 (16.1)	1,771 (16.0)
	50 to 59	165 (29.9)	3,296 (29.9)
	60 to 69	129 (23.4)	2,562 (23.2)
	70 to 79	81 (14.7)	1,611 (14.6)
	80 to 89	25 (4.5)	561 (5.1)
	90 or over	8 (1.4)	141 (1.3)
Low income		141 (25.5)	2,607 (23.6)
Rural residence		95 (17.2)	1,807 (16.4)
Substance use disorders*	Opioids	58 (10.5)	81 (0.7)
	Sedatives and hypnotics	14 (2.5)	16 (0.1)
	Stimulants	17 (3.1)	31 (0.3)
	Other	103 (18.7)	284 (2.6)
Romano comorbidity score*	Zero	202 (36.6)	6,038 (54.7)
	1 to 2	219 (39.7)	3,826 (34.7)
	3 or more	131 (23.7)	1,176 (10.7)
Other medical history*	Psychiatric illness	300 (54.3)	2,534 (23.0)
	Pneumonia	93 (16.8)	405 (3.7)
	Other respiratory illness	162 (29.3)	1,709 (15.5)
	HIV	<5	56 (0.5)
	Hepatitis C	15 (2.7)	27 (0.2)
	Cancer	52 (9.4)	822 (7.4)
Opioid prescription history‡	Methadone	7 (1.3)	20 (0.2)
	Buprenorphine/naloxone	<5	<5
	High dose opioid for pain	305 (55.3)	2,152 (19.5)
Continuous prescription opioid use, years	Under 1	61 (11.1)	1,876 (17.0)
	1 to under 2	92 (16.7)	2,362 (21.4)
	2 to under 3	53 (9.6)	1,422 (12.9)
	3 to under 4	47 (8.5)	1,006 (9.1)
	4 to under 5	33 (6.0)	797 (7.2)
	5 or more	266 (48.2)	3,577 (32.4)
Other prescription history‡	Sedatives and hypnotics	219 (39.7)	2,506 (22.7)
	Stimulants	10 (1.8)	146 (1.3)

Types of opioid overdose correspond to ICD-10 T40.0-T40.4 and T40.6. *Based on diagnoses at a physician or hospital visit in the 365 days before follow-up. ‡Based on dispensings in the 180 days prior to follow-up. High dose opioid use is defined by a dispensing of opioid pain medication of >90 oral morphine equivalents per day. Small cell sizes are denoted as '<5' or 0 as applicable. §includes buprenorphine, fentanyl, pethidine and tramadol ‖includes codeine, hydromorphone, morphine and oxycodone

Table 3. Number of hospital admissions for accidental opioid overdose and outcomes evaluated during overdose admission, by year

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2006-2015
(a) Overdose hospitalizations (n):											
Admission	~178	166	~200	211	207	251	274	284	290	372	2,433
Readmission	<5	6	<5	15	8	17	15	18	16	21	121
All	180	172	203	226	215	268	289	302	306	393	2,554
(b) Type of opioid overdose* (n):											
Heroin	28	27	34	28	28	35	35	56	67	96	434
Methadone	30	26	36	32	31	36	54	47	65	70	427
Synthetic opioid†	9	<7	<7	8	11	10	14	12	19	37	130
Other opioid‡	80	82	81	109	101	135	143	147	121	148	1,147
Unspecified/other	46	41	52	57	53	60	55	56	53	76	549
(c) Number of outcomes* (n):											
Encephalopathy	7	<5	<5	<5	<5	8	14	11	8	17	77
Respiratory failure	<6	<6	7	8	7	10	24	16	17	37	134
Aspiration pneumonia	20	17	18	21	33	31	38	30	36	44	288
Rhabdomyolysis	7	6	10	11	12	10	17	12	19	20	124
Acute renal failure	13	15	9	16	20	25	30	24	34	51	237
Death in hospital	8	<5	7	7	<5	7	9	9	12	13	80
Composite outcome§											
Admission with >=1 event	42	37	36	50	54	68	87	72	82	109	637
Total events	69	55	62	76	83	108	150	111	142	199	1,055
(d) Incidence proportion‖ (%):											
Encephalopathy	3.9	n/a	n/a	n/a	n/a	3.0	4.8	3.6	2.6	4.3	3.0
Respiratory failure	n/a	n/a	3.4	3.5	3.3	3.7	8.3	5.3	5.6	9.4	5.3
Aspiration pneumonia	11.1	9.9	8.9	9.3	15.3	11.6	13.1	9.9	11.8	11.2	11.3
Rhabdomyolysis	3.9	3.5	4.9	4.9	5.6	3.7	5.9	4.0	6.2	5.1	4.9
Acute renal failure	7.2	8.7	4.4	7.1	9.3	9.3	10.4	7.9	11.1	13.0	9.3
Death in hospital	4.4	n/a	3.4	3.1	n/a	2.6	3.1	3.0	3.9	3.3	3.1
Composite outcome†											
Admission with >=1 event	23.3	21.5	17.7	22.1	25.1	25.4	30.1	23.8	26.8	27.7	24.9

*To avoid small cell sizes, less common types of overdose (opium) and outcome (e.g., cardiac outcomes) have been omitted, or a value of '<5' was entered for counts and corresponding proportions were listed as 'n/a'. Where counts <5 could be deduced, values of '<6' or '<7' have been used or a tilde (~) was used for approximate values. †includes buprenorphine, fentanyl, pethidine and tramadol ‡includes codeine, hydromorphone, morphine and oxycodone §The "composite outcome" included encephalopathy, ARDS, respiratory failure, pulmonary hemorrhage, aspiration pneumonia, cardiac arrest, ventricular arrhythmia, heart failure, rhabdomyolysis, acute renal failure, or death ("total events" does not equal the sum of the other events reported, because some outcomes included in the composite outcome were not reported separately). ‖Incidence proportion describes the percentage of hospital admissions for accidental opioid overdose in which patients were diagnosed with each type of outcome in each period.

Table 4. Influence of readmission for accidental opioid overdose and year of overdose on neurological, respiratory, cardiac and other outcomes evaluated during overdose admission

	Events	(a) Opioid overdose readmission		(b) Admissions in 2015 vs 2006*	
		Crude OR	Adjusted OR (95% CI)	Crude OR	Adjusted OR (95% CI)
Primary outcome					
Neurological:					
Encephalopathy	77	0.52	0.58 (0.14, 2.51)	1.12	0.73 (0.28, 1.89)
Secondary outcomes					
Respiratory outcomes:					
Respiratory failure	134	1.10	0.93 (0.43, 2.04)	3.65	3.05 (1.15, 8.08)
Aspiration pneumonia	288	0.45	0.48 (0.21, 1.08)	1.01	0.88 (0.49, 1.59)
ARDs	19	n/a	n/a	n/a	n/a
Pulmonary hemorrhage	<5	n/a	n/a	n/a	n/a
Cardiac outcomes:					
Cardiac arrest	56	n/a	n/a	n/a	n/a
Ventricular arrhythmia	5	n/a	n/a	n/a	n/a
Heart failure	28	n/a	n/a	n/a	n/a
Other outcomes:					
Rhabdomyolysis	124	0.64	0.64 (0.24, 1.75)	1.33	0.96 (0.38, 2.43)
Acute renal failure	237	1.13	1.07 (0.60, 1.91)	1.97	1.86 (0.95, 3.66)
Paraplegia or tetraplegia	6	n/a	n/a	n/a	n/a
Death in hospital	80	0.77	0.86 (0.27, 2.76)	0.74	0.63 (0.24, 1.65)
Composite outcome†	637	0.82	0.83 (0.54, 1.26)	1.27	1.08 (0.71, 1.64)

Odds ratio (OR) estimates have been omitted, and replaced with 'n/a' for 'not available', for outcomes where estimation was not possible due to a small number of events in one or more exposure groups. *The 'Admissions in 2015 vs 2006' column reports the odds of each outcome occurring in association with an accidental opioid overdose hospitalization in 2015 as compared to 2006. †The "composite outcome" was defined as the occurrence of >=1 of the following within an admission: encephalopathy, ARDS, respiratory failure, pulmonary hemorrhage, aspiration pneumonia, cardiac arrest, ventricular arrhythmia, heart failure, rhabdomyolysis, acute renal failure, or death (corresponds to 'admission with >=1 event' under the composite outcome in table 3). Occurrences of the composite outcome do not equal the sum of other events, because some admissions included >1 type of event but this only counted once toward the composite outcome. OR=odds ratio. ARDS=adult respiratory distress syndrome

Table 5. Risk of neurological, respiratory, cardiac and other outcomes in 1 year following hospital admission for accidental opioid overdose in comparison to controls among patients with long-term prescription opioid use (>=180 days)

	Events		Odds ratios	
	Overdose patients (n=552)	Controls (n=11,040)	Crude	Adjusted (95% CI)
Primary outcome				
Neurological:				
Encephalopathy	<5	<5	n/a	n/a
Secondary outcome				
Respiratory outcomes:				
Respiratory failure	14	23	12.46	6.21 (2.24, 17.21)
Aspiration pneumonia	5	19	5.30	2.96 (0.90, 9.71)
ARDs	<5	9	n/a	n/a
Pulmonary hemorrhage	0	0	n/a	n/a
Cardiac outcomes:				
Cardiac arrest	0	5	n/a	n/a
Ventricular arrhythmia	0	5	n/a	n/a
Heart failure	9	95	1.93	0.99 (0.45, 2.15)
Other outcomes:				
Rhabdomyolysis	5	19	5.30	3.08 (0.87, 10.88)
Acute renal failure	16	103	3.18	1.66 (0.90, 3.05)
Paraplegia or tetraplegia	<5	6	n/a	n/a
All-cause mortality	22	96	4.73	2.13 (1.18, 3.86)
Composite outcome†	59	309	4.14	2.15 (1.48, 3.12)
Serious adverse events‡	315	3,489	2.84	1.97 (1.62, 2.39)

Odds ratio estimates have been omitted, and replaced with 'n/a' for 'not available', for outcomes where estimation was not possible due to a small number of events in one or more exposure groups. †The "composite outcome" was defined as an inpatient hospital diagnosis of one or more of the following: encephalopathy, ARDS, respiratory failure, pulmonary hemorrhage, aspiration pneumonia, cardiac arrest, ventricular arrhythmia, heart failure, rhabdomyolysis, acute renal failure, or death. ‡Serious adverse events were defined as all-cause hospitalization or death. ARDS=adult respiratory distress syndrome

SUPPLEMENTARY APPENDIX

Table S1. Opioid poisoning codes

ICD-10 codes indicating opioid poisoning, by category:[2]

Description	ICD-10 codes
Poisoning by opium	T40.0
Poisoning by heroin	T40.1
Poisoning by other opioids*	T40.2
Poisoning by methadone	T40.3
Poisoning by synthetic opioid†	T40.4
Poisoning by unspecified/other opioids	T40.6

*includes codeine, hydromorphone, morphine and oxycodone †includes buprenorphine, fentanyl, pethidine and tramadol

Accidental opioid poisoning was defined by meeting both of the following criteria.

- A hospital admission record is coded with an ICD-10 code opioid poisoning (**T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6**). For hospital admissions related to accidental opioid poisoning, the hospital diagnosis type must also be coded as M (most responsible diagnosis); 1 (pre-admit comorbidity); W, X or Y (service transfer diagnoses); or 6 (proxy most responsible diagnosis).
- The hospital admission record is also coded with an external cause ICD-10 code corresponding to accidental opioid poisoning (**X42**, Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified). Note: This is distinguished from codes corresponding to intentional self-harm (X62), harm from therapeutic use (Y45.0), or unknown intent (Y12).

Table S2. Diagnostic codes for exclusions

Description	ICD-9	ICD-10
Encephalopathy (anoxic brain damage, toxic encephalopathy or unspecified encephalopathy)	348.1, 349.82	G93.1, G92, G93.4
Acute respiratory distress syndrome (ARDS)	518.82	J80
Respiratory failure	518.81	J96.0, J96.9
Pulmonary hemorrhage	770.3	R04.8

Aspiration pneumonia	507.0	J69.0
Cardiac arrest	427.5	I46
Ventricular arrhythmia	427.1, 427.4	I47.0, I47.2, I49.0
Heart failure	428	I50
Rhabdomyolysis	728.88	M62.8, T79.6
Paraplegia or tetraplegia	344.0, 344.1	G82
Acute renal failure	584	N17
Intentional self-harm	n/a‡	X60 – X84

‡Only hospital diagnoses were used for identifying intentional self-harm, because E-codes which could be used are only supplementary codes and MSP data are typically coded with only one diagnostic code.

Table S3. Diagnostic codes for outcomes

Type of outcome	Diagnosis	ICD-10 Codes
Neurological	Encephalopathy (anoxic brain damage, toxic encephalopathy or unspecified encephalopathy)	G93.1, G92, G93.4
Pulmonary	Adult respiratory distress syndrome (ARDS)	J80
	Respiratory failure	J96.0, J96.9
	Pulmonary hemorrhage	R04.8
	Aspiration pneumonia	J69.0
Cardiac	Cardiac arrest	I46
	Ventricular arrhythmia	I47.0, I47.2, I49.0
	Heart failure	I50
Other	Rhabdomyolysis	M62.8, T79.6
	Paraplegia or tetraplegia	G82
	Acute renal failure	N17

Table S4. Diagnostic codes for covariates

Description	Subcategory (if applicable)	ICD codes
Mental or behavioural disorders due to psychoactive substance use	Opioids	ICD-9: 304.0, 304.7, 305.5 ICD-10: F11
	Sedatives and hypnotics	ICD-9: 304.1, 305.4 ICD-10: F13
	Stimulants	ICD-9: 304.2, 305.6, 304.4, 305.7 ICD-10: F14, F15
	Other (alcohol, cannabinoids, hallucinogens, volatile solvents, multiple drug use or use of other psychoactive substances)	ICD-9: 303, 304.3, 304.5, 304.6, 304.8, 304.9, 305.0, 305.2, 305.3, 305.8, 305.9 ICD-10: F10, F12, F16, F18, F19
Other psychiatric illness	Depression	ICD-9: 311, 296.2, 296.3 ICD-10: F32, F33
	Bipolar disorder/ mixed mania	ICD-9: 296.0, 296.1, 296.4, 296.9 ICD-10: F31
	Schizophrenia	ICD-9: 295 ICD-10: F20
	Personality disorders	ICD-9: 301 ICD-10: F60
	Other psychosis	ICD-9: 297 - 299 ICD-10: F21 – F29
Pneumonia (excluding aspiration pneumonia)		ICD-9: 480-486, 487.0 ICD-10: J10.0, J11.0, J12-J18
Other respiratory illness	COPD	ICD-9: 490-492, 494-496 ICD-10: J40-J44, J47
	Asthma	ICD-9: 493 ICD-10: J45
	Sleep apnea	ICD-9: 327.23, 780.57 ICD-10: G47.3, P28.3
HIV disease		ICD-9: 042 ICD-10: B20-B24
Hepatitis B		ICD-9: 070.2, 070.3 ICD-10: B16, B18.0, B18.1
Hepatitis C		ICD-9: 070.41, 070.44, 070.51, 070.54, 070.7 ICD-10: B17.1, B18.2
Cancer		ICD-9: 140-208, 209.0-209.3 ICD-10: C00-C96

Table S5. Prescription opioids

Opioids indicated for pain treatment	Opioid substitution medications
Buprenorphine (patch only)	Buprenorphine/ naloxone (trade name: Suboxone)
Codeine	Methadone
Fentanyl	
Hydromorphone	
Pethidine (also known as: meperidine)	
Morphine	
Oxycodone	
Tapentadol	
Tramadol	

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Title (p. 1) and abstract (p. 2) Abstract (pp. 2-3)	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Abstract (p. 2) Abstract (p. 2) Abstract (p. 2)
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Paragraphs 1-2 (p. 4)		
Objectives	3	State specific objectives, including any prespecified hypotheses	Paragraph 3 (p. 4)		
Methods					
Study Design	4	Present key elements of study design early in the paper	Study setting and design, paragraph 1 (p. 5)		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Study setting and design, paragraphs 2-4 (pp. 5-6)		
Participants	6	*(a) Cohort study* - Give the	Cohort study: Study	RECORD 6.1: The methods of study	Study setting and

		eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	setting and design, paragraphs 2-4 (pp. 5-6) Matching in secondary analysis: Study setting and design, paragraph 4 (p. 6)	population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	design, paragraphs 2-4; (pp. 5-6) Tables S1 and S2 (Supplementary appendix, pp. 1-2) n/a Not included
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	'Outcome measures' section (p.7) and Table S3 (Supplementary Appendix, p. 2); 'Covariates' section (p. 8) and Tables S4 and S5 (Supplementary appendix, pp. 3-4); 'Statistical analyses' section (pp. 8-9)	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	'Outcome measures' section (p. 7) and Table S3 (Supplementary Appendix, p. 2); 'Covariates' section (p. 8) and Tables S4 and S5 (Supplementary appendix, pp. 3-4); 'Statistical analyses' section (pp. 8-9)
Data sources/	8	For each variable of interest, give	'Data sources'		

measurement		sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	section indicates sources for types of variables (p. 7); details as under Variables above in this table (pp. 7-9); Supplementary Appendx, pp. 2-4)		
Bias	9	Describe any efforts to address potential sources of bias	'Discussion' section, paragraph 4 (p. 13) (potential selection bias)		
Study size	10	Explain how the study size was arrived at	Study setting and design, paragraphs 2-4 (population data for specific cohorts over 10 years) (pp. 5-6)		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	'Covariates' section (p. 8)		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed	(a) 'Covariates' and 'Statistical analyses' sections (pp. 8-9) (b) 'Statistical analyses', paragraphs 1-2 (pp. 8-9) (c) n/a (d) 'Statistical analyses', paragraph 2 (p. 9) e) 'Statistical analyses', paragraph 1 (pp. 8-9)		

		Cross-sectional study - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	'Data sources' section (p. 7) n/a
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	'Data sources' section (p. 7)
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	(a), (b) 'Patient characteristics' section (p. 10) (c) Not included	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	'Patient characteristics' section (p. 10)
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential	'Patient characteristics' section (p. 10) and Tables 1-2 (pp. 22-		

		confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	23) n/a Not included		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Tables 3-5 (pp. 24-26)		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	'Results' section (pp. 11-12) and Tables 3-5 (pp. 24-26) n/a Not included		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	'Results' section, paragraph 2 (p. 11); Table 4(b) (p. 25)		
Discussion					
Key results	18	Summarise key results with reference to study objectives	'Discussion', paragraphs 1 (p. 12)		

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	'Discussion', paragraph 3 (p. 13) 'Discussion', paragraph 3 (p. 13)	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	'Discussion', final paragraph (p. 13)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	'Conclusion' section (pp. 13-14)		
Generalisability	21	Discuss the generalisability (external validity) of the study results	'Discussion', paragraph 2 (pp. 12-13)		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	'Funding statement' (p. 15)		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Study protocol is available on request as noted in 'Data sharing statement' (p. 15)

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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Outcomes associated with hospital admissions for accidental opioid overdose in British Columbia: a retrospective cohort study

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Outcomes associated with hospital admissions for accidental opioid overdose in British Columbia: a retrospective cohort study

Short title: Outcomes associated with opioid overdose hospitalizations

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ABSTRACT

Objectives: To study the association between accidental opioid overdose and neurological, respiratory, cardiac and other serious adverse events and whether risk of these adverse events was elevated during hospital readmissions compared to initial admissions.

Design: Retrospective cohort study.

Setting: Population-based study using linked administrative data in British Columbia, Canada.

Participants: The primary analysis included 2,433 patients with 2,554 admissions for accidental opioid overdose between 2006 and 2015, including 121 readmissions within one year of initial admission. The secondary analysis included 538 patients discharged following a total of 552 accidental opioid overdose hospitalizations and 11,040 matched controls from a cohort of patients with >=180 days of prescription opioid use.

Outcome measures: The primary outcome was encephalopathy; secondary outcomes were adult respiratory distress syndrome, respiratory failure, pulmonary hemorrhage, aspiration pneumonia, cardiac arrest, ventricular arrhythmia, heart failure, rhabdomyolysis, paraplegia or tetraplegia, acute renal failure, death, a composite outcome of encephalopathy or any secondary outcome, and total serious adverse events (all-cause hospitalization or death). We analyzed these outcomes using generalized linear models with a logistic link function.

Results: 3% of accidental opioid overdose admissions included encephalopathy and 25% included >=1 adverse events (composite outcome). We found no evidence of increased risk of encephalopathy (odds ratio 0.57; 95% CI 0.13 to 2.49) or other outcomes during readmissions versus initial admissions. In the secondary analysis, <5 patients in each cohort experienced encephalopathy. Risk of the composite outcome (OR 2.15; CI 1.48 to 3.12) and all-cause mortality (OR 2.13; CI 1.18 to 3.86) were higher for patients in the year following overdose relative to controls.

Conclusions: We found no evidence that risk of encephalopathy or other adverse events was higher in readmissions compared to initial admissions for accidental opioid overdose. Risk of serious morbidity and mortality may be elevated in the year following an accidental opioid overdose.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A strength is that adverse events associated with accidental opioid overdose were collected from population data rather than adverse event reports.
- This study provides new data to understand the risk of encephalopathy from a larger sample than previously studied.
- The study investigated a wide range of neurological, respiratory, cardiac and other adverse events over a 10-year period.
- Analysis of accidental opioid overdoses was limited to overdoses that led to a hospital admission.
- We controlled for prescription drug use but lacked information on the actual level of drug exposure including illicit drug use.

A rise in opioid-related deaths in British Columbia (BC) contributed to the declaration of a public health emergency in the province.[1] Serious morbidity related to opioid overdose, in contrast, has received relatively little attention. The rate of hospitalizations due to opioid overdose in Canada rose by more than 30% from 2007-08 to 2014-15.[2]

Opioid overdose may lead to a range of neurological, respiratory, cardiac or other adverse events. The evidence linking these events to opioid poisoning has primarily, but not exclusively, been limited to case reports. Neurological events include cerebral hypoxia[3-5], anoxic encephalopathy,[6] toxic encephalopathy,[7-9] delayed encephalopathy,[10-11] and leukoencephalopathy[9,12-14] or delayed leukoencephalopathy.[15-19] Respiratory adverse events include adult respiratory distress syndrome (ARDS),[4,6,20] respiratory failure,[20-22] pulmonary hemorrhage[21,23-25] and aspiration pneumonia.[6,26,27] A retrospective cohort study of opioid overdose leading to intensive care unit admission found that most patients admitted experienced respiratory failure requiring mechanical ventilation, approximately 10 percent died, and among those who died half experienced hypoxic brain injury.[28] Adverse cardiac outcomes may include cardiac arrest,[29,30] ventricular arrhythmia,[31-33] and heart failure.[22,34,35] Other adverse effects related to opioid overdose may include rhabdomyolysis,[4,36-40], paraplegia or tetraplegia due to spinal cord injury,[41-43] and acute renal failure.[4,26,38,40]

We investigated neurological, respiratory, cardiac or other adverse outcomes among patients who were admitted to hospital for accidental opioid poisoning from 2006 to 2015 in BC. Our study examined outcomes that occurred during hospital admissions for accidental opioid poisoning and in the 365 days following discharge from admissions for opioid poisoning. We provide the frequency of these adverse events, assess the influence of repeated overdose, and

investigate whether risk of these outcomes increased over time. We hypothesized that repeated overdose would show a higher risk of adverse events than initial overdoses due to potential cumulative effects of exposure to high-dose opioids, and that risk of adverse events would increase over the period of our study due to increased use of more potent opioids in British Columbia.

METHODS

Study setting and design

We used a retrospective cohort study design to investigate the risk of neurological, respiratory, cardiac and other adverse events during hospital admissions for accidental opioid overdose or in the 1 year following discharge from overdose admissions. The source population for this study consisted of residents of BC who had been registered for provincial medical services for at least 1 year as of any time during 2006-2015.

We investigated outcomes associated with accidental opioid overdose both immediately following an overdose and in the year following an overdose. Our primary analysis focused on outcomes recorded during a hospital admission for an accidental opioid overdose to investigate outcomes immediately following, or shortly after, an overdose. Our secondary analysis focused on outcomes that occurred during the year following discharge from a hospital admission for accidental opioid overdose to investigate events that occurred after a delay following an overdose. Generally, our primary and secondary analyses examined the same neurological, respiratory, cardiac and other adverse events, but in these two different time periods. As described below, however, these two analyses varied in the cohorts studied and the analytical methods used to investigate outcomes.

In our primary analysis, we evaluated whether risk of the study outcomes was increased in repeat admissions for accidental opioid overdose in comparison to initial admissions. For this

analysis, we analyzed a cohort of patients who had been admitted to hospital during 2006-2015 for an accidental opioid overdose. Accidental opioid overdoses represent a subset of all opioid overdoses, which exclude those identified as resulting from intentional self-harm, therapeutic use (that is, occurred when the drug was used as prescribed), or unknown intent,[2] as defined by the International Classification of Disease (ICD), version 10 (diagnostic codes for accidental opioid overdose are found in Table S1 of the Supplementary Appendix). We selected diagnostic codes to identify accidental opioid overdose based on the codes used in a national study by the Canadian Institute for Health Information.[2] A validation study that tested ICD codes for opioid poisoning in electronic health records reported a positive predictive value of 81% for opioid overdoses and poisonings, although it did not test all of the codes that we used in our study.[44] Only patients who had not experienced any of the study outcomes in the year prior to their overdose admission were included in the study, in order to focus on incident outcomes. Patients were excluded if they had received a diagnosis for non-accidental opioid poisoning in the year prior to their overdose admission or a diagnosis of self-harm in their overdose admission or in the previous year, or if they had previously entered long-term or palliative care (diagnostic codes for exclusions are found in Table S2).

We conducted a secondary analysis to evaluate whether risk of study outcomes was elevated in the year following an accidental opioid overdose. In contrast to our primary analysis, this analysis focused on a cohort of patients with long-term prescription opioid use. From this cohort, we selected patients who had been hospitalized for an accidental opioid overdose and controls who had not experienced an overdose hospitalization. We defined a cohort of long-term opioid users to include patients with an episode of prescription opioid analgesic therapy lasting 180 days or more during 2006-2014, where an episode was defined by a series of opioid

dispensings with no more than 90 days between the end of the days' supply of one script and the beginning of another. Patients were eligible for selection into the "overdose cohort" or control group on or after the date of their first dispensing of opioid analgesic medication 180 days into an episode of opioid therapy. Patients were no longer eligible for selection into the study cohort after stopping use of opioid pain medication for a period of 90 days. We used a period of 180 days to define long-term therapy to try to ensure that we were including only patients who were taking these medications over an extended period, with the goal of including patients who were as similar as possible in the overdose cohort and control group. We allowed a grace period between the end of one prescription and the start of another to determine the end of therapy, because some patients might take their medication over a longer period than the recorded days' supply. We expected it would be less common for prescriptions to exceed 90 days, and setting the 'grace period' between prescriptions at 90 days assumed that some patients might continue to take their medication for twice that length of time.

In the secondary analysis, patients with long-term prescription opioid use as described above were selected to enter the overdose cohort, if they were admitted to hospital for an accidental opioid overdose and had been discharged from hospital during 2006-2014. We selected 20 controls for each member of the overdose cohort, matched on sex and age within 2 years. The date of each overdose patient's discharge from hospital following an overdose admission served as a "cohort entry date" for the overdose patient and that patient's matched controls. Patients were followed for up to 1 year starting the day after each patient's cohort entry date, and study outcomes were assessed during this follow-up period. Patients could enter the study more than once as a member of the overdose cohort and/or as a control, but it was only possible to enter the overdose cohort more than once if a readmission for accidental opioid

overdose occurred at least 1 year from a patient's prior overdose hospitalization. Patients were excluded if they had received a diagnosis of opioid poisoning, self-harm or any of the study outcomes in the year prior to cohort entry, or if they had previously entered long-term or palliative care. Patients were followed from cohort entry date until the earliest of diagnosis with a relevant study outcome, hospital admission or readmission for opioid poisoning, a diagnosis of self-harm, end of provincial health coverage, entry into long-term or palliative care, death, 365 days of follow-up, or 31 December 2015.

Data sources

We used de-identified, patient-level administrative health data from BC, which were linked with encrypted patient identifiers, to create the study cohorts and conduct analyses. Medical Services Plan (MSP) data included outpatient diagnoses, while the Canadian Institute for Health Information Discharge Abstract Database included hospital admissions and inpatient diagnoses and procedures. MSP registration data were used to determine study eligibility and to define patient demographics. BC PharmaNet data were used to identify a patient's prescription drug use and use of long-term or palliative care drug plans.

Outcome measures

The primary outcome in our study was encephalopathy, which was defined by an inpatient hospital diagnosis of anoxic brain damage, toxic encephalopathy or unspecified encephalopathy. Secondary outcomes included ARDS, respiratory failure, pulmonary hemorrhage, aspiration pneumonia, cardiac arrest, ventricular arrhythmia, heart failure, rhabdomyolysis, paraplegia or tetraplegia, acute renal failure, and death. We also included a composite outcome, which we defined as a diagnosis of encephalopathy and/or any of the secondary outcomes (diagnostic codes for outcomes are found in Table S3). In our secondary

analysis, we added the unplanned outcome of "serious adverse events," which was defined as hospitalization or death from any cause, to provide a more comprehensive measure of potential harm. Inpatient hospital data were used to ascertain whether an outcome diagnosis had occurred. Deaths were ascertained with hospital data and MSP registration data.

Covariates

We adjusted our analyses for patient characteristics, including demographic variables, medical history and prescription history. Demographic variables included sex, age category, low-income status, and rural residence. Medical history included variables indicating mental or behavioural disorders due to opioid use, stimulant use, and other substance use, and variables for a history of psychiatric illness, pneumonia, other respiratory illness, Romano comorbidity score (0, 1-2, >=3), and cancer (diagnostic codes for medical covariates are found in Table S4). Prescription history included a variable indicating past use of high-dose opioid pain medication (>90 mg of "oral morphine equivalents" per day, calculated using conversion factors recommended in a recent review of opioid utilization studies)[45] and a variable for lack of any prescription opioid pain medication use (opioid medications are listed in Table S5), and a variable for past use of sedative/hypnotic medication (identified by Anatomical Therapeutic Chemical code N05C). In the secondary analysis, the variable for mental and behaviour disorders due to stimulant use was excluded (due to a low prevalence in the control group), and prescription history consisted of variables for high-dose opioid use (>90 mg of "oral morphine equivalents" per day), duration of prescription opioid use (<1, 1 to <2, 2 to <3, 3 to <4, 4 to <5, or >=5 years) and prior sedative use. We used 90 mg of morphine equivalents per day as a cut-off to define high-dose prescription opioid use, because this reflected advice from the College of Physicians and Surgeons of British Columbia to avoid prescribing of doses above this level in

most cases not involving patients with active cancer or those receiving palliative care or end-of-life care.[46]

Statistical analyses

In the primary analysis, we estimated odds ratios to evaluate whether the risk of each outcome was elevated during repeat hospital admissions for accidental opioid overdose in comparison to initial admissions. We used generalized linear models with a logistic link function and a binomial error distribution. Repeat admissions or "readmissions" were any admissions for accidental opioid overdose that occurred within a year of a discharge for a previous admission. In the same models, we included a series of binary independent variables indicating the year in which each opioid overdose admission occurred, using the first year of the study, 2006, as a reference year. We inferred the odds of each study outcome occurring in association with an opioid overdose in 2015 in comparison to 2006 (based on the variable indicating an overdose occurred in 2015 versus the reference year), as a test of our hypothesis that the risk of the adverse events we investigated may have increased in recent years due to the use of more potent opioids. In a sensitivity analysis related to the outcome of acute kidney failure, we examined trends in diagnosis of acute kidney failure among the general population.

In the secondary analysis, we similarly estimated odds ratios to evaluate whether risk was increased in the 1-year period following a hospital admission for accidental opioid overdose, as compared to controls. The model included a series of binary independent variables for the year in which patients entered the study (according to date of discharge from an overdose patient's overdose admission or corresponding cohort entry date for each control patient), using 2006 as a reference year, to control for time-varying confounding. In additional models, we included interaction terms representing interaction between these "cohort entry year" variables and a

variable indicating whether a patient was in the overdose cohort (the "exposed" group), as a test for effect measure modification, to investigate whether risk of our study outcomes in the year following opioid overdose was elevated in more recent years.

All regression models used generalized estimating equations to adjust for "clustering effects" due to multiple observations from the same patients. We had planned to conduct analyses stratified on whether patients had a history of cancer, but due to a smaller than expected sample size we chose instead to control for cancer as a covariate.

Ethics approval

The study was approved by the University of British Columbia Clinical Research Ethics Board.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. As the study used routinely collected administrative health data, there were no study participants to share results with. There are no plans to disseminate the results of the research to the relevant patient community.

RESULTS

Patient characteristics

We identified 3,235 patients with a total of 3,519 hospital admissions involving accidental opioid overdose during 2006 to 2015. After excluding patients lacking 1 year of provincial medical services coverage prior to admission and applying other exclusion criteria (described above), the cohort for our primary analysis included 2,433 patients who had experienced 2,554 admissions for accidental opioid overdose, of which 121 were readmissions within a year of a previous admission (Table 1). The age of patients at time of overdose

admission ranged from 1 to 99 years (median 48; interquartile range [IQR] 32 to 61 years). Patients who were readmitted tended to have a poorer health status and were more likely to have been diagnosed with opioid use disorder and have used a high-dose prescription opioid.

For the secondary analysis, we identified a cohort of 247,883 patients with at least one episode of long-term prescription opioid use during 2006 to 2014. Our secondary analysis included 538 patients discharged following a total of 552 accidental opioid overdose hospitalizations and 11,040 matched controls from the cohort (Table 2). Ages ranged from 19 to 100 years (median 58; IQR 49 to 67 years), as no younger patients met the entry criteria for overdose during long-term prescription opioid use. Patients in the overdose cohort had a poorer health status than controls, and notably many patients had a history of psychiatric illness, high-dose prescription opioid use for pain, prescription opioid use of 5 years or more, and/or sedative/hypnotic medication use.

Frequency of adverse events associated with overdose admissions

The number of hospital admissions for accidental opioid overdose more than doubled over the period of our study, from 180 admissions in 2006 to 393 admissions 2015, including both initial admissions and readmissions (Table 3). We found that 3% of overdose admissions during this ten-year period included a diagnosis of encephalopathy, and 25% of overdose admissions included at least one of the adverse outcomes included in our composite outcome (Table 3).

Adverse events during admissions for accidental opioid overdose

In our primary analysis, we found no evidence of increased risk of encephalopathy during readmission for accidental opioid overdose in comparison to initial admission for accidental opioid overdose (adjusted OR 0.57; 95% CI 0.13 to 2.49) (Table 4). Women admitted to hospital

for accidental opioid overdose had a lower risk of encephalopathy than men (adjusted OR 0.46; 95% CI 0.26 to 0.81) (Table S6 in Supplementary Appendix). In addition, we observed no increase in risk of either death in hospital or our composite outcome during readmission for accidental opioid overdose, compared to initial admission (adjusted OR 0.86, 95% CI 0.27 to 2.76, for death in hospital, and adjusted OR 0.83, 95% CI 0.54 to 1.26, for the composite outcome). Similarly, results for other secondary outcomes did not indicate any increased risk during readmission for accidental opioid overdose, compared initial admission. (Table 4)

We included indicator variables for the year in which each accidental opioid overdose occurred in the regression models for our primary analysis, which provided a test of whether risk of the outcome in each model was higher in the final year of our study (2015) in comparison with the initial year of the study (2006). We found the risk of encephalopathy was not elevated in 2015 in comparison to 2006 (OR 0.73; CI 0.28 to 1.89) (Table 4). In contrast, respiratory failure in association with opioid overdose was approximately three times higher in 2015 in relation to 2006 (OR 3.05; CI 1.15 to 8.08), although the estimate was imprecise. While no other outcomes showed a significantly higher risk in the last year of the study, the point estimate for risk of acute renal failure was elevated but non-significant (OR 1.86; CI 0.95 to 3.66). In a sensitivity analysis, an examination of the general trend in incidence of acute renal failure showed a similar elevation in risk of acute renal failure in the general population of BC (relative risk 2.38; CI 2.30 to 2.47).

Adverse events in year following overdose admissions for accidental opioid overdose

In our secondary analysis, we compared patients in the year following discharge from an accidental opioid overdose admission to controls, among a cohort of patients with long-term prescription opioid use. Encephalopathy was diagnosed in fewer than five patients in each of the

cohorts in our secondary analysis (the overdose cohort and the control cohort), so we could not estimate an odds ratio to compare overdose patients with controls for this outcome. Our analyses suggested a doubling of the odds of experiencing one of the events in our composite outcome (OR 2.15; CI 1.48 to 3.12) or a serious adverse event (OR 1.97; CI 1.62 to 2.39), or dying from any cause (OR 2.13; CI 1.18 to 3.86), for patients in the year following a hospital admission for accidental opioid overdose, compared to controls (Table 5). Analyses of effect measure modification (not shown) did not indicate that year of cohort entry was an effect modifier in relation to risk of our study outcomes among overdose patients in the year following an overdose relative to control patients.

DISCUSSION

In our study, we found that encephalopathy was diagnosed in about 3% of accidental opioid overdose admissions from 2006 to 2015, and at least one of the adverse events in our composite outcome occurred in 25% of accidental opioid overdose admissions. We found no evidence that risk of encephalopathy or other adverse outcomes was increased in readmissions in comparison to initial admissions for accidental opioid overdose. We found that risk of respiratory failure was elevated in 2015 in relation to 2006. Since reports suggest that more potent prescription and illicit opioids have been used in BC toward the end of our study period,[47,48] the apparent increase in risk of respiratory failure may reflect exposure to more potent opioids; however, this increase in risk may have occurred due to co-ingestion of other substances[28] or due to other factors. While the risk of acute renal failure was non-significantly elevated in 2015 compared to 2006, a sensitivity analysis indicated this may reflect a general trend in diagnosis of acute kidney failure.[49] Our comparison of overdose patients to controls within a cohort of patients with long-term opioid use suggested that the risk of serious adverse events including

respiratory failure and death may be elevated in the year following an accidental opioid overdose.

A potential link between opioid overdose and encephalopathy has been reported in case reports and case series.[3,5,7-19] Additionally, a prospective observational study reported that 1 of 573 patients visiting the emergency department for opioid overdose suffered from cerebral anoxia, ARDS and death,[4] and a retrospective chart review reported that 2 of 42 ICU patients with heroin overdose suffered form anoxemic encephalopathy and death.[6] Our finding that 77 (3%) of 2,554 admissions related to accidental overdose included a diagnosis of encephalopathy provides additional data on this association.

We included both anoxic brain damage and toxic encephalopathy in the definition of encephalopathy in our study, because case reports raise concerns about a potential association between opioid overdose about these outcomes, and these diagnoses describe important brain injuries.[6-9] In addition, studies which use administrative health data face the limitation that coding of outcomes in the data will often not be precise, so we have included unspecified encephalopathy in the outcome definition. There is a lack of validation studies for either anoxic or toxic encephalopathy, so the specificity of the individual diagnostic codes we used and of our composite outcome is unknown. Inclusion of unspecified encephalopathy may lead to some outcome misclassification, but this definition will have greater sensitivity to detect encephalopathy when it has occurred. It is expected that any outcome misclassification would be similar across exposure groups in our primary analysis (that is, during an initial or repeat admission for accidental opioid overdose). This type of misclassification could bias the analysis toward a null effect.[50]

The association between respiratory failure and accidental opioid overdose in our study appears to be consistent with a recent U.S. study. While not directly reporting on respiratory failure, the US study found that 10.0% of emergency department visits for opioid overdose were associated with mechanical ventilation.[51] Our hospital admission data found that respiratory failure occurred in 9.4% of overdose admissions in 2015. In addition, a cohort study of 178 adults with opioid overdose leading to intensive care unit admission reported that 84.8% required mechanical ventilation.[28]

Our study provides new data on potential association between accidental opioid overdose and a range of serious adverse events. A strength of our study was that adverse events associated with overdose were collected from population data rather than adverse event reports. These data were more comprehensive than adverse event reports, because the data were collected routinely by the health care system rather than relying on reports from the public, health care providers or manufacturers and because the data available covered most of the population of the province. However, our study had some limitations. Our analysis of readmissions which occurred within one year of a previous admission excluded patients with adverse events in the year prior to readmission. However, this exclusion may have created selection bias by excluding patients who were more susceptible to these adverse events from the cohort of readmission patients. In addition, we analyzed data on accidental opioid hospitalizations but lacked data about overdoses that did not result in a hospital admission and lacked complete information about drug exposure including illicit drug use. We included patients with long-term use of prescription opioids in our secondary analysis based on the information in available administrative health databases; however, this excluded others with long-term opioid use who lacked ongoing prescriptions of their own but used opioids prescribed to others and/or non-prescription opioids. Lastly, our

analyses may have been subject to unmeasured confounders, such as co-ingestion of other drugs with opioids.

CONCLUSIONS

We found no increased risk of encephalopathy or other adverse events in repeat hospital admissions compared to initial admission for accidental opioid overdose. Our analysis suggests that accidental opioid overdoses were associated with risk of respiratory failure and that risk of respiratory failure associated with opioid overdose was higher in 2015 compared to 2006. The risk of serious adverse events including respiratory failure and death may be elevated in the year following an accidental opioid overdose.

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Author contributions: RM, CD and KB contributed to the study design. RM conducted the data analysis and drafted the manuscript. All authors (RM, KB, MM, and CD) contributed to the interpretation of the data, revised the work for important intellectual content, provided final approval for the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REFERENCES

1. Government of British Columbia. Provincial health officer declares public health emergency 2016 [updated April 14, 2016. News release]. Available from: https://news.gov.bc.ca/releases/2016HLTH0026-000568.
2. Canadian Centre for Health Information, Canadian Centre on Substance Abuse. Hospitalizations and emergency department visits due to opioid poisoning in Canada. Ottawa, ON: CIHI; 2016.
3. Voigt I. Fatal Overdose due to Confusion of an Transdermal Fentanyl Delivery System. case report. 2013;2013:154143.
4. Etherington J, Christenson J, Innes G, Grafstein E, Pennington S, Spinelli JJ, et al. Is early discharge safe after naloxone reversal of presumed opioid overdose? CJEM, Can. 2000;2(3):156-62.
5. Vila N, Chamorro A. Ballistic movements due to ischemic infarcts after intravenous heroin overdose: report of two cases. Clin Neurol Neurosurg. 1997;99(4):259-62.
6. Grigorakos L, Sakagianni K, Tsigou E, Apostolakos G, Nikolopoulos G, Veldekis D. Outcome of acute heroin overdose requiring intensive care unit admission. J Opioid Manag. 2010;6(3):227-31.
7. Morales Odia Y, Jinka M, Ziai WC. Severe leukoencephalopathy following acute oxycodone intoxication. Neurocrit Care. 2010;13(1):93-7.
8. Mills F, MacLennan SC, Devile CJ, Saunders DE. Severe cerebellitis following methadone poisoning. Pediatr Radiol. 2008;38(2):227-9.
9. Anselmo M, Campos Rainho A, do Carmo Vale M, Estrada J, Valente R, Correia M, et al. Methadone intoxication in a child: toxic encephalopathy? J Child Neurol. 2006;21(7):618-20.

10. Zanin A, Masiero S, Severino MS, Calderone M, Da Dalt L, Laverda AM. A delayed methadone encephalopathy: clinical and neuroradiological findings. J Child Neurol. 2010;25(6):748-51.

11. Shimizu F, Kawai M, Ogasawara J, Negoro K, Morimatsu M, Kanda T. [Delayed encephalopathy following acute fentanyl intoxication]. Rinsho Shinkeigaku. 2007;47(5):222-5.

12. Bellot B, Michel F, Thomachot L, Chaumoitre K, Battaglia F, Lagier P. Acute leukoencephalopathy after buprenorphine intoxication in a 2-year-old child. Europ J Paediatr Neurol. 2011;15(4):368-71.

13. Nanan R, von Stockhausen HB, Petersen B, Solymosi L, Warmuth-Metz M. Unusual pattern of leukoencephalopathy after morphine sulphate intoxication. Neuroradiology. 2000;42(11):845-8.

14. Foy L, Seeyave DM, Bradin SA. Toxic leukoencephalopathy due to transdermal fentanyl overdose. Pediatr Emerg Care. 2011;27(9):854-6.

15. Salazar R, Dubow J. Delayed posthypoxic leukoencephalopathy following a morphine overdose. J Clin Neurosci. 2012;19(7):1060-2.

16. Molloy S, Soh C, Williams TL. Reversible delayed posthypoxic leukoencephalopathy. AJNR Am J Neuroradiol. 2006;27(8):1763-5.

17. Shprecher DR, Flanigan KM, Smith AG, Smith SM, Schenkenberg T, Steffens J. Clinical and diagnostic features of delayed hypoxic leukoencephalopathy. J Neuropsychiatry Clin Neurosci. 2008;20(4):473-7.

18. Barnett MH, Miller LA, Reddel SW, Davies L. Reversible delayed leukoencephalopathy following intravenous heroin overdose. J Clin Neurosci. 2001;8(2):165-7.

19. Pirompanich P, Chankrachang S. Intravenous Heroin-Associated Delayed Spongiform Leukoencephalopathy: Case Report and Reviews of the Literature. J Med Assoc Thai. 2015;98(7):703-8.

20. Pichot C, Petitjeans F, Ghignone M, Quintin L. Swift recovery of severe acute hypoxemic respiratory failure under non-invasive ventilation. Anestezjol. 2015;47(2):138-42.

21. Cole JB, Dunbar JF, McIntire SA, Regelmann WE, Slusher TM. Butyrfentanyl overdose resulting in diffuse alveolar hemorrhage. Pediatrics. 2015;135(3):e740-3.

22. Liu SS, Kovell LC, Horne A, Jr., Chang D, Petronis JD, Zakaria S. A novel case of transient right ventricular failure in a patient with respiratory distress. J Intensive Care Med. 2013;28(3):185-8.

23. Ruzycki S, Yarema M, Dunham M, Sadrzadeh H, Tremblay A. Intranasal Fentanyl Intoxication Leading to Diffuse Alveolar Hemorrhage. J Med Toxicol. 2016;12(2):185-8.

24. Porter R, O'Reilly H. Pulmonary hemorrhage: a rare complication of opioid overdose. Pediatr Emerg Care. 2011;27(8):742-4.

25. Chaturvedi AK, Rao NG, Baird JR. A death due to self-administered fentanyl. J Anal Toxicol. 1990;14(6):385-7.

26. Eizadi-Mood N, Yaraghi A, Sharifian Z, Feizi A, Hedaiaty M, Sabzghabaee AM. Clinical Presentation and the Outcome of Therapy in a Cohort of Patients with Methadone Toxicity in Iran. Mater. 2015;27(4):276-9.

27. Shadnia S, Faiaz-Noori MR, Pajoumand A, Talaie H, Khoshkar A, Vosough-Ghanbari S, et al. A case report of opium body packer; review of the treatment protocols and mechanisms of poisoning. Toxicol. 2007;17(4):205-14.

28. Pfister GJ, Burkes RM, Guinn B, Steele J, Kelley RR, Wiemken TL, et al. Opioid overdose leading to intensive care unit admission: Epidemiology and outcomes. J Crit Care. 2016;35:29-32.

29. Nielsen K, Nielsen SL, Siersma V, Rasmussen LS. Treatment of opioid overdose in a physician-based prehospital EMS: frequency and long-term prognosis. Resuscitation. 2011;82(11):1410-3.

30. Boyd JJ, Kuisma MJ, Alaspaa AO, Vuori E, Repo JV, Randell TT. Outcome after heroin overdose and cardiopulmonary resuscitation. Acta Anaesthesiol Scand. 2006;50(9):1120-4.

31. Ray WA, Chung CP, Murray KT, Cooper WO, Hall K, Stein CM. Out-of-hospital mortality among patients receiving methadone for noncancer pain. JAMA Intern Med. 2015;175(3):420-7.

32. Butler B, Rubin G, Lawrance A, Batey R, Bell J. Estimating the risk of fatal arrhythmia in patients in methadone maintenance treatment for heroin addiction. Drug Alcohol Rev. 2011;30(2):173-80.

33. Daubin C, Quentin C, Goulle JP, Guillotin D, Lehoux P, Lepage O, et al. Refractory shock and asystole related to tramadol overdose. Clin Toxicol (Phila). 2007;45(8):961-4.

34. Garrett PM. Tramadol overdose and serotonin syndrome manifesting as acute right heart dysfunction. Anaesth Intensive Care. 2004;32(4):575-7.

35. Mitchell Heggs L, Genee O, Fichet J. Bi-ventricular failure following methadone overdose. Intensive Care Med. 2008;34(8):1553-4.

36. Melandri R, Re G, Lanzarini C, Rapezzi C, Leone O, Zele I, et al. Myocardial damage and rhabdomyolysis associated with prolonged hypoxic coma following opiate overdose. J Toxicol Clin Toxicol. 1996;34(2):199-203.

37. Zele I, De Tommaso I, Melandri R, Barakat B, Pezzilli R, Re G, et al. [Rhabdomyolysis during acute poisoning with drugs and narcotics. Experience with 7 clinical cases]. Minerva Med. 1992;83(12):847-52.

38. Sahni V, Garg D, Garg S, Agarwal SK, Singh NP. Unusual complications of heroin abuse: transverse myelitis, rhabdomyolysis, compartment syndrome, and ARF. Clin Toxicol (Phila). 2008;46(2):153-5.

39. Pascual Calvet J, Pou A, Pedro-Botet J, Gutierrez Cebollada J. [Non-infective neurologic complications associated to heroin use]. Arch Neurobiol (Madr). 1989;52 Suppl 1:155-61.

40. Rice EK, Isbel NM, Becker GJ, Atkins RC, McMahon LP. Heroin overdose and myoglobinuric acute renal failure. Clin Nephrol. 2000;54(6):449-54.

41. Kumar R, West DM, Jingree M, Laurence AS. Unusual consequences of heroin overdose: rhabdomyolysis, acute renal failure, paraplegia and hypercalcaemia. Br J Anaesth. 1999;83(3):496-8.

42. Riva N, Morana P, Cerri F, Gerevini S, Amadio S, Formaglio F, et al. Acute myelopathy selectively involving lumbar anterior horns following intranasal insufflation of ecstasy and heroin. J Neurol Neurosurg Psychiatry. 2007;78(8):908-9.

43. Sahni V, Garg D, Garg S, Agarwal SK, Singh NP. Unusual complications of heroin abuse: transverse myelitis, rhabdomyolysis, compartment syndrome, and ARF. Clin Toxicol (Phila). 2008;46(2):153-5.

44. Green CA, Perrin NA, Janoff SL, Campbell CI, Chilcoat HD, Coplan PM. Assessing the accuracy of opioid overdose and poisoning codes in diagnostic information from electronic health records, claims data, and death records. Pharmacoepidemiol Drug Saf. 2017;26(5):509-17.

45. Nielsen S, Degenhardt L, Hoban B, Gisev N. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. Pharmacoepidemiol Drug Saf. 2016;25(6):733-7.

46. College of Physicians and Surgeons of British Columbia. Professional standards and guidelines: Safe prescribing of drugs with potential for misuse/diversion. 2016 June 1, 2016 (revised Oct 28, 2016).

47. Smolina K, Gladstone E, Morgan SG. Determinants of trends in prescription opioid use in British Columbia, Canada, 2005-2013. Pharmacoepidemiol Drug Saf. 2016;25(5):553-9.

48. British Columbia Coroners Service. Illicit drug overdose deaths in BC: January 1, 2007 - Jun 30, 2017. Burnaby, BC; 2017 Aug 4, 2017.

49. Siew ED, Davenport A. The growth of acute kidney injury: a rising tide or just closer attention to detail? Kidney International. 2015;87(1):46-61.

50. Rothman KJ, Greenland S, Lash TL. Validity in epidemiologic studies. Modern epidemiology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008:128-147.

51. Hasegawa K, Brown DF, Tsugawa Y, Camargo CA, Jr. Epidemiology of emergency department visits for opioid overdose: a population-based study. Mayo Clin Proc. 2014;89(4):462-71.

Table 1. Characteristics of patients admitted to hospital for accidental opioid overdose, 2006-2015

Characteristic		Admission n (%)	Readmission n (%)
Hospitalizations		2,433	121
Type of opioid overdose	Opium	8 (0.3)	0
	Heroin	419 (17.2)	15 (12.4)
	Methadone	401 (16.5)	26 (21.5)
	Synthetic opioids§	123 (5.1)	7 (5.8)
	Other opioids‖	1,101 (45.3)	46 (38.0)
	Unspecified/other opioids	515 (21.2)	34 (28.1)
Sex	Female	1,134 (46.6)	54 (44.6)
	Male	1,299 (53.4)	67 (55.4)
Age (years)	Under 10	36 (1.5)	0
	10 to 19	80 (3.3)	<5
	20 to 29	371 (15.2)	16 (13.2)
	30 to 39	411 (16.9)	19 (15.7)
	40 to 49	415 (17.1)	15 (12.4)
	50 to 59	477 (19.6)	21 (17.4)
	60 to 69	329 (13.5)	36 (29.8)
	70 to 79	186 (7.6)	10 (8.3)
	80 or over	128 (5.3)	<5
Low income		719 (29.6)	35 (28.9)
Rural residence		325 (13.4)	17 (14.1)
Substance use disorders*	Opioids	192 (7.9)	25 (20.7)
	Sedatives and hypnotics	22 (0.9)	<5
	Stimulants	112 (4.6)	9 (7.4)
	Other	395 (16.2)	35 (28.9)
Romano comorbidity score*	Zero	1,380 (56.7)	54 (44.6)
	1 to 2	723 (29.7)	40 (33.1)
	3 or more	330 (13.6)	27 (22.3)
Other medical history*	Psychiatric illness	931 (38.3)	58 (47.9)
	Pneumonia	224 (9.2)	27 (22.3)
	Other respiratory illness	473 (19.4)	35 (28.9)
	HIV	42 (1.7)	<5
	Hepatitis C	33 (1.4)	<5
	Cancer	172 (7.1)	11 (9.1)
Opioid prescription history‡	Methadone	29 (1.2)	<5
	Buprenorphine/naloxone	30 (1.2)	<5
	High dose opioid for pain	569 (23.4)	33 (27.3)
	No use of opioids for pain	1,097 (45.1)	50 (41.3)
Other prescription history‡	Sedatives and hypnotics	571 (23.5)	37 (30.6)
	Stimulants	63 (2.6)	<5

Types of opioid overdose correspond to ICD-10 T40.0-T40.4 and T40.6 (some overdoses appear in >1 category). Readmissions are defined as additional accidental opioid overdose admissions within 365 days of prior admission. *Based on diagnoses at a physician or hospital visit in the 365 days before opioid overdose. ‡Based on dispensings in the 180 days prior to opioid overdose. High dose opioid use is defined by a dispensing of opioid pain medication of >90 oral morphine equivalents per day. Small cell sizes are denoted as '<5' or 0 as applicable. §includes buprenorphine, fentanyl, pethidine and tramadol ‖includes codeine, hydromorphone, morphine and oxycodone

Table 2. Characteristics of patients discharged from hospital after accidental opioid overdose and matched controls among patients with long-term prescription opioid use (>=180 days), 2006-2014

Characteristic		Overdose patients n (%)	Controls n (%)
Number of patients		552	11,040
Type of opioid overdose	Heroin	14 (2.5)	n/a
	Methadone	43 (7.8)	n/a
	Synthetic opioids§	42 (7.6)	n/a
	Other opioids‖	337 (61.1)	n/a
	Unspecified/other opioids	143 (25.9)	n/a
Sex	Female	332 (60.1)	6,640 (60.1)
	Male	220 (39.9)	4,400 (39.9)
Age, years	19 to 29	14 (2.5)	269 (2.4)
	30 to 39	41 (7.4)	829 (7.5)
	40 to 49	89 (16.1)	1,771 (16.0)
	50 to 59	165 (29.9)	3,296 (29.9)
	60 to 69	129 (23.4)	2,562 (23.2)
	70 to 79	81 (14.7)	1,611 (14.6)
	80 to 89	25 (4.5)	561 (5.1)
	90 or over	8 (1.4)	141 (1.3)
Low income		141 (25.5)	2,607 (23.6)
Rural residence		95 (17.2)	1,807 (16.4)
Substance use disorders*	Opioids	58 (10.5)	81 (0.7)
	Sedatives and hypnotics	14 (2.5)	16 (0.1)
	Stimulants	17 (3.1)	31 (0.3)
	Other	103 (18.7)	284 (2.6)
Romano comorbidity score*	Zero	202 (36.6)	6,038 (54.7)
	1 to 2	219 (39.7)	3,826 (34.7)
	3 or more	131 (23.7)	1,176 (10.7)
Other medical history*	Psychiatric illness	300 (54.3)	2,534 (23.0)
	Pneumonia	93 (16.8)	405 (3.7)
	Other respiratory illness	162 (29.3)	1,709 (15.5)
	HIV	<5	56 (0.5)
	Hepatitis C	15 (2.7)	27 (0.2)
	Cancer	52 (9.4)	822 (7.4)
Opioid prescription history‡	Methadone	7 (1.3)	20 (0.2)
	Buprenorphine/naloxone	<5	<5
	High dose opioid for pain	305 (55.3)	2,152 (19.5)
Duration of prescription opioid use, years	Under 1	61 (11.1)	1,876 (17.0)
	1 to under 2	92 (16.7)	2,362 (21.4)
	2 to under 3	53 (9.6)	1,422 (12.9)
	3 to under 4	47 (8.5)	1,006 (9.1)
	4 to under 5	33 (6.0)	797 (7.2)
	5 or more	266 (48.2)	3,577 (32.4)
Other prescription history‡	Sedatives and hypnotics	219 (39.7)	2,506 (22.7)
	Stimulants	10 (1.8)	146 (1.3)

Types of opioid overdose correspond to ICD-10 T40.0-T40.4 and T40.6. *Based on diagnoses at a physician or hospital visit in the 365 days before follow-up. ‡Based on dispensings in the 180 days prior to follow-up. High dose opioid use is defined by a dispensing of opioid pain medication of >90 oral morphine equivalents per day. Small cell sizes are denoted as '<5' or 0 as applicable. §includes buprenorphine, fentanyl, pethidine and tramadol ‖includes codeine, hydromorphone, morphine and oxycodone

Table 3. Number of hospital admissions for accidental opioid overdose and outcomes evaluated during overdose admission, by year

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2006-2015
(a) Overdose hospitalizations (n):											
Admission	~178	166	~200	211	207	251	274	284	290	372	2,433
Readmission	<5	6	<5	15	8	17	15	18	16	21	121
All	180	172	203	226	215	268	289	302	306	393	2,554
(b) Type of opioid overdose* (n):											
Heroin	28	27	34	28	28	35	35	56	67	96	434
Methadone	30	26	36	32	31	36	54	47	65	70	427
Synthetic opioid†	9	<7	<7	8	11	10	14	12	19	37	130
Other opioid‡	80	82	81	109	101	135	143	147	121	148	1,147
Unspecified/other	46	41	52	57	53	60	55	56	53	76	549
(c) Number of outcomes* (n):											
Encephalopathy	7	<5	<5	<5	<5	8	14	11	8	17	77
Respiratory failure	<6	<6	7	8	7	10	24	16	17	37	134
Aspiration pneumonia	20	17	18	21	33	31	38	30	36	44	288
Rhabdomyolysis	7	6	10	11	12	10	17	12	19	20	124
Acute renal failure	13	15	9	16	20	25	30	24	34	51	237
Death in hospital	8	<5	7	7	<5	7	9	9	12	13	80
Composite outcome§											
Admission with >=1 event	42	37	36	50	54	68	87	72	82	109	637
Total events	69	55	62	76	83	108	150	111	142	199	1,055
(d) Incidence proportion‖ (%):											
Encephalopathy	3.9	n/a	n/a	n/a	n/a	3.0	4.8	3.6	2.6	4.3	3.0
Respiratory failure	n/a	n/a	3.4	3.5	3.3	3.7	8.3	5.3	5.6	9.4	5.3
Aspiration pneumonia	11.1	9.9	8.9	9.3	15.3	11.6	13.1	9.9	11.8	11.2	11.3
Rhabdomyolysis	3.9	3.5	4.9	4.9	5.6	3.7	5.9	4.0	6.2	5.1	4.9
Acute renal failure	7.2	8.7	4.4	7.1	9.3	9.3	10.4	7.9	11.1	13.0	9.3
Death in hospital	4.4	n/a	3.4	3.1	n/a	2.6	3.1	3.0	3.9	3.3	3.1
Composite outcome†											
Admission with >=1 event	23.3	21.5	17.7	22.1	25.1	25.4	30.1	23.8	26.8	27.7	24.9

*To avoid small cell sizes, less common types of overdose (opium) and outcome (e.g., cardiac outcomes) have been omitted, or a value of '<5' was entered for counts and corresponding proportions were listed as 'n/a'. Where counts <5 could be deduced, values of '<6' or '<7' have been used or a tilde (~) was used for approximate values. †includes buprenorphine, fentanyl, pethidine and tramadol ‡includes codeine, hydromorphone, morphine and oxycodone §The "composite outcome" included encephalopathy, ARDS, respiratory failure, pulmonary hemorrhage, aspiration pneumonia, cardiac arrest, ventricular arrhythmia, heart failure, rhabdomyolysis, acute renal failure, or death ("total events" does not equal the sum of the other events reported, because some outcomes included in the composite outcome were not reported separately). ‖Incidence proportion describes the percentage of hospital admissions for accidental opioid overdose in which patients were diagnosed with each type of outcome in each period.

Table 4. Influence of readmission for accidental opioid overdose and year of overdose on neurological, respiratory, cardiac and other outcomes evaluated during overdose admission

	Events	(a) Opioid overdose readmission		(b) Admissions in 2015 vs 2006*	
		Crude OR	Adjusted OR (95% CI)	Crude OR	Adjusted OR (95% CI)
Primary outcome					
Neurological:					
Encephalopathy	77	0.52	0.57 (0.13, 2.49)	1.12	0.73 (0.28, 1.89)
Secondary outcomes					
Respiratory outcomes:					
Respiratory failure	134	1.10	0.93 (0.43, 2.04)	3.65	3.05 (1.15, 8.08)
Aspiration pneumonia	288	0.45	0.48 (0.21, 1.08)	1.01	0.88 (0.49, 1.59)
ARDs	19	n/a	n/a	n/a	n/a
Pulmonary hemorrhage	<5	n/a	n/a	n/a	n/a
Cardiac outcomes:					
Cardiac arrest	56	n/a	n/a	n/a	n/a
Ventricular arrhythmia	5	n/a	n/a	n/a	n/a
Heart failure	28	n/a	n/a	n/a	n/a
Other outcomes:					
Rhabdomyolysis	124	0.64	0.64 (0.24, 1.75)	1.33	0.96 (0.38, 2.43)
Acute renal failure	237	1.13	1.07 (0.60, 1.91)	1.97	1.86 (0.95, 3.66)
Paraplegia or tetraplegia	6	n/a	n/a	n/a	n/a
Death in hospital	80	0.77	0.86 (0.27, 2.76)	0.74	0.63 (0.24, 1.65)
Composite outcome†	637	0.82	0.83 (0.54, 1.26)	1.27	1.08 (0.71, 1.64)

Odds ratio (OR) estimates have been omitted, and replaced with 'n/a' for 'not available', for outcomes where estimation was not possible due to a small number of events in one or more exposure groups. *The 'Admissions in 2015 vs 2006' column reports the odds of each outcome occurring in association with an accidental opioid overdose hospitalization in 2015 as compared to 2006. †The "composite outcome" was defined as the occurrence of >=1 of the following within an admission: encephalopathy, ARDS, respiratory failure, pulmonary hemorrhage, aspiration pneumonia, cardiac arrest, ventricular arrhythmia, heart failure, rhabdomyolysis, acute renal failure, or death (corresponds to 'admission with >=1 event' under the composite outcome in table 3). Occurrences of the composite outcome do not equal the sum of other events, because some admissions included >1 type of event but this only counted once toward the composite outcome. OR=odds ratio. ARDS=adult respiratory distress syndrome

Table 5. Risk of neurological, respiratory, cardiac and other outcomes in 1 year following hospital admission for accidental opioid overdose in comparison to controls among patients with long-term prescription opioid use (>=180 days)

	Events		Odds ratios	
	Overdose patients (n=552)	Controls (n=11,040)	Crude	Adjusted (95% CI)
Primary outcome				
Neurological:				
Encephalopathy	<5	<5	n/a	n/a
Secondary outcome				
Respiratory outcomes:				
Respiratory failure	14	23	12.46	6.21 (2.24, 17.21)
Aspiration pneumonia	5	19	5.30	2.96 (0.90, 9.71)
ARDs	<5	9	n/a	n/a
Pulmonary hemorrhage	0	0	n/a	n/a
Cardiac outcomes:				
Cardiac arrest	0	5	n/a	n/a
Ventricular arrhythmia	0	5	n/a	n/a
Heart failure	9	95	1.93	0.99 (0.45, 2.15)
Other outcomes:				
Rhabdomyolysis	5	19	5.30	3.08 (0.87, 10.88)
Acute renal failure	16	103	3.18	1.66 (0.90, 3.05)
Paraplegia or tetraplegia	<5	6	n/a	n/a
All-cause mortality	22	96	4.73	2.13 (1.18, 3.86)
Composite outcome†	59	309	4.14	2.15 (1.48, 3.12)
Serious adverse events‡	315	3,489	2.84	1.97 (1.62, 2.39)

Odds ratio estimates have been omitted, and replaced with 'n/a' for 'not available', for outcomes where estimation was not possible due to a small number of events in one or more exposure groups. †The "composite outcome" was defined as an inpatient hospital diagnosis of one or more of the following: encephalopathy, ARDS, respiratory failure, pulmonary hemorrhage, aspiration pneumonia, cardiac arrest, ventricular arrhythmia, heart failure, rhabdomyolysis, acute renal failure, or death. ‡Serious adverse events were defined as all-cause hospitalization or death. ARDS=adult respiratory distress syndrome

SUPPLEMENTARY APPENDIX

Table S1. Opioid poisoning codes

ICD-10 codes indicating opioid poisoning, by category:[2]

Description	ICD-10 codes
Poisoning by opium	T40.0
Poisoning by heroin	T40.1
Poisoning by other opioids*	T40.2
Poisoning by methadone	T40.3
Poisoning by synthetic opioid†	T40.4
Poisoning by unspecified/other opioids	T40.6

*includes codeine, hydromorphone, morphine and oxycodone †includes buprenorphine, fentanyl, pethidine and tramadol

Accidental opioid poisoning was defined by meeting both of the following criteria.

- A hospital admission record is coded with an ICD-10 code opioid poisoning (**T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6**). For hospital admissions related to accidental opioid poisoning, the hospital diagnosis type must also be coded as M (most responsible diagnosis); 1 (pre-admit comorbidity); W, X or Y (service transfer diagnoses); or 6 (proxy most responsible diagnosis).
- The hospital admission record is also coded with an external cause ICD-10 code corresponding to accidental opioid poisoning (**X42**, Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified). Note: This is distinguished from codes corresponding to intentional self-harm (X62), harm from therapeutic use (Y45.0), or unknown intent (Y12).

Table S2. Diagnostic codes for exclusions

Description	ICD-9	ICD-10
Encephalopathy (anoxic brain damage, toxic encephalopathy or unspecified encephalopathy)	348.1, 349.82	G93.1, G92, G93.4
Acute respiratory distress syndrome (ARDS)	518.82	J80
Respiratory failure	518.81	J96.0, J96.9
Pulmonary hemorrhage	770.3	R04.8

Aspiration pneumonia	507.0	J69.0
Cardiac arrest	427.5	I46
Ventricular arrhythmia	427.1, 427.4	I47.0, I47.2, I49.0
Heart failure	428	I50
Rhabdomyolysis	728.88	M62.8, T79.6
Paraplegia or tetraplegia	344.0, 344.1	G82
Acute renal failure	584	N17
Intentional self-harm	n/a‡	X60 – X84

‡Only hospital diagnoses were used for identifying intentional self-harm, because E-codes which could be used are only supplementary codes and MSP data are typically coded with only one diagnostic code.

Table S3. Diagnostic codes for outcomes

Type of outcome	Diagnosis	ICD-10 Codes
Neurological	Encephalopathy (anoxic brain damage, toxic encephalopathy or unspecified encephalopathy)	G93.1, G92, G93.4
Pulmonary	Adult respiratory distress syndrome (ARDS)	J80
	Respiratory failure	J96.0, J96.9
	Pulmonary hemorrhage	R04.8
	Aspiration pneumonia	J69.0
Cardiac	Cardiac arrest	I46
	Ventricular arrhythmia	I47.0, I47.2, I49.0
	Heart failure	I50
Other	Rhabdomyolysis	M62.8, T79.6
	Paraplegia or tetraplegia	G82
	Acute renal failure	N17

Table S4. Diagnostic codes for covariates

Description	Subcategory (if applicable)	ICD codes
Mental or behavioural disorders due to psychoactive substance use	Opioids	ICD-9: 304.0, 304.7, 305.5 ICD-10: F11
	Sedatives and hypnotics	ICD-9: 304.1, 305.4 ICD-10: F13
	Stimulants	ICD-9: 304.2, 305.6, 304.4, 305.7 ICD-10: F14, F15
	Other (alcohol, cannabinoids, hallucinogens, volatile solvents, multiple drug use or use of other psychoactive substances)	ICD-9: 303, 304.3, 304.5, 304.6, 304.8, 304.9, 305.0, 305.2, 305.3, 305.8, 305.9 ICD-10: F10, F12, F16, F18, F19
Other psychiatric illness	Depression	ICD-9: 311, 296.2, 296.3 ICD-10: F32, F33
	Bipolar disorder/ mixed mania	ICD-9: 296.0, 296.1, 296.4, 296.9 ICD-10: F31
	Schizophrenia	ICD-9: 295 ICD-10: F20
	Personality disorders	ICD-9: 301 ICD-10: F60
	Other psychosis	ICD-9: 297 - 299 ICD-10: F21 – F29
Pneumonia (excluding aspiration pneumonia)		ICD-9: 480-486, 487.0 ICD-10: J10.0, J11.0, J12-J18
Other respiratory illness	COPD	ICD-9: 490-492, 494-496 ICD-10: J40-J44, J47
	Asthma	ICD-9: 493 ICD-10: J45
	Sleep apnea	ICD-9: 327.23, 780.57 ICD-10: G47.3, P28.3
HIV disease		ICD-9: 042 ICD-10: B20-B24
Hepatitis B		ICD-9: 070.2, 070.3 ICD-10: B16, B18.0, B18.1
Hepatitis C		ICD-9: 070.41, 070.44, 070.51, 070.54, 070.7 ICD-10: B17.1, B18.2
Cancer		ICD-9: 140-208, 209.0-209.3 ICD-10: C00-C96

Table S5. Prescription opioids

Opioids indicated for pain treatment	Opioid substitution medications
Buprenorphine (patch only)	Buprenorphine/ naloxone (trade name: Suboxone)
Codeine	Methadone
Fentanyl	
Hydromorphone	
Pethidine (also known as: meperidine)	
Morphine	
Oxycodone	
Tapentadol	
Tramadol	

Table S6. Influence of readmission for accidental opioid overdose and covariates on encephalopathy, compared to inital admission

Predictor variable		Adjusted OR (95% CI)
Exposure		
Repeat admission (vs initial admission)		0.57 (0.13, 2.49)
Covariates		
Sex	Female	0.46 (0.26, 0.81)
	Male	1.00
Age (years)	Under 25	1.02 (0.45, 2.28)
	25 to 39	1.35 (0.72, 2.54)
	40 to 49	1.00
	50 to 59	0.55 (0.24, 1.24)
	60 to 69	0.27 (0.07, 1.00)
	70 or above	0.11 (0.02, 0.76)
Cohort entry year	2006	1.00
	2007	0.28 (0.05, 1.41)
	2008	0.52 (0.15, 1.82)
	2009	0.55 (0.15, 1.97)
	2010	0.27 (0.05, 1.32)
	2011	0.77 (0.27, 2.19)
	2012	1.08 (0.41, 2.87)
	2013	0.73 (0.27, 2.01)
	2014	0.51 (0.17, 1.47)
	2015	0.73 (0.28, 1.89)
Income	Low income	0.44 (0.21, 0.92)
	Mid to high income	1.00
Residence	Rural	0.47 (0.17, 1.32)
	Urban	1.00
Substance use disorders*	Opioids	0.76 (0.29, 2.03)
	Sedatives and hypnotics	0.83 (0.44, 1.58)
	Stimulants	0.77 (0.24, 2.53)
Romano comorbidity score*	Zero	0.95 (0.51, 1.75)
	1 to 2	1.00
	3 or more	0.74 (0.20, 2.75)
Other medical history*	Psychiatric illness	0.84 (0.48, 1.48)
	Pneumonia	1.56 (0.60, 4.08)
	Other respiratory illness	0.79 (0.35, 1.78)
	Cancer	2.55 (0.66, 9.82)
Opioid prescription history†	High dose opioid for pain	0.32 (0.10, 0.97)
	Low to intermediate dose for pain	1.00
	No use of opioids for pain	0.95 (0.55, 1.64)
Other prescription history†	Sedatives and hypnotics	0.65 (0.30, 1.42)

Readmissions are defined as additional accidental opioid overdose admissions within 365 days of prior admission. *Based on diagnoses at a physician or hospital visit in the 365 days before opioid overdose. †Based on dispensings in the 180 days prior to opioid overdose. High dose opioid use is defined by a dispensing of opioid pain medication of >90 oral morphine equivalents per day.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Title (p. 1) and abstract (p. 2) Abstract (pp. 2-3)	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Abstract (p. 2) Abstract (p. 2) Abstract (p. 2)
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Paragraphs 1-2 (p. 4)		
Objectives	3	State specific objectives, including any prespecified hypotheses	Paragraph 3 (p. 4)		
Methods					
Study Design	4	Present key elements of study design early in the paper	Study setting and design, paragraph 1 (p. 5)		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Study setting and design, paragraphs 2-4 (pp. 5-6)		
Participants	6	*(a) Cohort study* - Give the	Cohort study: Study	RECORD 6.1: The methods of study	Study setting and

		eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	setting and design, paragraphs 2-4 (pp. 5-6) Matching in secondary analysis: Study setting and design, paragraph 4 (p. 6)	population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	design, paragraphs 2-4; (pp. 5-6) Tables S1 and S2 (Supplementary appendix, pp. 1-2) n/a Not included
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	'Outcome measures' section (p.7) and Table S3 (Supplementary Appendix, p. 2); 'Covariates' section (p. 8) and Tables S4 and S5 (Supplementary appendix, pp. 3-4); 'Statistical analyses' section (pp. 8-9)	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	'Outcome measures' section (p. 7) and Table S3 (Supplementary Appendix, p. 2); 'Covariates' section (p. 8) and Tables S4 and S5 (Supplementary appendix, pp. 3-4); 'Statistical analyses' section (pp. 8-9)
Data sources/	8	For each variable of interest, give	'Data sources'		

measurement		sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	section indicates sources for types of variables (p. 7); details as under Variables above in this table (pp. 7-9); Supplementary Appendx, pp. 2-4)		
Bias	9	Describe any efforts to address potential sources of bias	'Discussion' section, paragraph 4 (p. 13) (potential selection bias)		
Study size	10	Explain how the study size was arrived at	Study setting and design, paragraphs 2-4 (population data for specific cohorts over 10 years) (pp. 5-6)		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	'Covariates' section (p. 8)		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed	(a) 'Covariates' and 'Statistical analyses' sections (pp. 8-9) (b) 'Statistical analyses', paragraphs 1-2 (pp. 8-9) (c) n/a (d) 'Statistical analyses', paragraph 2 (p. 9) e) 'Statistical analyses', paragraph 1 (pp. 8-9)		

		Cross-sectional study - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	'Data sources' section (p. 7) n/a
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	'Data sources' section (p. 7)
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	(a), (b) 'Patient characteristics' section (p. 10) (c) Not included	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	'Patient characteristics' section (p. 10)
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential	'Patient characteristics' section (p. 10) and Tables 1-2 (pp. 22-		

		confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	23) n/a Not included		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Tables 3-5 (pp. 24-26)		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	'Results' section (pp. 11-12) and Tables 3-5 (pp. 24-26) n/a Not included		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	'Results' section, paragraph 2 (p. 11); Table 4(b) (p. 25)		
Discussion					
Key results	18	Summarise key results with reference to study objectives	'Discussion', paragraphs 1 (p. 12)		

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	'Discussion', paragraph 3 (p. 13) 'Discussion', paragraph 3 (p. 13)	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	'Discussion', final paragraph (p. 13)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	'Conclusion' section (pp. 13-14)		
Generalisability	21	Discuss the generalisability (external validity) of the study results	'Discussion', paragraph 2 (pp. 12-13)		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	'Funding statement' (p. 15)		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Study protocol is available on request as noted in 'Data sharing statement' (p. 15)

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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Outcomes associated with hospital admissions for accidental opioid overdose in British Columbia: a retrospective cohort study

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Outcomes associated with hospital admissions for accidental opioid overdose in British Columbia: a retrospective cohort study

Short title: Outcomes associated with opioid overdose hospitalizations

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ABSTRACT

Objectives: To study the association between accidental opioid overdose and neurological, respiratory, cardiac and other serious adverse events and whether risk of these adverse events was elevated during hospital readmissions compared to initial admissions.

Design: Retrospective cohort study.

Setting: Population-based study using linked administrative data in British Columbia, Canada.

Participants: The primary analysis included 2,433 patients with 2,554 admissions for accidental opioid overdose between 2006 and 2015, including 121 readmissions within one year of initial admission. The secondary analysis included 538 patients discharged following a total of 552 accidental opioid overdose hospitalizations and 11,040 matched controls from a cohort of patients with >=180 days of prescription opioid use.

Outcome measures: The primary outcome was encephalopathy; secondary outcomes were adult respiratory distress syndrome, respiratory failure, pulmonary hemorrhage, aspiration pneumonia, cardiac arrest, ventricular arrhythmia, heart failure, rhabdomyolysis, paraplegia or tetraplegia, acute renal failure, death, a composite outcome of encephalopathy or any secondary outcome, and total serious adverse events (all-cause hospitalization or death). We analyzed these outcomes using generalized linear models with a logistic link function.

Results: 3% of accidental opioid overdose admissions included encephalopathy and 25% included >=1 adverse events (composite outcome). We found no evidence of increased risk of encephalopathy (odds ratio 0.57; 95% CI 0.13 to 2.49) or other outcomes during readmissions versus initial admissions. In the secondary analysis, <5 patients in each cohort experienced encephalopathy. Risk of the composite outcome (OR 2.15; CI 1.48 to 3.12) and all-cause mortality (OR 2.13; CI 1.18 to 3.86) were higher for patients in the year following overdose relative to controls.

Conclusions: We found no evidence that risk of encephalopathy or other adverse events was higher in readmissions compared to initial admissions for accidental opioid overdose. Risk of serious morbidity and mortality may be elevated in the year following an accidental opioid overdose.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A strength is that adverse events associated with accidental opioid overdose were collected from population data rather than adverse event reports.
- This study provides new data to understand the risk of encephalopathy from a larger sample than previously studied.
- The study investigated a wide range of neurological, respiratory, cardiac and other adverse events over a 10-year period.
- Analysis of accidental opioid overdoses was limited to overdoses that led to a hospital admission.
- We controlled for prescription drug use but lacked information on the actual level of drug exposure including illicit drug use.

A rise in opioid-related deaths in British Columbia (BC) contributed to the declaration of a public health emergency in the province.[1] Serious morbidity related to opioid overdose, in contrast, has received relatively little attention. The rate of hospitalizations due to opioid overdose in Canada rose by more than 30% from 2007-08 to 2014-15.[2]

Opioid overdose may lead to a range of neurological, respiratory, cardiac or other adverse events. The evidence linking these events to opioid poisoning has primarily, but not exclusively, been limited to case reports. Neurological events include cerebral hypoxia[3-5], anoxic encephalopathy,[6] toxic encephalopathy,[7-9] delayed encephalopathy,[10-11] and leukoencephalopathy[9,12-14] or delayed leukoencephalopathy.[15-19] Respiratory adverse events include adult respiratory distress syndrome (ARDS),[4,6,20] respiratory failure,[20-22] pulmonary hemorrhage[21,23-25] and aspiration pneumonia.[6,26,27] A retrospective cohort study of opioid overdose leading to intensive care unit admission found that most patients admitted experienced respiratory failure requiring mechanical ventilation, approximately 10 percent died, and among those who died half experienced hypoxic brain injury.[28] Adverse cardiac outcomes may include cardiac arrest,[29,30] ventricular arrhythmia,[31-33] and heart failure.[22,34,35] Other adverse effects related to opioid overdose may include rhabdomyolysis,[4,36-40], paraplegia or tetraplegia due to spinal cord injury,[41-43] and acute renal failure.[4,26,38,40]

We investigated neurological, respiratory, cardiac or other adverse outcomes among patients who were admitted to hospital for accidental opioid poisoning from 2006 to 2015 in BC. Our study examined outcomes that occurred during hospital admissions for accidental opioid poisoning and in the 365 days following discharge from admissions for opioid poisoning. We provide the frequency of these adverse events, assess the influence of repeated overdose, and

investigate whether risk of these outcomes increased over time. We hypothesized that repeated overdose would show a higher risk of adverse events than initial overdoses due to potential cumulative effects of exposure to high-dose opioids, and that risk of adverse events would increase over the period of our study due to increased use of more potent opioids in British Columbia.

METHODS

Study setting and design

We used a retrospective cohort study design to investigate the risk of neurological, respiratory, cardiac and other adverse events during hospital admissions for accidental opioid overdose or in the 1 year following discharge from overdose admissions. The source population for this study consisted of residents of BC who had been registered for provincial medical services for at least 1 year as of any time during 2006-2015.

We investigated outcomes associated with accidental opioid overdose both immediately following an overdose and in the year following an overdose. Our primary analysis focused on outcomes recorded during a hospital admission for an accidental opioid overdose to investigate outcomes immediately following, or shortly after, an overdose. Our secondary analysis focused on outcomes that occurred during the year following discharge from a hospital admission for accidental opioid overdose to investigate events that occurred after a delay following an overdose. Generally, our primary and secondary analyses examined the same neurological, respiratory, cardiac and other adverse events, but in these two different time periods. As described below, however, these two analyses varied in the cohorts studied and the analytical methods used to investigate outcomes.

In our primary analysis, we evaluated whether risk of the study outcomes was increased in repeat admissions for accidental opioid overdose in comparison to initial admissions. For this

analysis, we analyzed a cohort of patients who had been admitted to hospital during 2006-2015 for an accidental opioid overdose. Accidental opioid overdoses represent a subset of all opioid overdoses, which exclude those identified as resulting from intentional self-harm, therapeutic use (that is, occurred when the drug was used as prescribed), or unknown intent,[2] as defined by the International Classification of Disease (ICD), version 10 (diagnostic codes for accidental opioid overdose are found in Table S1 of the Supplementary Appendix). We selected diagnostic codes to identify accidental opioid overdose based on the codes used in a national study by the Canadian Institute for Health Information.[2] A validation study that tested ICD codes for opioid poisoning in electronic health records reported a positive predictive value of 81% for opioid overdoses and poisonings, although it did not test all of the codes that we used in our study.[44] Only patients who had not experienced any of the study outcomes in the year prior to their overdose admission were included in the study, in order to focus on incident outcomes. Patients were excluded if they had received a diagnosis for non-accidental opioid poisoning in the year prior to their overdose admission or a diagnosis of self-harm in their overdose admission or in the previous year, or if they had previously entered long-term or palliative care (diagnostic codes for exclusions are found in Table S2).

We conducted a secondary analysis to evaluate whether risk of study outcomes was elevated in the year following an accidental opioid overdose. In contrast to our primary analysis, this analysis focused on a cohort of patients with long-term prescription opioid use. From this cohort, we selected patients who had been hospitalized for an accidental opioid overdose and controls who had not experienced an overdose hospitalization. We defined a cohort of long-term opioid users to include patients with an episode of prescription opioid analgesic therapy lasting 180 days or more during 2006-2014, where an episode was defined by a series of opioid

dispensings with no more than 90 days between the end of the days' supply of one script and the beginning of another. Patients were eligible for selection into the "overdose cohort" or control group on or after the date of their first dispensing of opioid analgesic medication 180 days into an episode of opioid therapy. Patients were no longer eligible for selection into the study cohort after stopping use of opioid pain medication for a period of 90 days. We used a period of 180 days to define long-term therapy to try to ensure that we were including only patients who were taking these medications over an extended period, with the goal of including patients who were as similar as possible in the overdose cohort and control group. We allowed a grace period between the end of one prescription and the start of another to determine the end of therapy, because some patients might take their medication over a longer period than the recorded days' supply. We expected it would be less common for prescriptions to exceed 90 days, and setting the 'grace period' between prescriptions at 90 days assumed that some patients might continue to take their medication for twice that length of time.

In the secondary analysis, patients with long-term prescription opioid use as described above were selected to enter the overdose cohort, if they were admitted to hospital for an accidental opioid overdose and had been discharged from hospital during 2006-2014. We selected 20 controls for each member of the overdose cohort, matched on sex and age within 2 years. The date of each overdose patient's discharge from hospital following an overdose admission served as a "cohort entry date" for the overdose patient and that patient's matched controls. Patients were followed for up to 1 year starting the day after each patient's cohort entry date, and study outcomes were assessed during this follow-up period. Patients could enter the study more than once as a member of the overdose cohort and/or as a control, but it was only possible to enter the overdose cohort more than once if a readmission for accidental opioid

overdose occurred at least 1 year from a patient's prior overdose hospitalization. Patients were excluded if they had received a diagnosis of opioid poisoning, self-harm or any of the study outcomes in the year prior to cohort entry, or if they had previously entered long-term or palliative care. Patients were followed from cohort entry date until the earliest of diagnosis with a relevant study outcome, hospital admission or readmission for opioid poisoning, a diagnosis of self-harm, end of provincial health coverage, entry into long-term or palliative care, death, 365 days of follow-up, or 31 December 2015.

Data sources

We used de-identified, patient-level administrative health data from BC, which were linked with encrypted patient identifiers, to create the study cohorts and conduct analyses. Medical Services Plan (MSP) data included outpatient diagnoses, while the Canadian Institute for Health Information Discharge Abstract Database included hospital admissions and inpatient diagnoses and procedures. MSP registration data were used to determine study eligibility and to define patient demographics. BC PharmaNet data were used to identify a patient's prescription drug use and use of long-term or palliative care drug plans.

Outcome measures

The primary outcome in our study was encephalopathy, which was defined by an inpatient hospital diagnosis of anoxic brain damage, toxic encephalopathy or unspecified encephalopathy. Secondary outcomes included ARDS, respiratory failure, pulmonary hemorrhage, aspiration pneumonia, cardiac arrest, ventricular arrhythmia, heart failure, rhabdomyolysis, paraplegia or tetraplegia, acute renal failure, and death. We also included a composite outcome, which we defined as a diagnosis of encephalopathy and/or any of the secondary outcomes (diagnostic codes for outcomes are found in Table S3). In our secondary

analysis, we added the unplanned outcome of "serious adverse events," which was defined as hospitalization or death from any cause, to provide a more comprehensive measure of potential harm. Inpatient hospital data were used to ascertain whether an outcome diagnosis had occurred. Deaths were ascertained with hospital data and MSP registration data.

Covariates

We adjusted our analyses for patient characteristics, including demographic variables, medical history and prescription history. Demographic variables included sex, age category, low-income status, and rural residence. Medical history included variables indicating mental or behavioural disorders due to opioid use, stimulant use, and other substance use, and variables for a history of psychiatric illness, pneumonia, other respiratory illness, Romano comorbidity score (0, 1-2, >=3), and cancer (diagnostic codes for medical covariates are found in Table S4). Prescription history included a variable indicating past use of high-dose opioid pain medication (>90 mg of "oral morphine equivalents" per day, calculated using conversion factors recommended in a recent review of opioid utilization studies)[45] and a variable for lack of any prescription opioid pain medication use (opioid medications are listed in Table S5), and a variable for past use of sedative/hypnotic medication (identified by Anatomical Therapeutic Chemical code N05C). In the secondary analysis, the variable for mental and behaviour disorders due to stimulant use was excluded (due to a low prevalence in the control group), and prescription history consisted of variables for high-dose opioid use (>90 mg of "oral morphine equivalents" per day), duration of prescription opioid use (<1, 1 to <2, 2 to <3, 3 to <4, 4 to <5, or >=5 years) and prior sedative use. We used 90 mg of morphine equivalents per day as a cut-off to define high-dose prescription opioid use, because this reflected advice from the College of Physicians and Surgeons of British Columbia to avoid prescribing of doses above this level in

most cases not involving patients with active cancer or those receiving palliative care or end-of-life care.[46]

Statistical analyses

In the primary analysis, we estimated odds ratios to evaluate whether the risk of each outcome was elevated during repeat hospital admissions for accidental opioid overdose in comparison to initial admissions. We used generalized linear models with a logistic link function and a binomial error distribution. Repeat admissions or "readmissions" were any admissions for accidental opioid overdose that occurred within a year of a discharge for a previous admission. In the same models, we included a series of binary independent variables indicating the year in which each opioid overdose admission occurred, using the first year of the study, 2006, as a reference year. We inferred the odds of each study outcome occurring in association with an opioid overdose in 2015 in comparison to 2006 (based on the variable indicating an overdose occurred in 2015 versus the reference year), as a test of our hypothesis that the risk of the adverse events we investigated may have increased in recent years due to the use of more potent opioids. In a sensitivity analysis related to the outcome of acute kidney failure, we examined trends in diagnosis of acute kidney failure among the general population.

In the secondary analysis, we similarly estimated odds ratios to evaluate whether risk was increased in the 1-year period following a hospital admission for accidental opioid overdose, as compared to controls. The model included a series of binary independent variables for the year in which patients entered the study (according to date of discharge from an overdose patient's overdose admission or corresponding cohort entry date for each control patient), using 2006 as a reference year, to control for time-varying confounding. In additional models, we included interaction terms representing interaction between these "cohort entry year" variables and a

variable indicating whether a patient was in the overdose cohort (the "exposed" group), as a test for effect measure modification, to investigate whether risk of our study outcomes in the year following opioid overdose was elevated in more recent years.

All regression models used generalized estimating equations to adjust for correlation of observations ("clustering effects") due to multiple observations from the same patients. We had planned to conduct analyses stratified on whether patients had a history of cancer, but due to a smaller than expected sample size we chose instead to control for cancer as a covariate.

Ethics approval

The study was approved by the University of British Columbia Clinical Research Ethics Board.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. As the study used routinely collected administrative health data, there were no study participants to share results with. There are no plans to disseminate the results of the research to the relevant patient community.

RESULTS

Patient characteristics

We identified 3,235 patients with a total of 3,519 hospital admissions involving accidental opioid overdose during 2006 to 2015. After excluding patients lacking 1 year of provincial medical services coverage prior to admission and applying other exclusion criteria (described above), the cohort for our primary analysis included 2,433 patients who had experienced 2,554 admissions for accidental opioid overdose, of which 121 were readmissions within a year of a previous admission (Table 1). The age of patients at time of overdose

admission ranged from 1 to 99 years (median 48; interquartile range [IQR] 32 to 61 years). Patients who were readmitted tended to have a poorer health status and were more likely to have been diagnosed with opioid use disorder and have used a high-dose prescription opioid.

For the secondary analysis, we identified a cohort of 247,883 patients with at least one episode of long-term prescription opioid use during 2006 to 2014. Our secondary analysis included 538 patients discharged following a total of 552 accidental opioid overdose hospitalizations and 11,040 matched controls from the cohort (Table 2). Ages ranged from 19 to 100 years (median 58; IQR 49 to 67 years), as no younger patients met the entry criteria for overdose during long-term prescription opioid use. Patients in the overdose cohort had a poorer health status than controls, and notably many patients had a history of psychiatric illness, high-dose prescription opioid use for pain, prescription opioid use of 5 years or more, and/or sedative/hypnotic medication use.

Frequency of adverse events associated with overdose admissions

The number of hospital admissions for accidental opioid overdose more than doubled over the period of our study, from 180 admissions in 2006 to 393 admissions 2015, including both initial admissions and readmissions (Table 3). We found that 3% of overdose admissions during this ten-year period included a diagnosis of encephalopathy, and 25% of overdose admissions included at least one of the adverse outcomes included in our composite outcome (Table 3).

Adverse events during admissions for accidental opioid overdose

In our primary analysis, we found no evidence of increased risk of encephalopathy during readmission for accidental opioid overdose in comparison to initial admission for accidental opioid overdose (adjusted OR 0.57; 95% CI 0.13 to 2.49) (Table 4). Women admitted to hospital

for accidental opioid overdose had a lower risk of encephalopathy than men (adjusted OR 0.46; 95% CI 0.26 to 0.81) (Table S6 in Supplementary Appendix). In addition, we observed no increase in risk of either death in hospital or our composite outcome during readmission for accidental opioid overdose, compared to initial admission (adjusted OR 0.86, 95% CI 0.27 to 2.76, for death in hospital, and adjusted OR 0.83, 95% CI 0.54 to 1.26, for the composite outcome). Similarly, results for other secondary outcomes did not indicate any increased risk during readmission for accidental opioid overdose, compared initial admission. (Table 4)

We included indicator variables for the year in which each accidental opioid overdose occurred in the regression models for our primary analysis, which provided a test of whether risk of the outcome in each model was higher in the final year of our study (2015) in comparison with the initial year of the study (2006). We found the risk of encephalopathy was not elevated in 2015 in comparison to 2006 (OR 0.73; CI 0.28 to 1.89) (Table 4). In contrast, respiratory failure in association with opioid overdose was approximately three times higher in 2015 in relation to 2006 (OR 3.05; CI 1.15 to 8.08), although the estimate was imprecise. While no other outcomes showed a significantly higher risk in the last year of the study, the point estimate for risk of acute renal failure was elevated but non-significant (OR 1.86; CI 0.95 to 3.66). In a sensitivity analysis, an examination of the general trend in incidence of acute renal failure showed a similar elevation in risk of acute renal failure in the general population of BC (relative risk 2.38; CI 2.30 to 2.47).

Adverse events in year following overdose admissions for accidental opioid overdose

In our secondary analysis, we compared patients in the year following discharge from an accidental opioid overdose admission to controls, among a cohort of patients with long-term prescription opioid use. Encephalopathy was diagnosed in fewer than five patients in each of the

cohorts in our secondary analysis (the overdose cohort and the control cohort), so we could not estimate an odds ratio to compare overdose patients with controls for this outcome. Our analyses suggested a doubling of the odds of experiencing one of the events in our composite outcome (OR 2.15; CI 1.48 to 3.12) or a serious adverse event (OR 1.97; CI 1.62 to 2.39), or dying from any cause (OR 2.13; CI 1.18 to 3.86), for patients in the year following a hospital admission for accidental opioid overdose, compared to controls (Table 5). Analyses of effect measure modification (not shown) did not indicate that year of cohort entry was an effect modifier in relation to risk of our study outcomes among overdose patients in the year following an overdose relative to control patients.

DISCUSSION

In our study, we found that encephalopathy was diagnosed in about 3% of accidental opioid overdose admissions from 2006 to 2015, and at least one of the adverse events in our composite outcome occurred in 25% of accidental opioid overdose admissions. We found no evidence that risk of encephalopathy or other adverse outcomes was increased in readmissions in comparison to initial admissions for accidental opioid overdose. We found that risk of respiratory failure was elevated in 2015 in relation to 2006. Since reports suggest that more potent prescription and illicit opioids have been used in BC toward the end of our study period,[47,48] the apparent increase in risk of respiratory failure may reflect exposure to more potent opioids; however, this increase in risk may have occurred due to co-ingestion of other substances[28] or due to other factors. While the risk of acute renal failure was non-significantly elevated in 2015 compared to 2006, a sensitivity analysis indicated this may reflect a general trend in diagnosis of acute kidney failure.[49] Our comparison of overdose patients to controls within a cohort of patients with long-term opioid use suggested that the risk of serious adverse events including

respiratory failure and death may be elevated in the year following an accidental opioid overdose.

A potential link between opioid overdose and encephalopathy has been reported in case reports and case series.[3,5,7-19] Additionally, a prospective observational study reported that 1 of 573 patients visiting the emergency department for opioid overdose suffered from cerebral anoxia, ARDS and death,[4] and a retrospective chart review reported that 2 of 42 ICU patients with heroin overdose suffered form anoxemic encephalopathy and death.[6] Our finding that 77 (3%) of 2,554 admissions related to accidental overdose included a diagnosis of encephalopathy provides additional data on this association.

We included both anoxic brain damage and toxic encephalopathy in the definition of encephalopathy in our study, because case reports raise concerns about a potential association between opioid overdose about these outcomes, and these diagnoses describe important brain injuries.[6-9] In addition, studies which use administrative health data face the limitation that coding of outcomes in the data will often not be precise, so we have included unspecified encephalopathy in the outcome definition. There is a lack of validation studies for either anoxic or toxic encephalopathy, so the specificity of the individual diagnostic codes we used and of our composite outcome is unknown. Inclusion of unspecified encephalopathy may lead to some outcome misclassification, but this definition will have greater sensitivity to detect encephalopathy when it has occurred. It is expected that any outcome misclassification would be similar across exposure groups in our primary analysis (that is, during an initial or repeat admission for accidental opioid overdose). This type of misclassification could bias the analysis toward a null effect.[50]

The association between respiratory failure and accidental opioid overdose in our study appears to be consistent with a recent U.S. study. While not directly reporting on respiratory failure, the US study found that 10.0% of emergency department visits for opioid overdose were associated with mechanical ventilation.[51] Our hospital admission data found that respiratory failure occurred in 9.4% of overdose admissions in 2015. In addition, a cohort study of 178 adults with opioid overdose leading to intensive care unit admission reported that 84.8% required mechanical ventilation.[28]

Our study provides new data on potential association between accidental opioid overdose and a range of serious adverse events. A strength of our study was that adverse events associated with overdose were collected from population data rather than adverse event reports. These data were more comprehensive than adverse event reports, because the data were collected routinely by the health care system rather than relying on reports from the public, health care providers or manufacturers and because the data available covered most of the population of the province. However, our study had some limitations. Our analysis of readmissions which occurred within one year of a previous admission excluded patients with adverse events in the year prior to readmission. However, this exclusion may have created selection bias by excluding patients who were more susceptible to these adverse events from the cohort of readmission patients. In addition, we analyzed data on accidental opioid hospitalizations but lacked data about overdoses that did not result in a hospital admission and lacked complete information about drug exposure including illicit drug use. We included patients with long-term use of prescription opioids in our secondary analysis based on the information in available administrative health databases; however, this excluded others with long-term opioid use who lacked ongoing prescriptions of their own but used opioids prescribed to others and/or non-prescription opioids. Lastly, our

analyses may have been subject to unmeasured confounders, such as co-ingestion of other drugs with opioids.

CONCLUSIONS

We found no increased risk of encephalopathy or other adverse events in repeat hospital admissions compared to initial admission for accidental opioid overdose. Our analysis suggests that accidental opioid overdoses were associated with risk of respiratory failure and that risk of respiratory failure associated with opioid overdose was higher in 2015 compared to 2006. The risk of serious adverse events including respiratory failure and death may be elevated in the year following an accidental opioid overdose.

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REFERENCES

1. Government of British Columbia. Provincial health officer declares public health emergency 2016 [updated April 14, 2016. News release]. Available from: https://news.gov.bc.ca/releases/2016HLTH0026-000568.
2. Canadian Centre for Health Information, Canadian Centre on Substance Abuse. Hospitalizations and emergency department visits due to opioid poisoning in Canada. Ottawa, ON: CIHI; 2016.
3. Voigt I. Fatal Overdose due to Confusion of an Transdermal Fentanyl Delivery System. case report. 2013;2013:154143.
4. Etherington J, Christenson J, Innes G, Grafstein E, Pennington S, Spinelli JJ, et al. Is early discharge safe after naloxone reversal of presumed opioid overdose? CJEM, Can. 2000;2(3):156-62.
5. Vila N, Chamorro A. Ballistic movements due to ischemic infarcts after intravenous heroin overdose: report of two cases. Clin Neurol Neurosurg. 1997;99(4):259-62.
6. Grigorakos L, Sakagianni K, Tsigou E, Apostolakos G, Nikolopoulos G, Veldekis D. Outcome of acute heroin overdose requiring intensive care unit admission. J Opioid Manag. 2010;6(3):227-31.
7. Morales Odia Y, Jinka M, Ziai WC. Severe leukoencephalopathy following acute oxycodone intoxication. Neurocrit Care. 2010;13(1):93-7.
8. Mills F, MacLennan SC, Devile CJ, Saunders DE. Severe cerebellitis following methadone poisoning. Pediatr Radiol. 2008;38(2):227-9.
9. Anselmo M, Campos Rainho A, do Carmo Vale M, Estrada J, Valente R, Correia M, et al. Methadone intoxication in a child: toxic encephalopathy? J Child Neurol. 2006;21(7):618-20.

10. Zanin A, Masiero S, Severino MS, Calderone M, Da Dalt L, Laverda AM. A delayed methadone encephalopathy: clinical and neuroradiological findings. J Child Neurol. 2010;25(6):748-51.

11. Shimizu F, Kawai M, Ogasawara J, Negoro K, Morimatsu M, Kanda T. [Delayed encephalopathy following acute fentanyl intoxication]. Rinsho Shinkeigaku. 2007;47(5):222-5.

12. Bellot B, Michel F, Thomachot L, Chaumoitre K, Battaglia F, Lagier P. Acute leukoencephalopathy after buprenorphine intoxication in a 2-year-old child. Europ J Paediatr Neurol. 2011;15(4):368-71.

13. Nanan R, von Stockhausen HB, Petersen B, Solymosi L, Warmuth-Metz M. Unusual pattern of leukoencephalopathy after morphine sulphate intoxication. Neuroradiology. 2000;42(11):845-8.

14. Foy L, Seeyave DM, Bradin SA. Toxic leukoencephalopathy due to transdermal fentanyl overdose. Pediatr Emerg Care. 2011;27(9):854-6.

15. Salazar R, Dubow J. Delayed posthypoxic leukoencephalopathy following a morphine overdose. J Clin Neurosci. 2012;19(7):1060-2.

16. Molloy S, Soh C, Williams TL. Reversible delayed posthypoxic leukoencephalopathy. AJNR Am J Neuroradiol. 2006;27(8):1763-5.

17. Shprecher DR, Flanigan KM, Smith AG, Smith SM, Schenkenberg T, Steffens J. Clinical and diagnostic features of delayed hypoxic leukoencephalopathy. J Neuropsychiatry Clin Neurosci. 2008;20(4):473-7.

18. Barnett MH, Miller LA, Reddel SW, Davies L. Reversible delayed leukoencephalopathy following intravenous heroin overdose. J Clin Neurosci. 2001;8(2):165-7.

19. Pirompanich P, Chankrachang S. Intravenous Heroin-Associated Delayed Spongiform Leukoencephalopathy: Case Report and Reviews of the Literature. J Med Assoc Thai. 2015;98(7):703-8.

20. Pichot C, Petitjeans F, Ghignone M, Quintin L. Swift recovery of severe acute hypoxemic respiratory failure under non-invasive ventilation. Anestezjol. 2015;47(2):138-42.

21. Cole JB, Dunbar JF, McIntire SA, Regelmann WE, Slusher TM. Butyrfentanyl overdose resulting in diffuse alveolar hemorrhage. Pediatrics. 2015;135(3):e740-3.

22. Liu SS, Kovell LC, Horne A, Jr., Chang D, Petronis JD, Zakaria S. A novel case of transient right ventricular failure in a patient with respiratory distress. J Intensive Care Med. 2013;28(3):185-8.

23. Ruzycki S, Yarema M, Dunham M, Sadrzadeh H, Tremblay A. Intranasal Fentanyl Intoxication Leading to Diffuse Alveolar Hemorrhage. J Med Toxicol. 2016;12(2):185-8.

24. Porter R, O'Reilly H. Pulmonary hemorrhage: a rare complication of opioid overdose. Pediatr Emerg Care. 2011;27(8):742-4.

25. Chaturvedi AK, Rao NG, Baird JR. A death due to self-administered fentanyl. J Anal Toxicol. 1990;14(6):385-7.

26. Eizadi-Mood N, Yaraghi A, Sharifian Z, Feizi A, Hedaiaty M, Sabzghabaee AM. Clinical Presentation and the Outcome of Therapy in a Cohort of Patients with Methadone Toxicity in Iran. Mater. 2015;27(4):276-9.

27. Shadnia S, Faiaz-Noori MR, Pajoumand A, Talaie H, Khoshkar A, Vosough-Ghanbari S, et al. A case report of opium body packer; review of the treatment protocols and mechanisms of poisoning. Toxicol. 2007;17(4):205-14.

28. Pfister GJ, Burkes RM, Guinn B, Steele J, Kelley RR, Wiemken TL, et al. Opioid overdose leading to intensive care unit admission: Epidemiology and outcomes. J Crit Care. 2016;35:29-32.

29. Nielsen K, Nielsen SL, Siersma V, Rasmussen LS. Treatment of opioid overdose in a physician-based prehospital EMS: frequency and long-term prognosis. Resuscitation. 2011;82(11):1410-3.

30. Boyd JJ, Kuisma MJ, Alaspaa AO, Vuori E, Repo JV, Randell TT. Outcome after heroin overdose and cardiopulmonary resuscitation. Acta Anaesthesiol Scand. 2006;50(9):1120-4.

31. Ray WA, Chung CP, Murray KT, Cooper WO, Hall K, Stein CM. Out-of-hospital mortality among patients receiving methadone for noncancer pain. JAMA Intern Med. 2015;175(3):420-7.

32. Butler B, Rubin G, Lawrance A, Batey R, Bell J. Estimating the risk of fatal arrhythmia in patients in methadone maintenance treatment for heroin addiction. Drug Alcohol Rev. 2011;30(2):173-80.

33. Daubin C, Quentin C, Goulle JP, Guillotin D, Lehoux P, Lepage O, et al. Refractory shock and asystole related to tramadol overdose. Clin Toxicol (Phila). 2007;45(8):961-4.

34. Garrett PM. Tramadol overdose and serotonin syndrome manifesting as acute right heart dysfunction. Anaesth Intensive Care. 2004;32(4):575-7.

35. Mitchell Heggs L, Genee O, Fichet J. Bi-ventricular failure following methadone overdose. Intensive Care Med. 2008;34(8):1553-4.

36. Melandri R, Re G, Lanzarini C, Rapezzi C, Leone O, Zele I, et al. Myocardial damage and rhabdomyolysis associated with prolonged hypoxic coma following opiate overdose. J Toxicol Clin Toxicol. 1996;34(2):199-203.

37. Zele I, De Tommaso I, Melandri R, Barakat B, Pezzilli R, Re G, et al. [Rhabdomyolysis during acute poisoning with drugs and narcotics. Experience with 7 clinical cases]. Minerva Med. 1992;83(12):847-52.

38. Sahni V, Garg D, Garg S, Agarwal SK, Singh NP. Unusual complications of heroin abuse: transverse myelitis, rhabdomyolysis, compartment syndrome, and ARF. Clin Toxicol (Phila). 2008;46(2):153-5.

39. Pascual Calvet J, Pou A, Pedro-Botet J, Gutierrez Cebollada J. [Non-infective neurologic complications associated to heroin use]. Arch Neurobiol (Madr). 1989;52 Suppl 1:155-61.

40. Rice EK, Isbel NM, Becker GJ, Atkins RC, McMahon LP. Heroin overdose and myoglobinuric acute renal failure. Clin Nephrol. 2000;54(6):449-54.

41. Kumar R, West DM, Jingree M, Laurence AS. Unusual consequences of heroin overdose: rhabdomyolysis, acute renal failure, paraplegia and hypercalcaemia. Br J Anaesth. 1999;83(3):496-8.

42. Riva N, Morana P, Cerri F, Gerevini S, Amadio S, Formaglio F, et al. Acute myelopathy selectively involving lumbar anterior horns following intranasal insufflation of ecstasy and heroin. J Neurol Neurosurg Psychiatry. 2007;78(8):908-9.

43. Sahni V, Garg D, Garg S, Agarwal SK, Singh NP. Unusual complications of heroin abuse: transverse myelitis, rhabdomyolysis, compartment syndrome, and ARF. Clin Toxicol (Phila). 2008;46(2):153-5.

44. Green CA, Perrin NA, Janoff SL, Campbell CI, Chilcoat HD, Coplan PM. Assessing the accuracy of opioid overdose and poisoning codes in diagnostic information from electronic health records, claims data, and death records. Pharmacoepidemiol Drug Saf. 2017;26(5):509-17.

45. Nielsen S, Degenhardt L, Hoban B, Gisev N. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. Pharmacoepidemiol Drug Saf. 2016;25(6):733-7.

46. College of Physicians and Surgeons of British Columbia. Professional standards and guidelines: Safe prescribing of drugs with potential for misuse/diversion. 2016 June 1, 2016 (revised Oct 28, 2016).

47. Smolina K, Gladstone E, Morgan SG. Determinants of trends in prescription opioid use in British Columbia, Canada, 2005-2013. Pharmacoepidemiol Drug Saf. 2016;25(5):553-9.

48. British Columbia Coroners Service. Illicit drug overdose deaths in BC: January 1, 2007 - Jun 30, 2017. Burnaby, BC; 2017 Aug 4, 2017.

49. Siew ED, Davenport A. The growth of acute kidney injury: a rising tide or just closer attention to detail? Kidney International. 2015;87(1):46-61.

50. Rothman KJ, Greenland S, Lash TL. Validity in epidemiologic studies. Modern epidemiology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008:128-147.

51. Hasegawa K, Brown DF, Tsugawa Y, Camargo CA, Jr. Epidemiology of emergency department visits for opioid overdose: a population-based study. Mayo Clin Proc. 2014;89(4):462-71.

Table 1. Characteristics of patients admitted to hospital for accidental opioid overdose, 2006-2015

Characteristic		Admission n (%)	Readmission n (%)
Hospitalizations		2,433	121
Type of opioid overdose	Opium	8 (0.3)	0
	Heroin	419 (17.2)	15 (12.4)
	Methadone	401 (16.5)	26 (21.5)
	Synthetic opioids§	123 (5.1)	7 (5.8)
	Other opioids‖	1,101 (45.3)	46 (38.0)
	Unspecified/other opioids	515 (21.2)	34 (28.1)
Sex	Female	1,134 (46.6)	54 (44.6)
	Male	1,299 (53.4)	67 (55.4)
Age (years)	Under 10	36 (1.5)	0
	10 to 19	80 (3.3)	<5
	20 to 29	371 (15.2)	16 (13.2)
	30 to 39	411 (16.9)	19 (15.7)
	40 to 49	415 (17.1)	15 (12.4)
	50 to 59	477 (19.6)	21 (17.4)
	60 to 69	329 (13.5)	36 (29.8)
	70 to 79	186 (7.6)	10 (8.3)
	80 or over	128 (5.3)	<5
Low income		719 (29.6)	35 (28.9)
Rural residence		325 (13.4)	17 (14.1)
Substance use disorders*	Opioids	192 (7.9)	25 (20.7)
	Sedatives and hypnotics	22 (0.9)	<5
	Stimulants	112 (4.6)	9 (7.4)
	Other	395 (16.2)	35 (28.9)
Romano comorbidity score*	Zero	1,380 (56.7)	54 (44.6)
	1 to 2	723 (29.7)	40 (33.1)
	3 or more	330 (13.6)	27 (22.3)
Other medical history*	Psychiatric illness	931 (38.3)	58 (47.9)
	Pneumonia	224 (9.2)	27 (22.3)
	Other respiratory illness	473 (19.4)	35 (28.9)
	HIV	42 (1.7)	<5
	Hepatitis C	33 (1.4)	<5
	Cancer	172 (7.1)	11 (9.1)
Opioid prescription history‡	Methadone	29 (1.2)	<5
	Buprenorphine/naloxone	30 (1.2)	<5
	High dose opioid for pain	569 (23.4)	33 (27.3)
	No use of opioids for pain	1,097 (45.1)	50 (41.3)
Other prescription history‡	Sedatives and hypnotics	571 (23.5)	37 (30.6)
	Stimulants	63 (2.6)	<5

Types of opioid overdose correspond to ICD-10 T40.0-T40.4 and T40.6 (some overdoses appear in >1 category). Readmissions are defined as additional accidental opioid overdose admissions within 365 days of prior admission. *Based on diagnoses at a physician or hospital visit in the 365 days before opioid overdose. ‡Based on dispensings in the 180 days prior to opioid overdose. High dose opioid use is defined by a dispensing of opioid pain medication of >90 oral morphine equivalents per day. Small cell sizes are denoted as '<5' or 0 as applicable. §includes buprenorphine, fentanyl, pethidine and tramadol ‖includes codeine, hydromorphone, morphine and oxycodone

Table 2. Characteristics of patients discharged from hospital after accidental opioid overdose and matched controls among patients with long-term prescription opioid use (>=180 days), 2006-2014

Characteristic		Overdose patients n (%)	Controls n (%)
Number of patients		552	11,040
Type of opioid overdose	Heroin	14 (2.5)	n/a
	Methadone	43 (7.8)	n/a
	Synthetic opioids§	42 (7.6)	n/a
	Other opioids‖	337 (61.1)	n/a
	Unspecified/other opioids	143 (25.9)	n/a
Sex	Female	332 (60.1)	6,640 (60.1)
	Male	220 (39.9)	4,400 (39.9)
Age, years	19 to 29	14 (2.5)	269 (2.4)
	30 to 39	41 (7.4)	829 (7.5)
	40 to 49	89 (16.1)	1,771 (16.0)
	50 to 59	165 (29.9)	3,296 (29.9)
	60 to 69	129 (23.4)	2,562 (23.2)
	70 to 79	81 (14.7)	1,611 (14.6)
	80 to 89	25 (4.5)	561 (5.1)
	90 or over	8 (1.4)	141 (1.3)
Low income		141 (25.5)	2,607 (23.6)
Rural residence		95 (17.2)	1,807 (16.4)
Substance use disorders*	Opioids	58 (10.5)	81 (0.7)
	Sedatives and hypnotics	14 (2.5)	16 (0.1)
	Stimulants	17 (3.1)	31 (0.3)
	Other	103 (18.7)	284 (2.6)
Romano comorbidity score*	Zero	202 (36.6)	6,038 (54.7)
	1 to 2	219 (39.7)	3,826 (34.7)
	3 or more	131 (23.7)	1,176 (10.7)
Other medical history*	Psychiatric illness	300 (54.3)	2,534 (23.0)
	Pneumonia	93 (16.8)	405 (3.7)
	Other respiratory illness	162 (29.3)	1,709 (15.5)
	HIV	<5	56 (0.5)
	Hepatitis C	15 (2.7)	27 (0.2)
	Cancer	52 (9.4)	822 (7.4)
Opioid prescription history‡	Methadone	7 (1.3)	20 (0.2)
	Buprenorphine/naloxone	<5	<5
	High dose opioid for pain	305 (55.3)	2,152 (19.5)
Duration of prescription opioid use, years	Under 1	61 (11.1)	1,876 (17.0)
	1 to under 2	92 (16.7)	2,362 (21.4)
	2 to under 3	53 (9.6)	1,422 (12.9)
	3 to under 4	47 (8.5)	1,006 (9.1)
	4 to under 5	33 (6.0)	797 (7.2)
	5 or more	266 (48.2)	3,577 (32.4)
Other prescription history‡	Sedatives and hypnotics	219 (39.7)	2,506 (22.7)
	Stimulants	10 (1.8)	146 (1.3)

Types of opioid overdose correspond to ICD-10 T40.0-T40.4 and T40.6. *Based on diagnoses at a physician or hospital visit in the 365 days before follow-up. ‡Based on dispensings in the 180 days prior to follow-up. High dose opioid use is defined by a dispensing of opioid pain medication of >90 oral morphine equivalents per day. Small cell sizes are denoted as '<5' or 0 as applicable. §includes buprenorphine, fentanyl, pethidine and tramadol ‖includes codeine, hydromorphone, morphine and oxycodone

Table 3. Number of hospital admissions for accidental opioid overdose and outcomes evaluated during overdose admission, by year

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2006-2015
(a) Overdose hospitalizations (n):											
Admission	~178	166	~200	211	207	251	274	284	290	372	2,433
Readmission	<5	6	<5	15	8	17	15	18	16	21	121
All	180	172	203	226	215	268	289	302	306	393	2,554
(b) Type of opioid overdose* (n):											
Heroin	28	27	34	28	28	35	35	56	67	96	434
Methadone	30	26	36	32	31	36	54	47	65	70	427
Synthetic opioid†	9	<7	<7	8	11	10	14	12	19	37	130
Other opioid‡	80	82	81	109	101	135	143	147	121	148	1,147
Unspecified/other	46	41	52	57	53	60	55	56	53	76	549
(c) Number of outcomes* (n):											
Encephalopathy	7	<5	<5	<5	<5	8	14	11	8	17	77
Respiratory failure	<6	<6	7	8	7	10	24	16	17	37	134
Aspiration pneumonia	20	17	18	21	33	31	38	30	36	44	288
Rhabdomyolysis	7	6	10	11	12	10	17	12	19	20	124
Acute renal failure	13	15	9	16	20	25	30	24	34	51	237
Death in hospital	8	<5	7	7	<5	7	9	9	12	13	80
Composite outcome§											
Admission with >=1 event	42	37	36	50	54	68	87	72	82	109	637
Total events	69	55	62	76	83	108	150	111	142	199	1,055
(d) Incidence proportion‖ (%):											
Encephalopathy	3.9	n/a	n/a	n/a	n/a	3.0	4.8	3.6	2.6	4.3	3.0
Respiratory failure	n/a	n/a	3.4	3.5	3.3	3.7	8.3	5.3	5.6	9.4	5.3
Aspiration pneumonia	11.1	9.9	8.9	9.3	15.3	11.6	13.1	9.9	11.8	11.2	11.3
Rhabdomyolysis	3.9	3.5	4.9	4.9	5.6	3.7	5.9	4.0	6.2	5.1	4.9
Acute renal failure	7.2	8.7	4.4	7.1	9.3	9.3	10.4	7.9	11.1	13.0	9.3
Death in hospital	4.4	n/a	3.4	3.1	n/a	2.6	3.1	3.0	3.9	3.3	3.1
Composite outcome†											
Admission with >=1 event	23.3	21.5	17.7	22.1	25.1	25.4	30.1	23.8	26.8	27.7	24.9

*To avoid small cell sizes, less common types of overdose (opium) and outcome (e.g., cardiac outcomes) have been omitted, or a value of '<5' was entered for counts and corresponding proportions were listed as 'n/a'. Where counts <5 could be deduced, values of '<6' or '<7' have been used or a tilde (~) was used for approximate values. †includes buprenorphine, fentanyl, pethidine and tramadol ‡includes codeine, hydromorphone, morphine and oxycodone §The "composite outcome" included encephalopathy, ARDS, respiratory failure, pulmonary hemorrhage, aspiration pneumonia, cardiac arrest, ventricular arrhythmia, heart failure, rhabdomyolysis, acute renal failure, or death ("total events" does not equal the sum of the other events reported, because some outcomes included in the composite outcome were not reported separately). ‖Incidence proportion describes the percentage of hospital admissions for accidental opioid overdose in which patients were diagnosed with each type of outcome in each period.

Table 4. Influence of readmission for accidental opioid overdose and year of overdose on neurological, respiratory, cardiac and other outcomes evaluated during overdose admission

	Events	(a) Opioid overdose readmission		(b) Admissions in 2015 vs 2006*	
		Crude OR	Adjusted OR (95% CI)	Crude OR	Adjusted OR (95% CI)
Primary outcome					
Neurological:					
Encephalopathy	77	0.52	0.57 (0.13, 2.49)	1.12	0.73 (0.28, 1.89)
Secondary outcomes					
Respiratory outcomes:					
Respiratory failure	134	1.10	0.93 (0.43, 2.04)	3.65	3.05 (1.15, 8.08)
Aspiration pneumonia	288	0.45	0.48 (0.21, 1.08)	1.01	0.88 (0.49, 1.59)
ARDs	19	n/a	n/a	n/a	n/a
Pulmonary hemorrhage	<5	n/a	n/a	n/a	n/a
Cardiac outcomes:					
Cardiac arrest	56	n/a	n/a	n/a	n/a
Ventricular arrhythmia	5	n/a	n/a	n/a	n/a
Heart failure	28	n/a	n/a	n/a	n/a
Other outcomes:					
Rhabdomyolysis	124	0.64	0.64 (0.24, 1.75)	1.33	0.96 (0.38, 2.43)
Acute renal failure	237	1.13	1.07 (0.60, 1.91)	1.97	1.86 (0.95, 3.66)
Paraplegia or tetraplegia	6	n/a	n/a	n/a	n/a
Death in hospital	80	0.77	0.86 (0.27, 2.76)	0.74	0.63 (0.24, 1.65)
Composite outcome†	637	0.82	0.83 (0.54, 1.26)	1.27	1.08 (0.71, 1.64)

Odds ratio (OR) estimates have been omitted, and replaced with 'n/a' for 'not available', for outcomes where estimation was not possible due to a small number of events in one or more exposure groups. *The 'Admissions in 2015 vs 2006' column reports the odds of each outcome occurring in association with an accidental opioid overdose hospitalization in 2015 as compared to 2006. †The "composite outcome" was defined as the occurrence of >=1 of the following within an admission: encephalopathy, ARDS, respiratory failure, pulmonary hemorrhage, aspiration pneumonia, cardiac arrest, ventricular arrhythmia, heart failure, rhabdomyolysis, acute renal failure, or death (corresponds to 'admission with >=1 event' under the composite outcome in table 3). Occurrences of the composite outcome do not equal the sum of other events, because some admissions included >1 type of event but this only counted once toward the composite outcome. OR=odds ratio. ARDS=adult respiratory distress syndrome

Table 5. Risk of neurological, respiratory, cardiac and other outcomes in 1 year following hospital admission for accidental opioid overdose in comparison to controls among patients with long-term prescription opioid use (>=180 days)

	Events		Odds ratios	
	Overdose patients (n=552)	Controls (n=11,040)	Crude	Adjusted (95% CI)
Primary outcome				
Neurological:				
Encephalopathy	<5	<5	n/a	n/a
Secondary outcome				
Respiratory outcomes:				
Respiratory failure	14	23	12.46	6.21 (2.24, 17.21)
Aspiration pneumonia	5	19	5.30	2.96 (0.90, 9.71)
ARDs	<5	9	n/a	n/a
Pulmonary hemorrhage	0	0	n/a	n/a
Cardiac outcomes:				
Cardiac arrest	0	5	n/a	n/a
Ventricular arrhythmia	0	5	n/a	n/a
Heart failure	9	95	1.93	0.99 (0.45, 2.15)
Other outcomes:				
Rhabdomyolysis	5	19	5.30	3.08 (0.87, 10.88)
Acute renal failure	16	103	3.18	1.66 (0.90, 3.05)
Paraplegia or tetraplegia	<5	6	n/a	n/a
All-cause mortality	22	96	4.73	2.13 (1.18, 3.86)
Composite outcome†	59	309	4.14	2.15 (1.48, 3.12)
Serious adverse events‡	315	3,489	2.84	1.97 (1.62, 2.39)

Odds ratio estimates have been omitted, and replaced with 'n/a' for 'not available', for outcomes where estimation was not possible due to a small number of events in one or more exposure groups. †The "composite outcome" was defined as an inpatient hospital diagnosis of one or more of the following: encephalopathy, ARDS, respiratory failure, pulmonary hemorrhage, aspiration pneumonia, cardiac arrest, ventricular arrhythmia, heart failure, rhabdomyolysis, acute renal failure, or death. ‡Serious adverse events were defined as all-cause hospitalization or death. ARDS=adult respiratory distress syndrome

SUPPLEMENTARY APPENDIX

Table S1. Opioid poisoning codes

ICD-10 codes indicating opioid poisoning, by category:[2]

Description	ICD-10 codes
Poisoning by opium	T40.0
Poisoning by heroin	T40.1
Poisoning by other opioids*	T40.2
Poisoning by methadone	T40.3
Poisoning by synthetic opioid†	T40.4
Poisoning by unspecified/other opioids	T40.6

*includes codeine, hydromorphone, morphine and oxycodone †includes buprenorphine, fentanyl, pethidine and tramadol

Accidental opioid poisoning was defined by meeting both of the following criteria.

- A hospital admission record is coded with an ICD-10 code opioid poisoning (**T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6**). For hospital admissions related to accidental opioid poisoning, the hospital diagnosis type must also be coded as M (most responsible diagnosis); 1 (pre-admit comorbidity); W, X or Y (service transfer diagnoses); or 6 (proxy most responsible diagnosis).
- The hospital admission record is also coded with an external cause ICD-10 code corresponding to accidental opioid poisoning (**X42**, Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified). Note: This is distinguished from codes corresponding to intentional self-harm (X62), harm from therapeutic use (Y45.0), or unknown intent (Y12).

Table S2. Diagnostic codes for exclusions

Description	ICD-9	ICD-10
Encephalopathy (anoxic brain damage, toxic encephalopathy or unspecified encephalopathy)	348.1, 349.82	G93.1, G92, G93.4
Acute respiratory distress syndrome (ARDS)	518.82	J80
Respiratory failure	518.81	J96.0, J96.9
Pulmonary hemorrhage	770.3	R04.8

Aspiration pneumonia	507.0	J69.0
Cardiac arrest	427.5	I46
Ventricular arrhythmia	427.1, 427.4	I47.0, I47.2, I49.0
Heart failure	428	I50
Rhabdomyolysis	728.88	M62.8, T79.6
Paraplegia or tetraplegia	344.0, 344.1	G82
Acute renal failure	584	N17
Intentional self-harm	n/a‡	X60 – X84

‡Only hospital diagnoses were used for identifying intentional self-harm, because E-codes which could be used are only supplementary codes and MSP data are typically coded with only one diagnostic code.

Table S3. Diagnostic codes for outcomes

Type of outcome	Diagnosis	ICD-10 Codes
Neurological	Encephalopathy (anoxic brain damage, toxic encephalopathy or unspecified encephalopathy)	G93.1, G92, G93.4
Pulmonary	Adult respiratory distress syndrome (ARDS)	J80
	Respiratory failure	J96.0, J96.9
	Pulmonary hemorrhage	R04.8
	Aspiration pneumonia	J69.0
Cardiac	Cardiac arrest	I46
	Ventricular arrhythmia	I47.0, I47.2, I49.0
	Heart failure	I50
Other	Rhabdomyolysis	M62.8, T79.6
	Paraplegia or tetraplegia	G82
	Acute renal failure	N17

Table S4. Diagnostic codes for covariates

Description	Subcategory (if applicable)	ICD codes
Mental or behavioural disorders due to psychoactive substance use	Opioids	ICD-9: 304.0, 304.7, 305.5 ICD-10: F11
	Sedatives and hypnotics	ICD-9: 304.1, 305.4 ICD-10: F13
	Stimulants	ICD-9: 304.2, 305.6, 304.4, 305.7 ICD-10: F14, F15
	Other (alcohol, cannabinoids, hallucinogens, volatile solvents, multiple drug use or use of other psychoactive substances)	ICD-9: 303, 304.3, 304.5, 304.6, 304.8, 304.9, 305.0, 305.2, 305.3, 305.8, 305.9 ICD-10: F10, F12, F16, F18, F19
Other psychiatric illness	Depression	ICD-9: 311, 296.2, 296.3 ICD-10: F32, F33
	Bipolar disorder/ mixed mania	ICD-9: 296.0, 296.1, 296.4, 296.9 ICD-10: F31
	Schizophrenia	ICD-9: 295 ICD-10: F20
	Personality disorders	ICD-9: 301 ICD-10: F60
	Other psychosis	ICD-9: 297 - 299 ICD-10: F21 – F29
Pneumonia (excluding aspiration pneumonia)		ICD-9: 480-486, 487.0 ICD-10: J10.0, J11.0, J12-J18
Other respiratory illness	COPD	ICD-9: 490-492, 494-496 ICD-10: J40-J44, J47
	Asthma	ICD-9: 493 ICD-10: J45
	Sleep apnea	ICD-9: 327.23, 780.57 ICD-10: G47.3, P28.3
HIV disease		ICD-9: 042 ICD-10: B20-B24
Hepatitis B		ICD-9: 070.2, 070.3 ICD-10: B16, B18.0, B18.1
Hepatitis C		ICD-9: 070.41, 070.44, 070.51, 070.54, 070.7 ICD-10: B17.1, B18.2
Cancer		ICD-9: 140-208, 209.0-209.3 ICD-10: C00-C96

Table S5. Prescription opioids

Opioids indicated for pain treatment	Opioid substitution medications
Buprenorphine (patch only)	Buprenorphine/ naloxone (trade name: Suboxone)
Codeine	Methadone
Fentanyl	
Hydromorphone	
Pethidine (also known as: meperidine)	
Morphine	
Oxycodone	
Tapentadol	
Tramadol	

Table S6. Influence of readmission for accidental opioid overdose and covariates on encephalopathy, compared to inital admission

Predictor variable		Adjusted OR (95% CI)
Exposure		
Repeat admission (vs initial admission)		0.57 (0.13, 2.49)
Covariates		
Sex	Female	0.46 (0.26, 0.81)
	Male	1.00
Age (years)	Under 25	1.02 (0.45, 2.28)
	25 to 39	1.35 (0.72, 2.54)
	40 to 49	1.00
	50 to 59	0.55 (0.24, 1.24)
	60 to 69	0.27 (0.07, 1.00)
	70 or above	0.11 (0.02, 0.76)
Cohort entry year	2006	1.00
	2007	0.28 (0.05, 1.41)
	2008	0.52 (0.15, 1.82)
	2009	0.55 (0.15, 1.97)
	2010	0.27 (0.05, 1.32)
	2011	0.77 (0.27, 2.19)
	2012	1.08 (0.41, 2.87)
	2013	0.73 (0.27, 2.01)
	2014	0.51 (0.17, 1.47)
	2015	0.73 (0.28, 1.89)
Income	Low income	0.44 (0.21, 0.92)
	Mid to high income	1.00
Residence	Rural	0.47 (0.17, 1.32)
	Urban	1.00
Substance use disorders*	Opioids	0.76 (0.29, 2.03)
	Sedatives and hypnotics	0.83 (0.44, 1.58)
	Stimulants	0.77 (0.24, 2.53)
Romano comorbidity score*	Zero	0.95 (0.51, 1.75)
	1 to 2	1.00
	3 or more	0.74 (0.20, 2.75)
Other medical history*	Psychiatric illness	0.84 (0.48, 1.48)
	Pneumonia	1.56 (0.60, 4.08)
	Other respiratory illness	0.79 (0.35, 1.78)
	Cancer	2.55 (0.66, 9.82)
Opioid prescription history†	High dose opioid for pain	0.32 (0.10, 0.97)
	Low to intermediate dose for pain	1.00
	No use of opioids for pain	0.95 (0.55, 1.64)
Other prescription history†	Sedatives and hypnotics	0.65 (0.30, 1.42)

Readmissions are defined as additional accidental opioid overdose admissions within 365 days of prior admission. *Based on diagnoses at a physician or hospital visit in the 365 days before opioid overdose. †Based on dispensings in the 180 days prior to opioid overdose. High dose opioid use is defined by a dispensing of opioid pain medication of >90 oral morphine equivalents per day.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Title (p. 1) and abstract (p. 2) Abstract (pp. 2-3)	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Abstract (p. 2) Abstract (p. 2) Abstract (p. 2)
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Paragraphs 1-2 (p. 4)		
Objectives	3	State specific objectives, including any prespecified hypotheses	Paragraph 3 (p. 4)		
Methods					
Study Design	4	Present key elements of study design early in the paper	Study setting and design, paragraph 1 (p. 5)		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Study setting and design, paragraphs 2-4 (pp. 5-6)		
Participants	6	*(a) Cohort study* - Give the	Cohort study: Study	RECORD 6.1: The methods of study	Study setting and

		eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	setting and design, paragraphs 2-4 (pp. 5-6) Matching in secondary analysis: Study setting and design, paragraph 4 (p. 6)	population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	design, paragraphs 2-4; (pp. 5-6) Tables S1 and S2 (Supplementary appendix, pp. 1-2) n/a Not included
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	'Outcome measures' section (p.7) and Table S3 (Supplementary Appendix, p. 2); 'Covariates' section (p. 8) and Tables S4 and S5 (Supplementary appendix, pp. 3-4); 'Statistical analyses' section (pp. 8-9)	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	'Outcome measures' section (p. 7) and Table S3 (Supplementary Appendix, p. 2); 'Covariates' section (p. 8) and Tables S4 and S5 (Supplementary appendix, pp. 3-4); 'Statistical analyses' section (pp. 8-9)
Data sources/	8	For each variable of interest, give	'Data sources'		

measurement		sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	section indicates sources for types of variables (p. 7); details as under Variables above in this table (pp. 7-9); Supplementary Appendx, pp. 2-4)		
Bias	9	Describe any efforts to address potential sources of bias	'Discussion' section, paragraph 4 (p. 13) (potential selection bias)		
Study size	10	Explain how the study size was arrived at	Study setting and design, paragraphs 2-4 (population data for specific cohorts over 10 years) (pp. 5-6)		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	'Covariates' section (p. 8)		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed	(a) 'Covariates' and 'Statistical analyses' sections (pp. 8-9) (b) 'Statistical analyses', paragraphs 1-2 (pp. 8-9) (c) n/a (d) 'Statistical analyses', paragraph 2 (p. 9) e) 'Statistical analyses', paragraph 1 (pp. 8-9)		

		Cross-sectional study - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	'Data sources' section (p. 7) n/a
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	'Data sources' section (p. 7)
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	(a), (b) 'Patient characteristics' section (p. 10) (c) Not included	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	'Patient characteristics' section (p. 10)
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential	'Patient characteristics' section (p. 10) and Tables 1-2 (pp. 22-		

		confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	23) n/a Not included		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Tables 3-5 (pp. 24-26)		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	'Results' section (pp. 11-12) and Tables 3-5 (pp. 24-26) n/a Not included		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	'Results' section, paragraph 2 (p. 11); Table 4(b) (p. 25)		
Discussion					
Key results	18	Summarise key results with reference to study objectives	'Discussion', paragraphs 1 (p. 12)		

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	'Discussion', paragraph 3 (p. 13) 'Discussion', paragraph 3 (p. 13)	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	'Discussion', final paragraph (p. 13)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	'Conclusion' section (pp. 13-14)		
Generalisability	21	Discuss the generalisability (external validity) of the study results	'Discussion', paragraph 2 (pp. 12-13)		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	'Funding statement' (p. 15)		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Study protocol is available on request as noted in 'Data sharing statement' (p. 15)

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.