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Title	Mortality after emergency department visits for opioid overdose: an analysis of the provincial overdose cohort in British Columbia
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Reviewer 1	Louise Overington
Institution	The Royal Ottawa Mental Health Centre, Substance Use and Concurrent Disorders
General comments (author response in bold)	<p>Reviewer Comments</p> <p>This study used data from the British Columbia (BC) Overdose Cohort to estimate the 12-month mortality risk of individuals presenting to an ED for overdose versus non-overdoes reasons. A secondary goal was to explore the 12-month mortality risk for individuals presenting to an ED for overdose based on final disposition. This article offers a clear comparison using a rich dataset. It provides evidence to target an intervention at the time of ED visit as this may help prevent negative patient outcomes. The main consideration is deepening the implications for practice section. For example, re-working parts of the discussion to clarify what interventions have been implemented and the outcome of these interventions.</p> <p>Thank you for these positive comments. We agree that our analysis of our rich, provincial dataset offers a unique opportunity to understand high-risk patients after overdose-related ED visits.</p> <p>We agree with the Reviewer’s suggestion to better develop implications for practice that flow from our analysis. In response, we have added a detailed description of evidence-based interventions that should be offered to persons following overdose-related ED visits to our Interpretation section.</p> <p>INTRODUCTION</p> <ul style="list-style-type: none"> • “For ED patients who present with opioid overdose, healthcare providers have an opportunity to initiate potentially lifesaving treatments.^{7,8}” <ul style="list-style-type: none"> o Can you provide brief examples of interventions that might be used or have been used in this situation (e.g., OAT, link to substance use treatment)? <p>Thank you for this comment. We have amended the referenced sentence as suggested:</p> <p>For ED patients who present with opioid overdose, healthcare providers have an opportunity to offer potentially lifesaving treatments, such as take-home naloxone kits and ED buprenorphine/naloxone inductions.</p> <p>STUDY POPULATION AND DEFINITIONS</p> <ul style="list-style-type: none"> • “Persons who did not have a non-fatal overdose-related ED visit comprised our comparison cohort” <ul style="list-style-type: none"> o This is confusing wording; consider using “non-overdose-related visit” (as you indicate later in the paragraph). We have made this suggested amendment. • Data from 2015-2016. Although you do note this in your limitations section – are more recent data available? If not, in the limitations section can you reflect on other things that have changed since this time period that might make effects the

study found more or less pronounced now.

We agree with this suggestion and have acknowledged the age of our data, an inherent limitation of any analyses of linked administrative health data, as well as historical changes that likely would impact our results, in our Limitations section as follows:

Finally, our analysis is restricted to overdoses that occurred in 2015/16, due to delays inherent in any analyses of linked administrative data where reporting and linkage need to be confirmed. Though we had data available to 2017, we chose 2015/16 as our index year to ensure one year of follow-up for all included subjects. Nonetheless, as 2015/16 was the year that increasing fentanyl prevalence was noted in the illicit drug supply, we expect that the results of our analyses are relevant to our current context. Subsequent evolution of the opioid overdose epidemic in BC with increasing fentanyl prevalence makes it likely that our analysis underestimates the current mortality following an overdose-related ED visit.

METHODS

• You indicate that 29 EDs in BC contributed data to NACRS. What percentage of EDs in this? Does this include EDs in rural locations of BC? If not, please indicate how this may impact the generalizability of your results in the limitations section.

Reporting to NACRS includes both urban and rural facilities, however the Reviewer is correct that a great majority of EDs reporting to NACRS comprise larger, urban EDs. For our 2014/15 data, 28 of 29 (97%) NACRS reporting facilities were urban and only 1 of 29 (3%) were rural, based on presence of “0” in the second character of the postal code.

Nonetheless, NACRS remains the most comprehensive provincial repository of ED visits, with an estimated 74% provincial coverage rate. We have added the following to the Limitations section to recognize the implications of relying on NACRS to identify our ED visits on the generalizability of our results:

Moreover, our reliance on NACRS to identify ED visits likely biased our sample to visits in larger, urban settings, as 97% (28/29) of reporting EDs in 2014/15 were urban. This may limit the generalizability of our results to smaller, rural EDs. Nonetheless, NACRS remains the most comprehensive available ED visit database, with an estimated coverage of 74% of ED visits in BC in 2015/16. Therefore, our provincial-scale analysis offers an important opportunity to understand the crucial issue of mortality post overdose-related ED visits.

STATISTICAL ANALYSES

• It may be helpful to include assumptions for the multivariate Cox regression.

We have added the following statement to our Statistical Analyses subsection of the Methods section to outline assumptions in our model:

	<p><i>Our Cox model did not account for censoring due to losses to follow-up: we assumed that persons with no recorded death remained alive, given persons needed three years of Client Roster data to be included in our analyses, and furthermore that we ascertained death from comprehensive provincial databases.</i></p> <p>INTERPRETATION</p> <ul style="list-style-type: none"> • You note potential interventions (OAT, referral). Consider discussing what other solutions have been proposed/implemented. <p>Thank you for this comment – we agree. We have added a detailed description of evidence-based and guideline-recommended ED interventions that should be routinely offered to ED patients following overdose-related visits.</p> <ul style="list-style-type: none"> • Consider elaborating on outpatient referral pathways and clinical interventions to include specific examples (e.g., Rapid access addiction medicine). <p>We have added a specific discussion of rapid access, low-barrier addictions clinic follow-up to our Interpretation section.</p> <ul style="list-style-type: none"> • You note limitations related to the impact of socioeconomic factors such as homelessness, income, or employment status on mortality. Can you briefly indicate how you think this may impact the results if you had access to this information? <p>Thank you for this suggestion. We have added the following to our</p> <p>Limitations section:</p> <p><i>In line with existing evidence, we would expect low socioeconomic status including low income and unstable housing to increase mortality risk.</i></p> <p>Table 1</p> <ul style="list-style-type: none"> • Spelling error (“visits”) in column header: “Non-overdose-related vjsjts (Discharged or left against medical advice)” <p>We have made this change.</p> <p>Table 3</p> <ul style="list-style-type: none"> • Consider adding a note to the table to define “Ref” <p>We have made this change.</p>
Reviewer 2	Stephen DiTommaso MD
Institution	Université de Montréal, Département de médecine familiale
General comments (author response in bold)	<p>The results of this study are predictable and not especially newsworthy, however tragic : patients coming to the ER for a drug overdose have a higher than average risk of dying during the subsequent year. I am actually surprised that the death rate isn't higher!</p> <p>Nevertheless, I do support publication of this study. The question is where, when, and how. Generalist clinician readers of the CMAJ will likely feel unfulfilled, and even helpless, unless offered a pathway toward concrete solutions. And health care planners may not continue reading this paper beyond the abstract, without the promise of guidance towards specific solutions.</p>

I'm not sure how much importance should be placed upon the statistical accuracy around the one-year death rate. Patterns of drug misuse, and the composition of drugs being misused, fluctuate dramatically. The rate of 5,4 % could be much higher or much lower depending on the season, the nature of the drugs which are available and affordable, contamination rates, and the catchment area (neighbourhood) around any given ER. The authors acknowledge this fact in their discussion of limitations. So much the better if the rates found by the authors correlate well with studies elsewhere. This is a credit to the authors, but that does not really matter very much to a clinician in the process of treating an overdose patient in his or her ER. The most effective interventions, if any, would be much the much the same if the one-year death rate were 4 %, or 5 %, or 6%, or 7 %, etc.

The practical implications of this study are important but unclear, and contingent on many factors, which the individual clinician is unlikely to be able to act upon during his or her busy ER shift. The authors do discuss possible solutions, but not comprehensively or specifically enough to help clinician readers change their clinical practice.

We appreciate the Reviewer's comments and criticisms, and thank them for their candid insights. In response:

-We do feel that our results add importantly to our collective national understanding of the high mortality risk experienced by persons following an overdose-related ED visit. Our study is the first to compare mortality of these patients to a comparison cohort drawn from a province-wide control group who presented to the ED with non-overdose related reasons. Our study also adds to the literature on this topic by specifically examining mortality following an overdose-related ED visit based on disposition status from the ED.

-We agree with the Reviewer's statement that mortality fluctuates with composition of the illicit drug supply, which is supported by a recent study (Irvine, 2019). We suspect that mortality following overdose-related ED visit is likely higher at present, given increasing prevalence of fentanyl, which adds urgency to the need for ED clinicians to identify these high-risk patients. As detailed above we have added the following statement to paragraph 3 of the Interpretation section, along with recent supporting references:

Given increasing fentanyl prevalence in BC's illicit drug supply since 2015(REF), and evidence of increased probability of fatal overdose when fentanyl-analogues are implicated, mortality following overdose-related ED visits is likely higher presently than in our analysis.

-We agree that clarifying and emphasizing the clinical implications of our work will strengthen our manuscript. To this end, we have added a detailed description of evidence-based, guideline-supported interventions that should be considered from the ED in the Discussion section. Furthermore, we have amended the last sentence of the Conclusion section to highlight the clinical implication of our study, as detailed above.

1) Urgent referral to detoxification services

After resuscitating an overdose patient in the ER, how exactly should ER staff go about making “an urgent intervention” ?

Most patients in the ER for drug misuse are repeat offenders, and they have usually cycled through the various detox facilities several times, which are usually widely known.

In my experience as a former ER physician in downtown Montreal, most patients to whom I administered naloxone for a narcotics overdose felt terrible and just wanted to leave ASAP, to take more heroin in order to relieve their iatrogenic withdrawal symptoms. The majority were rude, in a rush, and uninterested in discussing detox. The present study validates this observation : the very highest rate of post-overdose deaths occurred in patients leaving the ER against advice. In my experience, only a few overdose patients (mainly first-timers) were frightened, and open to discussion of ways to avoid repeated negative experiences. (I actually consulted our medical bioethics team to explore ways of retaining naloxone-resuscitated patients against their will for at least a few hours, to prevent rapid heroin re-injection and subsequent fatal overdose, and not to lecture them on the value of detox : my request was felt to breach patient rights and so denied.) So asking resuscitated patients to hang around the ER for any purpose is generally not feasible.

Conversely, I wonder how many patients who succumb to narcotics overdose have never gone through detox. Probably very few. It would be nice to see data.

I do not deny that referrals should be made. Of course they should be made. However is there any evidence to prove the benefits of “urgent referral” to detox as opposed to usual practice ? Are there any Canadian models to inspire the reader ?

I originally interpreted this study as a plea to ER staff to be less nonchalant (or less defeatist) before releasing resuscitated OD patients. However, I now believe that the rate limiting step in clinical practice is the poor availability of resources, and not the attitudes of ER staff. Are there even any detoxification centres available to ER patients on an urgent basis ?

Drug users are notoriously difficult to follow up. They often miss appointments, and they do not often have telephones or respond to them when called from unknown numbers. Simply firing off a referral and asking detox to call a patient back on an “urgent” basis is insufficient. And giving pamphlets and business cards of detox services to overdose patients as they leave the ER (as I always did) is also unlikely to have much impact.

So I am sceptical about the authors’ main recommendation (unproven), which is that rapid referrals will likely decrease post-discharge mortality.

We appreciate the Reviewer’s comments. We agree that improving access to supportive resources post-discharge is a key component of patients’ care following overdose.

There are many evidence-based ED interventions for patients with opioid use disorder that are recommended by national best practice guidelines and highlighted in a recent systematic review. Among these are initiation of ED buprenorphine/naloxone, and referral to rapid access, low-barrier addictions care, which have been shown to improve retention in care and to decrease illicit opioid use. We have added a detailed description and relevant references supporting evidence-based and guideline-supported ED interventions, including urgent addictions referral, to the Interpretation section. These interventions should be routinely considered in the treatment of ED patients with opioid use disorder.

We also respectfully point the Reviewer to the current national guideline that recommends against detoxification or withdrawal management alone as an isolated treatment option, due to evidence demonstrating increased mortality with this approach.

CRISM National Guideline for the Clinical Management of Opioid Use Disorder, 2018 (p. 21); Bruneau et al. Management of opioid use disorders: a clinical practice guideline. CMAJ, 2018:

Offering withdrawal management alone (i.e., detoxification without immediate transition to long-term addiction treatment) should be avoided, since this approach has been associated with increased rates of relapse, morbidity, and mortality (Quality of evidence: Moderate; Strength of recommendation: Strong).

2) Alternatives to urgent post-discharge referrals to detox

One potential solution is to post clinicians (not necessarily physicians) specializing in drug abuse within busy emergency rooms, so they can evaluate patients on the spot, and present patients with available services. This would take a load off of overworked ER staff, and also simplify the referral process. Whether this model would have an impact on drug misuse and mortality following discharge remains to be seen. Do any published reports support this model?

Another interesting solution would be start methadone or buprenorphine maintenance treatment in the ER, before discharge, as suggested by reference 7. I am unaware of the quality of evidence on this subject, but this treatment option is very attractive. Busy ER physicians won't generally have the time to initiate replacement therapy, but another hospital service certainly could. A problem we had at our inner-city hospital was the large number of repeat visits by patients who kept coming to the ER when they were in cold turkey, requesting methadone or other narcotics as a temporary measure, or coming back to the ER just a few days after signing themselves out of our detox unit and asking to be readmitted (we always refused). So a fast-start maintenance induction treatment in the ER would require strict conditions to avoid becoming a rotating door for on-again / off-again, impulsive patients tired of waiting for a spot in detox.

I believe that publication of this paper should be combined (in the same edition) with a paper explaining how rapid induction of narcotics maintenance treatment in an ER could be implemented. Standing alone, the current paper is much less

interesting to the general reader.

We agree that initiation of ED buprenorphine is an important and evidence-based intervention that should be considered for all patients following ED presentation for overdose.

We have added a discussion of ED opioid agonist treatment in addition to other guideline-supported care for patients with opioid use disorder, to the Interpretation section.

Additionally, we agree that exploring alternative solutions that integrate addictions specialists into EDs should be explored. To this effect, we have added references to recent studies examining this approach, and have added the following sentence to the Interpretation section:

Moreover, interventions that integrate addictions specialists in EDs to provide specialized care for patients with opioid use disorder merit further attention.

3) I did not examine the statistical analyses used by the authors.

Certainly, this study uses an impressive number of subjects : 3,593 OD patients and 216,453 non-OD visits.

However, I am not sufficiently proficient to criticize the statistical analyses employed by the authors.

In any case, the result is so self-evident, that I suspect the results would very similar irrespective of the data analyses used.

We thank the Reviewer for their recognition of the large sample size of our study. We are confident in the validity and rigor of our analytic methodology.

We respectfully disagree that the results of our analysis are self-evident. Our clinical experience in the ED is often that persons seen post overdose are not treated as high risk patients with initiation of evidence-based treatment options, liaisons to harm reduction services, discharge planning, urgent referral, and psychosocial supports. Comparatively, these patients often do not receive the same level of thorough disposition planning as patients with other medical illnesses, such as coronary artery disease or cancer. Given that patients experiencing overdose are relatively young, interventions initiated by emergency clinicians could have an important impact on quality-adjusted life years gained. We believe that our results provide an impetus for an important change in clinical practice and culture such that offering a range of evidence-based supports to persons following overdose-related visits becomes the norm, rather than the exception.

Conclusion

This paper is a useful contribution to medical knowledge in Canada. Should it be published in the CMAJ? I think so. However, I feel that the same issue of the

CMAJ should also contain one or more articles on practical ways that emergency departments can improve care to resuscitated overdose patients. Each article would potentiate the other. Each article standing alone would be less worthy of reading, and less likely to lead to improvements in care.

We appreciate the Reviewer's comment that our paper contributes to medical knowledge in Canada. We agree with the Reviewer's suggestion for improvement and have added a detailed description of the clinical implications of our findings, including practical and evidence-based ways that EDs can improve care of resuscitated overdose patients, in our Interpretation section. We hope that these edits help to contextualize and strengthen the importance of our results.