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Title: Opioid-related emergency department visits and deaths following a harm-reduction intervention: a retrospective observational cohort time-series analysis
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Reviewer 1: Meldon Kahan
Institution: Department of Family and Community Medicine, University of Toronto
General comments (author response in bold)

1. The results need further explanation. Deaths and ED visits markedly declined from pre to post implementation of the SCS in Edmonton and Calgary, but deaths and ED visits markedly increased in urban areas from pre to post implementation of the CBN programs. This is contradictory; I would think that Edmonton and Calgary make up the bulk of the urban population in Alberta. I understand that the CBN program started two years before the SCS program, but to me this doesn't satisfactorily explain the discrepancy.
We appreciate this new insight on our paper. We have attempted to address this discrepancy in the discussion and with a slope change analysis. Or data now shows that while visits and deaths may have continued to climb following CBN program implementation, the slope dramatically decreased, suggesting there was some lag time prior to the CBN program maturing and reaching full effectiveness. By contrast, the SCS programs were able to become effective within a short-time of opening, as their services were offered within the brick and mortar locations. This is explained in line 168-178, and line 205-206.

2. Overdose deaths and ED visits have increased dramatically in communities where fentanyl has been introduced. If these rates have really dropped in Edmonton and Alberta, this is critically important for public health planning. But it seems unlikely to me that SCS is the sole explanation fo this drop. One potentially confounding factor is the availability of opioid agonist treatment (OAT, which is not mentioned in the paper. Opioid agonist treatment with methadone and buprenorphine has been shown to reduce rates of overdose death and ED visits. It protects against overdose even among people who continue to use fentanyl, so it is a harm reduction intervention. The evidence for the effectiveness of OAT in preventing overdose death is far greater than the evidence for SCS. In a systematic review (Sordo 2017), the mortality rate while on methadone was 2.6 per 1000 patient years, rising to 12.7/1000 patient years while off methadone; see also Pearce 2020.
Thank you for highlighting these new programs that have an important impact on our study. The use of OAT and VODP is now explained in the discussion of the SCS in the paper and our Program Theory to highlight the wide impact of other factors on opioid overdose and death. See line 192-198.

3. A few years ago, Alberta started the Virtual Opioid Dependency Program, which allows individuals to start OAT on the same day, from any setting – home, ED or shelter. If the virtual program caused a spike in enrollment in OAT in Edmonton and Calgary, this could partly explain the reduction in ED visits and mortality.
Thank you for this previously unconsidered comment. We appreciate your insight. While it is possible the VODP may have contributed to reduced ED visits and mortality, the VODP was implemented earlier than the SCS intervention in the majority of examined locations, our analysis did not show reduction sot be true in

every municipality, suggesting VODP may not have been a large contributor to changes in deaths.

4. It would be helpful to know more about patient volumes in the SCS programs. How many unique clients did they serve, and how often on average did these clients visit the SCS programs? If the SCS only serves a small number of regular clients, then it is less plausible that the SCS was the sole cause of the drop in ED visits and overdose deaths.

This is now explained in our discussion. The urban sites serve many individuals, while this is not true of sites in Lethbridge. This is interesting because it was the urban areas that saw marked changes in deaths and ED visits (with the exception of Lethbridge). See line 167-178.

5. Regarding the CBN program, the authors acknowledge that they did not have data on how many kits were distributed in urban and rural areas. I would think this information would be easy to obtain and would be helpful in understanding the results. Also, the authors should comment on whether Alberta emergency departments distribute take-home naloxone kits to patients in the ED, or are they only distributed in community settings. If the latter, then the impact of CBN programs on overdose deaths will be limited. In other jurisdictions (including Ontario), take-home naloxone kits are rarely distributed in Eds and hospitals, and this diminishes the effectiveness of these programs. There is evidence that a large proportion of people who have died of an opioid overdose have visited the ED at least once in the previous year. There is also evidence that many patients who visit the ED for an opioid related problem have not picked up a take-home naloxone kit from a community pharmacy (Leece 2020, Hurt 2020, Moe 2021).

Thank you for highlighting this gap in reported information. It is now included in the introduction. Unfortunately, no further detailed information was available within our existing ethics request. Based on the work of Spackman et al, we believe it would take too long to obtain this modified data in time for inclusion in our study. See line 37-40.

Overall, I do recommend publication of this study. It is topical and it addresses a very important cause of potentially preventable death among young Canadian adults. However, this study is difficult to understand for clinical readers, and therefore I have some mixed feelings.

First of all, this dynamic subject is very difficult to investigate, due to multiple concurrent social trends and multiple concurrent health care interventions, many of which are described by the authors : the changing nature of the drugs being used, as well as the very different and evolving services and policies in different cities.

Secondly, I find the statistical analyses difficult to apply clinically, which is not the fault of the authors. The data are inconsistent depending on the outcome and the locale. Some outcomes improved and some worsened, while others didn’t change much after the interventions. Those which worsened might have worsened even more if it were not for the preventive interventions. Those which improved may have done so for reasons other than the interventions.

As a clinician reading this study, I am left with the impression that complications due to illicit drug consumption decreased (improved) but that it is very difficult to “prove” the extent of these benefits. It would be even more difficult to calculate cost-benefit analyses.

I am concerned that opponents to overdose prevention programmes will focus on the negative findings of this study and then argue for their closure, as being a “waste of good tax dollars”.
The authors do a good job of explaining the reasons why drug overdose prevention services may not have had the expected impact, but their (reasonable) explanations / theories are hard to prove, and they may not convince sceptics. In the end, there are just too many uncontrolled variables operating in all different directions, at the same time, so any definitive conclusions seem impossible. For example, ED visits for drug overdose are bad if they are dure to more overdoses, but they are good if they are due to more lives are being saved by naloxone administration. So should ED visits go up or go down or both (for different reasons)?
I would hope that government agencies would see the difficulties of performing this kind of study as a reason had to grant more funding and better research access to what the authors call “granular” data, which seems important given the high number of simultaneous variations being evaluated.
I credit the authors for being honest about the results that do not support drug overdose interventions, even if they try to “explain them away”.
The authors briefly mention the differences in approach by two services, one government funded and the other community funded. There are surely very many ways to deal with people at risk of drug overdose. While not the purpose of the present study, I would think that clinicians are hungry to know “what works and what doesn’t”. The scope of the present study may be too broad to answer that question, but the authors touch upon it when trying to explain regional variations in results.
Really, this is a rapidly evolving, unstable, and regionally heterogenous field. Drug overdose prevention services vary from clinic to clinic, all over the country. Unlike antihypertensive medications, surgical procedures, or many other health care interventions, it may be simply impossible to generalise the results of one service in one city at one point in time to any other context.
PS: I wonder if a definition should be offered of “interrupted time series analysis” for the benefits of non-researcher (clinical) readers. I certainly agree with the statement “. . . implementation (of interrupted time series analysis) can be challenging, particularly for non-statisticians” cited in the following reference:
Thank you for the comments and insight on both our results, paper, and the field we operate in. To address the above comments, we have offered a brief explanation of what an ITS is for layperson interpretation of results in the methods section. We hope this will help explain in rough terms what an ITS can do. We have also added a program theory to highlight how multifaceted drug addiction can be, in addition to a section on recommendations for future researchers and policymakers to ensure data is more accessible for research use. Line 83-84 and Supplemental Figure 1.

Reviewer 2: Elise Jackson
Institution: Internal Medicine Residency Program, The University of British Columbia
General comments (author response in bold)

1. The red lines on the graphs are not labelled - are these confidence intervals?
Thank you for catching this oversight on our part. We have now included a description in the titles of all figures.

2. Was the "expected trend" on the graphs just a continuation of the pre-intervention trend? I don't know if that was ever explicitly stated. Also, was the trend always linear, or

were any exponential? This would change the expected trend and possibly account for some of the difference between the the post-intervention trend vs. the expected trend.
The trend was always linear. Previous research and visual inspection of our data does not suggest an exponential approach to the study is appropriate.

3. You mention that once of the limitations is that you aren't able to say how many naloxone kits were actually used - is there at least any data on how many were at least distributed? And similarly, any data on how well utilized the SCS and OPS were? Analysing the data just as a binary of before vs. after the programs were implemented wouldn't necessarily accurately represent their effect on ED visits/deaths, and looking at actual utilization may also help to account for some of the variation between regions (as you mentioned, it may be influenced by trust in the organizations, and looking at rates of usage/attendance may more accurately capture this, if you could compare ED visits/deaths against actual usage)
Thank you for your comment. We hope that the additional information will improve the readability and generalizability of our paper. We have now included in the introduction information on the level of usage of both the SCS and CBN programs by kits distributed and visits to SCS sites. Unfortunately, the publicly available data is not sufficient to include in our analysis, as we cannot determine the number of visits or distributed kits by month. The data is also not granular enough to break down between municipalities like Lethbridge. See line 37-40.

4. Some small grammatical editing may be helpful, e.g. page 1 line 16-17 is a poorly worded and repetitive sentence
We have gone through the paper and made several minor changes to grammar.

Reviewer 3: Louise Overington
Institution: Substance Use and Concurrent Disorders, The Royal Ottawa Mental Health Centre
General comments (author response in bold)

The paper is framed as a contribution to existing evaluations of harm reduction interventions that have been adopted in recent years in the hopes of managing the ongoing opioid crisis. The specific context of the study is the Canadian province of Alberta, where the authors use information on energy room visits and opioid-related deaths as measures to assess whether the introduction of specific harm reduction programs have had desired impacts. Varying programs serve as the interventions being examined, and the study uses an interrupted time series analysis technique to check whether statistically significant slope changes occur post interventions for the two measures of interest. Overall, the paper stands to make a useful contribution. But I feel a few additional revisions are needed to ensure the contribution is clear and well explained to a general audience. My comments focus on changes that can help the authors improve their paper.
1. A first comment is the paper is a bit unclear on the level of analysis and how this level of analysis is a contribution in relation to existing work. In the final sentence of the introductory paragraph, the paper notes that it will focus on the municipal level rather than the local level. But there are two problems with this. First, local is not defined. Is this a standardized concept, where local means the same thing in different studies that have used it? How is it different from the municipal level? This needs to be clarified as this is a key justification for the current study. Second, the paper does not stick with this conceptual distinction in a clear way throughout the paper. Indeed, when it comes to

defining its research questions and specific research objectives, the paper uses the term local, e.g. “identifying changes in local opioid-related ED visit volume following SCS openings…” It was therefore very unclear what these terms mean and how the paper achieves its aim of doing something different from previous research. The authors need to address this in their revision.
Thank you for highlighting these potentially confusing terms. We hope these comments will help improve our readability. These terms have been changed and re-defined, with local being replaced by municipal and defined as within city limits. Previous reference to local research has been re-defined as reference to studies done within the neighbourhood an SCS site was located in. See line 23-25.

2. The second comment turns to the paper’s methods. The paper uses an interrupted time-series analysis to determine whether various measures have a shift in intercept pre and post intervention. I’d encourage the authors to add a little more discussion of the method to help readers appreciate how to interpret the results. Such a discussion could cover issues like the following. What are the assumptions of this modeling technique and why are they appropriate in this situation? Are there any omitted variables that might correlate with the interventions that could affect the results? For instance, are there any reasons to be concerned that there are trends that would be associated with seasons in Alberta. Would this differentially affect the interventions because they were rolled out at different times of the year? Another concern might be the assumption that interventions are uniform and consistently applied programs. Can we assume consistent application of the treatment from the date the programs started for the rest of the study period? Were there budgetary concerns at any point? Any other concerns with implementation that might suggest a diminishing effect over time? Or conversely, might the programs have built up over time, starting smaller and then increasing in their significance as the word got out about their effects? At least discuss these options would be good, and suggesting what would be needed to examine these sorts of questions further in future papers?
A statement addressing the fact changes in scale over time were not addressed is now included. To our understanding, there is no evidence to suggest either of the studied programs were scaled back over the course of the study. In fact, the opposite was true, with more sites and users reported over progressive time periods. See line 254-258.

3. A final comment turns to the findings about the supervised consumption sites. I wonder about the location of the Edmonton site. More could be discussed here. Are there any spatial patterns to opioid related deaths in urban areas in Alberta? Where is the Calgary facilitated located in relation to these areas as compared to the Edmonton site? Could this help explain pattern, as much as trust levels? I also wonder if the author could provide a little more additional interpretation here. Trust may be higher for the nonprofit, but I wonder if this is across the board with all individuals? Given what has happened in Edmonton seems very important to understand, more discussion of the potential causes of the decreased deaths in this case as compared to others would be a big help. Note, it would be important to connect some of this discussion back to the level of analysis issue raised above, as the discussion does not currently explain what is being found about the municipal level that is different from the local level, as it claimed would be a key contribution of the paper.
Thank you for highlighting this important contextual information not previously considered. The discussion has been modified to include the additional descriptive and interpretive information about the accessibility of SCS sites in the

two urban centres, as well as geographical contextual information. See line 167-178.