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Title	Availability of naloxone in Canadian pharmacies: a population-based survey
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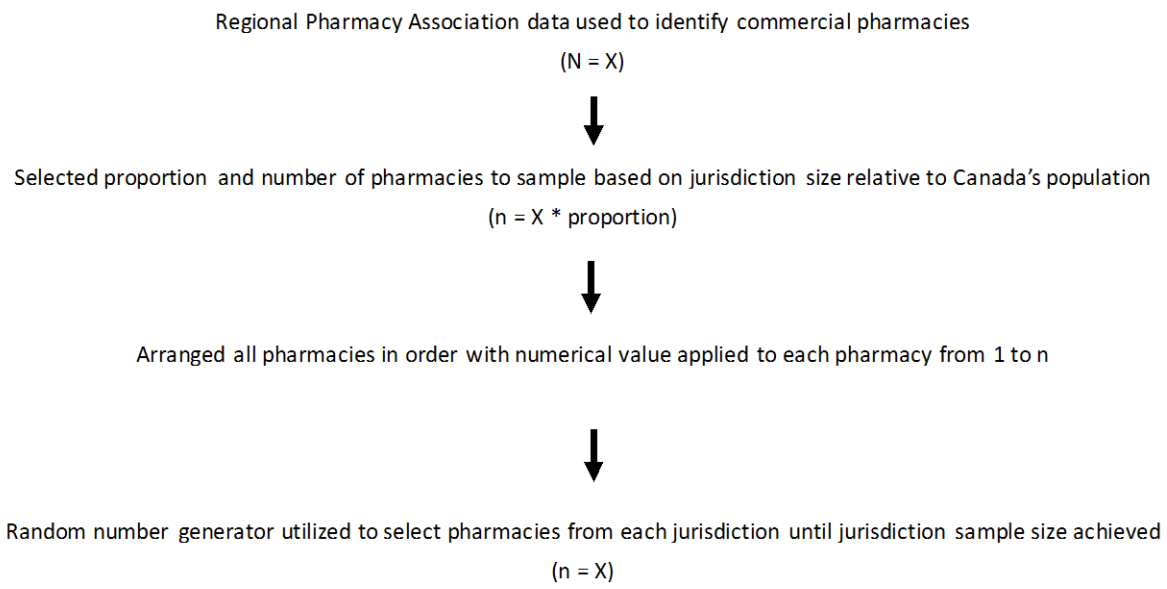
Reviewer 1	Z. Samaan
Institution	Department of Psychiatry and Behavioral Neurosciences, McMaster University, Hamilton, Ont.
General comments (author response in bold)	This manuscript used a survey style quality improvement initiative to identify the availability of naloxone in Canadian community pharmacies. Using a random sampling accounting for the population size per geographic area, the authors made telephone calls to 429 pharmacies asking about the availability of naloxone on the day of the call or the possibility of obtaining it within a week. The study rationale is based on the current Canadian opioid crisis and the increase in opioid-related overdose mortality. The availability of opioid antidote (naloxone) can save lives by making available for people at risk of overdose, that is why it was made accessible without a prescription, however, the cost of obtaining it and the availability in community pharmacies varied greatly among the provinces. This is important study highlighting the disparity among various regions of the country including access and cost of naloxone. The authors argued that their findings "emphasize the need for increased availability of naloxone across Canada". The manuscript is well written and the study is important however the conclusions are beyond the scope of this study as the lack of naloxone in the sampled pharmacies does not automatically mean that naloxone is not available through other means such as harm reduction sites. There are significant limitations need to be addressed and the study can be strengthened based on the following specifi comments: 1. Background and the study rationale: a. The rationale does not provide any data or evidence on the effectiveness of naloxone use in the community **We thank the reviewer for this comment. Naloxone can be highly effective in the community, with multiple studies illustrating a reduction in opioid-related mortality at the community level and thousands of opioid overdose "rescues" following the introduction of community-based naloxone programs. (7-11) We now cite these studies in the revised manuscript.** b. The frequency of its use by patients with chronic pain and prescribed opioids compared to patients with opioid use disorder, **We know of no studies specifically contrasting the frequency of use of naloxone among patients prescribed opioids for chronic pain and those with a documented opioid use disorder. Presumably, naloxone use in the former group would be considerably lower, even though roughly 1 in 4 misuse opioids in some way.(12) Importantly, these patients greatly outnumber those with a documented opioid use disorder. As discussed in our response to Reviewer 1, naloxone has an important public health role for these patients as well, and pharmacists are arguably the health professionals best positioned to promote its wider availability. It is not difficult to envision how this could save lives.** **Several studies demonstrate the acceptability of take-home naloxone for patients receiving opioids for chronic pain. (13,1 In these studies, most patients report that receiving education about opioid risks and having naloxone available in the event of overdose are beneficial, and that they would not be offended if offered the product.** c. There are no data provided on the frequency of dispensing naloxone by community pharmacies versus other sources such as harm reduction sites, supervised consumption sites, addiction clinics, emergency rooms, among others. **Please see our reply to Reviewer 1. While naloxone can be obtained from other sources, this is generally limited to patien with addiction.** d. How effective is naloxone when used in the community by lay persons in reducing mortality from an opioid overdose? **Naloxone can be highly effective when used in the community. Please see our response above.** e. Naloxone "kit" is not a kit although this term has been used it is a vial with naloxone, an instruction sheet, someone has to draw t drug into a syringe, etc.… what is the rate of proper use by lay persons? **We have removed reference to "kits". Although we are aware of no data examining proper use of naloxone by laypeople, this will surely be improved by pharmacists trained to deliver detailed instructions at the time naloxone is provided.** 2. Methods: a. What was the randomization method used to select the ~500 pharmacies? This was not mentioned in details, at the end of the "identification…" section the authors stated that they used random number generator to reduce "sampling bias" **In the revised manuscript, we have added a few sentences (page 4) and, should the editors wish it, a flow diagram describing the use of a random number generator to identify pharmacies. Briefly, all pharmacies within a jurisdiction wer numbered in sequence, and a random number generator (with n = the jurisdiction population size) was used to select site More detail is offered below in response 2f.** b. Why exclude the sites that disclosed the list of pharmacies dispensing naloxone? If randomization is used to select the pharmacies, should this be then balancing the distribution of those who do dispense and those who don't? **We excluded Alberta and Manitoba because they provided information online to identify pharmacies with naloxone. Although randomization reduced bias in the selection of pharmacies, it was done without knowledge of naloxone status, and would not be expected to yield balance in the availability of naloxone. In our view, presenting the full data on these provinces where available was the most accurate way of reporting this.** c. Why choose 500? **We chose 500 on the basis of pragmatism, because contacting all of Canada's ~10,000 pharmacies by phone would not hav been practical. Our sample represents nearly 5% of all community pharmacies in Canada.** d. Why choose a week as the duration to obtain naloxone if not ready on the day of call? **Most pharmacies can obtain drugs from their distributors within 1 to 2 business days. We chose a one week metric to avo exaggerating the extent of non-availability.** e. Under "identification" 2nd paragraph "…with a larger proportion of pharmacies sampled in PEI (n=5) and the Territories (n=5)", thought the authors set n=5 as the minimum unit, please clarify. **We thank the reviewer for this comment and now clarify this in the revised manuscript (page 4). Briefly, we set the minimum number of sites to sample within each jurisdiction at 5. Because of this, we deliberately sampled a larger proportion of pharmacies in less populous jurisdictions such as Prince Edward Island and the territories.**

f. Please provide a flow diagram of the selection process
A flow diagram has been added (in Appendix). Please see below.



g. Please use the reporting guidelines for quality improvement studies (SQUIRE) to improve the standard of reporting, transparency, and reproducibility. See the EQUATOR Network site.
We thank the reviewer for this suggestion and have adjusted our manuscript accordingly. We believe these changes have improved the transparency and the reproducibility of our work.

3. Results:

a. Second paragraph, 2nd line: please replace "ranged" which is a statistical term means the difference between max and min values, with varied.
We now use the word "varied" (page 5).

b. There is an important point that was a missed opportunity in this study which the perception of pharmacists of opioid use and naloxone dispensing. What is the level of training they receive
While an examination of pharmacists' attitudes toward naloxone would have been interesting, this was not the focus of our study. In th revised manuscript, we now outline in general terms the training process pharmacists complete, using Ontario and Alberta as examples. In brief, pharmacists must take an online training course that improves their understanding of the Take Home Naloxone program and explains the pharmacist's role as a participant. Such courses inform pharmacists about:

1) Principles of harm reduction,
2) How to identify at-risk individuals (such as those individuals receiving high doses of opioids,
3) Contents of a Take Home Naloxone kit,
4) Counseling and proper administration of naloxone

What are the unmet needs to implement the availability of naloxone in every pharmacy,
This has not been studied. If naloxone were used only for opioid addiction, it might not be needed in every pharmacy, particularly when several exist in close proximity. However, given its role in patients receiving high-dose opioids by prescription, a case can be made for making it available in every pharmacy. In the revised manuscript, we speculate about some of the unmet needs, including: 1) balancing supply and demand and 2) cost to corporations and distributors.

What are the associated concerns about risks associated with its use, any stigma associated with opioid use disorder that could impact th willingness of community pharmacists to obtain naloxone?
Naloxone is an exceedingly safe medication, with opioid withdrawal (unpleasant but temporary) as its primary adverse effect. Although opioid addiction is associated with stigma, it also represents an immediate threat to life, particularly wit the profusion of clandestinely-produced fentanyl in the illicit drug supply. In the revised manuscript, we have included th pharmacists may voice concern about precipitating withdrawal, but that the risks of opioid overdose and death greatly exceed the risk of opioid withdrawal.

4. Interpretation:
a. To increase naloxone access, the location and responsibility should not lie within the community pharmacies alone, there are many other sites and resources that were not captured by this study and therefore we can not conclude that access is limited because it is not available at every pharmacy. A more balanced argument with a clear acknowledgment of the current study limitations should be made.
See our response to Reviewer 1. Our revised discussion section notes the availability of naloxone from other sources, but also emphasizes that i) its distribution should not be limited to those with an opioid use disorder, and ii) its availability is particularly important in centres where supervised consumption sites, addiction clinics, etc. are less accessible.

Reviewer 2	Bruna Brands
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General comments (author response in bold)	This is an important, methodically sound study. The widespread availability of naloxone is an important initiative to address the opioid crisis. I have one minor question/comment. The Government of Canada web page on 'naloxone' (https://www.canada.ca/en/health-canada/services/substance-abuse/prescription-drug-abuse/opioids/naloxone.html accessed June 1, 2017) provides information on where t obtain naloxone in a particular province or territory. Although the webpage was last updated on March 21, 2017 the information in the links may have been updated since then. For example if you click on the link to British Columbia you are provided with a map of pharmacy locations where naloxone is available and the kits are free. This is quite a change from the situation reported in the manuscrip where 97% of pharmacies in British Columbia required a fee. It would have been interesting to have some further information as to wh and when this change occurred and how close were these changes to the posting of information on pharmacies in Alberta and Manitob where naloxone was available. **Our study was conducted between January and March 2017 when provincial and federal initiatives to address the opioid crisis were evolving, as they still are.** **In response to the reviewer's comment, we have again contacted the 32 pharmacies in British Columbia that originally ha naloxone and indicated a fee was required to receive it. Of these, all reaffirmed the need for a fee, which in some instanc was higher than previously stated. Moreover, some of these pharmacies no longer had naloxone on hand. These data indicate that Government of Canada's website is sometimes inaccurate with regard to both naloxone availability and cos How did the authors become aware of these postings? Did they routinely check the provincial websites or were they informed through other sources? This is relevant if one considers the short collection period and the fact that the authors rightly excluded the data from Alberta and Manitoba.** **We closely monitored the medical literature and provincial websites from December to March 2017, and expressly avoide modifying our sampling strategy over time to maintain consistency. Although some jurisdictions now provide access poin for naloxone, it is unclear if those databases accurately reflect naloxone access at the pharmacy level. An as-yet unpublished study from the Department of Pharmacology and Toxicology at the University of Toronto found that naloxon was often not available at pharmacies in the Greater Toronto Area indicated as sources on the governmental website. Ou study examined pharmacy level data on point of contact which is important and relevant to the consumer.** References 1. 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