

<b>Article details: 2019-0228</b>	
Title	<b>Influence of opioid prescribing standards on health outcomes among patients with long-term opioid use: a longitudinal cohort study</b>
Authors	Richard L. Morrow MA, Ken Bassett MD PhD, James M. Wright MD PhD, Greg Carney PhD, Colin R. Dormuth ScD
<b>Reviewer 1</b>	Dr. Ta-Liang Chen
Institution	Taipei Medical University, Health Policy Research Center, Taiwan
General comments and author response	This is a 2nd phase retrospective cohort evaluating the CPSBC standards and guidelines potentially affecting the adverse outcomes of hospitalization, emergency service visit and all-cause mortality associated with drug overdose and it was well designed, adjusted and beautifully written. This non-inferiority study implies the future modification for the guideline looking for more improvement in outcomes for the patients with opioid overdose.
<b>Reviewer 2</b>	Dr. Lisa Barbera
Institution	Tom Baker Cancer Centre, Radiation Oncology, Calgary, Alberta
General comments and author response	<p>This is a well written clear study describing the impact of a policy change in BC for opioid prescribing on opioid overdose hospitalization, all cause hospitalization, ED visits, opioid related mortality and all cause mortality. It is the second manuscript from this group with the same cohort. The first study evaluated changes in prescribing behavior of physicians. This paper focuses on outcomes.</p> <p>Minor comments:</p> <ol style="list-style-type: none"> <li>1. Why are residents of long term care excluded?</li> </ol> <p>Response: Our data sources lacked complete drug information for residents of long-term care facilities. Since phase 1 of our study included drug utilization outcomes, we excluded these patients to avoid outcome misclassification due to missing data.</p> <ol style="list-style-type: none"> <li>2. Morphine is not in the list of opioids in the first paragraph of the methods but presumably was included.</li> </ol> <p>Response: Yes, this correction has now been made.</p> <ol style="list-style-type: none"> <li>3. Figure S1 describing the cohort is excellent.</li> <li>4. How reliably are homeless people captured with this data? Does this potentially bias the cohort in any way?</li> </ol> <p>Response: We limited our study population to people with 1 year of provincial medical services coverage to ensure that we had sufficient data on patient covariates for 1 year prior to follow-up. However, it is possible that this excluded some homeless people who may not have registered for medical services coverage. This will not bias the analysis of the population that is included in the study, but it may reduce generalizability. We have now noted this in our Limitations section.</p> <ol style="list-style-type: none"> <li>5. The discussion mentions other research focusing on initiation of prescriptions, rather than focusing on users as this study does. Do the authors think this policy might have more impact on a population of opioid naïve individuals?</li> </ol>

	<p>Response: I believe you are referring to our suggestions for future research. One of our suggestions was that it would be valuable to know how the policy might affect use of non-opioid medications and non-pharmacologic treatments. However, we recognize the need to understand the impact of the policy on others not included in our study. In fact, we have conducted a similar analysis focused on patients diagnosed with certain chronic non-cancer pain conditions, and we will be seeking to publish our findings on that. Part of the rationale for that analysis is that it would include opioid-naïve individuals.</p>
<b>Reviewer 3</b>	Miss Natasha Baptist-Mohseni
Institution	McMaster University Faculty of Health Sciences, Hamilton
General comments and author response	<p>Very interesting study - only minor comments to make!</p> <p>1. Rework certain sentences (e.g., last sentence of first paragraph in introduction), as they are lengthy - I would consider breaking some up to help maintain flow. Various other grammatical errors to be corrected (see attached file for details).</p> <p>Response: I have made this change in the first paragraph and additional edits based on suggestions in the attached file.</p> <p>2. Main comment would be to consider whether it is a confound to have the same patients in both the historical control group and the experimental group.</p> <p>Response: A longitudinal design with repeated measures for each patient at intervals over time allows for the study of “change in response over time and factors that influence change.” (Fitzmaurice 2004) In this case, the main factor we are interested in is the introduction of the opioid prescribing standards and guidelines. Even without the addition of a control group, this design includes “unexposed time” (prior to the policy) and “exposed time” (following the policy) for many patients in the policy cohort of the study. As there are multiple observations for each individual in a repeated measures design, we have used generalized estimating equations to adjust for correlations among observations of the same individual.</p> <p>The addition of the historical control group with patients who are unexposed to the policy is important to our design as it provides a control for some factors that may vary over time, such as stopping of opioid medications by some patients during follow-up. As you mention, there is overlap with some patients from the policy cohort who are also in the historical control cohort. This may actually reduce confounding by making the control group more similar to the policy cohort than it would otherwise be. As in self-controlled designs such as a case crossover design, this would reduce confounding by controlling for factors (patient characteristics) which do not vary over time (e.g., a patient’s aversion to risky behaviour might be relatively stable over time).</p> <p>Reference:</p>

	Fitzmaurice GM, Laird NM, Ware JH. Applied longitudinal analysis. Hoboken, NJ: John Wiley & Sons; 2004.
<b>Reviewer 4</b>	Dr. Susan Baxter
Institution	Simon Fraser U, Faculty of Health Science
General comments and author response	<p>I commend the authors on submitting this piece as neutral or negative results rarely see the light of day. The amount of data you analyze is impressive and you explain your methods and process concisely and well. Your data is provided in enormous detail including readable tables and graphs which make parsing your subject demographics smooth. (I would do away with the graphs as in my view they add nothing meaningful, but by all means, keep them if they make you happy.) Having said that, I would nonetheless suggest a minor rewrite, as you need to guard against allowing your obvious dismay at your results to affect your tone or to allow your writing to veer into bias.</p> <p>1. Perhaps in an inverse echo of your own tone, this reviewer was rather disappointed at your lack of nuance in the discussion of your results. Not once does it seem to occur to you refer to these individuals whose data you were mining and emphasize that it was not the people being prescribed narcotics for pain who were at fault but the street drug supply since the policy did not seem to translate into any reductions in overdose and hospitalizations and so on.</p> <p>Response: I do realize that contamination of street drugs is an important factor contributing to overdoses in the province, and this is mentioned in the introductory paragraph of our manuscript. In our Discussion section, we also describe the contamination of street drugs as “[a] major contributing factor to the rise in opioid overdoses and deaths in BC.”</p> <p>2. In the Results section of your Abstract, you write that that “all-cause hospitalizations declined in level but may have increased in trend...” I have zero idea what this means and I doubt any reader would either. This either needs defining or deleting since your previous sentence states that you found “no impact on opioid overdose hospitalizations in level or in trend”. You can’t have it both ways.</p> <p>Response: I have reworded the methods slightly to emphasize that changes in level refer to sudden changes in rates following the policy and changes in trend refer to gradual monthly changes in rates following the policy. Hopefully those minor changes will help readers to understand what is being measured.</p> <p>I can clarify that opioid overdose hospitalizations are hospitalizations associated with a diagnosis of opioid overdose, whereas all-cause hospitalizations include hospital admissions for any reason. Our findings differed somewhat on these outcomes.</p> <p>3. I can’t speak to the College’s rationale for their policy but the article you cite as a probable source (your reference #12, “Opioids for Chronic Noncancer Pain, A Systematic Review and Meta-analysis, Busse et al) does not back up what you say it does. The conclusion of that article, in the Abstract, states that “opioid use</p>

was associated with statistically significant but small improvements in pain and physical functioning”. Busse et al clearly share your aversion to chronic pain treatment involving opioids with their addition of the qualifier “but small” in that sentence. (And frankly, I fail to see why “noncancer” pain is any less legitimate than any other kind of pain.)

Response: I have kept this reference but provided a description of its results to help ensure that it is accurately represented, as follows: “A systematic review published since the standards and guidelines were issued reported that opioids compared to placebo were associated with only small decreases in pain and improvements in physical functioning in treatment of chronic noncancer pain.”

4. This is perhaps a minor point, but I was somewhat puzzled by your not including morphine in your medications list as it is, to the best of my knowledge, a fairly common agent. Or did you include it in the study and simply not mention it? Also, why buprenorphine? It is a partial agonist/antagonist, not quite what you appear to mean by “opioid” in your article.

Response: I have corrected the manuscript to show that morphine was included in the study. Buprenorphine formulations indicated for pain were included rather than those indicated for treatment of dependence.

5. I am also surprised at your including neuropathies, diabetic and peripheral, in your medical history variables as my understanding is that opioids are contraindicated for neuropathy, at least according to various pain society guidelines.

Response: Neuropathies were less common than other chronic non-cancer pain conditions in our study population. However, opioids are sometimes used to treat neuropathies. For example, here are some stats from a study of diabetic peripheral neuropathy (DPN):

“Despite the neuropathy treatment guidelines that discourage use of opioids as first line treatment, opioids were used by over 50% of persons receiving a DPN pharmacologic treatment and opioids were the most frequently prescribed first line agents and is consistent with a recent study, that showed that opioids were used as first line agents in 28% of DPN patients.”

Reference:

Patil PR, Wolfe J, Said Q, Thomas J, Martin BC. Opioid use in the management of diabetic peripheral neuropathy (DPN) in a large commercially insured population. Clin J Pain. 2015;31(5):414-424.

6. I appreciate that you are merely reporting on your data but how you contextualize that data is your choice. Yours appears to have been to analyze catastrophic events such as hospitalizations and ER visits and listing demographics. No acknowledgement anywhere that the reality of pain is complex or that the College policy may have had adverse effects; that there may well have been a human cost. For instance, could there have been an increase in suicides? Requests for physician-assisted death? Or effects that were perhaps more ephemeral and difficult to measure such as being unable to work or function effectively? Again, I realize that your data cannot answer those questions but it

seems telling that you have not even considered the question.

Response: I realize that it is a limitation of our study that we have not been able to include an evaluation of pain management, and this has now been added to our Limitations section.

7. What you choose to highlight seems capricious at times. For instance, your data shows that the majority of patients were between age 40 and 74, which the reader can only find by reading through the tables. Some mention of this would seem germane in the body of the piece, since age is a major contributor in pain.

Response: I have added a sentence to the first paragraph of the Results section to highlight age and gender characteristics.

As a bit of a sidebar, I find it mildly ironic that the closure of thousands of pain clinics in North America (a “non-pharmacologic treatment”) over the past decades was largely the result of quantitative studies such as yours which insisted that there was little or no evidence of their efficacy. They were deemed irrelevant – and closed. Now, when opioids have become the go-to drug for pain, everyone is upset – and would like to see more multidisciplinary pain clinics.