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Title	Changes in the dispensing of opioid medications in Canada following the introduction of a tamper-deterrent formulation of long-acting oxycodone
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Reviewer 1	Prof. Heiner K. Berthold
Institution	Bielefeld Evangelical Hospital, Dept. of Internal Medicine and Geriatrics, Bielefeld, Germany
General comments (author response in bold)	The manuscript by Gomes et al. investigates whether dispensing patterns in opioids in Canada changes after the introduction of a tamper-deterrent formulation of oxycodone. The study addresses an important public health issue. They used a nation-wide representative data base and the statistical methodology is sound. Their main findings are that the introduction of the new formulation changes dispensing opioids but obviously compensatory other changes in opioids were observable. Their message to health policy decision makers is that an isolated single measure cannot resolve a complex problem. Moreover, they are describing substantial regional differences in prescribing which are only partially explained (outside the scope of the study). The manuscript is well written and is in my opinion important for the general readership among physicians. **We thank the reviewer for their supportive comments.** 1. Can they please give some references on the statistical models used? Can they please publish the final models in an electronic appendix? **We now include citations for the models and the final model specifications in our supplementary appendix.** 2. Lines 39-44 and Table 1: The final analyses of the provinces are done by comparing the first and the last observation period. Doing so, there is probably information lost on data in between. Isn't there an alternative using the time series procedures to perform these comparisons? **Our primary analysis undertook time series modeling to use all data over our study period to investigate the impact of OxyNeo® on the volume of opioid prescribed. In Table 1, we chose to report a number of other exposure measures of potential importance to the reader, but given the current length of the manuscript, felt that it would introduce too much complexity to the manuscript to report these measures monthly. Therefore, we chose to conduct a simple descriptive comparison in these outcomes at the beginning and end of our study period to provide the reader with an explanation for the factors driving the changes seen in the MME time series analyses. We believe that this will help inform the interpretation of our primary analysis of population exposure to opioids.**
Reviewer 2	Dr. Susan Baxter
Institution	Simon Fraser University, Burnaby, BC
General comments (author response in bold)	This is an excellent article; your research is thorough and quite staggeringly informative; I think your points regarding tamper-resistant formulations of long-acting opioids will be useful in drug policy decisions. In many ways this is perfect quantitative research in that it provides evidence for what one tended to believe but didn't actually know. **We thank the reviewer for their supportive comment.** Having said that, there are a few changes I would like to see. 1) Bias: You have admirably maintained a rational and neutral tone throughout, but in your Introduction there are a few sections where some bias seems to creep in. As such a few sentences either need to be removed or balanced. Notably, in the last line of your first para you write that "prescribing opioids in chronic non-cancer pain has become controversial ....[as they can lead to] abuse, addiction and premature death." True, but the initial use of these drugs was not capricious; it was a response to what the Canadian Pain Society (and others) have called the extremely poor management of pain in Canada; not only chronic pain but post-surgical or post-traumatic. I appreciate that the Introduction is a way for you to explain why your article matters in the grand scheme of things but at times a throwaway line can indicate unconscious bias. So you need to balance that line with one referring to the value of appropriate pain control and the role of opioids in that process. (You could use your own reference 5 - Moulin et al.) Conversely, you could simply delete that sentence altogether. Either way, neither your research nor your measured tone throughout makes that sentence appropriate. Along the same lines, your point about Canada and the U.S. having "the highest levels of prescription opioid consumption per capita" is somewhat misleading as Canada and the U.S. (and France) have the highest per capita consumption of every drug according to OECD figures. Given how careful you have been in the reporting of your data, this remark seems a trifle glib. Pain is multi-factorial and multi-faceted and, as you mention in your final sentence, access to non-drug treatments for chronic pain matters. This also varies widely within jurisdictions - as your research shows. So it stands to reason the U.S. and E.U., for instance, would approach the problem differently, with different treatment modalities. (My concern is that many readers will only read the Abstract and the first few paragraphs of any article; as such it behooves you to make the first section of your Introduction as balanced as possible.) Your research topic is important; you don't need to resort to emotive statements to make your point. This was especially noticeable given how reasoned and thoughtful your Conclusion is. **We thank the reviewer for making these suggestions and have revised our introduction slightly to be more selective in our statement. While we believe that the reviewer is correct that North America tends to have higher rates of drug prescribing more generally, in the case of opioids and their potential adverse effects, we believe that it is important to speak to this specifically in comparison with opioid prescribing trends elsewhere. We have changed this sentence slightly, but have not removed mention of the high per capita consumption rates of opioids, and comparisons to other jurisdictions as we believe that this is an important, well appreciated North American pattern which has driven rising opioid-related adverse events across Canada and the U.S.** Revised Text: Although opioids have an important clinical role in the treatment of acute and chronic pain, the use of these products to treat chronic non-cancer pain remains controversial, as their long-term use has been associated with significant side effects, which include abuse, addiction and premature death from accidental overdose.1,2 Canada and the United States have historically demonstrated high levels of prescription opioid consumption per capita3, with rates that are approximately double those observed in the European Union, Australia and New Zealand.4 In Canada, prescription opioid consumption increased nearly four-fold between 1999 and 2010,5 despite the proportion of Canadians who reported suffering from chronic pain not changing significantly over this period.6 In Ontario, the rate of opioid prescribing rose by 29% from 1991 to 2007, which was largely

	driven by an 850% rise in prescribing of oxycodone.7 2) Clarity and consistency: As long-acting oxycodone was OxyContin I am not sure as to why you don't refer to it as such. There's no reason you can't initially write OxyContin with the 'registered' mark next to it then simply write that from there on in it will be referred to as OxyContin (or OxyNeo when appropriate). Since oxycodone is the short-acting variety of the drug there are times when your reference to the long acting variety make for rather convoluted sentences and can be a bit confusing, especially when one reads quickly. In any event, whatever form you choose you need to be consistent. On page 12 you refer to OxyContin after having written "long acting oxycodone" throughout. My point here is that you need to edit your piece with the reader in mind. This is especially true for the Results section where you are including numbers of prescriptions and percentages. For instance, in the second line of your Results section, I first assumed the number referred to short acting oxycodone, not OxyContin which is what you actually mean. In short, your piece, especially the Methods and Results, needs some refining. **We thank the reviewer for pointing out this inconsistency. We have now replaced the term "long-acting oxycodone" with either OxyContin® or OxyNeo® wherever appropriate. There remain some instances where we are referring to long-acting oxycodone more generally (including OxyContin®, OxyNeo®, or generic formulations), and so have not made changes in these cases.** These minor points aside, your tone is measured and your research is thorough and interesting - deserving of a wide audience, not least policy wonks.