Article details: 2014-0103	
Title	Retrospective analysis of trends in dispensing of long-acting non-tamper-deterrent oxycodone near the USA-Canada border
Authors	Gomes, Tara (proxy) (contact); Paterson, Michael; Mukati, Mariam; Henry, David
Reviewer 1	MacLeod, Stuart M
Institution	
General comments	This is a very well written and lucid manuscript. The following comments present questions arising. The authors may wish to consider adding them to the discussion. 1. It may not be realistic to anticipate immediate changes in pattern of sales for cross-border diversion. It may be that the time interval following introduction of generic products is too short, although there appears to be no evolving pattern over the ensuing 14 months. 2. No discussion is provided about the pharmaceutical characteristics of the generic oxycodone introduced in November 2012. Is it entirely comparable to the earlier forms of oxycodone sold by the innovating company? Is it fully susceptible to tampering? 3. A possible explanation for the apparent lack of cross-border diversion may be significant difference in appearance of the generic product. Presumable a radically different appearance would affect 'marketability' for illicit sales. 4. The information provided in supplementary figures and tables is extremely interesting. It is notable that sales appear to be disproportionately high in three provinces, BC, Ontario and New Brunswick and, in two of these provinces, the uptake of generic NTD product has been more rapid. Clearly this is hard to interpret but it may be some indicator of greater illicit use in at least two provinces. 5. On page 6, line 55, the presentation of declining sales in BC should be specified as monthly.
Reviewer 2	Dalton, Bruce
Institution	Alberta Health Services - Calgary, Pharmacy
General comments	Thank you for the invitation to review this interesting study report. It is well written and the subject has important implications for narcotic policies. The authors met the applicable requirements in the STROBE checklist for observational trials. Overall, I believe that this study would be worthy of publication with some relatively easy changes, detailed below: 1. There were no statistical analyses performed. The authors acknowledge the limited amount of data from the period before precluded a time series analysis. Readers are left to estimate the relevance of fluctuations by visual analysis of the graphs. Are there no other statistical techniques that could be applied (t-test is not ideal for this situation but maybe better than none?). In addition, a power calculation would be of benefit for readers. Was an a priori hypothesis and relevant change defined? Ie. How much change would have been required to conclude that trafficking was occurring? 2.In addition, it is likely that improvements in the graphic representations could be made. Figures 1,2,3 and e Figures 1,5,6 show data lines almost contiguous to the x-axis. Hence the scale is inappropriate for these data to appreciate fluctuations and changes. These data lines represent areas of relatively low dispensing volumes. I believe it would be relevant to report the tablets dispensed as a function of the population in that geographic area per unit time. Indeed, in the interpretation section this is labeled "a population based study". Does that not require adoption of units that control for population? What relevance is reporting the population density of the dispensing areas (alone)? Alternatively, a log scale for the y axis could be used to better show changes in the low volume areas represented on the graphs. 3. A minor point of geography, but, Point Roberts, WA is only accessible by private boat or through Canada by land ie. not contiguous with the (rest of the) lower 48 states. As such the crossing is likely inappropriate to include in the study, unless the dispensing area is included due to proximity to the Blaine-Pacific Highway crossing. Its situation is similar to the Manitoba-Angle Inlet (Lake of the Woods) crossing which was not included. 4. There are further points which could be of interest to readers to include in the discussion. Since you did not observe an increase in prescriptions now, but previously observed one in the Detroit/Windsor area possibly related to cross-border trafficking, can you suggest a hypothesis of why this would not occur? Because prescribers are reluctant to write for generic NTD? Does this cast doubt on your previous findings or hypothesis that the excess oxycontin dispensed in Windsor was related to trafficking? For readers unfamiliar with pharmacy procedures, you could explain that only prescriptions from Canadian prescribers could be filled in Canadian pharmacies. Could there be a longer lag time for trafficking of generic NTD than would be detectable in

	this study and is a follow up study necessary? Are there current statistics on drugs of abuse in the US that could indicate a stable or change in the types and amounts of drugs of abuse?
Author response	Reviewer: Dr. Stuart M. MacLeod This is a very well written and lucid manuscript. The following comments present questions arising. The authors may wish to consider adding them to the discussion. 9. It may not be realistic to anticipate immediate changes in pattern of sales for cross-border diversion. It may be that the time interval following introduction of generic products is too short, although there appears to be no evolving pattern over the ensuing 14 months. Although we agree that we might not have seen an immediate change in oxycodone uptake at border crossings following the introduction of generic formulations, based on our past work, we believe that 14 months is sufficient to identify any major shifts that might happen as a result of cross-border trafficking. We believe that the absence of any such increase in any border crossing over our follow-up period is sufficient to suggest that no large scale trafficking occurred. around the introduction of generic oxycodone products in Canada. 10. No discussion is provided about the pharmaceutical characteristics of the generic oxycodone introduced in November 2012. Is it entirely comparable to the earlier forms of oxycodone sold by the innovating company? Is it fully susceptible to tampering? We thank the reviewer for mentioning this. The generic formulations of long-acting oxycodone are equivalent pharmacologically to the original OxyContin, and therefore they are comparable to this product, and have no tamper deterrent properties. We have clarified this in the manuscript. EDITED TEXT: In contrast to the US Food and Drug Administration (FDA),[7] Health Canada authorized marketing of generic non-tamper-deterrent (NTD) versions of LA oxycodone that are pharmacologically equivalent, and similar in appearance, to OxyContin in November 2012.[7] This reintroduction of long-acting oxycodone products with no tamper deterrent properties reopened the potential for prescribing behavior similar to that observed in Canada near the Detroit–Windsor Tunnel in 2010/11. 11. A possible explanation for the apparent lack of cross-border diversion may be significant difference in appearance of the generic product. Presumable a radically different appearance would affect 'marketability' for illicit sales. While a radical difference in appearance could delay the uptake of these products, the generic formulations of long-acting oxycodone were similar in shape and size to the original OxyContin (see examples here: http://www.opiateaddictionresource.com/media/images/oxycodone_er). While slight differences in colour or size may have delayed uptake of these products for illicit purposes, given their high demand as illicit drugs, we believe it is unlikely that this delay would have been substantial. Therefore, we believe that the 14 month follow-up period should have been sufficient to observe any large-scale cross-border activity. Inserted text: In contrast to the US Food and Drug Administration (FDA),[7] Health Canada authorized marketing of generic non-tamper-deterrent (NTD) versions of LA oxycodone that are pharmacologically equivalent, and similar in appearance, to OxyContin in November 2012.[7] 12. The information provided in supplementary figures and tables is extremely interesting. It is notable that sales appear to be disproportionately high in three provinces, BC, Ontario and New Brunswick and, in two of these provinces, the uptake of generic NTD product has been more rapid. Clearly this is hard to interpret but it may be some indicator of greater illicit use in at least two provinces. We believe that the interpretation of these figures may have been difficult due to the large differences in population sizes across provinces in Canada. We have therefore revised all figures to adjust oxycodone volumes by population size. With this new information, it appears that Ontario, Alberta and New Brunswick have slightly higher rates of LA oxycodone dispensing compared to other provinces studied. However, we do not believe this to be an indicator of greater illicit use of generic LA oxycodone in these provinces because the rate of dispensing either decreased (Ontario) or remained steady (New Brunswick) following the introduction of generic LA oxycodone, and, despite an increase in the rate of dispensing in Alberta after the introduction of generic LA oxycodone, we found that only 1.3% of all LA oxycodone dispensed in that province was for the non-tamper deterrent, generic formulation. Please see our response to #3 above for revised results section. 13. On page 6, line 55, the presentation of declining sales in BC should be specified as monthly. This change has been made.

	Reviewer: Dr. Bruce R. Dalton, Alberta Health Services 14. Thank you for the invitation to review this interesting study report. It is well written and the subject has important implications for narcotic policies. The authors met the applicable requirements in the STROBE checklist for observational trials. Overall, I believe that this study would be worthy of publication with some relatively easy changes, detailed below. We thank Dr. Dalton for his positive comments. 15. There were no statistical analyses performed. The authors acknowledge the limited amount of data from the period before precluded a time series analysis. Readers are left to estimate the relevance of fluctuations by visual analysis of the graphs. Are there no other statistical techniques that could be applied (t-test is not ideal for this situation but maybe better than none?). In addition, a power calculation would be of benefit for readers. Was an a priori hypothesis and relevant change defined? Ie. How much change would have been required to conclude that trafficking was occurring? Unfortunately, a t-test would not provide an accurate representation of whether a change occurred because this would require simply comparing one estimate pre- and post-introduction of generic LA oxycodone. A simple t-test assumes that the pre- and post-rates are statistically independent, which is not the case in this study design. Furthermore, because there were already downward trends in LA oxycodone use in most provinces over time, these t-tests would not provide an accurate representation of whether the rate of change was impacted over time. Furthermore, we examined dispensing across 50 prescribing regions which would introduce concerns around multiple hypothesis testing. Time series analysis would be most appropriate approach. However, we were unable to conduct these analyses because we did not have a sufficient number of data points to accurately establish trends prior to the introduction of generic LA oxycodone. IMS Brogan only retains data for the most recent 2 years, while suitably-powered time-series analyses typically require 20 to 40 data points prior to the intervention.1;2 However, we believe that – given the large number of LA oxycodone tablets dispensed over time, this analysis is not subject to a large degree of statistical uncertainty. We have included discussion of our inability to conduct statistical analyses/comparisons in the limitation section of our study. TEXT: Second, interventional time series analysis could not be performed due to limitations of data availability prior to the intervention of interest. 16. In addition, it is likely that improvements in the graphic representations could be made. Figures 1,2,3 and e Figures 1,5,6 show data lines almost contiguous to the x-axis. Hence the scale is inappropriate for these data to appreciate fluctuations and changes. These data lines represent areas of relatively low dispensing volumes. I believe it would be relevant to report the tablets dispensed as a function of the population in that geographic area per unit time. Indeed, in the interpretation section this is labeled "a population based study". Does that not require adoption of units that control for population? What relevance is reporting the population density of the dispensing areas (alone)? Alternatively, a log scale for the y axis could be used to better show changes in the low volume areas represented on the graphs. We agree with the reviewer that adjusting for population size would help elucidate patterns in smaller provinces. We have therefore updated our figures and results section to present rates per 1000 population. 17. A minor point of geography, but, Point Roberts, WA is only accessible by private boat or through Canada by land ie. not contiguous with the (rest of the) lower 48 states. As such the crossing is likely inappropriate to include in the study, unless the dispensing area is included due to proximity to the Blaine-Pacific Highway crossing. Its situation is similar to the Manitoba-Angle Inlet (Lake of the Woods) crossing which was not included. We thank the reviewer for pointing this out. We have removed the Point Roberts crossing from the analysis. 18. There are further points which could be of interest to readers to include in the discussion. Since you did not observe an increase in prescriptions now, but previously observed one in the Detroit/Windsor area possibly related to cross-border trafficking, can you suggest a hypothesis of why this would not occur? Because prescribers are reluctant to write for generic NTD? Does this cast doubt on your previous findings or hypothesis that the excess oxycontin dispensed in Windsor was related to trafficking? As the reviewer points out, in our previous study, we observed evidence of cross-border trafficking near the Detroit-Windsor tunnel. However, we did not find evidence of trafficking at any other border in Ontario. We hypothesized that this was because a small number prescribers and/or dispensers in the region were working with traffickers from across the border. Importantly, this high dispensing activity was quickly rectified once warnings were sent to prescribers and pharmacists in the region. Therefore, it is unlikely that those involved in trafficking in the Detroit-Windsor region in the past

	would attempt similar activity upon the introduction of generic LA oxycodone since they would be aware that regulators were monitoring this activity. Therefore, we do not believe that these findings cast doubt on the findings in our prior study, but instead suggest that the activity in the Detroit-Windsor area was highly regionalized, and did not continue once prescribers and dispensers were made aware of the activity. Inserted Text: This is likely a reflection of the highly regionalized nature of our past finding which was quickly rectified following warnings to pharmacists and prescribers. Furthermore, it is likely we did not observe another rise near the Detroit-Windsor Tunnel because those involved in past trafficking activities are now aware that their activities are being monitored. 19. For readers unfamiliar with pharmacy procedures, you could explain that only prescriptions from Canadian prescribers could be filled in Canadian pharmacies. Canadian pharmacies can only fill prescriptions written by registered medical practitioners who are licensed to practice in Canada. We have now clarified this in the manuscript. Inserted Text: Only prescriptions from prescribers licensed to practice in Canada can be filled in Canadian pharmacies. 20. Could there be a longer lag time for trafficking of generic NTD than would be detectable in this study and is a follow up study necessary? We do not believe this to be the case. Please see our response to reviewer 1 (#10) above. 21. Are there current statistics on drugs of abuse in the US that could indicate a stable or change in the types and amounts of drugs of abuse? With tightening of regulations governing prescription opioids it is possible that there may have been a shift towards heroin in the US. Therefore, if the popularity of prescription opioids as a street drug has declined, this could be one explanation for the lack of evidence of cross-border trafficking seen in our study. We have included this as a limitation in our study. Inserted text: Finally, it is possible that the most common drugs of abuse have shifted in the US following changes in opioid availability. If patients moved to using heroin instead of prescription opioids, this could impact demand for illicitly obtained LA oxycodone in the US.