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Title	**Influence of opioid prescribing standards on drug utilization among patients with chronic opioid use: a longitudinal cohort study**
Authors	Richard L. Morrow MA, Ken Bassett MD PhD, James M. Wright MD PhD, Greg Carney BSc, Colin R. Dormuth ScD
Reviewer 1	Dr. Evan Wood
Institution	BC Centre on Substance Use
Reviewer comments and author response	Comments to the Author Morrow and colleagues have described changes in prescribing behaviour coinciding with the BC College of Physicians and Surgeons changes to prescribing standards related to opioid drugs. Over 68,000 individuals were compared to approximately 68,000 historical controls. Overall, the study is well written. The author's main findings were that overage monthly utilization of opioids declined and discontinuation of opioids increased. Individuals on high-dose opioids were more likely to switch to lower dose opioids. There was no impact on discontinuation among those on high dose opioids. The authors interpret the findings to suggest that the policy change modestly reduced the utilization of opioids. My main suggestion for the manuscript would be to remove the description of the use of opioid agonist therapy. This is not an area where the authors have much content expertise (e.g. "opioid substitution" is a term that is frowned upon in this area - see Samet Lancet) and there were a constellation of changes that explain increased opioid agonist therapy use that are not accounted for in this analysis where the use of other prescription opioids is an excellent focus. Response: We have removed the analysis of opioid agonist therapy from the paper, based on this advice. I would also suggest that the manuscript would be improved by spending some energy on the literature regarding the use of opioids for chronic non-cancer pain. The NIH Pathways to Prevention review in Annals of Internal Medicine should be described as well as the SPACE trial from JAMA and the recent meta-analysis in JAMA by Busse. This could put the College's new prescribing standard in context. Response: We agree and have added a paragraph to the introduction with some additional context citing these sources. (pp. 3-4)
Reviewer 2	Dr. Ta-Liang Chen
Institution	Taipei Medical University, Health Policy Research Center
Reviewer comments and author response	Comments to the Author The objective of this study is to evaluate the impact of the CPSBC prescribing standards and the buprenorphine/naloxone policy on prescription drug utilization in patients with chronic opioid use. The study provides new information on the effects of opioid prescribing standards on drug utilization. However, there are some questions that need to be clarified in this manuscript: 1. Page 4 under "Study setting and design": The data of 47,416 patients are used in both intervention group and control group. Please provide reference(s) to prove this type of study design is not biased. Response: As stated in our response to the editor's query on overlap in the study cohort: In retrospective cohort studies, it is possible to adopt a design in which patients may enter the study more than once in either the same or a different exposure group, as long as the time attributed to each exposure group is correctly categorized. For example, a retrospective cohort study of isotretinoin and inflammatory bowel disease allowed patients to enter each of three exposure groups at different times: isotretinoin treatment, topical acne medication treatment and untreated individuals (Alhusayen et al 2013). Our longitudinal cohort study adopts a design used in a prior study of a drug

	reimbursement policy in British Columbia (Dormuth et al 2008). In the previous study, a policy cohort of long-term inhaler users was defined during a 6-month identification period and followed for up to 40 months, and a historical control cohort of long-term inhaler users was defined using the same criteria during a 6-month period occurring earlier in time and similarly followed for up to 40 months. Patients who were members of the historical control cohort were not excluded from membership in the policy cohort, if they could be defined as long-term inhaler users on both occasions. Only members of the policy cohort were exposed to a change in drug reimbursement, while the historical control group was not. In the previous study by Dormuth et al and in the current study, the statistical model includes variables to associate each observation of an individual with the appropriate cohort, which may differ for different observations. It is also a characteristic of longitudinal designs that individuals have repeated observations, which are correlated (Fitzmaurice et al 2004). In our study, we therefore used the generalized estimating equations to adjust for correlations among observations by individual. We have tried to better describe our study design (p. 4), citing Dormuth et al (2008) and Fitzmaurice et al (2004). References: Alhusayen RO, Juurlink DN, Mamdani MM, Morrow RL, Shear NH, Dormuth CR, et al. Isotretinoin use and the risk of inflammatory bowel disease: a population-based cohort study. J Invest Dermatol. 2013;133(4):907-12. Dormuth CR, Maclure M, Glynn RJ, Neumann P, Brookhart AM, Schneeweiss S. Emergency hospital admissions after income-based deductibles and prescription copayments in older users of inhaled medications. Clin Ther. 2008;30 Spec No:1038-50. Fitzmaurice GM, Laird NM, Ware JH. Applied longitudinal analysis. Hoboken, NJ: John Wiley & Sons; 2004. 2. Page 5 under “Outcome measures”: Please define the abbreviation “MME”. Response: This has now been added. (p. 6) 3. Table 1: It seems that less than 50% of study cohort had chronic pain. Can you explain the reasons of chronic opioid use for the rest of study cohort? Response: We have added a paragraph in the ‘Patient characteristics’ section of our manuscript to better describe the study population (second paragraph under ‘Patient characteristics’, p. 9), which now speaks to this question. 4. Page 8 under “Patient characteristics”: Please provide P-value to illustrate the differences when comparing opioid use between historical cohort and policy cohort. Response: At the request of the editors, we have added absolute standardized difference (ASD) to the reporting of characteristics in Table 1, which shows the correlation between which cohort the patient is in and measured characteristics is negligible (ASD<10% for all characteristics). That is, the policy cohort and historical control cohort are similar on these characteristics at cohort entry – which appears to address the concern raised here. 5. Page 8 under “Patient characteristics” and “Impact on drug utilization”: Patients were followed for 1 to 22 months. This means that some patients did not have data in “Post-policy period”. Does it cause bias when comparing opioid utilization between pre-policy period and post-policy period? Please explain. Response: We have included all patients who met the criteria for inclusion either the policy cohort or the historical control cohort, and followed patients until either the end of the study or until they met the criteria for censoring. As described under ‘Study setting and design’, (p. 5) we censored patients during follow-up if they lost medical services coverage, entered long-term or palliative care, died, or were diagnosed with cancer. While 90 percent of patients were followed for at least 16 months (noted on p. 9), some were censored prior to the post-policy period (or analogous period for historical controls). This censoring will not cause bias, because both the policy cohort and historical controls have been treated in the same way and loss to follow-up was similar in the two cohorts. Mean follow-up was 20.6 months for the policy cohort and 20.7 months for historical controls.

	6. Table 2: Also explain why the number of patients are different in the analysis items on (a) Opioid analgesic use and (b) Discontinuation. Shouldn't the patient number of these two be the same? Response: The analysis of discontinuation only includes patients with days supply of opioid medication that ends in a given month (this is described under 'Outcome measures' in the manuscript, p. 6). The reason for this is that only these patients can be considered to be at risk of stopping their opioid medication in that month. If no additional opioid prescription was filled in the 90 days following date on which the days' supply ended, then the patients was deemed to have discontinued (noted on p. 6).
Reviewer 3	Dr. Ifran Dhalla
Institution	University of Toronto, Department of Medicine
Reviewer comments and author response	Comments to the Author Major comments 1. I am not knowledgeable enough to properly review or critique the statistical methods used in this paper. The OR for opioid discontinuation of 1.24 is, on its face, surprisingly high given the difference of 2.6% vs. 2.5%. Similarly, the OR for initiation of opioid substitution is 1.87 but the difference is only 0.9% vs. 0.8%. So, it would be worth sending this paper to someone who really understands how time series data should be analyzed to see if the authors have used the right statistical methods. The rest of my review assumes the authors have used appropriate statistical methods. Response: The rates of discontinuation of 2.7% for the policy cohort and 2.6% for the historical control cohort refer to the rates during the pre-policy period, so this shows that the baseline rates of discontinuation were very similar at baseline. The OR refers to the impact on discontinuation of opioids during the post-policy period. These are referred to as pre-policy measures in Table 2 and in paragraph 2 of the 'Impact on drug utilization' section under Results in the manuscript (p. 10). The same applies to the other percentages you mention. 2. The way the paper reads, it seems that all differences between the two cohorts are attributed to the CPSBC standards and guidelines. But in fact, there have been lots of "co-interventions" including the CDC guidelines, various other articles, etc. Response: We have added wording to the Limitations section of the manuscript to note some of the key co-interventions which may have influenced opioid utilization. (pp. 12-13) 3. Figures 1 to 3 do not obviously show a clear effect of the policy. If there is an effect, it only comes out through statistical analysis, and not through visual inspection of the data - at least not to my eye. The authors might consider softening their conclusions or explaining more fully the apparent discrepancy between visual inspection of the graphs and the results. Response: The figures have been renumbered, since we have added a new Figure 1 to describe the study design. We believe that in fact the Figures provide an illustration and corroboration of our findings, as follows. • Monthly opioid analgesic use. We found a modest decrease in the level and trend of analgesic use, as reported in Table 2. Figure 2 shows that the lines depicting opioid use for the policy cohort (orange) and the historical control cohort (blue) diverge during the transition period and further diverge during the post-policy period. The change in opioid use can be seen by comparing the vertical distance between the lines at the mid-point of the pre-policy period and the mid-point of the post-policy period. We have added Figure S1 to the Appendix to help the reader to visualize the difference between a change in level versus a change in monthly trend. While the changes depicted in Figure S1 are somewhat idealized, hopefully this will be helpful. Changes to level and trend may occur simultaneously, which is not shown.

	• Discontinuation of opioids. We report an increase in the rate of discontinuation in Table 2 (OR 1.24; 95% CT 1.16 to 1.32). Figure 2 shows that monthly discontinuation for the policy cohort (yellow) diverges from discontinuation in the historical control cohort (grey) following the pre-policy period. The rate of stopping was already slightly higher for the policy cohort during the pre-policy period, but there is a clear difference shown in the vertical distance between these two lines following the pre-policy period. The one anomaly of this plot is that the stopping rates are slightly higher also in the first month of the prepolicy period for both cohorts; this suggests that we captured some patients who were relatively shorter-term users of the medications who stopped use at a higher rate for that month, but that occurred in both cohorts and should not have much impact on this result. • Switching from high-dose to lower dose opioids. We report an increase in switching from high-dose to lower dose opioids in Table 2 (OR 1.88; 95% CI 1.63 to 2.17). This finding is more pronounced that our other findings, and this is reflected in Figure 3. Rates of switching are similar among the two cohorts during the pre-policy period, but during the post-policy period, switching in the policy cohort (orange) jumps dramatically as compared to switching in the historical control cohort. This is shown in the vertical distance between these line orange and blue lines during the post-policy period. • Discontinuation of high-dose opioids. We have reworded how we have described our findings under 'Impact on drug utilization' in the Results section of the manuscript, to provide more detail and better explain these findings (p. 10). In brief, we did not find a clear association between the introduction of the opioid prescribing standards and guidelines and the rate of discontinuation of high-dose opioids. The adjusted ORs reported in Table 2 are non-significant but suggest an increase in the level of discontinuation (sudden change) but a decreasing trend (gradual change). Figure 3 may help to understand what is being picked up by the statistical model. It suggests there was a temporary increase in stopping of high-dose opioids among the policy cohort (the yellow line peaks in month 13) followed by a return to the pre-policy level of discontinuation. In contrast to overall opioid discontinuation shown in Figure 2, there is not a clear difference in high-dose opioid discontinuation as shown in Figure 3; that is, except for a temporary increase in stopping in month 13 in the policy cohort (yellow), which may be related to the policy, the yellow and grey lines do not show markedly different patterns. • Concurrent use of opioids and sedative/hypnotic medications. As we describe in paragraph 3 under 'Impact on drug utilization' (p. 10) and report in Table 2, we found an increase in the level of discontinuation of concurrent use of these medications (OR 1.37; 95% CI 1.27 to 1.49). This is reflected in Figure S2, which shows that prior to the policy, the rates of discontinuation are similar in the policy cohort (orange) and the historical control cohort (blue), whereas these lines diverge during the post-policy period. As we report in the Results section, the findings we report in Table 2 show 'the potential change in initiation of concurrent use of opioids and sedatives/hypnotics following the policy was unclear'. (p. 10) These findings suggest a modest increase in the level of initiation of about 10% followed by a decreasing monthly trend of about 2% per month. Due to this mixed result, we describe these findings as unclear. Figure S2 suggests that there may be a slight decline in the initiation of concurrent use of these medications during the post-policy period, but it is slight and should likely be described as unclear to avoid over-interpretation. Minor comments 1. Page 2. In the results section, the authors state that discontinuation "did not" increase but the point estimate on the OR is 1.2, which would in my view be clinically significant. So, it's probably more accurate to say something like "discontinuation appeared to more likely, but could not be precisely estimated." Response: We agree that our previous wording may have over-simplified this finding. We have qualified our description of these findings in the abstract to state that discontinuation of high-dose opioids "did not change significantly." (p. 2) We have also re-worded how to describe our findings for this outcome in the Results section of our manuscript. (p. 10) We have described our view of these results in more detail above under the bullet,

	'Discontinuation of high-dose opioids.' Our findings now state that we did not find a clear association between the introduction of the opioid prescribing standards and guidelines and the rate of discontinuation of high-dose opioids. (p. 10) This is not due just to statistical significance, but also considering the point estimates for level and trend effects and the plot of discontinuation of high-dose opioids (in Figure 3). 2. Page 4. Two opioid prescriptions in 6 months does not necessarily mean chronic opioid use. It might have been better to construct some sort of measure of continuous use. However, given the nature of the analysis, and the data presented in Table 1, I think the overly inclusive definition does not invalidate the findings. If anything, it probably biases the analyses slightly toward the null. My suggestion would be to discuss this issue in the limitations section. Response: We have added the following statement to the Limitation section: 'The definition of chronic opioid use that we used to define our study cohort likely captured some patients that were not long-term users of opioids; however, during the pre-policy period the percentage of patients who discontinued opioids each month was relatively low at about 2.5% for both cohorts.' (p. 12) 3. Given how many different types of standards there are, I think it's important to be clear that what is being studied here is the impact of regulatory standards. I'd suggest the authors consider including the word "regulatory" in the title and elsewhere in the paper. Response: We agree with this point and have adopted this terminology in the abstract (p. 1), introduction (pp. 3-4), conclusion (p. 13) and elsewhere in the manuscript.