Article details: 2014-0027/CMAJ-13-1713	
Title	**Impact of a Prescription Monitoring Program on the Prevalence of Inappropriate Prescriptions for Monitored Drugs**
Authors	Tara Gomes, David Juurlink, Zhan Yao, Ximena Camacho, J. Michael Paterson, Samantha Singh, Irfan Dhalla, Beth Sproule, Muhammad Mamdani
Reviewer 1	**Mahyar Etminan**
Institution	None listed.
General comments	This manuscript examines the effect of an intervention mainly the Ontario Narcotics Strategy on narcotic prescription misuse. This study found that the ONS was effective in reducing inappropriate narcotic prescriptions. Some of the authors have done a similar study using the British Columbia PharmaNet found similar results. The methodology is a classic 'time-series' analysis and I don't have any major issues with the methodology. I have the following questions/comments: 1-What is the rational for using a 7 day window to define inappropriate prescribing? Is there a value to look at prescriptions prescribed less than 5 days? Many Tylenol #3s (acetaminophen 325mg+codeine 30mg) are prescribed for a less than 7 day period. Also why not include methadone or buprenorphine (Suboxone) I suspect that the Ontario drug benefit database may not capture these directly but there is probably a way to look at these drugs?? 2-Where the drugs mentioned mutually exclusive? Would someone on a narcotic and a stimulant be counted twice? 3-Have similar studies outside Canada found similar findings? How would the results of these studies help drug policy makers outside Canada?
Reviewer 2	**Caleb Alexander**
Institution	University of Chicago, Medicine
General comments	General comment The authors conducted a time series analysis to examine the impact of the Ontario Narcotics Strategy on the prevalence of inappropriate publicly-funded monthly prescriptions for opioids, benzodiazepines and stimulants from January 2007 to May 2013. For the primary analysis, a prescription was considered inappropriate if dispensed within seven days of an earlier prescription for at least 30 tablets of a drug within the same class from a different physician and different pharmacy. They report relative reductions in the prevalence of inappropriate prescriptions of 35%, 49% and 60% for opioids, benzodiazepines and stimulants, respectively. They conclude implementation of a prescription monitoring program dramatically reduced the prevalence of prescriptions highly suggestive of misuse. Main specific comments 1. Introduction. The authors report the NMS was "phased in gradually". How does this inform their statistical approach and its interpretation? For example, they report many comparisons between October 2011 and April 2012 to assess the NSAA, yet wouldn't April 2011 include assessments of some effect of the NMS phase-in? Can the effects of these two interventions truly be isolated? 2. Introduction. It may be helpful to discuss the burden of prescription drug abuse in Ontario or Canada. This could provide a better sense of the context and reasoning behind the enactment of the NSAA and NMS. 3. The method of determining prescriptions "suggestive of misuse" is obviously quite limited, though it may be the best the authors have. With that said, there are many reasons that one might imagine patients could trigger this indicator for unobjectionable causes (e.g., medication intolerance, inadequate response, second opinion). Do the authors have any data to support its validity? Why not look at a variety of other potential outcomes of interest, ranging from more traditional measures of doctor shoppers to utilization such as more than 100 mg morphine equilvalents per day. Were these considered and examined? If not, why not? 4. The very low proportion of all controlled substances affected by these changes is noteworthy – less than 1%. Did the authors examine the effect of the policy changes on all prescribing within these classes? Why or why not?

	5. I think many public health experts would argue that these are just the tip of the iceberg – and that far more important are the 99% not examined. After all, considerable work, including some by these authors, demonstrates the high potential for aberrant use of opioids, for example, among a much broader population of users. 6. It might be helpful or the authors to include a greater number of sensitivity analyses. 7. Discussion. The claim that "the public health impact of reductions in this prevalence is substantial" seemed to speak beyond the data provided and was consistent with a few other areas where the interpretation of the data felt a little bit like a hard sell. 8. Limitations. The authors report that defining inappropriate use can be difficult, and then go on to say that "we expect this would apply equally prior to, and following the implementation of the NMS", and then go on to say "this limitation will not likely influence the trends in this study". But this seems to miss the forest for the trees. My concern isn't that the trends are artifactual, but rather, that without any ability to judge appropriatness, interpreting the desirability of their effect is next to impossible. 9. Results. The large amount of variability and high prevalence of inappropriate stimulant prescriptions compared to the other monitored drugs classes as well as the NMS implementation's lack of impact on DUR warnings for stimulants is noteworthy and worth highlighting in the results or discussion. 10. Discussion. Based on the results reported, the implementation of the NMS system had a larger impact on the prevalence of inappropriate prescriptions than the enactment of the NMAA in November 2011. The implications of this differential impact and its relevance to policy stakeholders may warrant discussion. 11. Conclusion. Although the definitions of the terms "misuse", "abuse", and "diversion" may vary, based on the definitions of inappropriate prescription used in this study, at least for the second definition of "inappropriate" prescriptions, it seems the authors detected a reduction in the prevalence prescriptions highly suggestive of "diversion" or "abuse" rather than "misuse". Would it be helpful to specify or distinguish between these terms? Smaller specific comments 12. The authors generally report and analyze pre-post comparisons of monthly counts. Did they consider reporting slopes and levels, as is often done with these types of time series? Doesn't the comparison of single months (e.g., November 2011 with April 2012) obscure more information contained within the series? 13. Overall, I had a bit of a tough time keeping in mind the various time periods that were being compared – it appears it was primarily October 2011 with April 2012 with May 2013. I wonder if the text, and/or a figure might be provided (or one of the current time series modified) so as to make this more clear for readers, should any have the same difficulty. 14. What was the rationale for the opioids and other drugs studied? For example, what about hydrocodone? Did the authors consider an analgesic other than NSAIDs, since so many NSAIDs are available over the counter? 15. Introduction. The authors are a bit generous in referencing prior studies evaluating the impact of PDMPs – most have had one or more serious limitations, whether based on very limited and non-representative samples, being reported in non-peer reviewed literature, using crude measures to assess PDMP implemention, or incorporating limited statistical methods to strengthen causal inference. 16. Results. The similarity between the results of the prior study, conducted in BC, and this one, are stunning (32.8% vs. 35.4% reduction in opioids; 48.6% vs. 48.5% reduction in benzos). 17. Would it be of interest to report the volume of opioids (or other controlled substances) per beneficiary that filled them, and the proportion of all beneficiaries in the province filling one over the time period, etc? 18. Introduction. The distinction between opioids and controlled substances is confusing, since opioids are controlled substances.

	19. Methods. Being unfamiliar with the NMS system, are all publicly-funded prescriptions captured regardless of payment type? Can patients with public drug coverage opt to pay for prescriptions in cash in full? Are these cash prescription also captured in the NMS? 20. Introduction. Do the authors have data on how often prescription information is disclosed to government officials as referenced in ref #11? 21. Introduction. It was a bit opaque as to whether pharmacists routinely are provided with the DUR messages. 22. What proportion of all prescriptions in Ontario are dispensed through the publicly funded program? 23. The methodologic approach seems sound and the team included a variety of helpful statistical checks. 24. Discussion, page 11, line 53. It may be helpful to change "absolute" to "true", "actual" or something similar, since the authors report relative changes throughout the report and it may be confusing to the reader.
Author response	Reviewer: 1 1) What is the rationale for using a 7 day window to define inappropriate prescribing? Ultimately, any specific choice of window has a degree of arbitrariness to it. However, based on clinical experience, it is highly unlikely that when an opioid is received within 7 days, and has both been prescribed by a different physician and dispensed by a different pharmacist, this situation represents misuse. Of note, the same 7 day window was used by Dormuth et al. in their analysis of inappropriate prescribing in British Columbia.1 Furthermore, this definition does not change over time, and therefore, any contamination of our analyses by potentially appropriate prescriptions would relate to both the periods prior to and following policy changes, and therefore would not impact the significance of our results. 2) Is there a value to look at prescriptions prescribed less than 5 days? Many Tylenol #3s (acetaminophen 325mg+codeine 30mg) are prescribed for a less than 7 day period. To clarify, we did not make any restrictions based on prescription duration, but only on quantity dispensed. In our primary analysis, for reasons described above, and to follow the methodology undertaken by Dormuth et al in their CMAJ publication1, we felt that the restriction to prescriptions with a quantity of 30 units, and a window of 7 days would be the most specific way of defining inappropriate use. 3) Also why not include methadone or buprenorphine (Suboxone) I suspect that the Ontario drug benefit database may not capture these directly but there is probably a way to look at these drugs?? We agree, and have now expanded our drug list to include all opioids that are listed on the monitored drug list. This includes methadone and buprenorphine among other opioids. A full list can be found here: http://www.health.gov.on.ca/en/pro/programs/drugs/monitored_productlist.aspx (June 14, 2013 edition). INSERTED TEXT (page 6): 4) We restricted our analysis to opioids, benzodiazepines, and stimulants monitored by the NMS, and excluded prescriptions with missing prescriber identifiers, and non-tablet formulations with the exception of fentanyl (full list available at http://www.health.gov.on.ca/en/pro/programs/drugs/monitored_productlist.aspx; June

	14, 2013 edition). 5) Were the drugs mentioned mutually exclusive? Would someone on a narcotic and a stimulant be counted twice? The analysis was conducted at the prescription level and so each prescription was assessed for its appropriateness. Therefore, someone receiving prescriptions for both opioids and stimulants would have all of their prescriptions for both drugs included in the analyses. This has been clarified in the text. INSERTED TEXT (page 8): All analyses were conducted at the prescription level, and therefore, if a patient was treated with drugs from multiple classes, (i.e. opioids, benzodiazepines, stimulants), all such prescriptions were considered separately. 6) Have similar studies outside Canada found similar findings? How would the results of these studies help drug policy makers outside Canada? A few studies have been published in the United States investigating the impact of prescription monitoring programs on prescription drug misuse and abuse. These studies are described briefly in the introduction of the manuscript (page 4). We are unaware of any other studies that have investigated similar questions outside of North America. As the issue of prescription drug abuse and misuse (particularly relating to opioids) becomes an increasing concern outside of North America, we believe that drug policy-makers will find the results from this manuscript to be useful in demonstrating the potential impact of regulations and prescription monitoring on behaviours related to misuse and abuse of prescription drugs. Reviewer: 2 1) Introduction. The authors report the NMS was "phased in gradually". How does this inform their statistical approach and its interpretation? For example, they report many comparisons between October 2011 and April 2012 to assess the NSAA, yet wouldn't April 2011 include assessments of some effect of the NMS phase-in? Can the effects of these two interventions truly be isolated? We thank the reviewer for mentioning this. The NMS was phased in, starting in April 16, 2012 and with full implementation required by May 12, 2012. Therefore, we do not expect the changes that occurred between November 2011 and April 2012 to be influenced by the NMS, but driven by the NSAA instead. We realize that this wasn't clear in the text and have updated the manuscript to make this clearer. INSERTED TEXT (Page 5): Pharmacies could begin submitting dispensing information through the NMS as of April 16, 2012, with full implementation on May 12, 2012. 2) Introduction. It may be helpful to discuss the burden of prescription drug abuse in Ontario or Canada. This could provide a better sense of the context and reasoning behind the enactment of the NSAA and NMS. We thank the reviewer for making this suggestion. We have included a discussion of this in the introduction of the manuscript.

	INSERTED TEXT (Page 4): Furthermore, Canada has one of the highest opioid consumptions per capita in the world.2 Increased use of these prescription drugs, along with trends highlighting the substantial risks of overdose death among those receiving prescriptions for these medications in Ontario have led to considerable concern among physicians, public health officials and regulatory authorities. 3) The method of determining prescriptions "suggestive of misuse" is obviously quite limited, though it may be the best the authors have. With that said, there are many reasons that one might imagine patients could trigger this indicator for unobjectionable causes (e.g., medication intolerance, inadequate response, second opinion). Do the authors have any data to support its validity? Why not look at a variety of other potential outcomes of interest, ranging from more traditional measures of doctor shoppers to utilization such as more than 100 mg morphine equivalents per day. Were these considered and examined? If not, why not? Although we agree that there may be reasons why a patient's prescription could trigger this indicator for an appropriate cause, based on our clinical experience as well as that of others we have spoken with, we believe that this would be rare (e.g. early refill with different prescriber and different pharmacist). Therefore, we do not believe that this would influence our findings to any great degree. Furthermore, it is unlikely that the "unobjectionable" activities described above would be impacted by the NSAA or NMS, and therefore changes observed in this analysis are likely driven by changes in truly inappropriate use. We have ensured that we use the term "potentially inappropriate prescribing" throughout the manuscript to clarify that some of these prescriptions may in fact be appropriate. We did consider other measures of inappropriate use, which is why we included a secondary analysis using a different definition that relied on pharmacy warning flags that would capture 'doctor shoppers' and 'pharmacy shoppers'. We did not look at the prevalence of use beyond 100mg MEQ for two reasons. First, this would not apply to stimulants or benzodiazepines, and so would limit our analysis to opioids. Second, we wanted to focus on measures relating to the practice of filling prescriptions for monitored drugs, since this is the key focus of the NSAA and the NMS. These policies did not impose specific restrictions or recommendations around maximum dose prescribed of these medications. For these reasons, we feel that the two key outcome definitions reported in this paper are the most appropriate for the hypotheses tested in this analysis. 4) The very low proportion of all controlled substances affected by these changes is noteworthy – less than 1%. Did the authors examine the effect of the policy changes on all prescribing within these classes? Why or why not? Although a very low proportion of prescriptions for monitored drugs fit our definition of inappropriate use over the entire study period (<2%), given the large number of prescriptions, this amounts to almost one million prescriptions over the study period. Furthermore, this study demonstrated that the policy changes implemented had a substantial impacton the prescribing in these classes. For example, the prevalence of opioid prescriptions meeting our definition of "inappropriate" was only 1.6% overall in the study period, but it fell 40.3% between October 2011 (prior to any regulatory changes) and the end of our study period. We did not extend our definition to look at all prescribing within these classes because it would be difficult to know if any changes observed were being driven by the most concerning prescribing behaviour (e.g. early refills with evidence of doctor and pharmacy shopping). Therefore, although we agree with the reviewer that our definition of potentially inappropriate use is likely an underestimate of true inappropriate use, we believe that this method is the best way of assessing the impact of these policies on particularly troublesome prescribing behaviour in this population, and aligns with research already done in this area.1 We have updated the limitation section of our manuscript to clarify some of these issues: AMENDED TEXT (PAGE 13): These definitions were designed to be conservative and specific, and are likely to misclassify prescriptions of shorter duration, or those that met only one of the multi-

	doctoring or poly-pharmacy requirements. Furthermore, our study excluded prescriptions with missing prescriber identifiers, which may be more likely to be inappropriate. Therefore, our study likely underestimates the true prevalence of inappropriate prescribing of monitored drugs in Ontario. However, the consistency of findings between the two definitions of inappropriate use, along with the null finding among our tracer drug class (NSAIDs) suggest a true association between regulatory and prescription monitoring changes in Ontario and reductions in inappropriate prescribing. 5) I think many public health experts would argue that these are just the tip of the iceberg – and that far more important are the 99% not examined. After all, considerable work, including some by these authors, demonstrates the high potential for aberrant use of opioids, for example, among a much broader population of users. We agree with the reviewer that we are likely underestimating the true prevalence of inappropriate use, and were careful to discuss this clearly in the interpretation section of our manuscript. However, for the reasons outlined in our response to #4 above, we feel that our approach to this analysis is most appropriate to evaluate the hypothesis that these policies impacted prescribing behaviour. Furthermore, prior to the introduction of the NMS, only publically funded prescriptions for monitored drugs were captured in electronic databases, and therefore analyses in a broader population are unfortunately not feasible. 6) It might be helpful or the authors to include a greater number of sensitivity analyses. Based on Reviewer #1 and #2's comments, we have included a sensitivity analysis where our definition for the primary outcome was loosened to classify prescriptions as inappropriate if they would have led to the issuance of either a double-doctoring or a poly-pharmacy warning. The methods and results sections have been updated to reflect these changes and are included below: INSERTED TEXT: Page 7-8: In a sensitivity analyses, we broadened the definition in the primary analysis such that prescriptions were flagged as potentially inappropriate if they were issued by either a different doctor or a different pharmacy. Page 11-12: In our sensitivity analysis, we loosened the criteria on potentially inappropriate prescriptions to require only double doctoring or polypharmacy. Using these loosened criteria, 2.8% of opioid prescriptions, 1.0% of benzodiazepine prescriptions, and 1.2% of stimulant prescriptions were deemed potentially inappropriate over the study period. For both opioids and benzodiazepines, the results were consistent with the primary analysis. Among opioids, we found a significant reduction in the proportion of potentially inappropriate prescriptions following the enactment of the NSAA (5.6% reduction from October 2011 to April 2012; p=0.03), but no further significant reduction after the implementation of the NMS (p=0.44). Similarly, among benzodiazepines, we found a significant reduction in the proportion of potentially inappropriate prescriptions after both the enactment of the NSAA (12.5% reduction from October 2011 to April 2012; p<0.001) and the implementation of the NMS (19.8% reduction from April 2012 to May 2013; p=0.03). However, among stimulant prescriptions, the sensitivity analysis found a significant impact of the enactment of the NSAA (28.0% reduction from October 2011 to April 2012; p=0.02), but no further impact of the NMS (p=0.22). This is in contrast to the primary analysis, where the NSAA had a marginally non-significant impact, and the NMS had a significant impact on reducing potentially inappropriate prescribing. 7) Discussion. The claim that "the public health impact of reductions in this prevalence is substantial" seemed to speak beyond the data provided and was consistent with a few other areas where the interpretation of the data felt a little bit like a hard sell.

	We agree and have softened the wording in the discussion in several places. 8) Limitations. The authors report that defining inappropriate use can be difficult, and then go on to say that "we expect this would apply equally prior to, and following the implementation of the NMS", and then go on to say "this limitation will not likely influence the trends in this study". But this seems to miss the forest for the trees. My concern isn't that the trends are artifactual, but rather, that without any ability to judge appropriatness, interpreting the desirability of their effect is next to impossible. We agree that for the reasons described, the trends are likely not artifactual. With respect to judging the appropriateness of the prescriptions, we feel that the definition of inappropriate use implemented in this study is extremely strict, and it is unlikely that many appropriate prescriptions would fall within these criteria. As explained earlier, we specifically chose this definition to ensure that we were not capturing a large amount of potentially appropriate prescriptions where the desirability of changes over time could be debated. Furthermore, we believe that the consistency of the findings between our primary, secondary and sensitivity analyses, along with the correlation between our findings and those conducted in British Columbia reinforce the validity of the findings. 9) Results. The large amount of variability and high prevalence of inappropriate stimulant prescriptions compared to the other monitored drugs classes as well as the NMS implementation's lack of impact on DUR warnings for stimulants is noteworthy and worth highlighting in the results or discussion. The variability in the stimulant data is due to the much smaller number of prescriptions in this drug class (1,066,834 prescriptions) compared to the other classes included in this study (49,578,359 and 21,469,883 prescriptions for opioids and benzodiazepines, respectively). Therefore, this introduces more noise into the data. INSERTED TEXT (page 14): Third, due to the small number of stimulant prescriptions identified in this analysis, there is considerable variation in estimates of inappropriate stimulant use over time. Despite this, we were able to specify robust time series models that evaluated the impact of the policy interventions in our analysis. 10) Discussion. Based on the results reported, the implementation of the NMS system had a larger impact on the prevalence of inappropriate prescriptions than the enactment of the NMAA in November 2011. The implications of this differential impact and its relevance to policy stakeholders may warrant discussion. We have updated our primary analyses in response to several other reviewer comments, and in these updated analyses, we have found that both the NSAA and the NMS had significant impacts on the trends in prevalence of inappropriate prescribing of monitored drugs in Ontario. Based on these findings, we do not believe that it would be fair to describe one intervention as having a greater impact than another. Given this, we believe that the discussion of the results in the manuscript accurately reflects the findings of these analyses and so have not made any changes. 11) Conclusion. Although the definitions of the terms "misuse", "abuse", and "diversion" may vary, based on the definitions of inappropriate prescription used in this study, at least for the second definition of "inappropriate" prescriptions, it seems the authors detected a reduction in the prevalence prescriptions highly suggestive of "diversion" or "abuse" rather than "misuse". Would it be helpful to specify or distinguish between these terms? We agree that the definitions of these terms may vary, and therefore have focused the manuscript on the terms "inappropriate use" and "suggestive of misuse". As we are unable to specifically determine in our data whether the drugs are being abused or diverted, we have been careful in the use of these terms in the manuscript. We believe that the way in which these terms are used is standard within the opioid literature, and therefore haven't included any specific definitions in the revised manuscript. If the editors feel more clarification is needed, we will attempt to do so. 12) The authors generally report and analyze pre-post comparisons of monthly counts. Did they consider reporting slopes and levels, as is often done with these types of time series? Doesn't the comparison of single months (e.g., November 2011 with April 2012) obscure more information contained within the series?

	The approach of reporting slopes is typically undertaken when a segmented regression is conducted. For time series analyses using ARIMA methods, we typically don't report slopes because there are many slopes over a given timeframe. Instead, the standard reporting for this approach is level changes at the time of the intervention along with p-values. As a result, we have left the reporting of our results in this format. 13) Overall, I had a bit of a tough time keeping in mind the various time periods that were being compared – it appears it was primarily October 2011 with April 2012 with May 2013. Iwonder if the text, and/or a figure might be provided (or one of the current time series modified) so as to make this more clear for readers, should any have the same difficulty. We understand that this may be confusing. We have created a figure with explanatory legend to help the reader clarify each of the comparisons which is included in the Supplementary Appendix. 14) What was the rationale for the opioids and other drugs studied? For example, what about hydrocodone? Did the authors consider an analgesic other than NSAIDs, since so many NSAIDs are available over the counter? We have now expanded our list of opioids, benzodiazepines and stimulants to include all drugs that are listed in the Ontario Public Drug Programs' list of monitored drugs. The rationale for this is that these are the drugs identified by the OPDP in their policies and being tracked by the NMS. We selected NSAIDs as a tracer exposure class because there is no expected reason for misuse or abuse of drugs within this class. In Ontario, only ibuprofen and naproxen are available over the counter. We don't expect that the availability of these medications over the counter would impact the validity of this tracer exposure. Therefore, this is a good choice for a tracer exposure since any suggestion of a change in prescription trends in this drug class would call into question the validity of our other findings. Given the null finding in this study for the NSAID class, we feel that this reinforces the observed association between policy changes in Ontario and reductions in inappropriate prescribing of monitored drugs. 15) Introduction. The authors are a bit generous in referencing prior studies evaluating the impact of PDMPs – most have had one or more serious limitations, whether based on very limited and non-representative samples, being reported in non-peer reviewed literature, using crude measures to assess PDMP implemention, or incorporating limited statistical methods to strengthen causal inference. While we agree that the literature in this field is scarce, and some studies may have limitations that question the validity of their findings, we cited these studies to provide thereader with information as to what evaluations had been conducted, and to highlight the lack of consistency in literature describing the impact of PDMPs. We have included a comment on the quality of this literature being variable to address the reviewer's concern. INSERTED TEXT (page 4): Although some studies suggest a significant impact of these programs on the supply of monitored drugs and rates of drug abuse and misuse7-9, their quality is variable, and their success relies on a variety of factors, including the accessibility of data to healthcare providers, pharmacist engagement, and the involvement of law enforcement.5;7;10;11 16) Results. The similarity between the results of the prior study, conducted in BC, and this one, are stunning (32.8% vs. 35.4% reduction in opioids; 48.6% vs. 48.5% reduction in benzos). We agree with the reviewer – the congruency between the findings in both studies is interesting, and – we believe – reassuring. However, in the updated analyses, using a broader definition of exposure drugs, the percentage reported in our study has increased somewhat compared to the BC data. This has now been described in the discussion. INSERTED TEXT (page 12): Although the BC PharmaNet system captures all drugs (compared to the limited list of

	drugs monitored by the Ontario NMS), Dormuth et al. reported a 33% reduction in inappropriate opioid prescribing and a 49% reduction in inappropriate benzodiazepine prescribing, which is consistent with, but slightly lower than our findings of 40% and 58%, respectively. This suggests that, although the products available and the rates of use and abuse of these drugs (particularly opioids) have changed substantially since that time, the value of prescription monitoring programs that allow pharmacists access to real-time data on patient prescribing history remains high. 17) Would it be of interest to report the volume of opioids (or other controlled substances) per beneficiary that filled them, and the proportion of all beneficiaries in the province fillingone over the time period, etc? We have reported the total number of beneficiaries filling at least one prescription over the study period in the first sentence of the results (see text below). We do not feel that it would add anything substantial to the manuscript to also report the volume of opioids dispensed per beneficiary since this is beyond the scope of our primary objectives for this study. Furthermore, calculation of these volumes would become complicated because conversion factors between drug strengths are not well established for all medications included in this analysis. Therefore, we have not included this measure. MANUSCRIPT TEXT (page 8): Over the 77-month study period, 49,578,359 opioid prescriptions, 21,469,883 benzodiazepine prescriptions and 1,066,834 stimulant prescriptions were dispensed to 1,706,502, 928,240, and 34,902 public drug plan beneficiaries, respectively. 18) Introduction. The distinction between opioids and controlled substances is confusing, since opioids are controlled substances. We have clarified this as "narcotics and other controlled substances" in the introduction. We believe that it is important to specifically identify narcotics in the text since both policies specifically refer to 'narcotics' in their names, despite the fact that they apply to all monitored drugs. 19) Methods. Being unfamiliar with the NMS system, are all publicly-funded prescriptions captured regardless of payment type? Can patients with public drug coverage opt to pay for prescriptions in cash in full? Are these cash prescription also captured in the NMS? The NMS system captures all prescriptions for monitored drugs, regardless of how they have been paid for (cash, private insurance, public drug program). This has been clarified in the text. INSERTED TEXT (page 5): Another key component of this legislation is the Narcotics Monitoring System (NMS), which captures prescriber, pharmacist and patient information for all narcotics and other controlled drugs dispensed in Ontario, regardless of payment type (e.g. cash, private insurance or public drugprogram). 20) Introduction. Do the authors have data on how often prescription information is disclosed to government officials as referenced in ref #11? Prescription data are required to be submitted to the NMS by the pharmacist at the time of filling the prescription, and this data is automatically relayed to the provincial public drug program. 21) Introduction. It was a bit opaque as to whether pharmacists routinely are provided with the DUR messages. Pharmacists are routinely provided with DUR messages. We have revised the text in the introduction to make this clearer. INSERTED TEXT (page 5): This information could lead to educational interventions, and the reporting of potential misconduct or criminal activity to regulatory and law enforcement agencies. Although full patient profiles for all prescriptions in the NMS system are accessible to physicians and pharmacists, pharmacists are now provided with more information in the Drug

	Utilization Review (DUR) messages (alerts) that includes the conflicting drugs, quantities and other dispensing pharmacies. 22) What proportion of all prescriptions in Ontario are dispensed through the publicly funded program? In 2011, 43% of drug costs were paid for through the Ontario Public Drug Program. We have included this in the text of the manuscript. INSERTED TEXT (page 13): First, our findings are limited to publically funded prescription drugs (which accounts for approximately 43% of all drug costs in Ontario), and may not be generalizable to the entire population. 23) The methodologic approach seems sound and the team included a variety of helpful statistical checks. We thank the reviewer for their comment. 24) Discussion, page 11, line 53. It may be helpful to change "absolute" to "true", "actual" or something similar, since the authors report relative changes throughout the report and it may be confusing to the reader. This change has been made. INSERTED TEXT (page 12): Given our conservative definitions, the true number of inappropriate prescriptions is likely to be even higher.