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Title	Comparing opioid prescribing and adverse events for opioid naive patients treated by emergency and family physicians
Authors	Bjug Borgundvaag MD PhD, Shelley McLeod PhD(c), Wayne Khuu MPH, Catherine Varner MD MSc, Mina Tadrous PharmD PhD, Tara Gomes MHSc
Reviewer 1	Christopher Maher
Institution	The George Institute for Global Health, Musculoskeletal Division, Sydney, Australia
General comments (author response in bold)	This is clearly an important issue and the introduction nicely justifies the need for this work. I have some questions about the methods. Some are areas of uncertainty and others relate to aspects of the methods that I think are not optimal. It does not look like you adjusted for any confounders. Is that true? I would prefer some adjustment for important confounders. If that is not possible please discuss as a limitation of your study. **Thank you for this suggestion. We did not adjust for confounders in our analyses. This is because we aimed to provide a basic description of opioid prescribing patterns by emergency and family physicians and to *explore* the relationship between association of initiation and subsequent opioid toxicity and dose escalation. In particular, we were interested in differences in these outcomes regardless of differences in patient characteristics to provide an understanding of the relative contribution of each practice setting to these outcomes. One reason for this approach is that our hypothesis is not that the setting itself (i.e. ED vs. primary care) influences these future risks, but that the patient mix and prescriber practices that are common in each of these settings influence these future risks. Therefore, in this case, it is not appropriate to adjust for confounders, but to describe the relative distribution of outcomes in each setting.** **We have added the following text to the limitations section of our manuscript:** **"Because the aim of this investigation was to provide a basic description of opioid prescribing patterns by EP's and FP's, and to explore the relationship between opioid initiation setting and subsequent opioid toxicity and dose escalation, we did not adjust for independent factors associated with toxicity".** You elected to exclude people who were prescribed >200mgMEU on the grounds that these people had already experienced the event for one of your analyses. That is true for one of your 3 objective. For your first two objectives ("describe and compare opioid prescribing patterns by emergency and family physicians and to explore the relationship between setting of initiation and hospital admission for opioid toxicity") including these people is not a problem and in my view excluding them removes some really important information. I would encourage you to repeat the analyses so these people are included for these two objectives. **We appreciate this insightful comment. We elected to exclude patients with an initial dose exceeding 200 mgMEQ for several reasons. Firstly, this would be an extraordinarily high dose for an opiate naïve patient to be initiated on under any circumstance and would likely be suggestive of a data error in our databases. Second, it might be possible that the patient was not opioid naive, was on chronic opioid treatment that was paid through cash or private insurers, and subsequently became eligible for ODB coverage (ie it was a continuation of existing opioid treatment). While it might be possible for some patients to have been initiated on doses exceeding 200 mgMEQ, we feel that there is a strong possibility that these data simply represent data errors or populations who are not truly opioid naïve. Therefore, we believe that it is best to exclude them from any further analysis.** One aspect of the study that was unclear was whether you could measure opioid poisoning deaths in the cohort. Please clarify. If you cannot, it is a potential limitation that possibly confounds this study if you ignore it eg one group may have less ED opioid related toxicity events, but more deaths (once you are dead you cannot attend with a toxicity event). I would like some information and discussion on this issue. **Thank you for this important comment. Opioid-related death data was not available to us when conducting this study, so we were unable to study this outcome. We have however expanded our analysis to include the number of deaths in each group, however we have not adjusted for other potential causes of death, and therefore this data should be interpreted with caution.** **We have subsequently added the following text to the end of the first paragraph in the results section** **"While we have no details on the number of deaths due to opioid poisoning between the two groups, we observed no difference in the rate of death between the EP and FP groups over the course of the study (n=30 (0.1%) vs n=91 (0.2%) SD = 0.03 respectively)."** Please tell us what % of population aged 15-64 your sample covers. **In 2015/16 there were approximately 900,000 individuals under the age of 65 covered by the ODB program (http://www.health.gov.on.ca/en/public/programs/drugs/publications/opdp/docs/odb_report_16.pdf). Census data from this same year indicates roughly 9.4 individuals in Ontario between the ages of 15 to 65 (http://www5.statcan.gc.ca/cansim/a47). Based on this information, approximately 10% of the general 15-65 year old population in the Province of Ontario is covered by the Ontario Drug Benefit Program We have added the following text to the second paragraph on the methods section under "Setting":** **"The cohort of patients in this study represents approximately 10% of the total population of the Province of Ontario aged 15-65."** You describe participants as opioid naïve; but they are not naïve to this medicine. The inclusion was not taking it in last 12 months. Needs a better term if possible. **Thank-you for this comment. Opioid Naive is the standard term which has been used in the literature to describe the population of patients who are not known to have been prescribed opioids for the period prior to the index visit, and has been widely used in most published studies describing an interval of between 6-12 months to establish a new course of opioid treatment. As a result, we have chosen to continue to use this term in the manuscript, and have ensured that we define clearly what we mean by naïve in our methods.** In Table 1 you provide previous med use (in last 180 days). I would like to know if they are concurrently taking them with opioid particularly benzos as guidelines warn against this as it is so dangerous. For example CDC guide notes: "Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible". If understanding concurrent use is possible I think it would definitely add to your important paper. **Thank you for highlighting this important point. Without doubt, concurrent use of benzodiazepine medications and prescription opioids places patients at increased risk for adverse events.** **In response to this query, we have re-analyzed our data and determined that 4,693 and 7,962 (13.5% vs 17.3% SD 0.11) individuals in the EP and FP groups respectively had an active prescription for a benzodiazepine at time of**

	initiating opioids. We have amended our manuscript in the following places: **Table 1: Line added Benzodiazepines (Active prescription with numbers and %'s))** **Paragraph 1 results New Text included** **"4,693 (13.5%) and 7,952 (17.3%) of individuals in the EP and FP groups respectively had active prescriptions for a benzodiazepine at the time their initial opioid prescription was obtained."** **Paragraph 3 interpretation has been revised as follows (new text highlighted).** **"Our study demonstrates that a large number of patients in both the EP and FP groups have known risk factors associated with adverse outcomes related to opioid use. Nearly half of each group had documented anxiety or sleep disorders, and approximately one fifth had received a prescription for a benzodiazepine within the previous 180 days (13.5% and 17.3% of EP and FP patients had active prescriptions for benzodiazepines when they were first prescribed opioids)."**
Reviewer 2	Kelly Grinrod
Institution	University of Waterloo, School of Pharmacy, Kitchener, Ont.
General comments (author response in bold)	General comments: This is a very well written article. The paper describes a prospective cohort study that uses administrative data from Ontario to compare opioid prescribing between family physicians and emergency medicine physicians. It also offers clear recommendations for areas that educators and policy makers can intervene (e.g., opioids for low back pain). -The main concern we noted was that patients over 65 are excluded and there is not clear justification for this. From a clinical perspective, opioid prescribing in seniors is also a concern especially as it relates to chronic conditions such as osteoarthritis, low back pain and diabetic neuropathy. This is also relevant considering that you found that older individuals in your current cohort were more likely to receive an opioid prescription from a family physician. **Thank you for this thoughtful comment, and we completely agree, and this is an area that requires additional research. Patients over the age of 65 are a complex group that we believe require separate consideration. In addition to the fact that older patients in our cohort were more likely to get an opioid prescribed, there are, as you point out, many special considerations for this group: prevalence of chronic conditions, reduced ability to clear these drugs due to impaired hepatic/renal function, increased sensitivity to sedative effects of opioids etc. Clearly more research is needed in this area. We chose to focus this manuscript on the <65 age group because our past research has demonstrated that 97% of accidental opioid-related deaths occur in this demographic. Therefore, we believe that this is the most important population to study at this time.** -Why was the cut-off of 200mEQ used rather than the 90mEQ included in the new guidelines? Is there a reference that the 200mEQ is based on? **Thank-you for this comment. The threshold cutoff of 200mgMEQ corresponds to the "watchful dose" published in the 2010 Canadian guidelines which were in place over the course of this study's accrual and follow-up window. For this reason, we believe that it is the most appropriate threshold to use. In response to your comment, we have made reference to these new guidelines in the second paragraph of our interpretation section which now reads:** **"In this study, almost 30% of all opioid prescriptions provided by EPs exceeded a dose of 50 mg MEQs. While there are no guidelines for opioid prescribing for acute pain, recently published Canadian prescribing guidelines for chronic non-cancer pain recommend that initial prescriptions not exceed the 50 mg MEQs threshold (and in most cases should not exceed 90 mg MEQ's)."** -Very interesting that one of the top 3 reasons for a family physician to prescribe an opioid was a "psychiatric reason". The other indications listed are for pain but this is the only one of the 6 (for both EP and FP prescribing) that is not an actual indication for opioids. The discussion focuses more on opioids not being first line for the other conditions but the finding about psychiatric conditions deserves more attention. It's also unclear how you linked the prescriptions to each of these codes. For example, if the patient was being seen for a psychiatric condition but also had chronic pain, then this finding is misleading. **Thank you for your thoughtful comment. It is an interesting observation that one of the most common diagnostic codes associated with opioid prescribing by family physicians relates to "psychiatric diagnoses". Anxiety neurosis, hysteria, neurasthenia, obsessive compulsive neurosis and reactive depression are all attributed to the OHIP diagnostic code 300. The diagnostic codes were linked to the visit which was attributed to the index opioid prescription, however patients may have other ongoing conditions, and only one diagnosis can be recorded by the billing physician. Therefore, it is possible that the physician saw a patient with a psychiatric diagnosis and an acute pain condition, and chose to list the psychiatric diagnosis on their billing instead of the pain condition. Despite this, it is surprising that this population would be so frequently prescribed opioids that this diagnosis would be one of the most common captured in our cohort, particularly given that unstable psychiatric diagnoses are well-known risk factors for problematic opioid use.** **In response to your suggestion, we have added the following sentence to our limitations section:** **"It is well known that patients with concurrent psychiatric conditions are at increased risk for adverse outcomes related to opioid prescribing, and current Canadian guidelines recommend against opioid prescribing until the active psychiatric disorder has been stabilized (ref Canadian guidelines) Our observation that psychiatric conditions were a common cause for opioid prescribing by FP's requires further investigation. We are not able to determine what the cause for these prescriptions were, however since physicians can only apply a single diagnostic code to a visit it is possible that a patient seen for a primary psychiatric condition had a concurrent painful condition, or that an underlying psychiatric condition was felt to result in a somatic pain complaint.**