

Title: Patterns of prescription opioid dispensation among Red River Métis in Manitoba: a retrospective longitudinal cross-sectional study

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Reviewer 1 Comments

Reviewer: Meldon Kahan

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I don't have any concerns about the methodology used in the study, but I do not think that their conclusions and recommendations are supported by their findings.

The authors have made the assumption that higher doses and longer duration of treatment are causing opioid-related harms. For example, they state, "the use of stronger opioids is on the rise, and longer durations of opioid use among Metis may contribute to this population disproportionately experiencing opioid-related harms". Later, they state that "Our findings highlight the disproportionate burden of opioid-related harms in Indigenous communities in Canada." The paper did not, in fact, examine opioid-related harms; it only looked at opioid dose and duration. The evidence does not support a simple relationship between dose and harm.

We acknowledge that we overstated the relationship between opioid dispensation patterns and opioid-related harms in the paper. We have presented our findings slightly differently in the revised paper and have rewritten the interpretation and conclusion sections to better describe the implications of our results.

The authors assume that the somewhat higher rates of opioid prescribing and higher dose per prescription for the Metis population versus the general population means that physicians serving Metis patients are prescribing inappropriately. This is not necessarily true. The most common reason for chronic opioid prescriptions is chronic pain due to osteoarthritis. Perhaps the Metis population have a higher prevalence of osteoarthritis, due to increased rates of MSK injuries, greater involvement in heavy physical labour, and/or higher rates of obesity. The longer duration of prescriptions could be because prescribers were writing relatively fewer short-term prescriptions for acute pain. Acute pain prescriptions tend to have lower MED than prescriptions for chronic pain, where the dose tends to increase over weeks or months.

Acknowledged. There could be many reasons why Metis receive more opioid prescriptions, and the relevant paragraph has been rewritten to reflect this.

The authors also assume that the dose of prescription opioids is causally related to the rate of overdose deaths. This is not supported by the evidence.

The authors note that there was a 55% increase in overdose deaths from 2016-2018, but the rate of prescribing among the study population declined from 2006 to 2018, so it is not clear how prescription opioids are contributing to the marked increase.

On the contrary, the evidence strongly indicates that fentanyl and other non-prescribed opioids are the major factors in the increase. This is in marked contrast to the increase in opioid overdose deaths from 1995 to 2010. The study by Dhalla in CMAJ demonstrated that the increase in prescribing of OxyContin was closely correlated with the rise in oxycodone-related overdose deaths.

We have revised the interpretation and conclusion sections to better describe the implications of

our results.

The authors point out that the Metis population has higher rates of opioid poisonings than the general population, referring to the Carriere study. They state, 'In Manitoba, the rate of opioid-related overdose among those with an active opioid prescription is 62.9%...'. This cannot be correct. I looked at the abstract of the paper by Gomes (reference 3). This was an analysis of patients hospitalized with opioid overdose in Canada. I think the paper was saying that among those who overdosed, 62.9% had an active opioid prescription. Note that this does not mean that the active opioid prescription caused the overdose death; even if a prescribed opioid was present in the serum at the time of death, the overdose could be due to illicit opioids such as fentanyl.

Thank you for pointing out this error. This sentence has been corrected.

The authors correctly point out that higher doses of opioids are correlated with higher rates of overdose, but an important confounding factor that needs to be considered. Patients with opioid use disorder tend to be prescribed high opioid doses. They also take opioids in a hazardous manner compared to pain patients: they often combine opioids with alcohol or benzodiazepines, or they inject or crush oral opioids, or they binge on the opioid. In fact, a patient is very unlikely to die of an overdose if they are on a high but stable opioid dose and are compliant with the prescriber's instructions. That's because physicians titrate the opioid dose slowly, so patients have time to build up tolerance to the CNS depressant effects of the opioid.

Good point. We've added this potential confounder to our discussion.

The paper doesn't address the possibility that a significant portion of the Metis population on prescribed opioids have a prescription opioid use disorder. The paper's table on comorbidities indicates that the Metis population has somewhat higher rates of anxiety, depression and substance use disorders than the general population; these are known risk factors for opioid use disorder. As mentioned above, patients with opioid use disorder are more likely to use their opioid in a risky manner. In other words, the reason for greater rates of opioid-related harms among the Metis population is because of higher rates of opioid use disorder, not because their mean opioid dose is somewhat higher.

We've added this consideration to the paper and plan to investigate it in a future analysis. This paper is the first in a series of studies on opioid use and was meant to provide baseline information on opioid dispensations in an often-overlooked population, but we will be exploring more of the underlying story in future papers.

The authors state that they intend to use this paper to influence policy. If, as the authors assume, higher opioid doses equate to higher opioid-related harms, then the solution would be to persuade or require physicians to lower their doses. But the evidence suggests that this would have serious unintended consequences. A retrospective cohort study was conducted on 1.4 million patients in the Veterans Health Administration in the US who received an outpatient opioid prescription between 2013 and 2014 (Olivia 2020). The sample had 2,887 deaths from overdose or suicide. Stopping opioids was associated with an increased risk of death, and the longer the duration of opioid treatment the greater the risk: Hazard ratios for stopping opioid treatment were 1.67 (stopping in < 30 days), 2.80 (31-90 days), 3.95 (91-400 days), and 6.77 (> 400 days). The likely explanation is that opioid tapering and discontinuation cause a withdrawal syndrome, with marked exacerbation of pain, depression and anxiety, and cravings. The pain exacerbation and depression could trigger suicidal ideation, especially in patients with an underlying mood disorder. Patients who have discontinued opioids for a week or more are at high risk of overdose if they find another source for their opioid, because they have lost tolerance to the CNS depressant effects of the opioid.

We've revised our conclusions and added more nuance to our stated plans to work with Metis

health leadership. Our planned future analyses will also give us a more detailed picture of opioid use in Manitoba before we pursue any potential change to policy.

If the authors wish to use prescribing data to further an understanding of the opioid crisis and its impact on the Metis population, they should look at the prescribing of opioid agonist therapy (OAT) with buprenorphine and methadone. Controlled trials and systematic reviews have shown that people with opioid use disorder are at far lower risk of overdose while on OAT than when off it (Sordo 2017, Pearce 2020). I suspect that prescribing rates of buprenorphine are lower among Metis individuals than among others in Manitoba.

This would indicate that the Metis population have a relative lack of access to lifesaving medication, which is a serious inequity.

Whether or not the authors undertake an analysis of prescribing of OAT, it is important that they understand which interventions are effective in mitigating the opioid crisis, and which could make things worse. Patients who are receiving analgesic benefit from an opioid and are not having major side effects from it should be left on that dose, even if the dose is high. Patients who have a prescription or illicit opioid use disorder should be offered OAT; tapering or discontinuing their opioid will increase their risk of overdose death. The most effective public policy approach is to ensure that all individuals and communities have access to comprehensive, high quality opioid agonist treatment.

Thank you for this suggestion. This is an important consideration and we will include it in our planned future analyses.

Reviewer 2 Comments

Reviewer: Stephanie Sinclair

Institution: First Nations Health and Social Secretariat of Manitoba, Research

Research is needed to provide evidence to support the calls for action. Agree that one should not compare Metis and First Nations, but rather use all other Manitobans as the comparison group.

Thank you for reviewing the paper.

