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Comparing the contribution of prescribed opioids to opioid-related hospitalizations across Canada: A multi-jurisdictional cross-sectional study

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ABSTRACT

Background: The Canadian opioid crisis is a complex, multifaceted problem involving prescribed, diverted and illicitly manufactured opioids. This study sought to characterize the contribution of prescribed opioids to opioid-related hospitalizations in Canada.

Methods: We conducted a cross-sectional study of all individuals who were admitted to hospital for opioid toxicity in British Columbia (BC), Manitoba and Ontario between April 2015 and March 2016. We used prescription claims to ascertain active prescription opioid use at time of hospital admission. In secondary analyses, we defined recent opioid prescriptions as those that were dispensed in the 30 and 180 days up to and including admission, and the prevalence of active co-prescription of benzodiazepines with opioids at time of overdose.

Results: We identified 2599 instances of opioid toxicity over the study period. In BC, 34.1% of hospital visits for overdose occurred in people with an active opioid prescription, compared to 52.2% (47 of 90) in Manitoba and 52.8% (804 of 1524) in Ontario. However, active opioid prescriptions prior to overdose varied significantly by age and sex. Co-prescription of opioids and benzodiazepines prior to overdose ranged from 17.1% in BC to 35.6% in Manitoba.

Conclusions: There remains an important ongoing contribution of prescribed opioids to overdoses across Canada, but non-prescribed opioids play a growing role, particularly in BC. These findings underscore the importance of more judicious opioid prescribing, harm reduction programs, and improved access to addiction care for people with an opioid use disorder.

1. Introduction

In Canada, over 2800 deaths were opioid-related in 2016, and 13 people are hospitalized every day from an opioid-related toxicity event (Canadian Institute for Health Information and Canadian Centre on Substance Abuse, 2016; Government of Canada, 2017). Although these rates have risen considerably across the country over the past two decades, considerable geographic variation exists in the rates of fatal and non-fatal overdoses (Alberta Health, 2017; British Columbia Coroners Service, 2017a, b; Canadian Institute for Health Information and Canadian Centre on Substance Abuse, 2016; Gomes et al., 2017). In particular, British Columbia (BC) has experienced particularly high rates of both non-fatal and fatal opioid overdoses (20.6 illicit drug deaths per 100,000 population in 2016) (British Columbia Coroners Service, 2017b), with steep increases in illicit drug-related deaths since late 2015 primarily attributed to the profusion of clandestinely-produced fentanyl analogs in the illicit drug supply (British Columbia Coroners Service, 2017a, b). In contrast, rates of opioid overdose are lower in Ontario and Manitoba, with 6.2 and 5.2 opioid-related deaths per 100,000 population reported in 2016 in Ontario (Public Health Ontario, 2017) and Manitoba, (Manitoba Health Seniors and Active Living, 2017) respectively.

Although increasing rates of opioid addiction and overdose have been historically attributed to overprescribing of opioids, the recent emergence of illicitly manufactured fentanyl and its analogs, along with changing access to prescribed opioids has created a complex

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environment in which both prescribed and illicit opioids contribute to opioid-related harms across Canada. However, little is known about the relative contributions of different drug sources to opioid overdoses and how this varies across the country. This is particularly important as policy-makers prioritize the development of programs and policies to address this rising public health emergency in Canada that is reliant on an understanding of the underlying drivers of this issue (Government of Canada, 2016). Therefore, we sought to characterize the contributions of prescribed opioids to opioid-related hospitalizations in Canada and describe the geographic variation in these trends across the country.

2. Methods

2.1. Setting

We conducted population-based cross-sectional studies of all individuals who were admitted for acute care to hospital for an opioid overdose between April 1, 2015, and March 31, 2016, in BC and Ontario; and between July 1, 2015, and March 31, 2016, in Manitoba (to ensure complete prescription drug records over the accrual period). In a secondary analysis, we explored trends over time beginning April 1, 2013, in BC and Ontario, where earlier data were available. The study protocol was approved by the research ethics board of Sunnybrook Health Sciences Centre, Toronto, Ontario and is reported in accordance with the STROBE guidelines.

2.2. Data sources

We used the Canadian Institute for Health Information's (CIHI's) National Prescription Drug Utilization Information System (NPDUIS) and the Ontario Narcotics Monitoring System (NMS) to identify all prescriptions for opioids and benzodiazepines dispensed from community pharmacies over the study period. This captures all drugs dispensed in the community, except for medications that are dispensed and used while an inpatient in a hospital setting. All provinces studied require that individuals provide a form of identification (generally a provincial health insurance card) at the time of their prescription being dispensed, which can be used to link individual-level prescription history to health services utilization. We linked these prescription databases to the CIHI Discharge Abstract Database, which contains details on all diagnoses and procedures occurring during inpatient hospitalizations in each province of interest. All Ontario datasets were linked using unique, encoded health card numbers, and were analyzed at the Institute for Clinical Evaluative Sciences (ICES, www.ices.on.ca). The datasets from Manitoba and BC were linked similarly and were analyzed at CIHI.

2.3. Identification of patients

We identified all individuals of any age who were admitted to an acute hospital in Ontario, BC, or Manitoba for an opioid overdose. Opioid overdoses were defined as an inpatient stay with a preadmission International Classification of Diseases, 10th revision (ICD-10) diagnosis code of T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6. We excluded people with "suspected" diagnoses, as well as those who had invalid patient identifiers, for whom it would be impossible to link to opioid prescription records. We defined the index date as the date of hospital admission. For people with multiple admissions over our study period, we selected the first such admission for this analysis.

2.4. Opioid exposure definition

We defined prescription opioid exposure at the time of overdose using three complementary approaches. The primary analysis considered "active" opioid prescriptions as those with a prescription duration (days' supply) overlapping the index date. In secondary analyses, we defined recent opioid prescriptions as those dispensed in the i) 30 days and ii) 180-days prior to and including index date.

In our primary analysis among people with an active opioid prescription at index date, we determine the type of opioid dispensed, and the number of days between the last opioid dispensing and the hospital admission date. Finally, because concomitant benzodiazepine use is a well-established risk factor for opioid overdose (Park et al., 2015), we identified active benzodiazepine prescriptions as those with days' supply overlapping the index date and reported the prevalence of individuals with co-prescription of opioids and benzodiazepines on the index date.

2.5. Secondary analysis

In a secondary analysis, we replicated our primary analysis in each of the previous two fiscal years (i.e., April 2013 to March 2014, and April 2014 to March 2015) in Ontario and BC to explore changes in the contribution of prescribed opioids to opioid-related hospitalizations over time. Manitoba was not included in this analysis as prescription data for the entire province was not available prior to April 2015.

2.6. Statistical analysis

We calculated rates of opioid-related hospitalizations (per 100,000 population) in fiscal year 2015/16 using provincial population estimates from Statistics Canada for the year 2015. (Statistics Canada, 2018) We summarized patient demographic characteristics (including age, sex, neighborhood household income quintile (1 = lowest income quintile; 5 = highest income quintile) and urban location of residence) using descriptive statistics in each study province. People with missing data were categorized separately. In our primary analysis, we reported the prevalence of active prescriptions prior to opioid-related hospitalization in each province, overall, and stratified by age group (0–24, 25–34, 35–44, 45–64, 65+), sex, the intention of overdose, income quintile, and location of residence (urban vs. rural). Intention of overdose was determined using the following ICD-10 diagnosis codes recorded in the Discharge Abstract Database: accidental (X42), intentional (X62), and undetermined or unknown. In a secondary analysis, we reported the prevalence of recent opioid prescriptions and active concomitant opioid and benzodiazepine prescriptions prior to and including the index date, by province. We used chi-square statistics to characterize pairwise differences in these proportions between Ontario and the other two provinces and to compare the proportion of persons who had active opioid prescriptions between categories in the stratified analyses. In our secondary analysis, we used the Cochran-Armitage test to identify any trends in prevalence over time.

All analyses used a type 1 error rate of 0.05 as the threshold for statistical significance and were performed using SAS statistical software (version 9.4; SAS Institute Inc., Cary, North Carolina).

3. Results

In fiscal year 2015/16, we identified a total of 2599 inpatient hospitalizations related to an opioid overdose, of which 37.9% (N = 985; annual rate 21.0 per 100,000 population) occurred in BC, 58.6% (N = 1524; annual rate 11.1 per 100,000 population) occurred in Ontario, and 3.5% (N = 90; 6.9 per 100,000 population) occurred in Manitoba. The annualized rate in Manitoba rose to 9.2 per 100,000 population after adjusting for the shorter (9-months) study period. On average, subjects were 47.5 years of age at the time of hospitalization, and 51.5% were male. Demographic characteristics differed by province, with those hospitalized in Ontario tending to be older (mean age 49.4 vs. 44.7 and 45.7 in BC and Manitoba, respectively) while those in Manitoba were more likely to be female (57.8% vs. 51.6% and 42.8% in Ontario and BC, respectively) (Table 1). In general, opioid-related hospitalizations were concentrated among lower-income individuals and those residing in urban locations in all provinces studied.

Table 1
Demographic characteristics of individuals admitted to hospital for opioid toxicity. Fiscal year 2015.

Characteristic	British Columbia N = 985	Manitoba* N = 90	Ontario N = 1524
Age, mean (SD) years	44.7 (18.1)	45.7 (17.8)	49.4 (19.0)
Age group (N, %) in years			
0-24	147 (14.9%)	13 (14.4%)	172 (11.3%)
25-34	194 (19.7%)	14 (15.6%)	211 (13.8%)
35-44	162 (16.5%)	13 (14.4%)	198 (13.0%)
45-64	332 (33.7%)	36 (40.0%)	611 (40.1%)
65+	150 (15.2%)	14 (15.6%)	332 (21.8%)
Sex (N, %)			
Female	422 (42.8%)	52 (57.8%)	787 (51.6%)
Male	563 (57.2%)	38 (42.2%)	737 (48.4%)
Neighborhood income quintile			
1 (lowest)	234 (23.8%)	53 (58.9%)	515 (33.8%)
2	226 (22.9%)	14 (15.6%)	358 (23.5%)
3	166 (16.9%)	7 (7.8%)	242 (15.9%)
4	170 (17.3%)	8 (8.9%)	219 (14.4%)
5 (highest)	106 (10.8%)	7 (7.8%)	172 (11.3%)
Missing	83 (8.4%)	1 (1.1%)	18 (1.2%)
Location of residence			
Rural	126 (12.8%)	35 (38.9%)	209 (13.7%)
Urban	789 (80.1%)	54 (60.0%)	1314 (86.2%)
Missing	70 (7.1%)	1 (1.1%)	1 (0.1%)

Abbreviations: SD, Standard Deviation.
* Manitoba data only includes hospitalizations between July 1 2015 to March 31 2016 to allow for sufficient lookback for past prescription records.

Table 2
Recent Opioid Prescribing and Concomitant Benzodiazepine Prescribing among Opioid-Related Hospitalizations. Fiscal Year 2015.

Exposure Definition	British Columbia N = 985	Manitoba‡ N = 90	Ontario N = 1524
Active Opioid Prescription	336 (34.1%) *	47 (52.2%)	804 (52.8%)
Recent Opioid Prescription:			
30 days	409 (41.5%) *	50 (55.6%)	926 (60.8%)
180 days	549 (55.7%) *	**	1112 (73.0%)
Both Opioid and Benzodiazepine Active Prescriptions	168 (17.1%) *	32 (35.6%) *	395 (25.9%)

* Denotes statistically significant difference ($p < 0.05$) in comparison with Ontario.
‡ Manitoba data only includes hospitalizations between July 1 2015 to March 31 2016 to allow for enough lookback for past prescription records.
** Due to limitations in lookback data in Manitoba, statistic cannot be calculated.

Overall, the prevalence of active opioid prescribing prior to an opioid-related hospitalization was high in all provinces studied but was much lower in BC (34.1%) compared to both Manitoba (52.2%) and Ontario (52.8%) ($p < 0.05$; Table 2). Among those with an active opioid prescription, the median time between the last opioid dispensing and overdose was 3 days in both BC and Manitoba (interquartile range IQR 1 to 7 and 1 to 10, respectively), and 4 days (IQR 1 to 12 days) in Ontario. The most commonly prescribed opioids were hydromorphone, codeine, oxycodone, and methadone, but the relative contribution of these drugs varied slightly by province (Table 3). In our secondary analysis describing the prevalence of co-prescribed opioids and benzodiazepines, we found considerable inter-provincial variation, ranging from 35.6% in Manitoba to 17.1% in BC (Table 2). Finally, when considering any opioid prescription dispensed in the prior 30 days or 180 days, we found a high degree of previous opioid prescribing in all provinces. In BC, 55.7% of people hospitalized for opioid toxicity received a prescription opioid in the preceding 6 months, compared to 73.0% in Ontario ($p < 0.05$; Table 2).

Table 3
Type of prescribed active opioid dispensed prior to opioid-related hospitalization.

Type of opioid prescribed	British Columbia N = 336	Manitoba‡ N = 47	Ontario N = 804
Oxycodone	46 (13.7%)	10 (21.3%)	238 (29.6%)
Fentanyl	23 (6.9%)	< 5	86 (10.7%)
Hydromorphone	91 (27.1%)	11 (23.4%)	277 (34.5%)
Codeine	88 (26.2%)	20 (42.6%)	91 (11.3%)
Morphine	52 (15.5%)	5 (10.6%)	132 (16.4%)
Methadone	75 (22.3%)	< 5	125 (15.5%)
Buprenorphine/Naloxone	7 (2.1%)	0	15 (1.9%)
Tramadol	12 (3.6%)	< 5	20 (2.5%)
Cough	< 5	0	7 (0.9%)
Other	5 (1.5%)	0	10 (1.2%)

Drug types are not mutually exclusive as people may have multiple active opioid prescriptions at time of overdose.
‡ Manitoba data only includes hospitalizations between July 1 2015 to March 31 2016 to allow for enough lookback for past prescription records.

We observed some notable differences in patterns of active opioid prescribing in our stratified analyses. In both Manitoba and Ontario, accidental overdoses were more likely to have an active opioid prescription compared to intentional overdoses (62.9% vs. 35.3% [$p = 0.04$] in Manitoba and 60.5% vs. 39.4% [$p < 0.001$] in Ontario), however, there were no similar differences observed in BC (Table 4). There were also significant differences in prescription opioid involvement by age, with older age generally being associated with a higher likelihood of active prescription opioids at time of overdose ($p < 0.001$ in Ontario and BC). For example, in Ontario, only 9.9% of people aged ≤24 who was hospitalized for an opioid overdose had an active opioid prescription, as compared with 73.2% of those aged 65 or older (Table 4). Finally, we observed differences in prescription opioid involvement by sex and province. In BC and Ontario, the prevalence of active opioid prescriptions was significantly higher among women compared to men (41.7% vs. 28.4% in BC and 57.2% vs. 48.0% in Ontario; $p < 0.001$). In contrast, in Manitoba, there were no significant differences in active prescription opioid involvement by sex ($p = 0.36$).

Finally, in our secondary analysis of trends over time, we found a significant trend towards fewer active opioid prescriptions at the time of opioid-related hospitalizations in BC (reduction from 44.4% in FY2013/14 to 34.1% in FY2015/16; $p < 0.001$). In contrast, no such trend was evident in Ontario (prevalence 54.2% in FY2013/14, 52.8% in FY2015/16; $p = 0.22$) (Table 5).

4. Discussion

In this population-based study involving 3 provinces collectively representing more than half of the Canadian population, we found considerable differences in the contribution of prescribed opioids to opioid-related hospitalizations. In particular, only one-third of people hospitalized for an opioid overdose in BC had an active opioid prescription at the time of hospitalization compared to slightly more than half of those hospitalized in Manitoba and Ontario. Despite these differences, similar trends were observed in the age-stratified analyses, with younger individuals consistently much less likely to have an active opioid prescription at the time of overdose compared to older adults.

Our findings align with geographic patterns of illicitly produced fentanyl across North America, which was initially concentrated in areas with high prevalence of white powder heroin (Fairbairn et al., 2017). Specifically, BC was the first province in Canada to report broad illicit fentanyl involvement in opioid-related deaths (British Columbia

Table 4
Prevalence of prescribed opioids prior to an opioid-related hospitalization in Ontario, British Columbia, and Manitoba, overall and stratified by intention of overdose, age, sex, location of residence, and income quintile. Fiscal Year 2015.

Characteristic		British Columbia		Manitoba[‡]		Ontario	
		N	Active opioid prescription	N	Active opioid prescription	N	Active opioid prescription
Intention of overdose	**Accidental**	**N = 505**	177 (35.1%)	**N = 35**	22 (62.9%)	**N = 742**	449 (60.5%)
	Intentional	**N = 327**	105 (32.1%)	**N = 34**	12 (35.3%)	**N = 442**	174 (39.4%)
	Other/ Unknown	**N = 153**	54 (35.3%)	**N = 21**	13 (61.9%)	**N = 340**	181 (53.2%)
	P-value	*0.65*		*0.04*		*< 0.001*	
Age	**0-24**	**N = 147**	10 (6.8%)	**N = 13**	0	**N = 172**	17 (9.9%)
	25-34	**N = 194**	31 (16.0%)	**N = 14**	< 5	**N = 211**	55 (26.1%)
	35-44	**N = 162**	37 (22.8%)	**N = 13**	5-10[*]	**N = 198**	80 (40.4%)
	45-64	**N = 332**	151 (45.5%)	**N = 36**	23 (63.9%)	**N = 611**	409 (66.9%)
	65 +	**N = 150**	107 (71.3%)	**N = 14**	13 (92.9%)	**N = 332**	243 (73.2%)
	P-value	*< 0.001*		–[**]		*< 0.001*	
Sex	**Female**	**N = 422**	176 (41.7%)	**N = 52**	25 (48.1%)	**N = 787**	450 (57.2%)
	Male	**N = 563**	160 (28.4%)	**N = 38**	22 (57.9%)	**N = 737**	354 (48.0%)
	P-value	*< 0.001*		*0.36*		*< 0.001*	
Location of Residence	**Urban**	**N = 789**	278 (35.2%)	**N = 54**	29 (53.7%)	**N = 1,307**	686 (52.5%)
	Rural	**N = 126**	50 (39.7%)	**N = 35**	18 (51.4%)	**N = 216**	118 (54.6%)
	P-value	*0.33*		*0.83*		*0.48*	
Income Quintile	**1 (lowest)**	**N = 234**	98 (41.9%)	**N = 53**	31 (58.5%)	**N = 499**	267 (53.5%)
	2	**N = 226**	81 (35.8%)	**N = 14**	9 (64.3%)	**N = 334**	184 (55.1%)
	3	**N = 166**	57 (34.3%)	**N = 7**	< 5	**N = 243**	127 (52.3%)
	4	**N = 170**	54 (31.8%)	**N = 8**	< 5	**N = 226**	126 (55.8%)
	5 (highest)	**N = 106**	32 (30.2%)	**N = 7**	< 5	**N = 201**	95 (47.3%)
	P-value	*0.16*		–[**]		*0.05*	

[‡] Manitoba data only includes hospitalizations between July 1, 2015 to March 31, 2016 to allow for enough lookback for past prescription records.
[*] In cases where only one record is suppressed (i.e. value from 1 through 4), the record with the next lowest value is suppressed as well, in order to avoid residual disclosure according to CIHI policies.
[**] P-value cannot be calculated due to suppressed cells.

Coroners Service, 2017a), which supports our finding of reduced prescribed opioid involvement in opioid-related hospitalizations in that province over time and compared to elsewhere in Canada. However, despite this high contribution of non-prescribed opioids to overdose rates in BC, more than half of the people included in our study received a prescription opioid in the six months preceding overdose. This is also evident in Ontario, where nearly three-quarters of people hospitalized for an opioid overdose had been prescribed an opioid in the past 6 months, while only half had an active prescription at the time of overdose. These trends highlight the continued role of prescription opioids in overdoses across the country and suggest that a considerable portion of the observed overdoses may be occurring among people who have recently transitioned from prescribed to illicitly-obtained opioids. This would align with emerging concerns that restrictions to prescribed opioids and physician decisions to abruptly discontinue opioids in their patients are driving people to the illicit market (Fogger and McGuinness, 2014; Smith, 2017), and suggests that future policies need to carefully consider the strong inter-relationship between the prescribed and illicit opioid markets across Canada.

Understanding the relative contributions of prescribed and illicit opioids to opioid overdose is a high priority for policy-makers and program managers who aim to develop appropriate clinical and policy responses to this issue. In our study, a large proportion of opioid overdoses requiring hospitalization involved a non-prescribed opioid, particularly among men, youth, and young adults. This aligns with research conducted in Canada and the U.S. demonstrating a higher prevalence of harm from illicit drug use and diversion among youth compared to adults. (Hall et al., 2008; Office of Research and Surveillance Controlled Substances and Tobacco Directorate, 2014) These findings suggest that the relative contribution of prescribed and non-prescribed opioids to opioid-related hospitalizations varies across demographic groups. This supports the need for tailored interventions that consider patient characteristics and contributors to problematic opioid use, including post-discharge continuity of care, access to addiction treatment, identification of harm reduction opportunities, and other community supports (Sharma et al., 2017).

Finally, we also observed significant geographic variation in the prevalence of benzodiazepine prescriptions prior to opioid overdose in our analysis. The lower prevalence of recent benzodiazepine prescriptions in BC is consistent with previously reported findings of low benzodiazepine involvement in illicit opioid-related deaths (Gladstone et al., 2016) and may, therefore, be reflective of the higher contribution of illicit opioids to overdoses in this province compared to Ontario and Manitoba. Overall, the high degree of recent benzodiazepine

Table 5
Prevalence of prescribed opioids prior to an opioid-related hospitalization in Ontario and British Columbia over time.

Exposure Definition	British Columbia				Ontario			
	FY2013/14 N = 796	FY2014/15 N = 808	FY2015/16 N = 985	P-value trend	FY2013/14 N = 1,445	FY2014/15 N = 1,449	FY2015/16 N = 1524	P-value trend
Active Opioid Prescription	353 (44.4%)	334 (41.3%)	336 (34.1%)	< .001	783 (54.2%)	762 (52.6%)	804 (52.8%)	0.22
Recent Opioid Prescription:								
30 days	402 (50.5%)	396 (49.0%)	409 (41.5%)	< .001	891 (61.7%)	864 (59.6%)	926 (60.8%)	0.31
180 days	524 (65.8%)	519 (64.2%)	549 (55.7%)	< .001	1075 (74.4%)	1037 (71.6%)	1112 (73.0%)	0.20
Both Opioid and Benzodiazepine Active Prescriptions	210 (26.4%)	183 (22.7%)	168 (17.1%)	< .001	386 (26.7%)	409 (28.2%)	395 (25.9%)	0.31

prescriptions in all provinces (36% in Manitoba, 26% in Ontario and 17% in BC) is concerning given the risks associated with this medication combination which are highlighted in clinical guidelines across North America (Busse et al., 2017; Dowell et al., 2016).

This study has several strengths including its use of linked population-based databases that allow us to identify all opioids dispensed and all opioid-related hospitalizations across three provinces in Canada. However, several limitations also merit discussion. First, prescription data from Manitoba was only available from April 2015 onwards and, therefore, we were unable to study trends in prescribed opioid prevalence over time, or prevalence of opioid prescribing in the 180 days prior to overdose. Second, we did not have access to the results of hospital laboratory tests performed during the index admission, so cannot confirm whether opioids prescribed at the time of overdose led to the toxicity event or whether additional opioids were also contributing factors. Third, complete emergency department data were not available for all the study provinces and, therefore, we were unable to explore the role of prescribed opioids in overdoses that are treated in the emergency department and did not lead to an inpatient hospital stay. Finally, linked, population-level hospital and prescribing data were not available at CIHI for other Canadian provinces and territories. Thus, while the generalizability of our findings to other jurisdictions is currently unknown, our study could be replicated in other provinces and territories in future.

5. Conclusions

As the opioid environment continues to evolve across North America, clinicians and government officials increasingly require information on the relative contributions of prescribed, diverted and illicitly manufactured opioids to tailor their policy response appropriately. While this study demonstrates the important ongoing contribution of prescribed opioids to overdoses across Canada, it also illuminates the growing role of non-prescribed opioids to this issue, and the important differences that exist both geographically and between demographic groups. It is essential that future policy responses to the current opioid crisis in Canada are multi-faceted to address the different drivers of overdose across diverse populations.

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Contributors

Wayne Khuu, Diana Craiovan, and Kathy Lee had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were responsible for study design, interpretation of findings critical revision of the article and final approval of the manuscript. Tara Gomes was responsible for drafting the article. Diana Martins, Wayne Khuu, Diana Craiovan and Kathy Lee were responsible for acquisition of data.

Conflicts of interest

Dr. Muhammad Mamdani has received honoraria from Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, and Bayer. Dr. David Juurlink reports being a volunteer member of Physicians for Responsible Opioid Prescribing and has received payment for expert testimony and lectures related to opioids. All other authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2018.06.028.

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