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Research article

Patterns, Changes, and Trends in Prescription Opioid Dispensing in Canada, 2005–2016

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Background: Levels of prescription opioid (PO) dispensing have been rising in Canada – also in global comparison – since the mid-2000s, and are co-occurring with extensive PO-related morbidity and mortality. Previous analyses have demonstrated correlations between PO dispensing and related harm levels, yet also distinct heterogeneous interprovincial PO-dispensing patterns, in regards to quantities and individual PO formulations. Several system-level interventions have been implemented recently (since 2012) to address high PO-use levels and related harms in Canada; the effects of these interventions on PO-dispensing levels remain largely unexamined.

Objectives: Our aim was to examine over-time patterns and trends of levels of PO dispensing quantitatively (in defined daily doses [DDDs]) for 'strong' and 'weak' opioids and qualitatively (by individual PO formulations) by province and Canada total, for the period of 2005–2016.

Methods: We examined annual PO-dispensing levels, by 'weak' and 'strong' POs (individual PO formulations, but excluding methadone), by province and for Canada total, from 2005–2016. Raw dispensing information for POs were obtained from IMSQuintiles CompuScript [new name: IQVIA], based on monthly retail dispensing data from a representative sample of community pharmacies covering about 80% of all dispensing episodes in Canada. These data were converted into annual dispensing values in DDDs (DDD/1,000 population/day), based on standard methodology, for the PO formulation groups of interest. Patterns and trends of 'strong' and 'weak' POs and individual PO formulations were examined descriptively, aided by segmented regression analyses to identify significant break-points in over-time trends. In addition, changes in 'strong'/'weak' PO dispensing ratios between 2005 and 2016 were examined.

Results: 'Weak' PO use remained largely stable across Canada over the study period. For 'strong' PO dispensing, half of the provinces featured consistent increases, while remaining provinces presented initial increases with subsequently reverting downward trends at divergent levels. Dispensing of individual 'strong' PO formulations varied interprovincially; specifically, substantial decreases for oxycodone co-occurred with increases in other 'strong' PO formulations. The dispensing ratios for 'strong'/'weak' POs increased significantly across jurisdictions between 2005 and 2016 ($P < .05$).

Limitations: Retail pharmacy-based data do not cover the total – but the large majority – of PO dispensing in Canada. There are limitations to DDD/1,000 population/day as a comparative measurement unit for PO dispensing. The causal contribution of interventions associated with changes in PO dispensing observed cannot be verified with the data available.

Conclusions: Heterogeneous trends for PO dispensing, driven mostly by variations in 'strong' PO use, continue to be observed provincially across Canada. Recent changes in PO dispensing are likely influenced by recent intervention efforts (e.g., PO de-scheduling, monitoring, guidelines) aiming to reduce PO-related harms, which, however, have shown limited impact on PO-dispensing levels to date.

Key words: Opioids, prescribing, dispensing, interventions, policy, population, monitoring, Canada

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The availability and use of prescription opioids (POs) receive widespread global attention for several distinct reasons: first, the medical availability of POs is largely limited to the world's wealthiest nations, with about 80% of the global population having inadequate or no access at all; second, PO-use levels have rapidly risen in most industrialized countries; and third, rising levels of PO availability have translated into expanded PO-related harm outcomes on population levels, such as: non-medical use, disorders and treatment seeking, and overdose mortality (1-6). Concretely, PO-related overdose mortality has dramatically risen in North America (i.e., the US and Canada) over the past decade, exceeding deaths from other common injuries and/or chronic diseases (7-9). In the US, the volume of opioid-related deaths has negatively impacted life-expectancy in select sub-populations (10,11).

Over the past decade, international comparisons of PO consumption levels consistently document the highest rates in North America; levels of PO use and associated harms (e.g., overdose mortality) have also been increasing in other wealthy nations but at lower rates (1,2,7,9,12-15). More fine-grained analyses have examined PO-use patterns intranationally, e.g., in lower-level jurisdictions, by prescriber source or for different PO formulations. While commonly descriptive, some analyses have assessed determinants of interjurisdictional differences or the effects of specific interventions targeting high levels of PO use (e.g., prescription monitoring programs [PMPs], prescribing standard enforcement, PO re-scheduling) at system levels (16-18). To selectively illustrate, over the period of 2000–2015, the prescription amounts of common PO types in the US have vastly changed over time and differed by state and prescriber source (19). Differential levels were also associated with various system determinants or interventions (e.g., prescription monitoring) (19-21). Similarly, changes in prescribing patterns of certain PO-formulations – specifically hydrocodone – have been observed subsequent to intensified scheduling controls; these, however, have commonly co-occurred with increases in dispensing of other 'strong' opioid formulations (22-24). Substantial increases in PO prescribing, particularly 'strong' POs, have occurred in different Commonwealth countries (e.g., Australia, England, and Scotland) post-2000 (13,25-29).

Canada has featured the world's second highest PO consumption levels over the past decade, accompanied by even steeper increases than the US (3,15). PO-related morbidity (e.g., hospitalizations, treatment seeking) and mortality (e.g., overdose fatalities) have substantially increased there, resulting in what has been described as 'epidemic' or even regional 'public health emergency' states (e.g., in British Columbia) (9,30-32). PO-dispensing patterns in Canada (e.g., 2005–2010) have substantially varied by PO formulation type and province. Additionally, PO-dispensing levels have correlated with population-level (e.g., mortality, morbidity) harm outcomes (6,33-35). Recently, various interventions to improve control of PO availability and related adverse outcomes have been implemented at different jurisdictional levels, such as descheduling select PO formulations (e.g., slow-release oxycodone) from provincial public formularies, implementing PMPs, and revising PO-prescribing guidelines (35-37). To date, data regarding the impact of these interventions suggest limited and mixed effects; longer-term impacts have not yet been systematically assessed.

PO-dispensing trends can be assessed with different measures. The simplest measure includes prescription counts, however, it does not account for formulation strength or amounts (17,38). Others include population-based rates in defined daily doses (DDDs) or morphine equivalents, both of which consider PO formulations' analgesic strength. While based on approximations with variable specificity, they allow for more standardized comparisons in use levels for different PO formulation groups (39-43).

In this context, the objective of this paper is to assess trends and patterns in PO use in Canada (specifically at the provincial level) for the time period of 2005–2016. This time period captures pre-existing PO-prescribing trends, as well as trends possibly affected by recent interventions aiming at PO consumption and related adverse consequences.

Methods

The present analyses are based on annual PO-dispensing data from retail pharmacies in Canada (here specifically: the 10 Canadian provinces) from January 2005 to December 2016. Raw data were obtained from the QuintilesIMS CompuScript retail prescription database, which monitors prescription-based transactions for branded and generic medications (44). About 80%, i.e., the large majority, of the total of POs in Canada are dispensed by way of retail pharmacies (other routes include hospital- or emergency care-based dispensing not captured by the present data) (33). The CompuScript panel is drawn from a representative and stratified base

sample of about 6,000 retail pharmacies (representing about two-thirds of the total of retail pharmacies) across Canada. This includes a continuously refreshed sub-sample which provides the pharmaceutical dispensing data to capture the large majority of all prescriptions at the national level (44,45). Following quality-control checks, QuintilesIMS projected the monthly sample data, based on patented geospatial projection methodology, to the universe of pharmacies by province; the sampling error is estimated to be mostly lower but not exceeding 5–10% in select circumstances. Given the sampling approach described, the degree of representativeness of data for the actual total of POs dispensed is considered high.

Annual aggregate PO dispensing data were provided in summary totals of both the number of PO prescriptions and the number of units dispensed by region (provinces), molecule (codeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone), product name (including 173 different products), form (solid, liquid, etc.), and product strength. Data for the different PO types dispensed were converted to DDDs per 1,000 population per day (DDD/1,000/day) values – the assumed average maintenance dose per day for a drug used for its main indication for an average adult – according to the World Health Organization's (WHO) Anatomical Therapeutic Chemical classification and DDD measurement methodology. This average is based on relevant information for each PO product dispensed in combination with relevant annual population statistics for the Canadian jurisdictions under study (39,46). Furthermore, based on the WHO's pain ladder, codeine formulations and its combination products were defined as 'weak' opioids, whereas hydrocodone, hydromorphone, oxycodone, fentanyl, meperidine, and morphine formulations were defined as 'strong' opioids for the purpose of combination analysis (47). By applying provincial population estimates (48), we computed the annual dispensing rates for both PO ('weak' and 'strong') categories, as well as each PO formulation, by province and for Canada total, in DDD/1,000/day values, for over-time and interjurisdictional comparison. Methadone formulations were excluded from the analyses since it is primarily used for addiction (i.e., opioid maintenance) and rarely for pain treatment, and thus its dispensing greatly varies between provinces and includes biases for comparison.

We conducted descriptive analyses for annual dispensing levels for different PO formulation categories, including low- and high-ranking values, by province and over-time (Figs. 1, 2). These examinations were complemented by segmented regression analyses, to

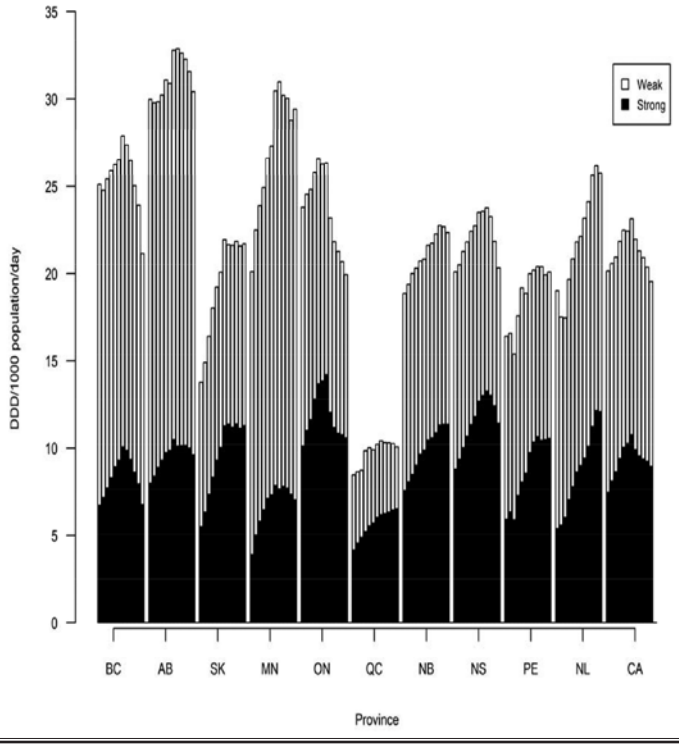

Fig. 1. *Annual dispensing rates of 'strong' and 'weak' POs (in DDD/1,000/day) by province and Canada total, 2005–2016.* Notes: Light bars represent 'weak' POs, and dark bars represent 'strong' POs. Bars are displayed for Canadian provinces west to east and chronologically for years 2005–2016. For full names and acronyms of provinces, see Table 1. CA represents Canada (total).

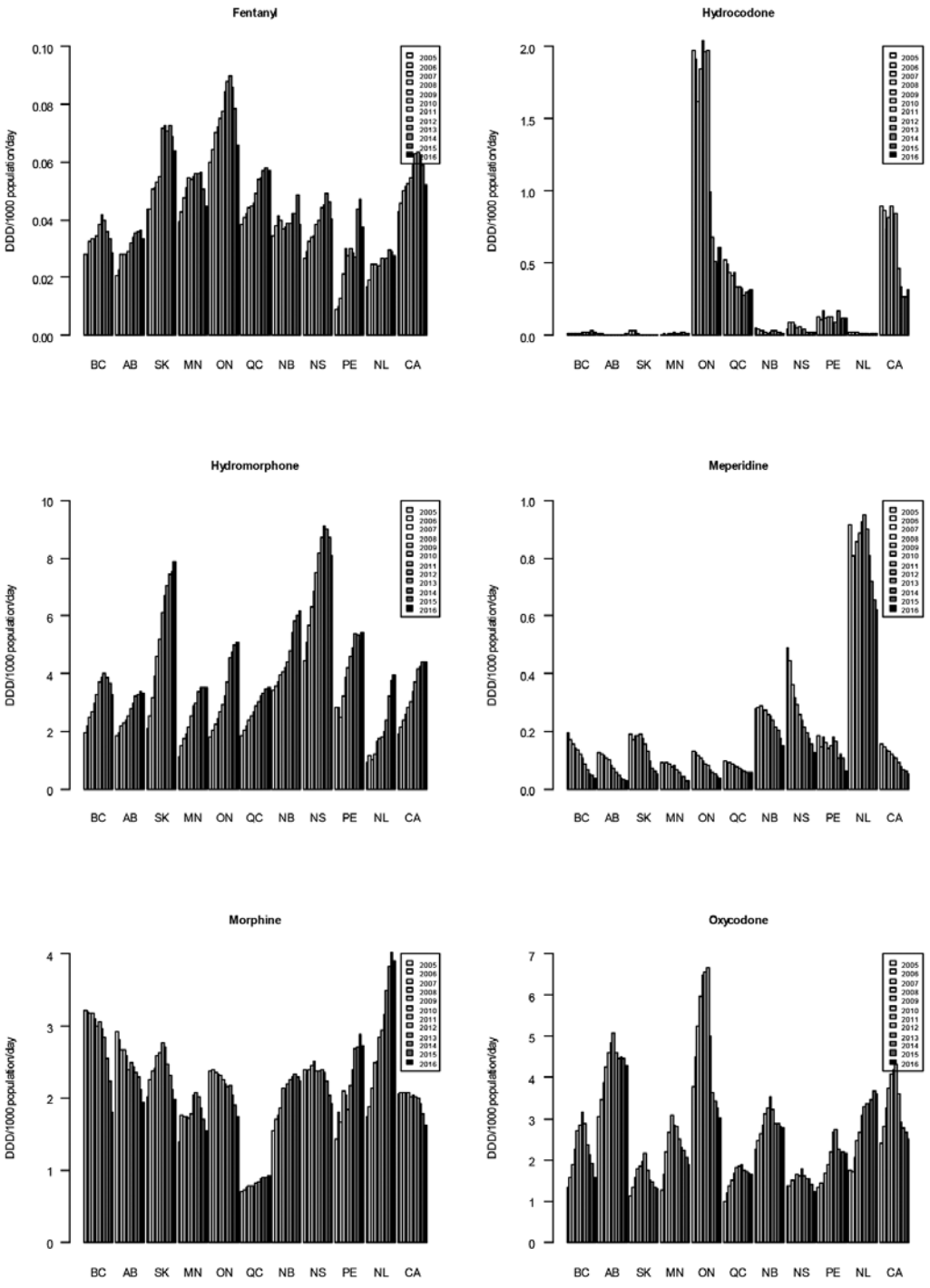

Fig. 2. *Annual dispensing rates (in DDD/1,000/day) of select 'strong' opioid formulations by province and Canada total, 2005–2016.*
Notes: Bars are displayed for Canadian provinces west to east and chronologically for years 2005–2016. For full names and acronyms of provinces, see Table 1. CA represents Canada (total).

specifically examine whether the individual dispensing trend-lines contained significant break-points, as opposed to simple linear model. Segmented regression analysis is an algorithm-based method that fits separate straight line segments to subsets of the sequential data-points (49). For this analysis, the R package segmented was used (50,51). In addition, we calculated and compared the annual ratios of the dispensing of 'strong'/'weak' POs by province from 2005 and 2016, respectively (Table 1). Changes in these ratios (10 pairs) were tested for significance by the McNemar exact test.

Ethical approval was not required for the present study, since only aggregate non-personalized medications dispensing data were included in the analyses.

Results

Over-time trends and interprovincial patterns for PO dispensing by 'weak' (codeine) and 'strong' PO formulations were examined over time (by year for the period 2005–2016), by province and Canada total.

For 'weak' opioids (codeine), all provinces except for 3 (SK, MN, NL; see Table 1 for a list of the provinces' names and corresponding acronyms) featured lower levels of dispensing in 2016 compared with 2005. Significant changes in dispensing trends (all decelerating) were identified by segmented analyses for 8 provinces. 'Weak' opioid dispensing was highest in AB (22.0 DDD/1,000/day) in 2005 and in MN (22.4 DDD/1,000/day) in 2016, while lowest in QC (4.3 and 3.6 DDD/1,000/day) at both times, reflecting a more than 5-fold difference between highest and lowest province, respectively (Fig. 1).

Each of the provinces (and Canada total) indicated higher rates of 'strong' PO dispensing in 2016 compared to 2005; 6 provinces (BC, AB, SK, MN, ON, NB) featured higher peak rates pre-2016. Segmented analyses detected a significant (decelerating) trend change in all provinces except one (NL). 'Strong' PO dispensing was highest in ON (10.1 DDD/1,000/day) in 2005 and in NL (12.1 DDD/1,000/day) in 2016; it was lowest in MN (3.9 DDD/1,000/day) in 2005 and QC (6.5 DDD/1,000/day) in 2016, indicating about a factor-2 difference between highest and lowest value.

The same trends and patterns were examined for individual 'strong' PO formulations (Fig. 2). For fentanyl products, all provinces indicated higher dispensing levels in 2005 compared with 2016, while indicating peak levels for dispensing pre-2016. Segmented analyses indicated a significantly decelerating trend in all except 2 provinces (NB and PE). Fentanyl dispensing was highest in ON (0.06 and 0.07 DDD/1,000/day) in both 2005 and 2016, and lowest in PE (0.01 DDD/1,000/day; 2005) and NL (0.03 DDD/1,000/day; 2016), with assimilating trends in differences.

Hydrocodone formulations were dispensed at substantially higher levels in 3 provinces (ON, QC, and PE) compared to others, with ON featuring disproportionally highest levels (2.0 DDD/1,000/day in 2005 and 0.6

Table 1. *Rates (in DDD/1,000/day) and changes in dispensing of 'strong' and 'weak' POs, and ratios, by province and Canada total, 2005 and 2016.*

Province	'Strong' Opioids (DDD/1,000/day)			'Weak' Opioids (DDD/1,000/day)			Ratios ('Strong'/'Weak' Opioids)		
	2005	2016	Change (%)	2005	2016	Change (%)	2005	2016	Change (%)
British Columbia (BC)	6.7	6.8	+1.5	18.4	14.4	-21.7	0.36	0.47	+30.6
Alberta (AB)	8.0	9.6	+20.0	22.0	20.8	-5.5	0.36	0.46	+27.8
Saskatchewan (SK)	5.5	11.3	+105.5	8.3	10.4	+25.3	0.66	1.09	+65.2
Manitoba (MN)	3.9	7.0	+79.4	16.2	22.4	+38.3	0.24	0.31	+29.2
Ontario (ON)	10.1	10.6	+5.0	13.7	9.4	-31.4	0.74	1.13	+52.7
Quebec (QC)	4.2	6.5	+54.8	4.3	3.6	-16.3	0.98	1.81	+84.7
New Brunswick (NB)	7.6	11.4	+50.0	11.3	11.0	-2.7	0.67	1.04	+55.2
Nova Scotia (NS)	8.8	11.4	+29.5	11.3	8.9	-21.2	0.78	1.28	+64.1
Prince Edward Island (PE)	5.9	10.6	+79.7	10.5	9.5	-9.5	0.56	1.12	+100.0
Newfoundland (NL)	5.4	12.1	+124.1	13.6	13.7	+0.7	0.40	0.88	+120.0
Canada (CA)	7.5	9.0	+20.0	12.7	10.6	-16.5	0.59	0.85	+44.1

DDD/1,000/day in 2016), yet also substantial declines throughout the examination period.

Hydromorphone formulation dispensing rates increased in each of the provinces for the observation period, with increases ranging from 73% (BC) to 433% (NL). Segmented analyses indicated significant trend changes – with all but 3 (ON, NB, NL) decelerating – in each of the provinces. Hydromorphone dispensing levels were lowest in NL (0.9 DDD/1,000/day) in 2005 and in AB (3.3 DDD/1,000/day) in 2016, and highest in NS (4.5 and 8.1 DDD/1,000/day, respectively) in both years.

Meperidine was dispensed at substantially higher levels in NL (0.92 DDD/1,000/day in 2005 and 0.62 DDD/1,000/day in 2016) and at lowest levels in MN (0.09 DDD/1,000/day in 2005 and 0.02 DDD/1,000/day in 2016). Each of the provinces indicated consistent downward trends in meperidine dispensing throughout the examination period.

Dispensing levels for morphine formulations increased in 5 provinces (MN, QC, NB, PE, NL) and decreased in the other 5 (BC, AB, SK, ON, NS) throughout the study period. Segmented analyses indicated a trend change (all but one [QC] decelerating), except in 2 provinces (NL and PE). Morphine dispensing was highest in BC (3.2 DDD/1,000/day; 2005) and NL (3.9 DDD/1,000/day; 2016) and lowest in QC (0.7 and 0.9 DDD/1,000/day; both years), indicating a difference of greater than magnitude of 3 in both years.

For oxycodone formulations, all but 2 provinces (ON and NS) featured higher dispensing levels in 2016 compared to 2005; each of the provinces featured respective peak levels in oxycodone dispensing pre-2016. A recent decelerating trend change was detected for each of the provinces. Oxycodone dispensing was highest in ON (3.8 DDD/1,000/day; 2005) and AB (4.3 DDD/1,000/day; 2016) and lowest in QC (1.0 DDD/1,000/day; 2005) and NS (1.2 DDD/1,000/day; 2016).

Between 2005 and 2016, the ratios of 'strong'/'weak' POs (in DDD/1,000/day) dispensed increased in each of the provinces, by rates between 27.8% (AB) and 120.0% (NL); this ratio had been < 1 in all provinces in 2005 but was > 1 in the majority (6) of provinces in 2016 (McNemar exact test $P = .0412$) (Table 1).

Discussion

Our study examined national and provincial patterns and trends in PO dispensing over-time in Canada, including 10 provinces, for the past decade. These examinations extend previous work in this area and provide fundamentally important data on PO dispensing in Canada, especially in light of recent interventions. Featuring the second highest PO-dispensing levels in the world, Canada also associates with a PO-related 'public health crisis' consisting of extensive adverse outcomes (i.e., morbidity and mortality) at the population level (9,15,30,33,35). The high levels of PO-dispensing have been identified as a crucial structural driver and determinant of these PO-related harm outcomes (6,33,52).

A few noteworthy changes, compared to previously described patterns and trends, were identified in regards to 'weak' PO (codeine) dispensing. Its patterns are largely stable intraprovincially – with a couple of provincial outliers featuring a notable increase and decrease, respectively – but also featuring substantial (e.g., > 4-fold) interprovincial differences between highest- and lowest-use provinces. These observations come in the context of Canada historically featuring among the highest codeine-use levels in the world, despite consistent questioning regarding the therapeutic efficacy and safety of codeine medications and their availability regulations (53,54).

Several primary observations come with regards to key developments related to the dispensing of 'strong' POs. First, our study observed an overall heterogeneous or inconsistent trend in dispensing patterns of 'strong' POs between the provinces. Here, about half the provinces featured consistent and substantial increases in 'strong' PO dispensing (e.g., more than doubling in NL), whereas the others indicated substantial increases in dispensing in the first half, yet, subsequent decreases in the second half of the study period (e.g., BC or ON, where dispensing levels in 2016 have reversed close to the 2005 levels). While these pattern developments continue to be rather heterogeneous – as also indicated in other data sources, e.g., provincial PO expenditure data – they also feature somewhat of an interprovincial 'assimilation' in 'strong' PO-dispensing trends over-time. In other words, the interprovincial ranges or differences in 'strong' PO-dispensing rates were substantially less variable in 2016 (i.e., less than a 2-fold difference) than they were in 2005 (15,33,55,56). Nevertheless, the interprovincial variations in PO dispensing within the same country continue to be stark and are not easily explained in terms of their causal drivers.

Key differences and changes concerning dispensing of 'strong' POs are furthermore observed for specific individual 'strong' PO-formulations. First, we observed extensive interprovincial differences in regards to select PO formulations (e.g., hydrocodone, meperidine, or morphine) by as high as factor-4 or greater in some

instances. These differences are not easily explained, but may include possible differences in provincial formularies (i.e., inconsistent listings of drugs eligible for reimbursement from public drug plans) or in medical practice or culture (which are difficult to empirically measure or compare) (57). However, the overall lowest PO-dispensing rates are consistently observed in Quebec, the only francophone (and much more Eurocentric) province in Canada, mirroring the generally lower PO-use levels relative to rates observed in North America (58-60). Secondly, substantial and largely interrelated changes in individual 'strong' PO-dispensing levels were observed. These included considerable decreases in oxycodone dispensing in most provinces, yet, simultaneous substantial increases in hydromorphone, fentanyl, and – to some extent – morphine formulations primarily in the second half of the study period (i.e., post-2011). These latter observations suggest a 'substitution effect,' where reductions in the dispensing of oxycodone occur in parallel with increases in the other 'strong' PO formulations. Similar effects have been observed in other jurisdictions, for example, including tightened scheduling and more restrictive controls implemented for hydrocodone formulations followed by shifts to other PO-prescribing in the US (22-24).

The described changes in specific PO-dispensing patterns ought to be viewed and understood in the wider context of key developments in PO-related harms and interventions in Canada, especially in the past 5 years. While there had been indications of substantial PO-related problems (e.g., non-medical use, increasing treatment demand, overdose deaths) in Canada pre-2010, these received little attention until about 2012 (61). In the wake of rising morbidity and mortality harms, select policy and other interventions have been implemented since 2012. These included the descheduling of slow-release oxycodone formulations (OxyContin, Purdue Pharma, Stamford, CT) – which until then was considered the PO formulation responsible for a lion's share of PO-related harms in Canada – from the public drug formularies of most provinces in 2012 (62-64). In addition, several provinces (e.g., ON) implemented PMPs, or intensified PMP data-based monitoring, of and interventions towards physicians with erratic PO prescribing (37,65). Recently, more restrictive PO prescribing guidelines have been introduced in North America and established as professional standards in select provinces (e.g., BC and NS) (66,67). In addition, capped high-dose prescribing of certain PO formulations (ON) were implemented and various provincial action plans regarding PO-related harms were launched (most of which however consisted of 'downstream measures,' i.e., expanded opioid disorder treatment, naloxone provision, overdose surveillance, etc.) (36). Furthermore, these measures occurred in the wider context of extensive media attention and coverage (e.g., investigative feature reports) and generally heightened popular awareness on high levels of PO prescribing and related harms (e.g., overdose mortality) in recent years (15,36).

Concretely, the descheduling of slow-release oxycodone formulations (2012) was followed by steep reductions in oxycodone-dispensing in the years following. However, these decreases were – partially – compensated by subsequent shifts to and increases in other 'strong' PO dispensing in most provinces, suggesting an at least partial 'substitution effect' (62,63). The consistent observation of substitution effects raises questions about the utility of such specific control interventions narrowly focusing on a single PO formulation and especially its benefit for reducing PO-related (e.g., overdose mortality) harms. Indeed, oxycodone-related deaths decreased, yet mortality related to other POs have strongly increased in many provinces (15). At the same time, overall reductions in 'strong' PO dispensing have been observed – some in the context of an overall bifurcated picture – in several provinces in the past 5 years, including some of those (e.g., BC, ON, and, to some degree, AB) where extensive policy measures and other interventions have been implemented yet extensive public health (especially overdose mortality) harms continue to be experienced (9,68,69).

The above details present themselves within the wider reality that Canada's overall 'strong' PO-dispensing levels, despite incremental recent declines, were substantially increased in 2016 compared to a decade earlier, and continue to be higher than in any country other than the US (where substantial decreases have been recorded in recent years) (1,3,33). Both recent and more restrictive North American evidence-based guidelines for opioid prescribing, as well as available scientific data, suggest that PO-dispensing levels in Canada continue to far exceed good clinical practice (67,70,71). On this basis, data suggest these excessive PO-use levels persist as primary drivers of high and many continuously increasing levels of key PO-related harms (e.g., non-medical use, various morbidity and treatment demand, and overdose mortality) (6,8,30,35,72-74). While some incremental reductions in 'strong' PO-use levels are noted and likely attributable to recently imple-

mented interventions, these policy measures – whether 'upstream' or 'downstream' – have not yet managed to broadly restrain PO-use levels nor to effectively reduce these adverse public health outcomes (36). Evidence-based adjustments of PO use and dispensing within the medical system are certainly among the main actions that have yet to decisively and successfully occur – e.g., by targeted action from governments and/other medial regulators – towards these ends in Canada.

References

1. Berterame S, Erthal J, Thomas J, Fellner S, Vosse B, Clare P, Hao W, Johnson DT, Mohar A, Pavadia J, Samak AK, Sipp W, Sumyai V, Suryawati S, Toufiq J, Yans R, Mattick RP. Use of and barriers to access to opioid analgesics: A worldwide, regional, and national study. *Lancet* 2016; 387:1644-1656.
2. Duthey B, Scholten W. Adequacy of opioid analgesic consumption at country, global, and regional levels in 2010, its relationship with development level, and changes compared with 2006. *J Pain Symptom Manage* 2014; 47:283-297.
3. International Narcotics Control Board (INCB). Availability of internationally controlled drugs: Ensuring adequate access for medical and scientific purposes. Vienna, Austria: International Narcotics Control Board (INCB); 2016. Available: www.incb.org/documents/Publications/AnnualReports/AR2015/English/Supplement-AR15_availability_English.pdf. Accessed: 09/30/2017.
4. Fischer B, Keates A, Bühringer G, Reimer J, Rehm J. Non-medical use of prescription opioids and prescription opioid-related harms: Why so markedly higher in North America compared to the rest of the world? *Addiction* 2014; 109:177-181.
5. Okie S. A flood of opioids, a rising tide of deaths. *N Engl J Med* 2010; 363:1981-1985.
6. Fischer B, Jones W, Rehm J. High correlations between levels of consumption and mortality related to strong prescription opioid analgesics in British Columbia and Ontario, 2005–2009. *Pharmacoepidemiol Drug Saf* 2013; 22:438-442.
7. Rudd RA, Aleshire N, Zibbell JE, Matthew Gladden R. Increases in drug and opioid overdose deaths — United States, 2000-2014. *MMWR* 2016; 64:1378-1382.
8. King NB, Fraser V, Boikos C, Richardson R, Harper S. Determinants of increased opioid-related mortality in the United States and Canada, 1990-2013: A systematic review. *Am J Public Health* 2014; 104:e32-e42.
9. Gomes T, Greaves S, Martins D, Bandola D, Tadrous M, Singh S. Latest trends in opioid-related deaths in Ontario: 1991 to 2015. Toronto, Canada: Ontario Drug Policy Research Network (ODPRN); 2017.
10. National Centre for Health Statistics. Health, United States, 2013: With special feature on prescription drugs. Maryland, USA: U.S. Department of Health and Human Services; 2014.
11. Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proc Natl Acad Sci USA* 2015; 112:78-83.
12. International Narcotics Control Board (INCB). Report of the International Narcotics Control Board for 2016. New York, USA: International Narcotics Control Board (INCB); 2016. Available: www.incb.org/documents/Publications/AnnualReports/AR2016/English/AR2016_E_ebook.pdf. Accessed: 09/20/2017.
13. Blanch B, Pearson SA, Haber PS. An overview of the patterns of prescription opioid use, costs and related harms in Australia. *Br J Clin Pharmacol* 2014; 78:1159-1166.
14. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). European drug report 2016: Highlights. Lisbon, Portugal: European Monitoring Centre for Drugs and Drug Addiction (EMCDDA); 2016. Available: www.emcdda.europa.eu/publications/edr/trends-developments/2016_en. Accessed: 10/01/2017.
15. Murphy Y, Goldner EM, Fischer B. Prescription opioid use, harms and interventions in Canada: A review update of new developments and findings since 2010. *Pain Physician* 2015; 18:E605-E614.
16. Leong M, Murnion B, Haber P. Examination of opioid prescribing in Australia from 1992 to 2007. *Intern Med* 2009; 39:676-681.
17. Volkow ND, McLellan TA. Characteristics of opioid prescriptions in 2009. *JAMA* 2011; 305:1299-1301.
18. Kenan K, Mack K, Paulozzi L. Trends in prescriptions for oxycodone and other commonly used opioids in the United States, 2000-2010. *Open Med* 2012; 6:e41-e47.
19. Mack KA, Zhang K, Paulozzi L, Jones C. Prescription practices involving opioid analgesics among Americans with Medicaid, 2010. *J Health Care Poor Underserved* 2015; 26:182-198.
20. McDonald DC, Carlson K, Izrael D. Geographic variation in opioid prescribing in the US. *J Pain* 2012; 13:988-996.
21. Reifler LM, Droz D, Bailey JE, Schnoll SH, Fant R, Dart RC, Bucher Bartelson B. Do prescription monitoring programs impact state trends in opioid abuse/misuse? *Pain Med* 2012; 13:434-442.
22. Jones CM, Lurie PG, Throckmorton DC. Effect of US drug enforcement administration's rescheduling of hydrocodone combination analgesic products on opioid analgesic prescribing. *JAMA Intern Med* 2016; 176:399-402.
23. Pergolizzi JV, Breve F, Taylor R Jr, Zampogna G, LeQuang J. The aftermath of hydrocodone rescheduling: Intentional and unintended consequences. *Int J Anesth Res* 2017; 5:377-382.
24. Seago S, Hayek A, Pruszynski J, Newman MG. Change in prescription habits after federal rescheduling of hydrocodone combination products. *Proc (Bayl Univ Med Cent)* 2016; 29:268.
25. Ruscitto A, Smith BH, Guthrie B. Changes in opioid and other analgesic use 1995–2010: Repeated cross-sectional analysis of dispensed prescribing for a large geographical population in Scotland. *Eur J Pain* 2015; 19:59-66.
26. Hollingworth SA, Symons M, Khatun M, Loveday B, Ballantyne S, Hall WD, Najman JM. Prescribing databases can be used to monitor trends in opioid analgesic prescribing in Australia. *Aust N Z J Public Health* 2013; 37:132-138.
27. Islam MM, McRae IS, Mazumdar S, Taplin S, McKetin R. Prescription opioid analgesics for pain management in Australia: 20 years of dispensing. *Intern Med* 2016; 46:955-963.
28. Berecki-Gisolf J, Hassani-Mahmooei B, Clapperton A, McClure R. Prescrip-

tion opioid dispensing and prescription opioid poisoning: Population data from Victoria, Australia 2006 to 2013. *Aust N Z J Public Health* 2016. 41:85-91.

29. Zin CS, Chen LC, Knaggs RD. Changes in trends and pattern of strong opioid prescribing in primary care. *Eur J Pain* 2014; 18:1343-1351.
30. Canadian Institute for Health Information (CIHI). Hospitalizations and emergency department visits due to opioid poisoning in Canada. Ottawa, Canada: Canadian Institute for Health Information (CIHI); 2016. Available: https://secure.cihi.ca/free_products/Opioid%20Poisoning%20Report%20%20EN.pdf. Accessed: 10/10/2017.
31. BC Center for Disease Control (BCCDC). The BC public health opioid overdose emergency. Vancouver, Canada: BC Center for Disease Control (BCCDC); 2017. Available: www.bccdc.ca/resource-gallery/Documents/Educational%20Materials/Epid/Other/Public%20Surveillance%20Report_2017_03_17.pdf. Accessed: 10/10/2017.
32. Gomes T, Mamdani MM, Dhalla IA, Cornish S, Paterson JM, Juurlink DN. The burden of premature opioid-related mortality. *Addiction* 2014; 109:1482-1488.
33. Fischer B, Jones W, Krahn M, Rehm J. Differences and over-time changes in levels of prescription opioid analgesic dispensing from retail pharmacies in Canada, 2005–2010. *Pharmacoepidemiol Drug Saf* 2011; 20:1269-1277.
34. Gomes T, Juurlink D, Moineddin R, Gozdyra P, Dhalla I, Paterson M, Mamdani M. Geographical variation in opioid prescribing and opioid-related mortality in Ontario. *Healthc Q* 2011; 14:22-24.
35. Fischer B, Jones W, Rehm J. Trends and changes in prescription opioid analgesic dispensing in Canada 2005–2012: An update with a focus on recent interventions. *BMC Health Serv Res* 2014; 14:90.
36. Fischer B, Rehm J, Tyndall M. Effective Canadian policy to reduce harms from prescription opioids: Learning from past failures. *CMAJ* 2016; 188:1240-1244.
37. Gomes T, Juurlink D, Yao Z, Camacho X, Paterson JM, Singh S, Dhalla I, Sproule B, Mamdani M. Impact of legislation and a prescription monitoring program on the prevalence of potentially inappropriate prescriptions for monitored drugs in Ontario: A time series analysis. *CMAJ Open* 2014; 2:256-261.
38. Manchikanti L, Helm S 2nd, Fellows B, Janata JW, Pampati V, Grider JS, Boswell MV. Opioid epidemic in the United States. *Pain Physician* 2012; 15:ES9-ES38.
39. WHO Collaborating Centre for Drug Statistics Methodology. Definition and general considerations. Norwegian Institute of Public Health: World Health Organization (WHO); 2016. Available: www.whocc.no/ddd/definition_and_general_considera/. Accessed: 09/28/2017.
40. Rønning M, Blix HS, Harbø BT, Strøm H. Different versions of the anatomical therapeutic chemical classification system and the defined daily dose--are drug utilisation data comparable? *Eur J Clin Pharmacol* 2000; 56:723-727.
41. Pereira J, Lawlor P, Vigano A, Dorgan M, Bruera E. Equianalgesic dose ratios for opioids: A critical review and proposals for long-term dosing. *J Pain Symptom Manage* 2001; 22:672-687.
42. Michael G DeGroote National Pain Centre. Canadian guideline for safe and effective use of opioids for chronic noncancer pain appendix B-8: Opioid conversion and brand availability in Canada. National Pain Centre: Hamilton, Canada: McMaster University; 2017. Available: http://nationalpaincentre.mcmaster.ca/opioid/cgop_b_app_b08.html. Accessed: 10/19/2017.
43. Nielsen S, Gisev N, Bruno R, Hall W, Cohen M, Larance B, Campbell G, Shanahan M, Blyth F, Lintzeris N, Pearson S, Mattick R. Defined daily doses (DDD) do not accurately reflect opioid doses used in contemporary chronic pain treatment. *Pharmacoepidemiol Drug Saf* 2017; 26:587-591.
44. IMS Brogan (IMSB). IMSB Canadian Compuscript Audit. 2016. Available at: www.imsbrogancapabilities.com/.
45. Canadian Compuscript. Montreal, Canada: IMS Brogan. 2016. Available at: www.imsbrogancapabilities.com/en/market-insights/compuscript.html.
46. World Health Organization (WHO). ATC/DDD index. WHO Collaborating Centre for Drug Statistics Methodology: Norwegian Institute of Public Health; 2016. Available: www.whocc.no/atc_ddd_index/. Accessed: 10/20/2017.
47. World Health Organization (WHO). WHO's pain ladder. 2017. Available: www.who.int/cancer/palliative/painladder/en/. Accessed: 10/20/2017.
48. Statistics Canada. Table 051-0001 - Estimates of population, by age group and sex for July 1, Canada, provinces and territories; 2016. Available: www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo02a-eng.htm. Accessed: 10/21/2017.
49. Muggeo VM. Estimating regression models with unknown break-points. *Stat Med* 2003; 22:3055-3371.
50. Muggeo VM. Segmented: An R package to fit regression models with broken-line relationships. *R News* 2008; 8:20-25.
51. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2016.
52. Fischer B, Jones W, Urbanoski K, Skinner R, Rehm J. Correlations between prescription opioid analgesic dispensing levels and related mortality and morbidity in Ontario, Canada, 2005-2011. *Drug Alcohol Rev* 2014; 33:19-26.
53. MacDonald N, MacLeod SM. Has the time come to phase out codeine? *CMAJ* 2010; 182:1825.
54. Isaac P, Seto W, Lanctot KL. Use and abuse of prescription opioids in Canada 1978 to 1989. *Can J Clin Pharmacol* 1995; 2:81-86.
55. Morgan S, Smolina K, Mooney D, Raymond C, Bowen M, Gorczynski C, Basham KA. The Canadian Rx atlas. 3rd ed. UBC Centre for Health Services and Policy Research, Vancouver, 2013.
56. Gomes T, Paterson JM, Caetano P, Sketris I, Henry D. CNODES analysis: Safety of oral opioid use in Canada part 1: Changes in the dispensing of oral opioid drugs in Canadian provinces between 2008 and the end of 2013. Montreal, Canada: Canadian Network for Observational Drug Effect Studies (CNODES); 2015.
57. Demers V, Melo M, Jackevicius C, Cox J, Kalavrouziotis D, Rinfret S, Humphries KH, Johansen H, Tu JV, Pilote L. Comparison of provincial prescription drug plans and the impact on patients' annual drug expenditures. *CMAJ* 2008; 178:405-409.
58. Breivik H, Eisenberg E, O'Brien T; OPENMinds. The individual and societal burden of chronic pain in Europe: The case for strategic prioritisation and action to improve knowledge and availability of appropriate care. *BMC Public Health* 2013; 13:1229.
59. Cherny NI, Baselga J, de Conno F, Radbruch L. Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in Europe: A report from the ESMO/EAPC Opioid Policy Initiative. *Ann Oncol* 2010; 21:615-626.
60. van Amsterdam J, van den Brink W. The misuse of prescription opioids: A threat for Europe? *Curr Drug Abuse Rev* 2015;

8:3-14.

61. Fischer B, Argento E. Prescription opioid related misuse, harms, diversion and interventions in Canada: A review. *Pain Physician* 2012; 15:ES191-ES203.
62. Fischer B, Keates A. 'Opioid drought', Canadian-style? Potential implications of the 'natural experiment' of delisting oxycontin in Canada. *Int J Drug Policy* 2012; 23:495-497.
63. Fischer B, Vojtila L, Kurdyak P. Delisting' Oxycontin® to reduce prescription opioid related harms in Ontario (Canada) - gauging impacts five years later. *Pharmacoepidemiol Drug Saf* 2017; 26:1-4.
64. Dhalla IA, Mamdani MM, Sivilotti ML, Kopp A, Qureshi O, Juurlink DN. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *CMAJ* 2009; 181:891-896.
65. Furlan AD, MacDougall P, Pellerin D, Shaw K, Spitzig D, Wilson G, Wright J. Overview of four prescription monitoring/review programs in Canada. *Pain Res Manag* 2014; 19:102-106.
66. Furlan AD, Williamson OD. New Canadian guidance on opioid use for chronic pain: Necessary but not sufficient. *CMAJ* 2017; 189:E650-E651.
67. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain — United States, 2016. *MMWR* 2016; 65:1-49.
68. Health A. Opioids and substances of misuse: Alberta report, 2017 Q1. Edmonton, Canada: Alberta Health; 2017. Available: https://open.alberta.ca/dataset/1cfed7da-2690-42e7-97e9-da175d36f3d5/resource/9549f390-c78e-4794-8662-ca53e49b587e/download/Opioids-Substances-Misuse-Report-2017-Q1-Final.pdf. Accessed: 10/10/2017.
69. BC Coroners Service. Illicit drug overdose deaths in BC: January 1, 2017-April 30, 2017. Burnaby, Canada: Ministry of Public Safety & Solicitor General; 2017.
70. Busse J, Guyatt GH, Carrasco A, Akl E, Agoritsas T, da Costa B, et al. The 2017 Canadian guideline for opioids for chronic non-cancer pain. Hamilton, Canada: National Pain Centre, McMaster University; 2017.
71. Kaye AD, Jones MR, Kaye AM, Ripoll JG, Galan V, Beakley BD, Calixto F, Bolden JL, Urman RD, Manchikanti L. Prescription opioid abuse in chronic pain: An updated review of opioid abuse predictors and strategies to curb opioid abuse: Part 1. *Pain Physician* 2017; 20:S93-S109.
72. Government of Canada. National report: Apparent opioid-related deaths (2016). Ottawa, Canada: Government of Canada; 2017. Available: www.canada.ca/en/health-canada/services/substance-abuse/prescription-drug-abuse/opioids/national-report-apparent-opioid-related-deaths.html. Accessed: 10/10/2017.
73. Paulozzi LJ. Prescription drug overdoses: A review. *J Safety Res* 2012; 43:283-289.
74. Sauber-Schatz EK, Mack KA, Diekman ST, Paulozzi LJ. Associations between pain clinic density and distributions of opioid pain relievers, drug-related deaths, hospitalizations, emergency department visits, and neonatal abstinence syndrome in Florida. *Drug Alcohol Depend* 2013; 133:161-166.