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Research

Changes in the dispensing of opioid medications in Canada following the introduction of a tamper-deterrent formulation of long-acting oxycodone: a time series analysis

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Abstract

Background: In February 2012, a reformulated tamper-deterrent form of long-acting oxycodone, OxyNeo, was introduced in Canada. We investigated the impact of the introduction of OxyNeo on patterns of opioid prescribing.

Methods: We conducted population-based, cross-sectional analyses of opioid dispensing in Canada between 2008 and 2016. We estimated monthly community pharmacy dispensing of oral formulations of codeine, morphine, hydromorphone and oxycodone, and a transdermal formulation of fentanyl, and converted quantities to milligrams of morphine equivalents (MMEs) per 1000 population. We used time series analysis to evaluate the effect of the introduction of OxyNeo on these trends.

Results: National dispensing of long-acting opioids fell by 14.9% between February 2012 and April 2016, from 36 098 MMEs to 30 716 MMEs per 1000 population ($p < 0.01$). This effect varied across Canada and was largest in Ontario (reduction of 22.8%) ($p = 0.01$) and British Columbia (reduction of 30.0%) ($p = 0.01$). The national rate of oxycodone dispensing fell by 46.4% after the introduction of OxyNeo ($p < 0.001$); this was partially offset by an increase of 47.8% in hydromorphone dispensing ($p < 0.001$). Although dispensing of immediate-release opioids was a substantial contributor to overall population opioid exposure across Canada, it was unaffected by the introduction of OxyNeo ($p > 0.05$ in all provinces).

Interpretation: The findings suggest that the introduction of a tamper-deterrent formulation of long-acting oxycodone in Canada, against a background of changing public drug benefits, was associated with sustained changes in selection of long-acting opioids but only small changes in the quantity of long-acting opioids dispensed. This illustrates the limited effect a tamper-deterrent formulation and associated coverage policy can have when other, non–tamper-deterrent alternatives are readily available.

Although opioids have an important clinical role in the treatment of acute and chronic pain, the use of these products to treat chronic noncancer pain remains controversial, as their long-term use has been associated with substantial side effects, including abuse, addiction and premature death from accidental overdose.[1,2] Canada and the United States have historically high levels of prescription opioid consumption per capita,[3] with rates that are about double those observed in the European Union, Australia and New Zealand.[4] In Canada, prescription opioid consumption increased nearly fourfold between 1999 and 2010,[5] despite the fact that the proportion of Canadians who reported experiencing chronic pain did not change substantially over this period.[6] In Ontario, the rate of opioid prescribing rose by 29% between 1991 and 2007; the increase was largely driven by an 850% increase in prescribing of oxycodone.[7]

This rising prevalence of oxycodone prescribing in Ontario has been attributed to the addition of long-acting oxycodone (OxyContin) to the provincial drug benefit formulary in 2000, raising serious concerns regarding its potential misuse and abuse.[7] The ability to circumvent the long-acting properties of the oxycodone tablet by chewing

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or grinding the pills for inhalation or injection has been widely cited as a contributing factor to rising rates of opioid addiction and overdose across North America.[8,9] In February 2012, the manufacturer of OxyContin discontinued its production and replaced it with a new formulation, OxyNeo, in an attempt to address concerns related to the misuse of their controlled-release oxycodone product. Specifically, OxyNeo tablets were hardened to make them more difficult to misuse (i.e., crush, chew), and, when dissolved, these tablets form a gel that is difficult to inject.[10] In the US, Purdue Pharma similarly reformulated OxyContin 2 years earlier. The response of the Canadian public drug insurance plans to the new formulation varied, with provinces such as Alberta granting OxyNeo the same full benefit status afforded to OxyContin, while others severely restricted access because of concerns regarding the historically high rates of oxycodone misuse.[11] Given that OxyNeo was the first opioid with tamper-deterrent properties in Canada, and because opioid-prescribing practices vary widely across Canada,[12] we performed a study to explore the impact of the introduction of OxyNeo against a background of changing provincial drug insurance plan formulary changes on the quantity of opioids prescribed across the country.

Methods

Setting and design

We conducted a population-based, repeated cross-sectional analysis of prescribing of long-acting opioids across Canada between May 1, 2008, and Apr. 30, 2016. We studied dispensing of oral formulations of codeine, morphine, hydromorphone and oxycodone, and a transdermal formulation of fentanyl (Table 1). Propoxyphene and meperidine were excluded given their limited prescribing during the study period, and methadone and buprenorphine were excluded as they are used primarily to treat opioid use disorder in Canada.

Sources of data

We used the QuintilesIMS CompuScript database to identify monthly quantities of retail pharmacy prescriptions for all eligible opioid analgesics dispensed during the study period. This database captures data from a representative sample of about 6000 community pharmacies and projects prescription quantities dispensed at the national and provincial level. These projections incorporate information about the number of pharmacies in each region, the distance between participating pharmacies and the size of the pharmacies. These data are continuously monitored and verified by QuintilesIMS to ensure that they are within the standards set for quality control, are representative at both the provincial and national level and are regularly used for research purposes.[12,13] Specifically, at the national level, over 79% of prescriptions dispensed are captured by this panel of pharmacies, with a sampling error rate of about 3% (QuintilesIMS). The sampling error for monthly estimates at the provincial level can reach higher levels, although it generally does not exceed 5%–10%.

Outcomes

We calculated the total quantity of opioid dispensed each month by multiplying the units by the formulation strength and expressed the quantity in milligrams of morphine equivalents (MMEs) using conversion ratios reported by the National Opioid Use Guideline Group.[14] With fentanyl patches, conversion into estimates of MMEs can be difficult given that the patches are meant to be used over 3 days but are sometimes used for shorter periods. In this study, we assumed that all patches were used for 3 days, accepting that this may overestimate MME exposure in some people. Our primary measures of interest were the rate of dispensing of long-acting opioids by province and the national rate of dispensing of long-acting opioids stratified by opioid type. In a secondary analysis, we analyzed trends in dispensing of immediate-release opioids by province and prescribing of long-acting opioids by opioid type for each province sepa-

Table 1: Characteristics of opioid formulations included in the study

		Long-acting opioid formulations		Short-acting opioid formulations	
Drug	Morphine conversion factor	Formulation	Unit dosage range	Formulation	Unit dosage range
Oxycodone	1.71	Oral	5–80 mg	Oral	2.5–20 mg
Hydromorphone	4.5	Oral	3–32 mg	Oral	1–8 mg
Morphine	1	Oral	10–200 mg	Oral	1–60 mg
Fentanyl	12 µg/h: 52	Transdermal	12–100 µg/h	–	–
	25 µg/h: 97				
	37 µg/h: 157				
	50 µg/h: 202				
	75 µg/h: 292				
	100 µg/h: 382				
Codeine	0.15	Oral	50–200 mg	Oral	5–60 mg

rately. We report dispensing rates as MMEs dispensed per 1000 population, using Statistics Canada census population estimates[15] as the denominator.

We compared patterns of dispensing of long-acting opioids in the first (May to October 2008) and last (November 2015 to April 2016) 6-month periods of the study by province to establish any changes that occurred over the study period. Measures captured at each observation point included opioid prescription rate, average number of opioid units dispensed per prescription and opioid quantity (in MMEs) dispensed per prescription. We calculated ratios (last 6 months/initial 6 months) of the prescription rate and quantities dispensed as measures of variance over time.

Statistical analysis

We used time series analysis to characterize the impact of the introduction of OxyNeo to the provincial drug insurance plan formularies on the rate of dispensing of long-acting and immediate-release opioids in Canada using a ramp function in interventional autoregressive integrated moving average models.[16,17] All models were fitted with the use of data from the beginning of the study period to April 2013. We excluded data after this time point to avoid modelling more remote shifts in prescribing. We examined model fit using white noise probabilities, autocorrelation functions and the Ljung–Box test (see Appendix 1, available at www.cmajopen.ca/content/5/4/E800/suppl/DC1, for fit of specific models). All analyses used a type 1 error rate of 0.05 as the threshold for statistical significance and were carried out with the use of SAS statistical software version 9.3 (SAS Institute).

Results

Over the 8-year study period, 1 739 057 621 long-acting opioid tablets and transdermal patches were dispensed in Canada. The quantity dispensed differed by opioid type, with oxycodone tablets accounting for 726 477 071 (41.8%) of all units dispensed, hydromorphone for 443 604 461 units (25.5%), morphine for 408 648 392 units (23.5%), codeine for 99 856 627 units (5.7%) and fentanyl patches for 60 471 070 units (3.5%). In addition, 7 350 703 901 immediate-release opioid tablets were dispensed.

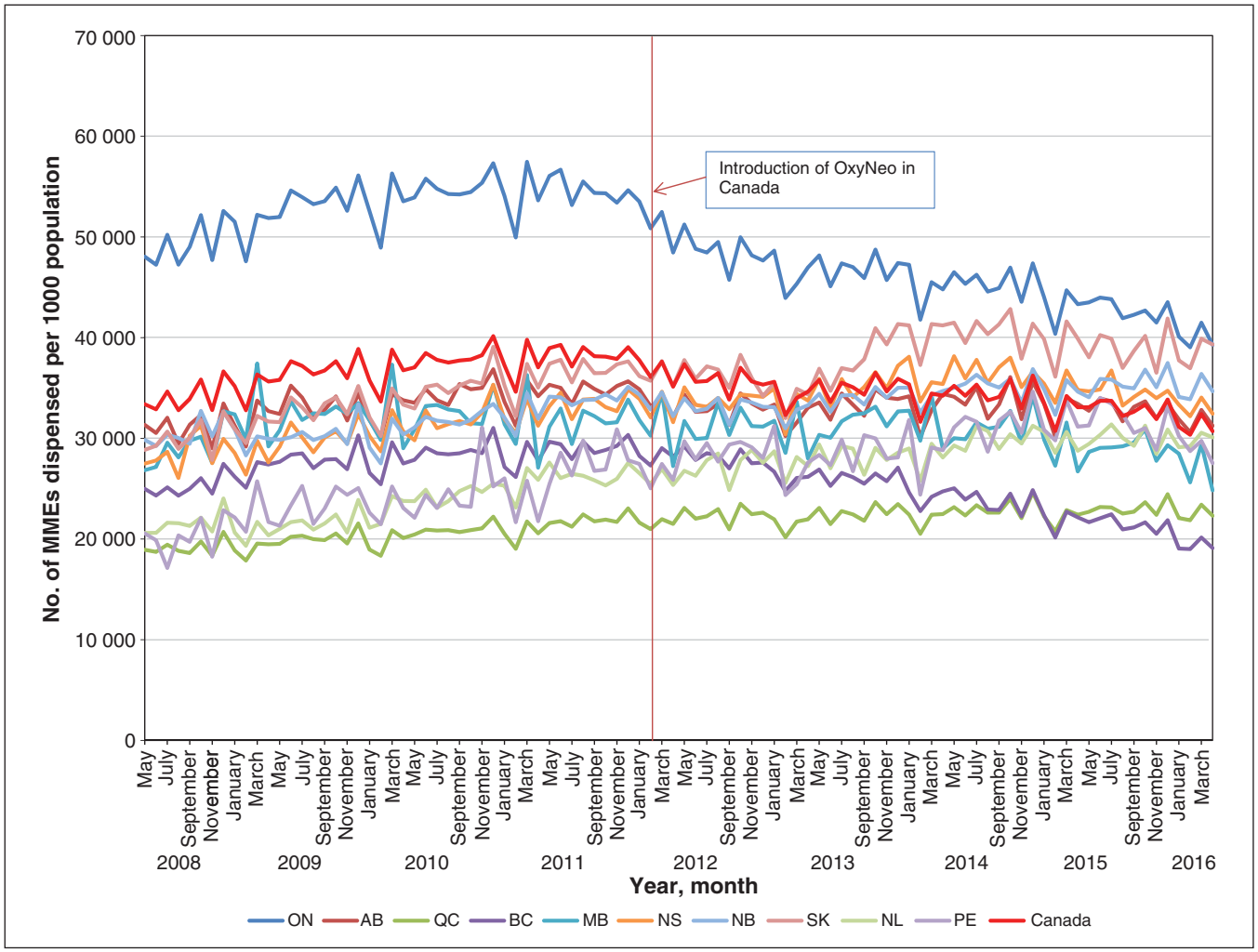

Figure 1: Rate of dispensing of long-acting opioids (in milligrams of morphine equivalents [MMEs] per 1000 population) in Canada, May 2008–April 2016, by province.

Overall use varied substantially by province (Figure 1). Ontario exhibited the highest levels of opioid dispensing throughout the study period, and Quebec consistently had the lowest levels. The monthly quantity of long-acting opioid dispensed fell by 14.9% between February 2012 (introduction of OxyNeo) and April 2016, from 36 098 MMEs per 1000 population to 30 716 MMEs per 1000 population ($p < 0.01$). However, this impact varied across Canada. In Ontario and British Columbia, there were significant reductions in the overall quantity of long-acting opioids dispensed between February 2012 and April 2016, with rates falling by 22.8% (from 50 865 to 39 288 MMEs per 1000 population) ($p = 0.01$) and 30.0% (from 27 306 to 19 107 MMEs per 1000 population) ($p = 0.01$), respectively. There were also significant changes in the rate of prescribing of long-acting opioids in Saskatchewan ($p = 0.01$), Quebec ($p < 0.01$) and New Brunswick ($p = 0.05$); however, these latter impacts were small, and overall rates of use of long-acting opioids continued to rise in those provinces over the study period. In contrast, there were no significant changes in rates of dispensing of immediate-release formulations after OxyNeo was introduced ($p > 0.05$ in all models) (Figure 2), with rates climbing in most provinces. Although the rate of dispensing of immediate-release opioids declined over time in Nova Scotia and BC, the introduction of OxyNeo did not appear to be driving these changes ($p = 0.4$ and 0.8, respectively).

Changes in the quantity of long-acting opioids dispensed varied considerably by opioid type. The national rate of oxycodone prescribing fell by 46.4% after the introduction of OxyNeo, from 14 140 MMEs per 1000 in February 2012 to 7585 MMEs per 1000 at the end of the study period ($p < 0.001$) (Figure 3). In contrast, the rate of hydromorphone dispensing increased by 47.8%, from 4890 MMEs to 7227 MMEs per 1000 population over this same period ($p < 0.001$), which indicates a likely partial substitution for oxycodone. We observed no significant changes in the dispensed quantities of long-acting morphine ($p = 0.1$), codeine ($p = 0.7$) or fentanyl ($p = 0.7$). By the last month of the study period, fentanyl made the largest single contribution to overall community exposure to long-acting opioids (37.5% [11 510 MMEs per 1000 population]), followed by oxycodone (24.7% [7585 MMEs per 1000 population]), hydromorphone (23.5% [7227 MMEs per 1000 population]), morphine

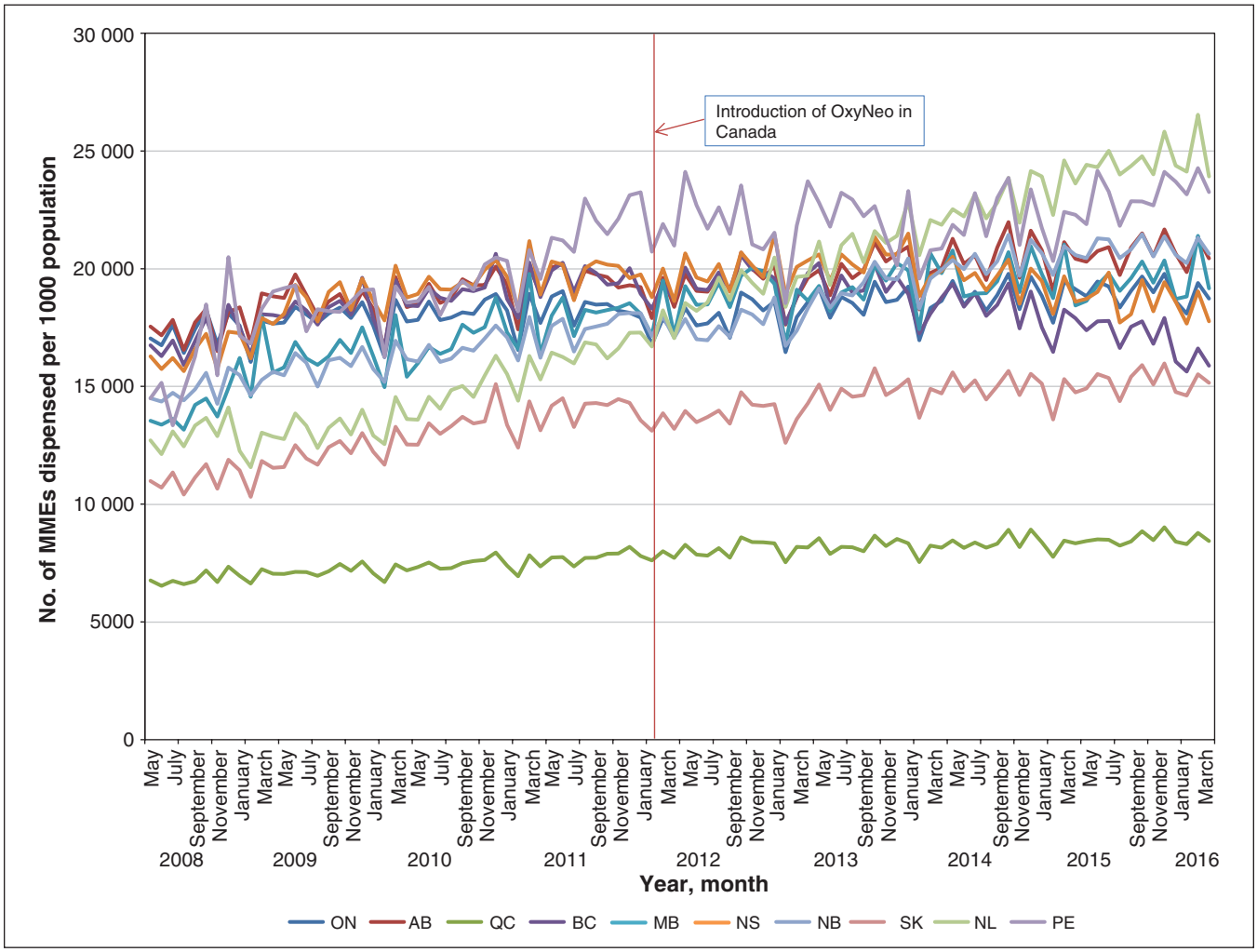

Figure 2: Rate of dispensing of immediate-release opioid dispensing (in milligrams of morphine equivalents [MMEs] per 1000 population) in Canada, May 2008–April 2016, by province.

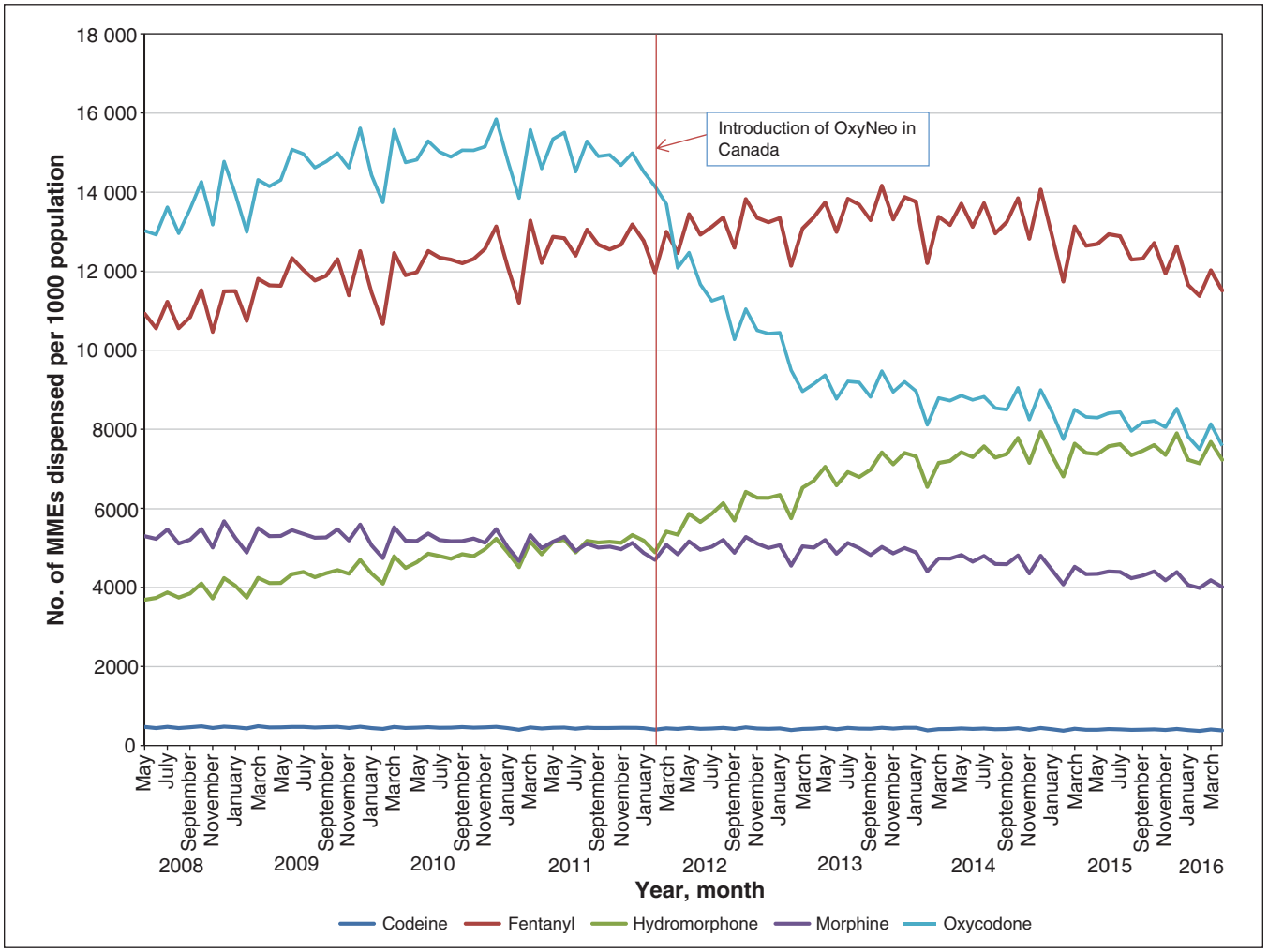

Figure 3: Rate of dispensing of long-acting opioids (in milligrams of morphine equivalents [MMEs] per 1000 population) in Canada, May 2008–April 2016, by opioid type.

(13.0% [4011 MMEs per 1000 population]) and codeine (1.2% [383 MMEs per 1000 population]).

In the first 6 months of the study period, the number of units and the quantity of opioid dispensed per prescription varied considerably between provinces (Table 2). In Quebec, the average number of units dispensed per prescription was 32, with each prescription having 2153 MMEs on average. In contrast, in all the other provinces, the average number of opioid units dispensed per prescription ranged from 53 (BC) to 74 (Nova Scotia), and the average opioid quantity per prescription varied from 3162 MMEs (BC) to 4508 MMEs (Ontario). Although the rate of prescribing of long-acting opioids (prescriptions per 1000 population) increased over the study period, the number of units and total quantity (in MMEs) dispensed per prescription declined. The largest changes in prescription quantity were observed in Quebec, Ontario, BC and Nova Scotia, where the opioid quantity dispensed per prescription fell by 43.9% (Nova Scotia) to 47.5% (Quebec). In the last 6 months of the study period, Quebec continued to exhibit the lowest quantity of opioids dispensed per prescription (25 units per prescription; 1131 MMEs per prescription).

Before the introduction of OxyNeo, OxyContin accounted for the highest levels of population exposure to long-acting opioids in all provinces except for Saskatchewan, Manitoba and Quebec, where fentanyl dominated, and Nova Scotia, where hydromorphone dominated (Appendix 1). In provinces where OxyContin accounted for the greatest opioid exposure, there was a reduction in oxycodone quantity dispensed after OxyNeo was introduced. However, the extent of the decline varied. In Alberta, despite a rapid decline in dispensing, oxycodone remained dominant at the end of the study period. In contrast, in Ontario, BC and Prince Edward Island, declines in oxycodone exposure meant that fentanyl became the dominant long-acting opioid, and, in New Brunswick, hydromorphone became the dominant opioid.

Interpretation

In this population-based study spanning 8 years, we found that the introduction of OxyNeo against a background of changes in public drug benefit policy in some Canadian provinces was associated with significant reductions in the quantity

Table 2: Summary of long-acting opioid prescription patterns by province at the beginning and end of the study period

	May 2008–October 2008				November 2015–April 2016				Overall comparisons	
Province	No. of prescriptions	No. of prescriptions per 100 000	No. of units per prescription	No. of MMEs per prescription	No. of prescriptions	No. of prescriptions per 100 000	No. of units per prescription	No. of MMEs per prescription	% change prescription rate	% change no. of MMEs per prescription
British Columbia	206 016	4579	53	3162	258 498	5492	40	1672	19.9	–47.1
Alberta	149 800	3952	71	4490	221 583	5236	58	3038	32.5	–32.3
Saskatchewan	48 198	4520	56	3792	68 742	6016	53	2761	33.1	–27.2
Manitoba	50 867	4123	59	4041	61 860	4744	50	2553	15.1	–36.8
Ontario	840 124	6334	63	4508	1 047 412	7549	48	2397	19.2	–46.8
Quebec	412 153	5147	32	2153	648 582	7819	25	1131	51.9	–47.5
New Brunswick	41 005	5427	56	3309	54 297	7194	52	2462	32.6	–25.6
Nova Scotia	38 344	4060	74	4186	66 800	7063	52	2347	74.0	–43.9
Prince Edward Island	5096	3538	67	3261	7578	5157	66	2750	45.8	–15.7
Newfoundland and Labrador	18 830	3586	54	3473	32 144	6084	46	2515	69.6	–27.6
Average		4527	59	3638		6236	49	2362	37.8	–35.1

Note: MME = milligrams of morphine equivalent.

of long-acting opioids dispensed, with prescribing of long-acting oxycodone declining dramatically and being partially replaced by increased dispensing of long-acting hydromorphone. Furthermore, our finding of no corresponding increase in dispensing of immediate-release opioids suggests that declining oxycodone dispensing outweighed increased rates of dispensing of other long-acting opioids.

These findings suggest that the introduction of a tamper-deterrent agent may have driven dispensing patterns toward other similar opioids within the same class that do not have tamper-deterrent properties. However, we cannot determine the extent to which accompanying changes to public drug formularies influenced these patterns. Recently, 2 large studies from the US also showed significant reductions in the quantity of long-acting oxycodone dispensed following the introduction of a tamper-deterrent formulation.[18,19] In contrast to our findings, the authors reported no corresponding rise in the quantity of other long-acting opioids dispensed. These differences may be at least partially explained by changes in the public funding of OxyNeo in Canada, which may have led more patients to switch from oxycodone to an alternative opioid. We observed considerable interprovincial variation in the impact of the introduction of OxyNeo, which likely reflects both differences in patterns of opioid prescribing before this change and differences in provincial drug insurance plan policies (see Appendix 1 for a summary of listing status in each province). In particular, the national trend toward lower dispensing quantity of long-acting opioids was driven by 2 of the largest provinces in Canada, Ontario and BC. In both provinces, there were immediate, dramatic reductions in dispensing of long-acting oxycodone, such that by June 2012, only 4 months after the introduction of OxyNeo, oxycodone was no longer the dominant opioid in either province. This was likely driven, at least in part, by strict reimbursement criteria implemented in both provinces.[20,21] Although we observed similar patterns of reduced dispensing of long-acting oxycodone in other provinces, the impact on overall opioid quantity dispensed outside of Ontario and BC was minimal. In most provinces, this is because dispensing of long-acting oxycodone was low, even before the tamper-deterrent formulation was introduced, and, therefore, small shifts away from oxycodone had limited impact on the total quantity of long-acting opioid dispensed. Two exceptions to this were New Brunswick and Alberta. In New Brunswick, long-acting oxycodone was high but was substantially influenced by the new formulation and strict reimbursement restrictions for this new product on the provincial drug insurance plan.[11] Conversely, in Alberta, dispensing of long-acting oxycodone was high, and, despite a small decline in quantity in February 2012, it remained that way throughout the study period. This may have been due to the listing of tamper-deterrent long-acting oxycodone as a full benefit in Alberta, which did not require clinicians to shift patients to alternative opioids.[11]

These findings highlight the complex effects that can occur with the introduction of new tamper-deterrent agents in a medication class where other, non–tamper-deterrent options are provided. It appears that the introduction of a tamper-deterrent agent along with accompanying changes to listing status on public drug insurance programs in several provinces was associated with both significant replacement of oxycodone with other long-acting opioids and an overall reduction in the quantity of long-acting opioids dispensed. In the US, similar changes in opioid prescribing patterns following the introduction of tamper-deterrent oxycodone have been associated with increased reports of using heroin to get "high"[22] and accelerated rates of heroin overdoses.[18] Although the impact of this

new formulation on patient outcomes in Canada has not been studied, recent reports have shown that hospital admissions for heroin overdoses rose by 38% between fiscal years 2011/12 and 2012/13 in Canada and that heroin involvement in opioid-related deaths nearly doubled between 2012 and 2015 in Ontario.[23,24] Despite our inability to determine the extent to which this was driven by changes in patterns of dispensing of long-acting opioids, these findings highlight a need for further exploration of the potential consequences of these shifts on patient outcomes.

Strengths and limitations

A key strength of this study is its capacity to report on quantity of prescribing of long-acting opioids across Canada over an 8-year period. However, several limitations bear mention. First, because our data included prescriptions dispensed from community pharmacies, we were unable to determine the impact of the introduction of OxyNeo on opioid prescribing in hospitals. Second, we did not have patient-level data and were thus unable to measure effects on the number of people prescribed opioids. This is important in the case of fentanyl, in which the high level of calculated population exposure may be concentrated in a relatively small number of people who are each receiving high opioid dosages. Third, we relied on projected estimates of prescription dispensing quantities, which include a small amount of sampling error. However, in Quebec, the province with the lowest rate of opioid prescribing, about 95% of all pharmacies are captured in the IMS Health Canada sample, which suggests that sampling bias is not the explanation for our finding of relatively low rates of dispensing in that province. Fourth, we did not specifically study changes in drug plan funding for opioids in our analysis and so could not determine how such changes influenced the observed trends in prescribing. Fifth, the Compuscript database does not have data from the territories in Canada, and therefore we were unable to include them in this analysis. Finally, we restricted our analyses to oral and transdermal opioid formulations with reliable morphine equivalence ratios. Given that these represent the majority of opioids prescribed across Canada, we do not expect that this exclusion influenced our findings.

Conclusion

The findings of this large, nationally representative study of opioid prescription patterns suggest that the introduction of a tamper-deterrent formulation of long-acting oxycodone, against a background of changes in public drug benefit policy, was associated with statistically significant, sustained changes in selection of long-acting opioids but only modest changes in the quantities of long-acting opioids dispensed. This illustrates the limited effect a tamper-deterrent formulation and associated coverage policy can have when other, non–tamper-deterrent alternatives are readily available. The considerable interprovincial variation shows the added influence of factors such as drug insurance policy and clinical practice on patterns of opioid use. These findings are of high importance given the potential for patient harm when switching between opioids of differing potency, as well as the potential for patients to transition to illicit opioids when access to prescription opioids is restricted.

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Supplemental information: For reviewer comments and the original submission of this manuscript, please see www.cmajopen.ca/content/5/4/E800/suppl/DC1.