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

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Short Title: Patterns of Opioid Dispensing Across Canada

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ABSTRACT

BACKGROUND:

In February 2012, a reformulated 'tamper-deterrent' form of long-acting oxycodone was introduced. We investigated trends in prescribing of opioid products in Canada, and the impact of the introduction of tamper-deterrent oxycodone on these patterns.

METHODS:

We conducted population-based, repeated cross-sectional analyses of dispensing of long-acting and immediate-release opioids in Canadian provinces between 2008 and 2016. We estimated monthly community pharmacy dispensing of oral and transdermal codeine, morphine, hydromorphone, oxycodone, and fentanyl, and converted quantities to mg morphine equivalents (MME) per 1000 population. We used time series analysis to evaluate the impact of tamper-deterrent oxycodone on these trends.

RESULTS:

After the introduction of tamper-deterrent oxycodone, national dispensing of long-acting opioids fell 14.9% from 36,098 MME to 30,716 MME per 1000 population in April 2016 ($p<0.01$). These effects varied and were largest in Ontario (23% reduction; $p=0.01$) and British Columbia (30% reduction; $p=0.01$). The national dispensing rate of oxycodone fell 39% after the introduction of a tamper-deterrent formulation ($p<0.001$), which was partially offset by a 48% rise in dispensing of hydromorphone ($p<0.001$). Although dispensing of immediate release opioids was a significant contributor to overall population opioid exposure across Canada, it was unaffected by the introduction of

tamper-deterrent oxycodone ($p>0.05$ in all provinces).

INTERPRETATION:

The introduction of tamper-deterrent oxycodone led to modest reductions in overall dispensing of long-acting opioids in some Canadian provinces. These changes were overshadowed by major differences in product choice and levels of opioid dispensing between provinces, underscoring the importance of regional pharmaceutical coverage and clinical practice policies.

INTRODUCTION

Opioids are a class of analgesics generally recognized as being the optimum treatment for moderate to severe pain associated with cancer.[1,2] In the early 1990s, there was a critical shift in practice to include opioids in the treatment of chronic non-cancer pain, which has driven an increase in the prescribing and consumption of opioids over the last 20 years.[3-5] Prescribing opioids in chronic non-cancer pain remains controversial, as their long-term use has been associated with significant side effects, which include abuse, addiction and premature death from accidental overdose.[6,7]

Canada and the United States have the highest levels of prescription opioid consumption per capita[8], with rates that are approximately double those observed in the European Union, Australia and New Zealand.[9] In Canada, prescription opioid consumption increased nearly four-fold between 1999 and 2010[10], despite the proportion of Canadians who reported suffering from chronic pain not changing significantly over this period.[11] In Ontario, the rate of opioid prescribing rose by 29% from 1991 to 2007, which was largely driven by an 850% rise in prescribing of oxycodone.[12] This rising prevalence of oxycodone prescribing in Ontario has been associated with the addition of long-acting oxycodone (OxyContin®) to the provincial drug benefit formulary in 2000, raising serious concerns regarding its potential misuse and abuse.[12] In particular, the ability to circumvent the long-acting properties of the oxycodone tablet by chewing or grinding the pills for inhalation or injection has been widely criticized as a contributing factor to rising rates of opioid addiction and overdose across North America.[13,14] In February 2012, the manufacturer of OxyContin® discontinued its production and replaced it with a tamper-deterrent formulation, OxyNeo®, that was designed to be more difficult

to misuse. 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.[15]

Given that OxyNeo® was the first opioid with tamper-deterrent properties in Canada, and because opioid prescribing practices vary widely across Canada[16], the Canadian Network for Observational Drug Effect Studies (CNODES) explored the impact of the introduction of OxyNeo® on opioid prescribing patterns across the country.

METHODS

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

We used the QuintileIMS CompuScript database to identify monthly retail pharmacy prescription quantities for all eligible opioid analgesics dispensed during the study period. This database captures data from a representative sample of approximately 6,000 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. Projections are conducted at the level of drug identification number (DIN), thus allowing the estimate of prescription quantities by opioid medication

and strength. These data are continuously monitored and verified by QuintilesIMS to ensure that they are within the standards set for quality control, they are representative at both the provincial and national level, and are regularly used for research purposes.[16,17].

We captured the number of units (i.e. tablets or transdermal patches) dispensed of each opioid by month and strength. The total quantity of opioid dispensed each month was calculated by multiplying the units by the formulation strength and expressed in milligrams of morphine equivalents (MME) using conversion ratios reported in the Canadian National Opioid Use Guideline Group.[18] Our primary measures of interest were the rate of long-acting opioid dispensing by province, and the national rate of long-acting opioid dispensing stratified by opioid type. In a secondary analysis, we analyzed trends in immediate-release opioid dispensing by province, and long-acting opioid prescribing by opioid type for each province separately. Dispensing rates were reported as MME dispensed per 1000 population, using Statistics Canada census population estimates as the denominator.

Patterns of long-acting opioid dispensing were compared 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 our study period. Measures captured at each observation point included opioid prescription rate, average number of opioid units dispensed per prescription and opioid quantity (in MME) dispensed per prescription. We calculated ratios of the prescription rate and quantity dispensed as a measure of variance over time.

Statistical Analysis

We used time series analysis to characterize the impact of the introduction of tamper-deterrent long-acting oxycodone to the drug formulary in February 2012 on the rate of long-acting and immediate-release opioid dispensing in Canada using a ramp function in interventional autoregressive integrated moving average (ARIMA) models. All models were fitted using data from the beginning of our study period to April 2013. We excluded data after this to avoid modeling more remote shifts in prescribing that we believed were unlikely to be immediately related to the introduction of OxyNeo®. Model fit was examined using white noise probabilities, autocorrelation functions and the Ljung-Box test. All analyses used a type 1 error rate of 0.05 as the threshold for statistical significance and were carried out using SAS statistical software (v 9.3; SAS Institute, Cary, NC).

RESULTS

Over the eight-year study period, a total of 1,739,057,621 tablets and transdermal patches for long-acting opioids were dispensed in Canada. The quantity dispensed differed by opioid type, with oxycodone tablets accounting for 42% (726,477,071), hydromorphone for 26% (443,604,461), morphine for 23% (408,648,392), codeine for 6% (99,856,627), and fentanyl patches for 3% (60,471,070) of all long-acting opioid units dispensed. In addition, 7,350,703,901 tablets for immediate-release opioids were dispensed in Canada.

Overall usage varied substantially by province (Figure 1). Ontario exhibited the highest levels of opioid dispensing throughout the 8 years of the study and Quebec consistently had the lowest levels, which were generally less than half of those seen in

Ontario. Dispensing levels fell in several provinces in the last 12 months of the study, with British Columbia's (B.C.'s) rate falling below that of Quebec in February 2015.

Upon the introduction of tamper-deterrent long-acting oxycodone in February 2012, the monthly quantity of long-acting opioid dispensing fell 14.9% from 36,098 MME per 1000 population to 30,716 MME per 1000 population in April 2016 ($p<0.01$). However, this impact varied across Canada. In Ontario and B.C., introduction of tamper-deterrent long-acting oxycodone was associated with significant reductions in the overall quantity of long-acting opioids dispensed, with rates falling by 23% (from 50,865 MME to 39,288 MME per 1000 population; $p=0.01$) and 30% (from 27,306 MME to 19,107 MME per 1000 population; $p=0.01$), respectively. The introduction of OxyNeo® also was associated with significant changes in the rate of long-acting opioid prescribing in Saskatchewan ($p=0.01$), Quebec ($p<0.01$) and New Brunswick ($p=0.05$); however, these latter impacts were small and temporary, and overall rates of long-acting opioid use continued to rise in these provinces over the study period. In contrast, the introduction of OxyNeo® had no impact on rates of immediate-release dispensing (Figure 2; $p>0.05$ in all models), with rates climbing in most provinces. Although the rate of immediate-release opioid dispensing declined over time in Nova Scotia and B.C., the introduction of OxyNeo® did not appear to be driving these changes ($p=0.42$ and 0.85, respectively).

Despite overall reductions in national rates of long-acting opioid dispensing, changes in the quantity of opioid dispensed varied considerably by opioid type. The national rate of long-acting oxycodone prescribing fell by 39% after the introduction of OxyNeo®, from 14,140 MME per 1000 (February 2012) to 7,585 MME per 1000 at the end of our study period ($p<0.001$; Figure 3). In contrast, the rate of hydromorphone

dispensing climbed 48% from 4,890 MME to 7,227 MME per 1000 population between February 2012 and the end of our study period ($p<0.001$), indicating a likely partial substitution for oxycodone. We observed no impact of the new oxycodone formulation on the dispensed quantities of long-acting morphine ($p=0.09$), codeine ($p=0.73$) or fentanyl ($p=0.70$). By the last month of our study period, fentanyl made the largest single contribution to overall community opioid exposure (37%; 11,510 MME per 1000 population), followed by oxycodone (25%; 7,585 MME per 1000 population), hydromorphone (24%; 7,227 MME per 1000 population), morphine (13%; 4,011 MME per 1000 population), and codeine (1%; 383 MME per 1000 population). This high value for MME for fentanyl contrasts with the low numbers of dispensed units noted earlier due to the high potency of this drug, and the use of patches over a three-day period.

In the first 6 months of our study period (May to October 2008), the number of units and the quantity (in MME) dispensed per prescription varied considerably between provinces (Table 1). In Quebec, the average number of units dispensed per prescription was 32, with each prescription having 2,153 MME opioid on average. In contrast, in all other provinces across Canada, the average number of opioid units dispensed per prescription ranged from 53 (B.C.) to 74 (Nova Scotia) and the average opioid quantity per prescription varied from 3,162 MME (B.C.) to a high of 4,508 MME (Ontario). Although the rate of long-acting opioid prescribing (prescriptions/1000 population) increased over the study period, the number of units and total quantity (in MME) dispensed per prescription declined. The largest changes in prescription quantity were observed in Ontario, Quebec, B.C. and Nova Scotia where the opioid quantity dispensed per prescription fell by between 43.9% (Nova Scotia) and 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; 1,131 MME per prescription).

Before the introduction of OxyNeo® in February 2012, oxycodone accounted for the highest levels of population exposure to long-acting opioids (expressed as MME/1000 population) in all provinces, except for Manitoba, Saskatchewan, and Quebec where fentanyl dominated, and Nova Scotia where hydromorphone dominated (see Supplementary Appendix). In provinces where oxycodone accounted for the greatest opioid exposure, the introduction of OxyNeo® led to a reduction in oxycodone quantity dispensed. However, the extent of the decline varied. In Alberta, despite a rapid decline in dispensing, oxycodone remained dominant at the end of our study period. In contrast, in Ontario, B.C., and Prince Edward Island, declines in oxycodone exposure led to fentanyl becoming the dominant opioid (in terms of MME/1000 population); and in New Brunswick, hydromorphone became the dominant opioid.

DISCUSSION:

In this population based study spanning 8 years, we found that the introduction of OxyNeo®, together with associated changes in public drug benefit policy in some provinces, led to significant reductions in the quantity of long-acting opioids dispensed in Canada, with long-acting oxycodone dispensing falling dramatically and being partially replaced by increased dispensing of long-acting hydromorphone. Furthermore, we observed a small, but significant reduction in the overall quantity of long-acting opioids dispensed in Canada, and no corresponding increase in immediate-release opioid dispensing suggesting that declining oxycodone dispensing outweighed increased rates of dispensing of other long-acting opioids.

These findings suggest that the introduction of one tamper-deterrent agent will drive dispensing patterns towards other similar opioids within the same class that do not have tamper-deterrent properties. Recently, two large studies from the U.S. also reported significant reductions in the quantity of long-acting oxycodone dispensed following the introduction of a tamper-deterrent formulation. However, in contrast to our findings, they reported no corresponding rise in the quantity of other long-acting opioids dispensed.[19,20] These differences may be at least partially explained by changes in the public funding of long-acting oxycodone in Canada after the introduction of the tamper-deterrent formulation, which may have led more patients to switch from oxycodone to an alternative opioid. The rate of long-acting oxycodone dispensing fell by 39% in Canada, compared to approximately 29% in the U.S.[20] Furthermore, a U.S. study among patients with opioid dependence reported a dramatic reduction in use of OxyContin as a primary drug of abuse following the introduction of tamper-deterrent oxycodone, followed by a significant rise in the abuse of other opioids such as fentanyl, hydromorphone, and heroin.[21] This suggests that among people dependent on opioids in the U.S., the abuse-deterrent formulation of oxycodone was likely replaced with alternative opioids, both prescription and illicit.[21]

We observed considerable inter-provincial variation in the impact of introducing tamper-deterrent long-acting oxycodone which likely reflects both differences in patterns of opioid prescribing prior to this change and differences in provincial drug insurance plan policies. In particular, the national trend towards lower dispensing quantity of long-acting opioids was driven by two of the largest provinces in Canada – Ontario and B.C. In both provinces, there were immediate, dramatic reductions in dispensing of long-

acting oxycodone such that by June 2012, only 5 months after the introduction of tamper-deterrent long-acting oxycodone, 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.[22,23] Although patients could continue to access this drug through private drug insurance and cash payment, listing status on public drug formularies often drives broader prescribing patterns. While we observed similar patterns of reduced long-acting oxycodone dispensing in other provinces, the impact on overall opioid quantity dispensed outside of Ontario and B.C. was minimal. In most provinces, this is because long-acting oxycodone dispensing was low, even prior to the introduction of the tamper-deterrent formulation, 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 dispensing was high, but was significantly impacted by the new formulation and strict reimbursement restrictions for this new product on the provincial drug insurance plan.[15] Conversely, in Alberta, long-acting oxycodone dispensing was high, and despite a small drop in quantity in February 2012, it remained this way throughout the study period. This may be due to the listing of tamper-deterrent long-acting oxycodone as a full benefit in Alberta, leading to minimal requirements for clinicians to shift patients to alternative opioids.[15]

These findings highlight the complex impacts that can occur with the introduction of new tamper-deterrent agents in a medication class where other, non-tamper-deterrent options continue to exist. It appears that the combination of a tamper-deterrent agent, along with accompanying changes to listing status on public drug insurance programs in

several provinces led to both significant replacement of oxycodone with other long-acting opioids, and an overall reduction in the quantity of long-acting opioids dispensed, nationally. In the U.S., 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[24], and accelerated rates of heroin overdoses.[19] Although the impact of this new formulation on patient outcomes in Canada has not been studied, recent reports have found that hospitalizations 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.[25,26] Despite our inability to determine the extent to which this was driven by changes in long-acting opioid dispensing patterns, this highlights a need for further exploration of the potential consequences of these shifts on patient outcomes.

Aside from the influence of tamper-deterrent oxycodone, our study highlights important differences between provinces in the utilization of long-acting opioids. Dispensing levels remained higher in Ontario than in other provinces throughout the study, although the gap closed markedly with the fall in oxycodone use after 2012. Quebec had the lowest levels of use until the end of the study when it was surpassed by British Columbia. Examination of prescription characteristics suggested that the fall in population exposures was achieved by reduced quantities of opioid per prescription rather than a reduction in the numbers of prescriptions written. This is particularly notable in Quebec, where it is common practice to issue a prescription for about half the number of days as in other provinces.[27]

Strengths and Limitations

A key strength of this study is its capacity to report on quantity of long-acting opioid prescribing across Canada over an 8-year period. However, several limitations require further discussion. First, our data include prescriptions dispensed from community pharmacies. Therefore, we are unable to determine the impact of tamper-deterrent long-acting oxycodone on opioid prescribing in hospitals. Second, we did not have patient-level data, and were thus unable to measure impacts on the number of individuals prescribed opioids in our study. This is important in the case of fentanyl where the high level of calculated population exposure may be concentrated in a relatively small number of individuals who are each receiving high opioid doses. Third, conversion of fentanyl patches into estimates of MME can be difficult given that these patches are meant to be used over 3 days, but can sometimes be used for a shorter period. In this study, we assumed that patches would be used for three days, and calculated opioid quantity (in MME) accordingly. Finally, we restricted our analyses to oral opioid formulations with reliable morphine equivalence ratios. However, these represent the vast majority of opioids prescribed across Canada, and thus we do not expect that this exclusion would influence our findings.

CONCLUSION

This large, nationally-representative study of opioid prescription patterns found that the introduction of a tamper-deterrent formulation of oxycodone, together with changes in public drug benefit policy, led to significant, sustained changes in long-acting opioid selection but only small changes in the quantity of long-acting opioids dispensed. This illustrates the limited impact a tamper-deterrent formulation and associated coverage policy can have when other non-tamper-deterrent alternatives are readily available. The

considerable inter-provincial variation demonstrates the added influence of drug insurance policy, clinical practice, and other factors 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. Policy makers and public health officials should consider the potential unintended consequences of introducing tamper-deterrent opioid formulations in the absence of other patient and clinician supports, such as training for healthcare professionals on non-opioid pain management, access to treatment for opioid use disorder and access to non-drug alternatives for chronic pain management.

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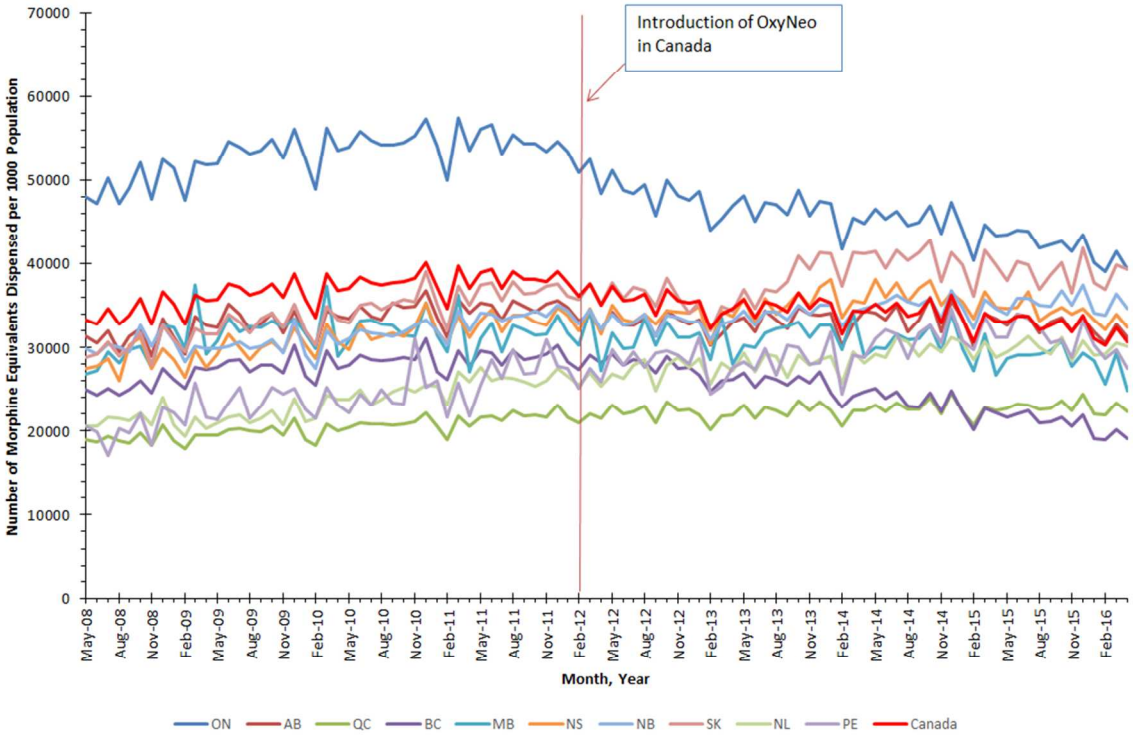
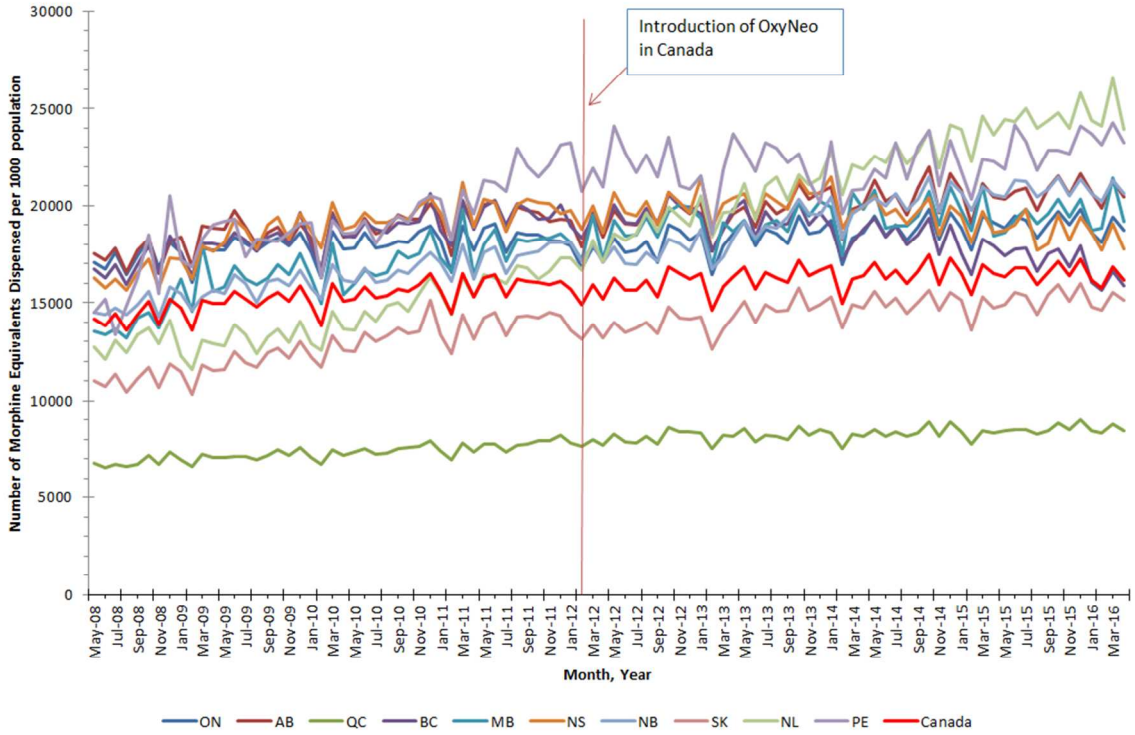
Figure 1. Rate of Long-Acting Opioid Dispensing (MEQ per 1000 population), by Province, All Opioids



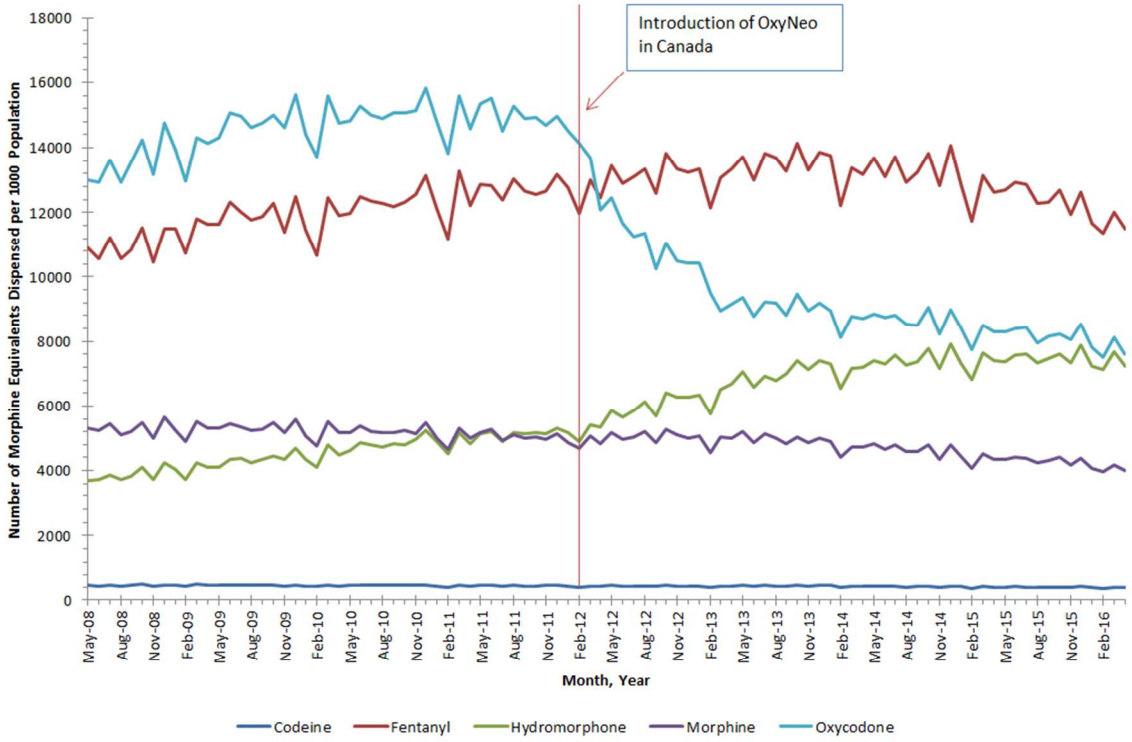
Legend. The rate of long-acting opioid dispensing by province from May 2008 to April 2016. Ontario attained the highest rate of opioid dispensing throughout the study period, and British Columbia had the lowest rate by the end of the study period.

Figure 2. Rate of Immediate-Release Opioid Dispensing (MEQ per 1000 population), by Province, All Opioids



Legend. The rate of immediate-release opioid dispensing by province from May 2008 to April 2016. Newfoundland & Labrador attained the highest rate of dispensing by the end of the study period and Quebec had the lowest rate of dispensing throughout the study period.

Figure 3. National Rate of Opioid Dispensing (MEQ per 1000 population), by LA Opioid Type.



Legend. The national rates of dispensing long-acting opioids from May 2008 to April 2016. Introduction of OxyNeo in Canada in February 2012led to significant reductions in the volume of oxycodone dispensed, and a significant increase in the volume of hydromorphone dispensed.

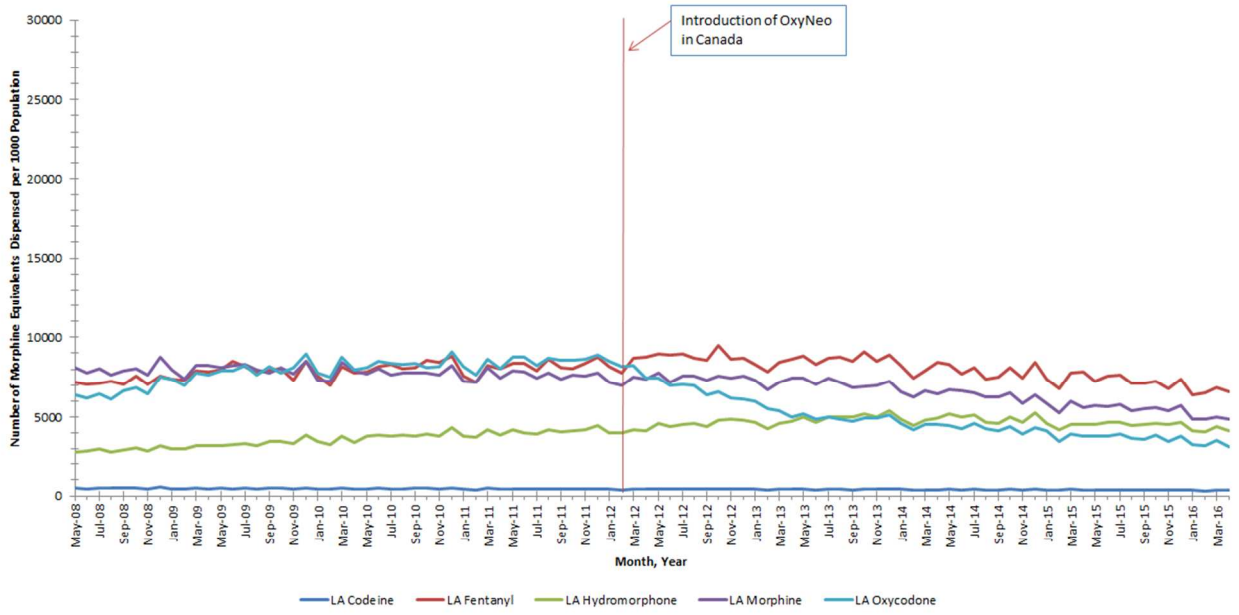
Table 1. Summary of long-acting opioid prescription patterns by province at the beginning and end of study period

	May 2008 to October 2008				November 2015 to April 2016				Overall Comparisons	
Province	Prescriptions	Prescriptions per 100,000	Units/Rx	MME/Rx	Prescriptions	Prescriptions per 100,000	Units/Rx	MME/Rx	% Change Rx Rate	% Change MME/Rx
Ontario	840,124	6,334	63	4,508	1,047,412	7,549	48	2,397	19.2	-46.8
Alberta	149,800	3,952	71	4,490	221,583	5,236	58	3,038	32.5	-32.3
Quebec	412,153	5,147	32	2,153	648,582	7,819	25	1,131	51.9	-47.5
British Columbia	206,016	4,579	53	3,162	258,498	5,492	40	1,672	19.9	-47.1
Manitoba	50,867	4,123	59	4,041	61,860	4,744	50	2,553	15.1	-36.8
Nova Scotia	38,344	4,060	74	4,186	66,800	7,063	52	2,347	74.0	-43.9
New Brunswick	41,005	5,427	56	3,309	54,297	7,194	52	2,462	32.6	-25.6
Saskatchewan	48,198	4,520	56	3,792	68,742	6,016	53	2,761	33.1	-27.2
Newfoundland and Labrador	18,830	3,586	54	3,473	32,144	6,084	46	2,515	69.6	-27.6
Prince Edward Island	5,096	3,538	67	3,261	7,578	5,157	66	2,750	45.8	-15.7
Average		**4,527**	**59**	**3,638**		**6,236**	**49**	**2,362**	**37.8**	**-35.1**

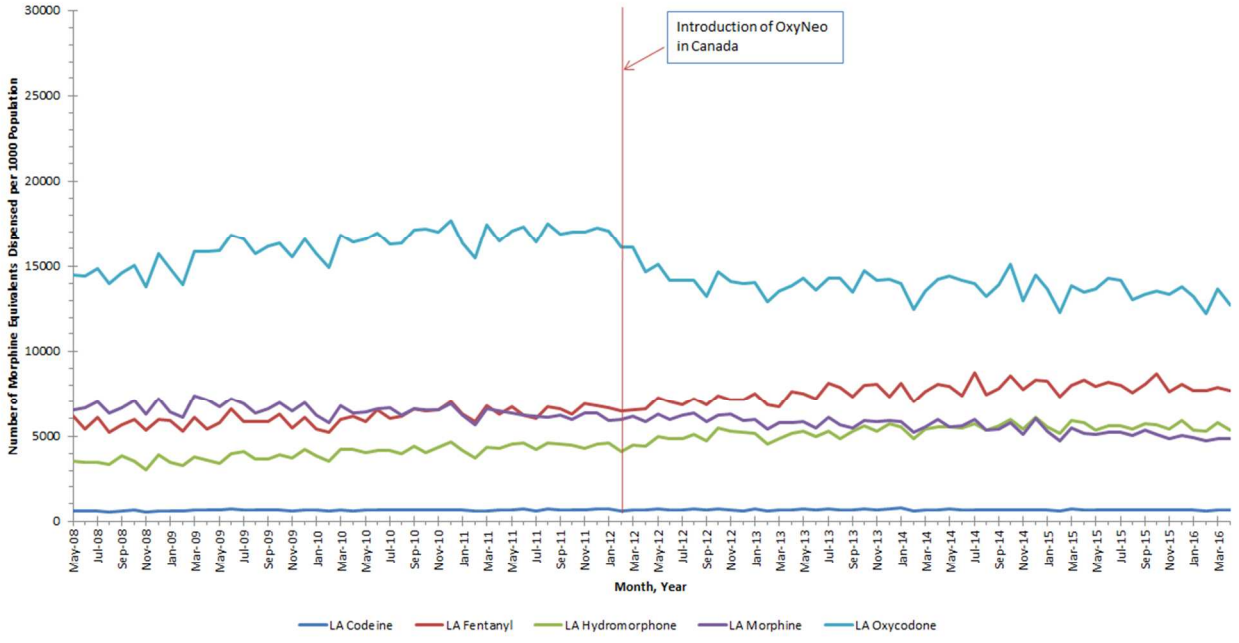
*Rx signifies prescription and MME signifies mg Morphine Equivalents

Supplementary Appendix: Rate of Long-Acting Opioid Prescribing by drug and province

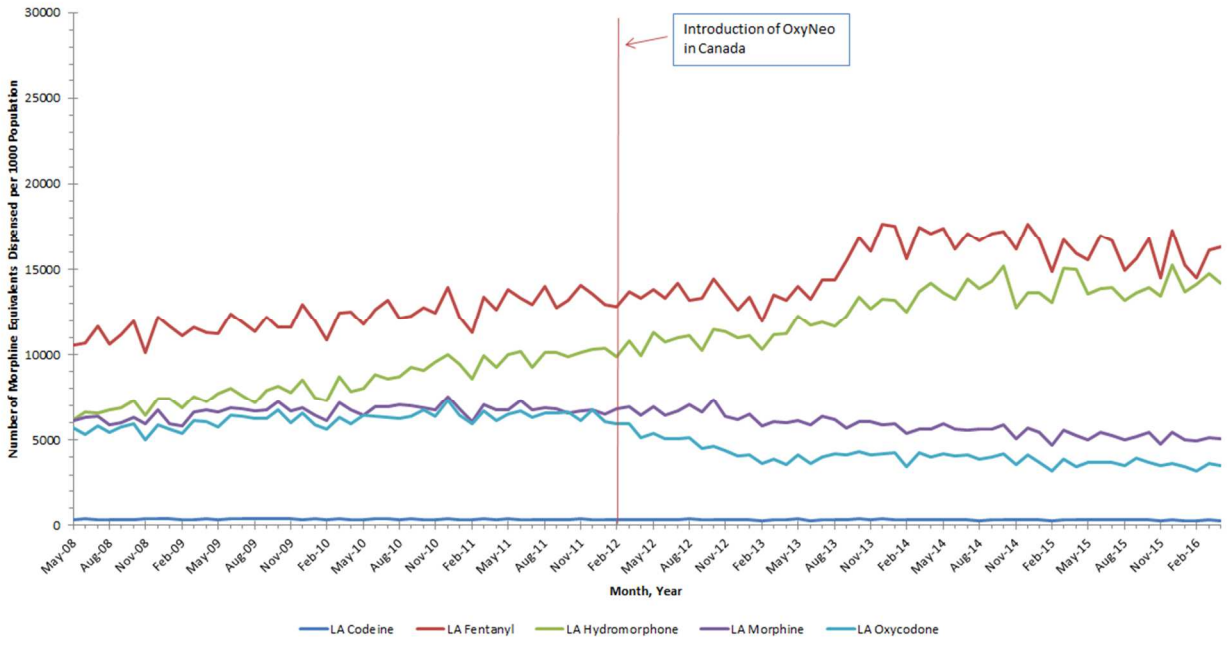
eFigure 1: British Columbia Rate of Opioid Dispensing (MEQ per 1000 population), by LA Opioid Type



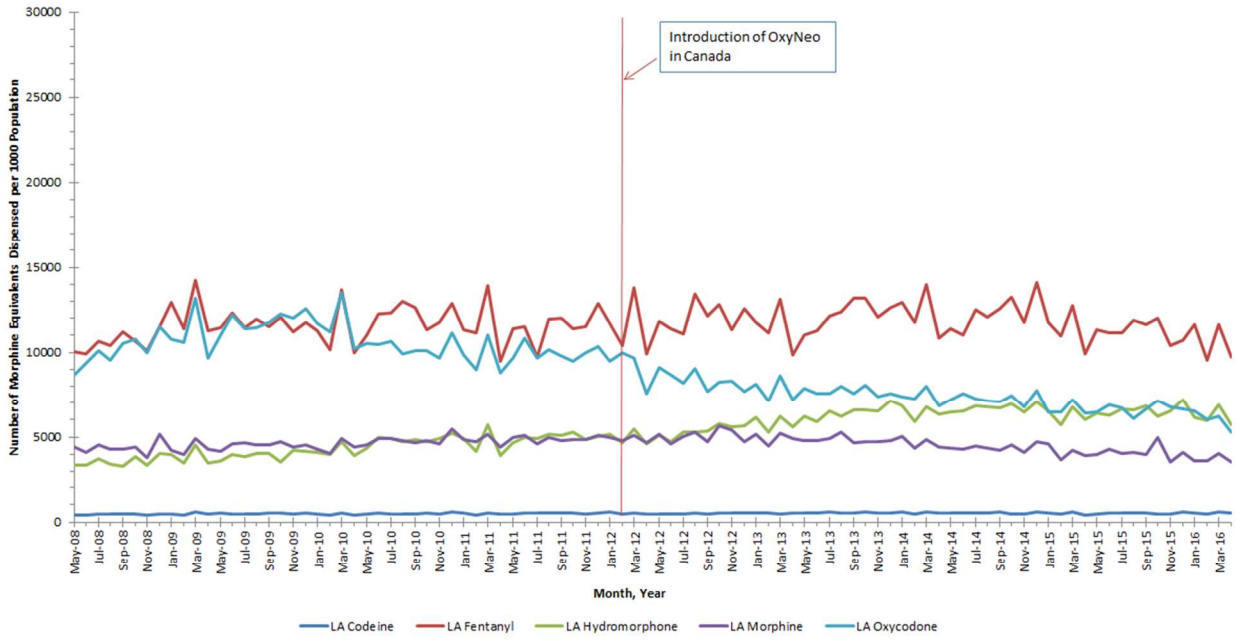
eFigure 2: Alberta Rate of Opioid Dispensing (MEQ per 1000 population), by LA Opioid Type



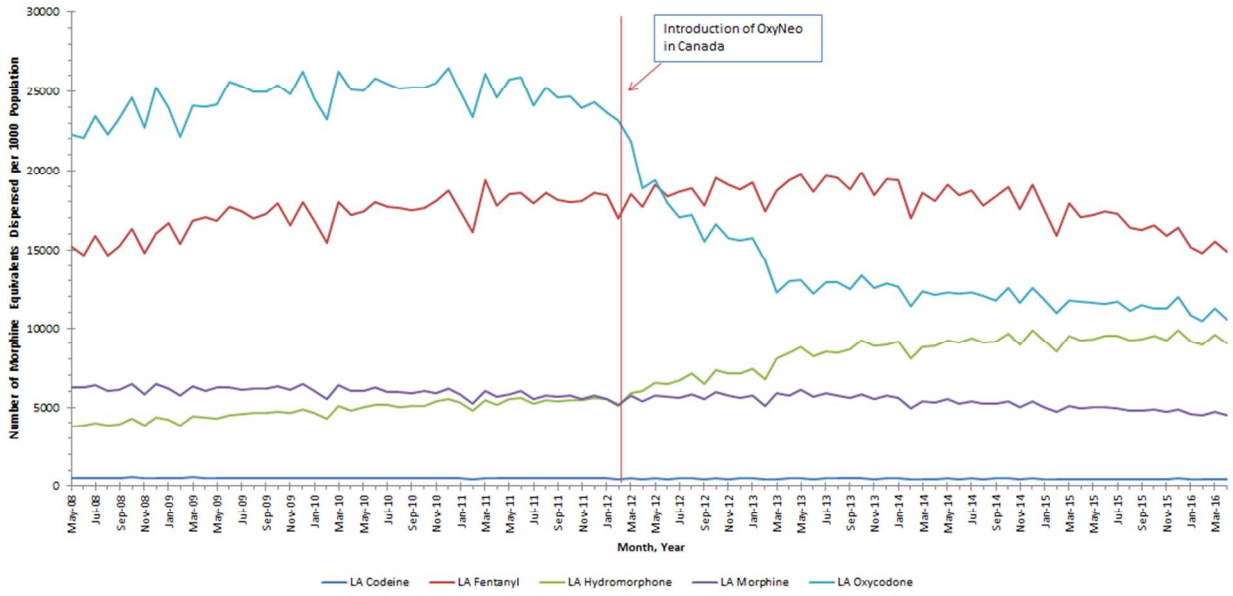
eFigure 3: Saskatchewan Rate of Opioid Dispensing (MEQ per 1000 population), by LA Opioid Type



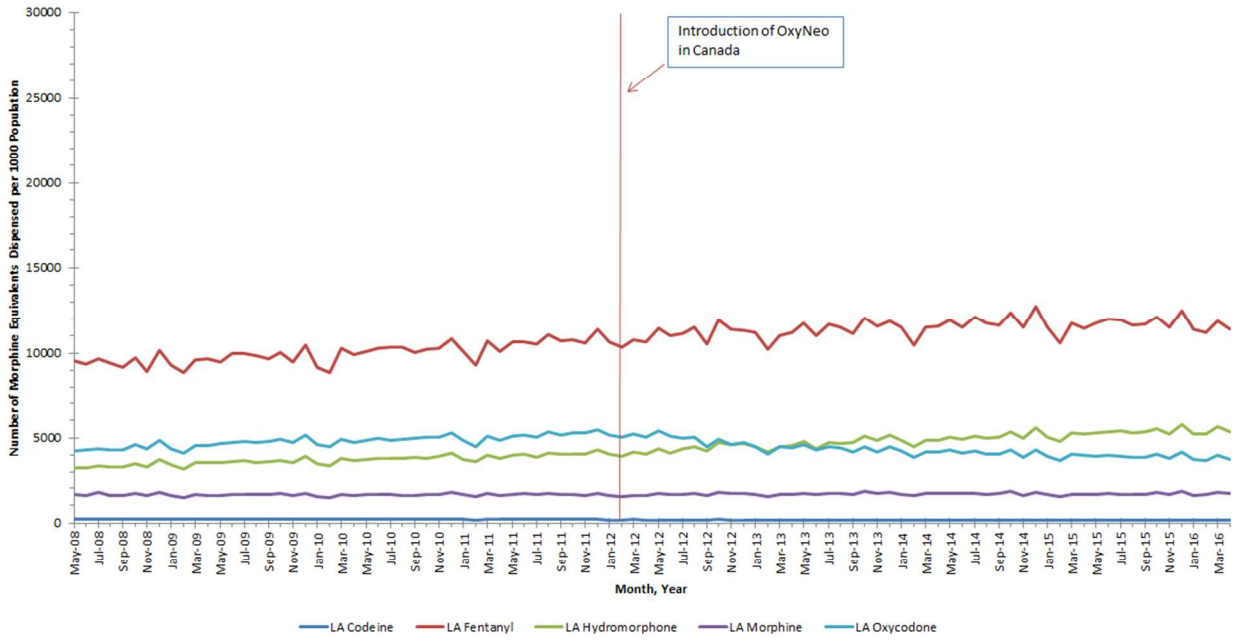
eFigure 4: Manitoba Rate of Opioid Dispensing (MEQ per 1000 population), by LA Opioid Type



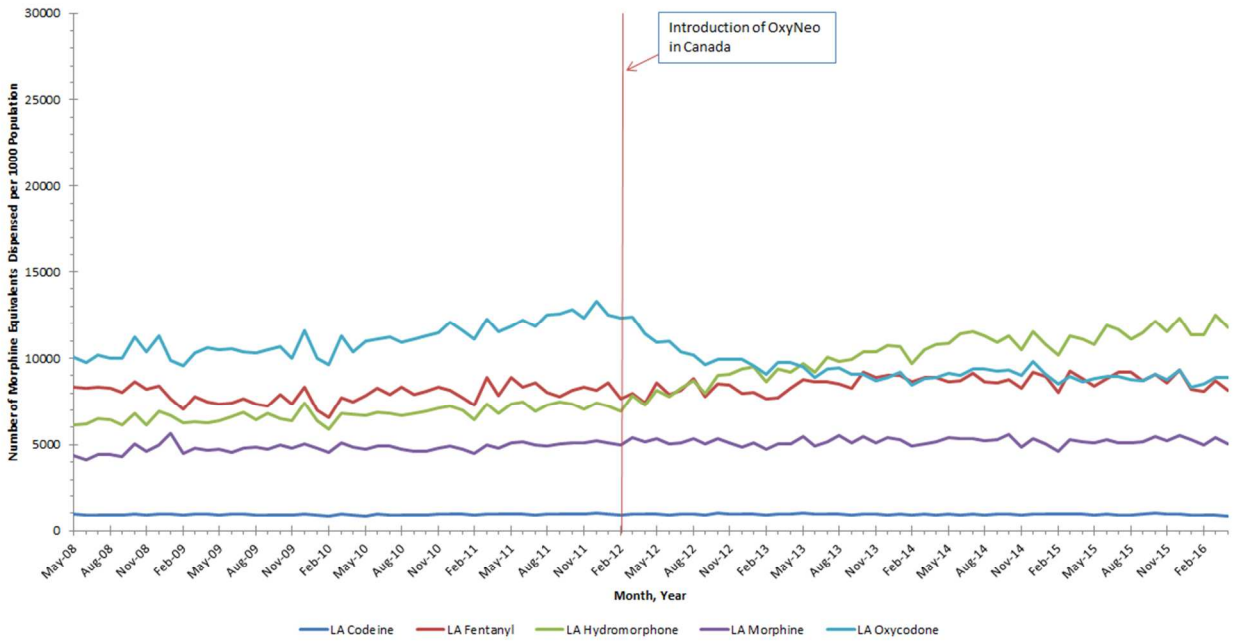
eFigure 5: Ontario Rate of Opioid Dispensing (MEQ per 1000 population), by LA Opioid Type



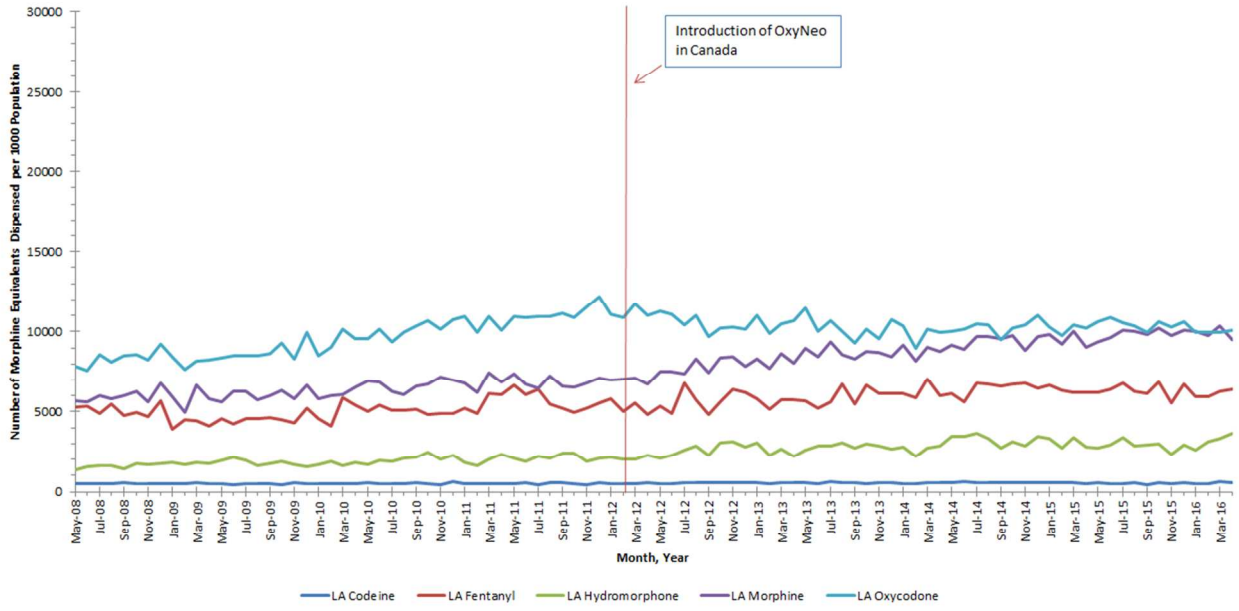
eFigure 6: Quebec Rate of Opioid Dispensing (MEQ per 1000 population), by LA Opioid Type



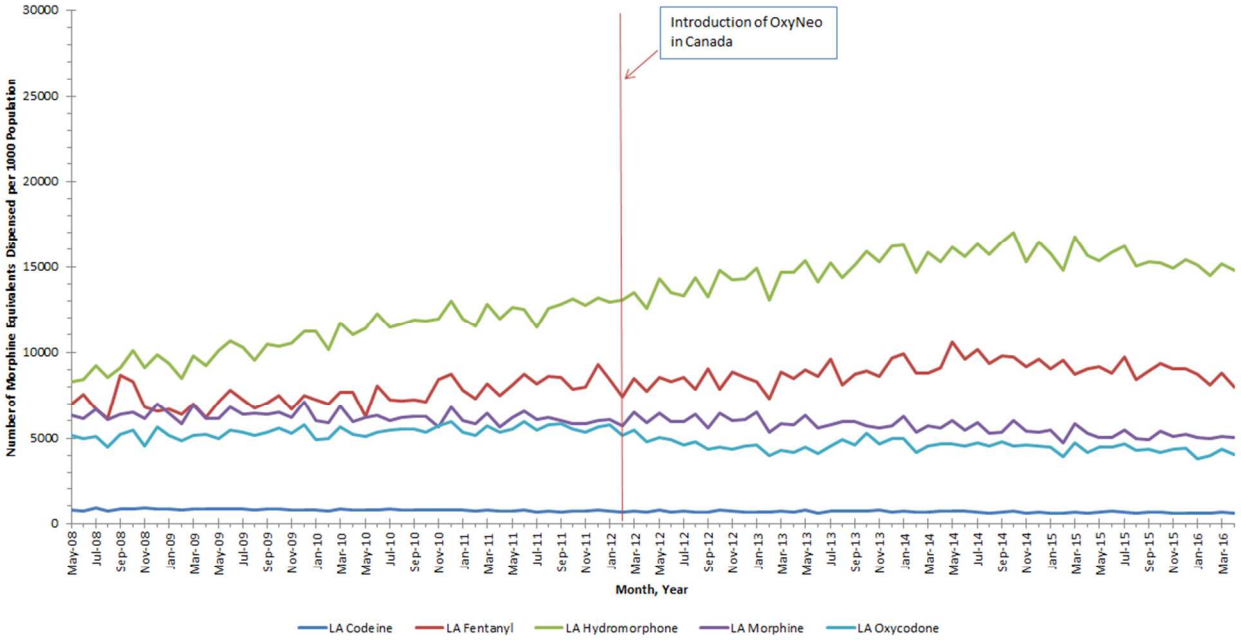
eFigure 7: New Brunswick Rate of Opioid Dispensing (MEQ per 1000 population), by LA Opioid Type



eFigure 8: Newfoundland & Labrador Rate of Opioid Dispensing (MEQ per 1000 population), by LA Opioid Type



eFigure 9: Nova Scotia Rate of Opioid Dispensing (MEQ per 1000 population), by LA Opioid Type



eFigure 10: Prince Edward Island Rate of Opioid Dispensing (MEQ per 1000 population), by LA Opioid Type