The impact of regulatory discussion on low-dose codeine purchasing in Canada: time series analysis

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ABSTRACT

Background: Low-dose codeine products can be purchased without a prescription in most of Canada, despite ongoing regulatory discussions regarding their potential rescheduling. Due to their over-the-counter (OTC) status, little is known about the amount of these products sold across the country.

Methods: We examined population-adjusted monthly purchasing of codeine products from January 2014 to October 2019 using the IQVIA Canadian Drug Store and Hospital Purchases Audit (CDH) database, stratified by province and OTC status. We used interventional autoregressive integrated moving average models to examine the impact of communications by regulators and a Manitoba rescheduling policy on these patterns.

Results: Over the study period, 24,120 kilograms of codeine (3.025 billion units) and 937,867kg of acetaminophen were sold through OTC low-dose codeine products across Canada. Health Canada's 2016 announcement of proposed regulatory change did not significantly impact OTC codeine purchasing ($p=0.57$). However, initiation of a 60-day public comment period in September 2017 was associated with a roughly 44% decrease in OTC codeine purchasing ($p=0.03$). In Manitoba, there was a dramatic decrease in the purchasing of the same codeine formulations after rescheduling in February 2016 ($p<0.001$). We observed no significant change in the rate of purchasing of higher dose codeine formulations in response to scheduling changes in Manitoba ($p=0.22$).

Conclusions: More than half a billion OTC codeine tablets are purchased in Canada each year. Given the potential risks of codeine dependence and acetaminophen toxicity

with these products, and the impacts of Manitoba's rescheduling in 2016, a national rescheduling strategy should be considered.

BACKGROUND

Introduction:

In Canada, the opioid crisis has affected every region of the country[1]. Recently, all provinces (excluding Quebec) have made efforts to monitor opioid prescribing through implementation of prescription monitoring programs[2-4]. However, over-the-counter (OTC) low-dose codeine purchases are not accounted for in these systems. While codeine is prescription-only in many countries, lower strengths are available OTC in others, including the United Kingdom, Canada, and Ireland[5]. The accessibility of OTC codeine formulations reinforces the perception of safety that can contribute to hazardous use[6], dependence[5, 7], and other harms, including from the ASA or acetaminophen with which it is combined[7, 8].

In Canada, *The Controlled Drugs and Substances Act* defines OTC (Schedule II) codeine preparations as those containing not more than 8 mg or its equivalent of codeine phosphate per unit of solid form or not more than 20 mg codeine phosphate per 30 mL liquid preparation[9]. Additionally, these products must contain two or more additional medicinal ingredients of specified quantities[9]. The most commonly sold OTC codeine preparations in Canada contain codeine, acetaminophen and caffeine. While intended to prevent inappropriate use, the requirement for OTC codeine products to be combined with other medicinal ingredients places consumers at risk of toxicity from these drugs in addition to opioid-related harm[8, 10], particularly hepatotoxicity caused by acetaminophen[11, 12].

In Canada, the federal government is responsible for determining the conditions of sale of drug products, such as the requirement for a prescription. Following this, provincial and territorial governments can further specify additional conditions of sale,

but those conditions must be more restrictive than federal legislation[13]. On February 1, 2016, the College of Pharmacists of Manitoba mandated that all low-dose codeine preparations previously considered OTC would require a prescription by either a pharmacist or other prescriber[14]. Similar regulations have been proposed on a provincial[15] and national[16] level, and are supported by professional pharmacy and medical associations[17, 18].

In July 2016, Canada's Minister of Health proposed regulatory changes that would require a prescription for low-dose codeine products, and in September 2017, the Canadian Department of Health opened a 60-day comment period for the proposed regulatory change[16]. Changes to the scheduling of OTC codeine products are still being proposed, with ongoing consultations involving stakeholders[19].

In order to limit the risk of harm from these products, it is important to understand the volume of products being sold across the country and the impacts, if any, of restrictions or proposed rescheduling on their sale. We examined trends in the purchasing of low-dose codeine products across Canada from 2014 to 2019, evaluating the impact of federal regulatory proposals on these patterns of use as well as the impact of Manitoba's 2016 policy change requiring a prescription for these products.

METHODS

Setting

We conducted a population-based time series analysis of low-dose codeine purchasing by pharmacies and hospitals across Canadian provinces from January 1st, 2014 to October 31st, 2019. Data regarding codeine consumption in the Canadian

territories were not available for this analysis. Due to the aggregate nature of the source data, research ethics approval was not required.

Data Sources

We used the IQVIA Canadian Drug Store and Hospital Purchases Audit (CDH) database during the study period. Sampling is based on a projected audit, covering over one-third of retail pharmacies and 88% of hospitals, with data subsequently stratified by size and region and then projected to determine total purchasing[20]. We used Statistics Canada annual population estimates to generate population-adjusted purchasing rates in each province[21].

Outcomes

Our primary outcomes were the impact of i) the federal regulatory proposal regarding a change to prescription-only status and ii) the subsequent 60-day period of public comment on the monthly volume of low-dose codeine purchased across Canadian provinces. For this analysis, we excluded data from Manitoba because low-dose codeine products were rescheduled as prescription only during the study period. The volume of low-dose codeine "units" dispensed allowed for standardization between liquid and solid dosage forms. We defined one unit as 8 milligrams of codeine, the standard dose in one OTC tablet.

In a secondary analysis, we investigated the impact of Manitoba's February 2016 policy change requiring a prescription for low-dose codeine. We examined several measures, including the monthly purchasing volume of low-dose codeine, of higher-dose codeine products (which have always required a prescription), and of all codeine strengths combined. We sought to determine whether restrictions the sale of OTC

codeine products was associated with a compensatory increase in the use of higher-dose codeine products.

Statistical Analysis

We used interventional autoregressive integrated moving average (ARIMA) models to examine the impact of regulatory proposals and policy changes on monthly purchasing of codeine at a population-adjusted rate in Canadian provinces. We differenced the time series and used the augmented Dickey-Fuller test to confirm stationarity. We selected model parameters using the residual autocorrelation function (ACF), partial autocorrelation function (PACF), and inverse autocorrelation function (IACF) correlograms. We chose the final model using the autocorrelation plots, the Ljung-Box chi-square test for white noise, and R-squared estimate of fit. In the primary analysis, we modeled Health Canada's proposed regulatory changes (July 2016) and the opening of the 60-day comment period on these regulatory changes (September 2017) as ramp functions to test for gradual changes in trends.

In our secondary analysis of codeine purchasing in Manitoba, we analyzed the impact of the February 2016 scheduling change on monthly sales of codeine-containing product. In separate models, we used a step intervention function to test for an immediate change in total codeine purchasing, a step intervention function to test for an immediate change in low-dose codeine purchasing, and a ramp intervention function to test for a gradual slope change in purchasing of higher-dose codeine products. All analyses were completed using SAS Enterprise Guide version 9.4 (SAS Institute, Cary, NC) and the SAS/ETS Time Series Forecasting System.

RESULTS

Over the study period, 24,120 kilograms of codeine (3.025 billion units) together with 937,867 kilograms of acetaminophen were sold as OTC low-dose codeine products across Canadian provinces. After population-adjustment, this amounts to approximately 88 codeine tablets dispensed OTC for every resident of Canadian provinces over a period of approximately 5 years.

Impact of selected opioid policies and interventions

In our primary analysis of low-dose codeine purchasing across Canada, we found that the proposed regulatory change announced in 2016 did not significantly impact low-dose codeine purchasing (p=0.574). In contrast, the subsequent announcement of a 60-day comment period in September 2017 was associated with a 43.5% decrease in low-dose codeine purchasing (from 1.38 to 0.78 units per resident between August 2017 and October 2019; p=0.03) (**Figure 1**).

In the secondary analysis of Manitoba trends, the February 2016 policy change was associated with an immediate 92% reduction in purchasing of low-dose codeine products (from 3.50 to 0.27 units per resident between January 2016 and February 2016; p<0.001) (**Figure 1)**. The scheduling change was not associated with compensatory changes in purchasing of higher-dose prescription codeine formulations (p=0.22; **Supplementary Appendix**).

Cross-provincial comparison of low-dose codeine purchasing

In the final year of our study period (November 1, 2018 to October 31, 2019), 375,847,016 units of low-dose codeine preparations were sold across Canada, representing 3,007 kilograms of codeine and 114,703 kilograms of acetaminophen. In Manitoba, where codeine products were only available with a prescription over the last

year of our study period, low-dose products accounted for 3.3% of all codeine sold by weight, compared to 21.7% in all other Canadian provinces where low-dose codeine products remained available for over-the-counter sale (**Table 1**). We identified considerable inter-provincial variability in the rate of OTC codeine purchasing. The annual rate of OTC codeine purchasing ranged from 1.6 units per person in Quebec to 17.3 units per person in British Columbia. The percentage of codeine attributable to low-dose preparations also varied by province, from 6.9% of all codeine purchased in Alberta to 44.6% of all codeine purchased in Ontario.

DISCUSSION

In this population-based study, we found that more than 375 million low-dose codeine tablets were dispensed without a prescription in Canada in the most recent 1-year period of 2018/2019. This approximates 10 tablets sold for every resident within Canada's provinces. Over one-fifth of all codeine dispensed (by weight) in the Canadian provinces was sold without a prescription. Interestingly, although the announcement regarding proposed national regulatory changes to OTC codeine products had no impact on OTC codeine accessibility, the initiation of a public commenting period was associated with reduced purchasing. In addition, rescheduling of low-dose codeine products in Manitoba was associated with an immediate and striking decrease in the total volume of these products sold, with no compensatory increase in higher-dose prescription codeine purchasing, and a significant decrease in the volume of codeine purchased overall. This demonstrates the potential impact of rescheduling if applied nationally in Canada.

The decrease in codeine purchasing observed following the opening of a comment period suggests that the engagement of stakeholders in regulatory discussion influenced

consumption trends. This may indicate that media coverage and communication to clinicians regarding the potential regulatory changes increased public awareness of the potential risks of codeine and may have influenced consumption trends and pharmacist counselling recommendations. This finding of reduced sales of low-dose codeine products is suggestive of a therapeutic area in which consumers and healthcare providers are willing to consider alternative therapies. Ongoing policy discussions should consider this as an indication of the ability for pharmacists and patients to adapt to changing regulation around these products if introduced nationally.

This is further reinforced by our findings in Manitoba, which are consistent with a study evaluating the 2018 rescheduling of low-dose codeine in Australia[22]. In both of these studies, purchasing of low-dose codeine preparations declined immediately following the policy change with no compensatory change in purchasing of high-dose formulations. The consistency of these findings suggests that rescheduling low-dose codeine preparations may reduce potentially inappropriate or unsafe use of these products without shifts in treatment towards higher strength alternatives.

Although Canadian data are lacking, treatment of acute and chronic pain is likely the principal reason for seeking over-the-counter codeine products. This assertion is supported by studies finding that 34% to 70% of individuals cite pain control as the principal reason for using these products in survey studies conducted in Australia and the UK, respectively[23, 24]. Accordingly, gaps in access to pain management modalities is a possible unintended consequence OTC codeine rescheduling and a corresponding shift to other, potentially less safe alternatives.

In Australia, the rescheduling of codeine products led to significant increases in non-opioid OTC analgesic use[25], suggesting that in some patients, safer approaches were used to manage pain. However, more data are needed to determine whether chronic

pain patients previously accessing OTC codeine were able to successfully manage their pain with non-opioid analgesics, or whether they transitioned to more potent opioids.

Our study has several limitations. First, the data represents codeine purchasing by pharmacies, and may not be reflective of consumption patterns as products may expire and be discarded, or be purchased by an individual and not completely consumed. However, pharmaceutical purchasing analysis methods are often used in antimicrobial stewardship analyses as they strongly correlate with consumption patterns[26], and such data are likely to provide an estimate of community consumption. Finally, we could not determine whether the rescheduling of low-dose codeine in Manitoba led to adverse patient outcomes, including opioid withdrawal, use of illicit opioids, or adverse outcomes from increased use of alternative analgesics. Future research is needed to further explore the impacts of this policy change.

Conclusion

Despite a trend towards lower use over time, the overall volume of low-dose codeine purchasing by pharmacies remains high, with an annual rate of 10 tablets being purchased by pharmacies for every resident of Canadian provinces in 2019. Despite a lack of a national regulatory change, Manitoba's rescheduling of these products in 2016 demonstrates the potential for rapid, large decreases in low-dose codeine purchasing across Canada if such a change was implemented. Given the risks of medication-related harm and dependence associated with low-dose codeine products, there is an opportunity for federal regulatory changes to improve medication safety across Canada.

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DISCLOSURES

The statements, findings, conclusions, views, and opinions expressed in this report are based in part on data obtained under license from IQVIA Solutions Canada Inc. concerning the following information service(s): CDH, data period November 1st, 2013, to October 31st, 2019. All Rights Reserved. The statements, findings, conclusions, views, and opinions expressed herein are not necessarily those of IQVIA Inc. or any of its affiliated or subsidiary entities.

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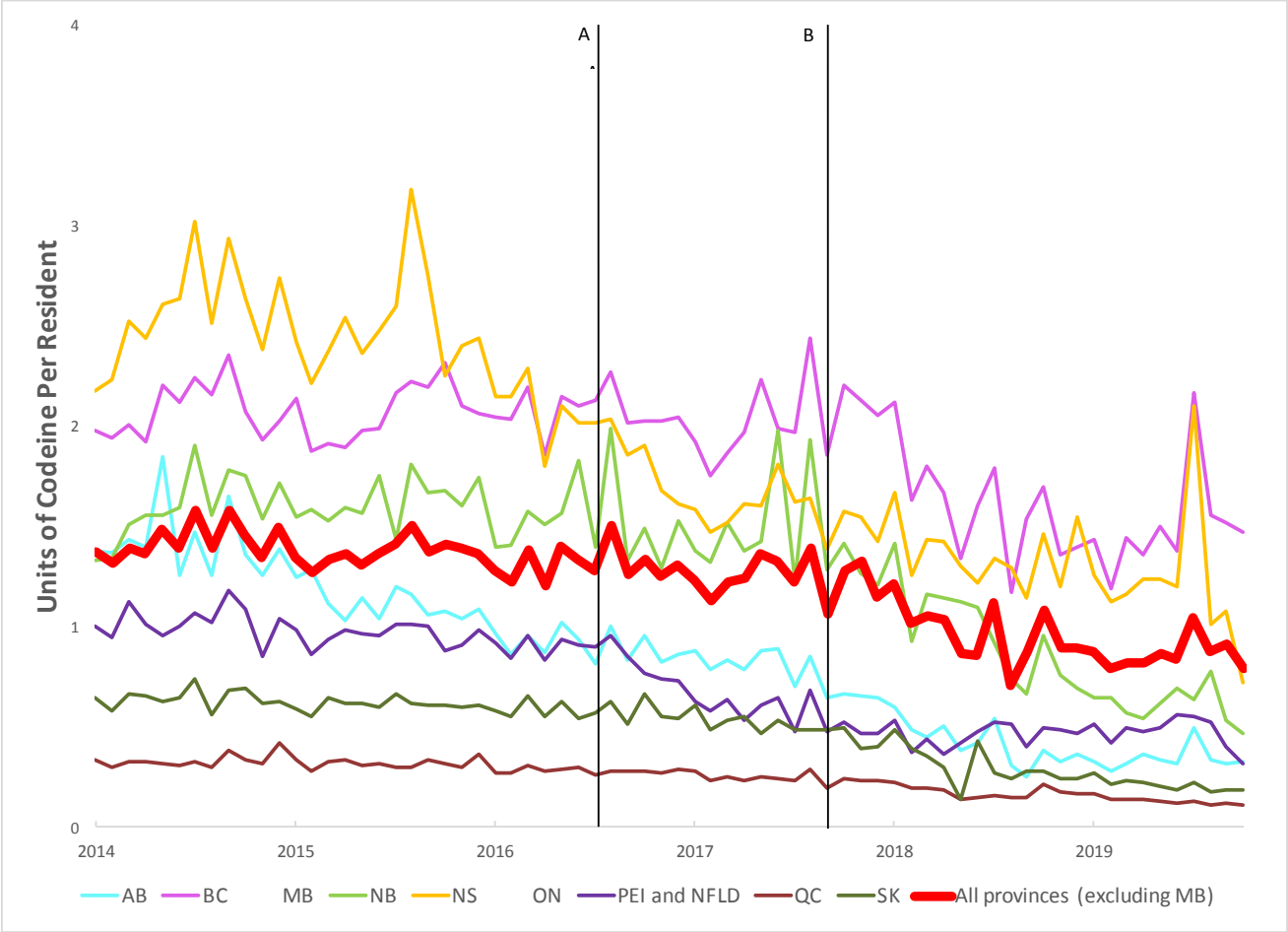
TABLES and FIGURES

Table 1: Descriptive characteristics for provincial low-dose codeine product sales between November 2018 and October 2019

Province	Units of Codeine (8mg)			Codeine sales		Acetaminophen sales	
	Number of Units (N)	Rate (units per resident	%* of total codeine sold as OTC	Kilograms	Rate (mg per resident)	Kilograms	Rate (mg per resident)
Alberta	17,688,955	4	7	142	32	5,375	1,230
British Columbia	89,681,975	18	38	718	142	26,500	5,225
Manitoba	2,175,128	12	3	17	13	753	550
New Brunswick	5,836,590	8	22	47	60	1,788	2,301
Nova Scotia	14,369,659	15	41	115	118	4,462	4,594
Ontario	225,685,892	16	45	1,806	124	69,698	4,785
PEI and NFLD	3,853,873	6	12	31	45	1,443	2,127
Quebec	13,570,422	2	19	109	13	3,730	440
Saskatchewan	2,984,521	3	9	24	20	954	813
All Provinces	**375,847,016**	**10**	**22**	**3,007**	**80**	**114,703**	**2,452**

***reported as a percent of total mass of codeine sold**

Figure 1. Low-dose codeine purchasing (units per resident) among Canadian Provinces from January 2014 to October 2019

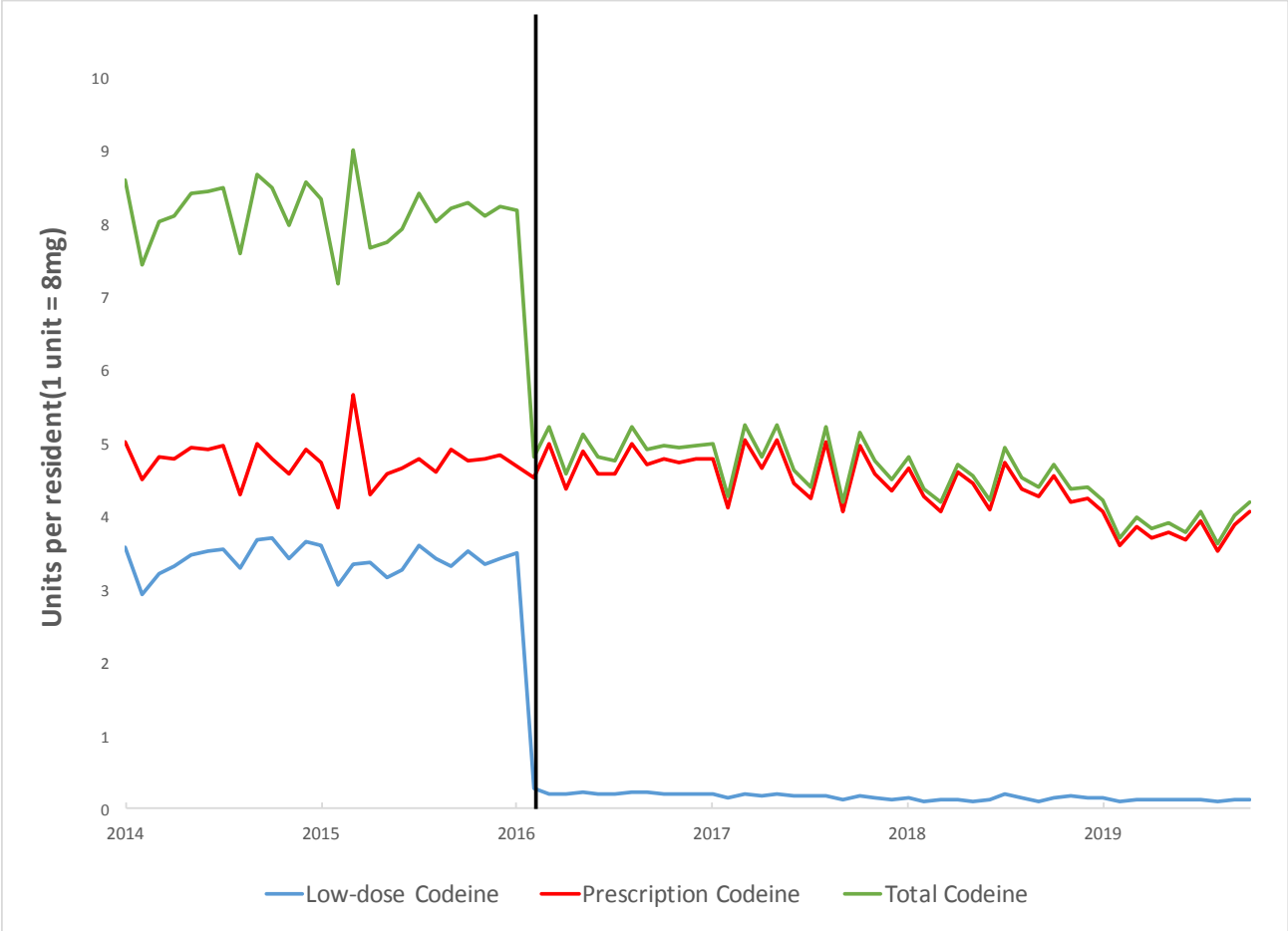


Vertical bars indicate policy changes which were modelled to assess for their impact on overall sale trends where:

A = Canadian proposal of regulatory changes: July 17th, 2016

B = Canadian Department of Health 60-day commenting period opens: September 9th, 2017

Figure 2. Codeine purchasing (OTC and prescription strength) in Manitoba from January 2014 to October 2019



Vertical bar indicates policy change to require a prescription for all codeine products regardless of strength