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Research

Off-label postpartum use of domperidone in Canada: a multidatabase cohort study

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Abstract

Background: Trends in off-label postpartum use of domperidone and the impact of safety advisories on its use remain unknown. Our objectives were to describe postpartum use of domperidone in Canada, to evaluate the impact of Health Canada advisories on prescribing patterns, and to describe the association between domperidone use and a composite end point of sudden cardiac death or ventricular tachycardia (VT) among postpartum patients.

Methods: We conducted a multidatabase cohort study involving pregnant patients with live births between 2004 and 2017 using administrative health databases from 5 Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba and Ontario). We excluded patients with less than 1 year of prepregnancy database history and with approved indications for domperidone. We assessed domperidone use in the 6 months postpartum and the impact of the 2012 and 2015 Health Canada advisories on prescribing via interrupted time series analysis. We estimated crude rates of VT and sudden cardiac death.

Results: We included 1 190 987 live births. Mean maternal age was 28.6 (standard error 0.6) years. Domperidone use increased over time, from 7% in 2003–2005 to 12% in 2009–2011, when it plateaued. The 2012 advisory was followed by a drop in use and a reduction in slope, and the 2015 advisory had a more modest impact. Crude analysis suggests that domperidone may be associated with increased VT or sudden cardiac death (0.74 v. 0.37 per 10 000 person-years; difference per 10 000 person-years: 0.37, 95% confidence interval –0.67 to 1.41).

Interpretation: Postpartum domperidone use increased between 2004 and 2017, with prescribing attenuated after Health Canada advisories and a very low absolute rate of VT or sudden cardiac death. These findings suggest that Health Canada advisories affected prescribing; any potential increase in VT or sudden cardiac death with use of domperidone is small and could not be confirmed in this large study. **Study registration:** ClinicalTrials.gov, no. NCT04024865

Domperidone is an antiemetic and prokinetic drug prescribed for nausea, vomiting and dyspepsia related to motility disorders.[1] Given its dopamine antagonist action, domperidone increases prolactin concentration and augments lactation.[2] Consequently, it is often used off label to promote lactation among postpartum patients with insufficient supply of breast milk. A population-based study reported a substantial and growing frequency of postpartum domperidone use between 2002 and 2011 in British Columbia, with about 20% of patients in 2011 filling at least 1 prescription in the first 6 months postpartum.[3] However, trends in postpartum use of domperidone in more recent years and in other jurisdictions remain understudied.

The increasing use of domperidone has coincided with concerns regarding its cardiac safety.[4–8] Cardiac events of concern include QT interval prolongation, torsades de pointes, serious ventricular arrhythmia and sudden cardiac death. The US Food and Drug Administration issued warnings regarding domperidone's unapproved use to increase milk production in 2004. Health Canada issued advisories regarding domperidone's cardiac risks in March 2012 and January 2015,[9,10] and the European Medicines Agency (EMA) released its recommendations in March 2014.[11] These safety advisories were based on evidence of increased arrhythmic events among older adults, who typically have a

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large comorbidity burden and frequent comedication use. However, evidence regarding the safety of domperidone in other populations such as postpartum patients, who may be less susceptible to its QT interval–prolonging effects, remains limited. The association between domperidone and cardiac events has been examined in a previous observational study involving postpartum patients.[11] Although the study identified a signal of potential harm (hazard ratio [HR] 2.25, 95% confidence interval [CI] 0.84 to 6.01), methodological limitations (i.e., exposure misclassification, outcome misclassification and imprecise estimates) render the study's results difficult to interpret.

Our objectives were to describe domperidone use among postpartum patients in Canada, to evaluate the impact of the Health Canada advisories on prescribing patterns, and to describe the association between domperidone use and the risk of a composite end point of sudden cardiac death or ventricular tachycardia (VT) among postpartum patients.

Methods

Study design

This study was conducted by the Canadian Network for Observational Drug Effect Studies (CNODES).[12] We conducted a multidatabase retrospective cohort study using administrative health databases from 5 Canadian provinces (BC, Alberta, Saskatchewan, Manitoba and Ontario), following a common protocol with distributed data. Using this approach, we developed a protocol collaboratively that was then adapted and implemented at each of the network's participating sites.[13]

Data sources

Canada has a publicly funded health care system that is administered provincially, with government drug insurance plans varying by province; CNODES has data-sharing agreements with 7 provinces (BC, Alberta, Saskatchewan, Manitoba, Ontario, Quebec and Nova Scotia).[12] Two Canadian CNODES sites were unable to participate in the present study: Quebec had data-access delays, and, at the time of study initiation, Nova Scotia drug data were limited to individuals aged 65 years and older. Data from Ontario were limited to recipients of social assistance.

From the 5 included provinces, we used linked, individual-level data on hospitalizations, physician visits, medication dispensations and vital status. Data sources were linked at the individual level using unique encoded identifiers derived from each person's health insurance number. The data sources are highly complete and accurate,[14,15] and are used extensively in pharmacoepidemiology.[12] Data sources used at each site are described in Appendix 1, Supplemental Table 1 (available at www.cmajopen.ca/content/9/2/E500/suppl/DC1).

Study population

In each province, we identified a cohort of all pregnancies ending with a hospital-delivered live birth between Apr. 1, 2004, and Sept. 30, 2017. The discharge date defined cohort entry. Exclusion criteria were maternal age less than 15 or greater than 55 years at cohort entry; less than 365 days of database history before conception (defined using the recorded gestational age or, if missing, defined as 273 days before term births and 245 days before preterm births[16]); health insurance coverage ending on or before cohort entry; no record of a newborn discharged alive; duplicate pregnancies caused by overlapping records or records reclassified as having outcomes other than live birth after the adjudication of overlapping records; a domperidone dispensing in the year before conception or during pregnancy (unless in the 6 months immediately after a previous birth); a diagnosis of Parkinson disease, Lewy body disease or other diseases that cause autonomic dysfunction or use of antiparkinsonian agents[17] before cohort entry; a diagnosis of gastroparesis in the year before conception or during pregnancy; and a diagnosis of VT before cohort entry.

Patients were followed until an event or censoring because of death, a diagnosis of an approved indication for domperidone (Parkinson disease or gastroparesis), emigration from the province, end of the 6-month follow-up or end of the study period (Sept. 30, 2017), whichever occurred first. Patients were permitted to contribute more than 1 observation.

Exposure

Exposure was defined using a time-fixed approach in which all observations were classified by the presence or absence of any dispensing for domperidone during the 6-month follow-up; previous studies suggest that most patients who start domperidone postpartum do so within the first 2 months.[3] In the safety analyses, exposure was defined using a time-varying approach; all person-moments of follow-up were classified as currently exposed or not currently exposed to domperidone. Current exposure was defined by a domperidone dispensation for which its duration plus a 7-day grace period overlapped with the day of follow-up being classified.

Outcome

The primary safety outcome was a composite end point of VT or sudden cardiac death, with a composite end point used to increase precision. The 3-step procedure used to identify VT or sudden cardiac death is described in Appendix 1, Supplemental Figure 1. Briefly, cases of a first recorded VT or sudden cardiac death were identified as possible events. The administrative data of these patients were then manually reviewed by reviewers blinded to patient domperidone use, to confirm that the events met the definition of VT or sudden cardiac death. The date of the first recorded VT diagnosis or sudden cardiac death defined the event date. Secondary outcomes were the individual end points of VT, sudden cardiac death and all-cause mortality.

The algorithm used *International Classification of Diseases, 9th Revision* (ICD-9-CM) and the Canadian version of *International Statistical Classification of Disease and Related Health Problems, 10th Revision* (ICD-10-CA) diagnostic codes in all sites, with Ontario also using modified ICD-8 codes.[18–20] The

diagnostic codes used are reported in Appendix 1, Supplemental Table 2.

Statistical analysis

Characteristics of patients who did and did not use domperidone were summarized at each site. The definitions used to operationalize these characteristics are reported in Appendix 1, Supplemental Table 3. We defined the prevalence of use as the percentage of patients who received a domperidone dispensation in the 6 months postpartum, with analyses stratified by province and by calendar period (2003–2005, 2006–2008, 2009–2011, 2012–2014 and 2015–2017). We described use overall, by dosage (> 30 mg/d v. ≤ 30 mg/d) and by duration (> 14 d v. ≤ 14 d) of the first treatment episode, defined by the prescription duration or, in the case of multiple prescriptions, their duration allowing for up to a 7-day gap between the end of one prescription and the start of the next.

We used interrupted time series analysis[21] to assess the impact of the Mar. 2, 2012, and Jan. 20, 2015, Health Canada advisories[9,10] on prescribing practices, comparing the rate of initiation before versus after the advisories with the estimates we would have expected to observe in their absence. We estimated the rate of domperidone initiation by quarter. We then used generalized least squares models that allow for a first-order autoregressive structure (to account for correlation between consecutive quarters) to examine the immediate impact and change in slope (i.e., trend) associated with the advisories. The impact of the advisories was examined overall, by dosage and by duration of the first treatment episode. In addition, we described the dosage and duration distributions before and after each advisory. Saskatchewan prescription data contained quantity dispensed but not duration, and we were unable to assume World Health Organization–defined daily doses[22] to estimate duration as we were studying off-label use. We therefore used the mean daily dose from Ontario to estimate duration in Saskatchewan. Province-specific results were pooled using DerSimonian and Laird random-effects models,[23] with the amount of between-province heterogeneity estimated using the I^2 statistic.

We had planned to assess the cardiac safety of domperidone using a prevalent new-user design.[24] However, given the small number of events in each province, this approach was deemed infeasible. Consequently, we estimated crude rate ratios and rate differences for each outcome across provinces, with exposure defined using the previously described time-varying approach.

In post-hoc sensitivity analyses, we repeated our interrupted time series analyses with a dependent variable of ln(prescription rate) to estimate relative reductions in geometric means at the time of the advisories. In addition, we repeated analyses using linear models rather than interrupted time series analyses to explore the impact of our choice of model structure on model fit.

Ethics approval

Research ethics board approvals were obtained at each participating institution, except at ICES in Ontario, where research ethics board approval was not legally required.

Results

A total of 1 190 987 pregnancies (Figure 1) ended with a live birth from 801 959 patients (Appendix 1, Supplemental Figure 2). Patients had been exposed to domperidone in 137 401 observations and had not been exposed in 1 053 586 observations. Table 1 and Appendix 1, Supplemental Table 4

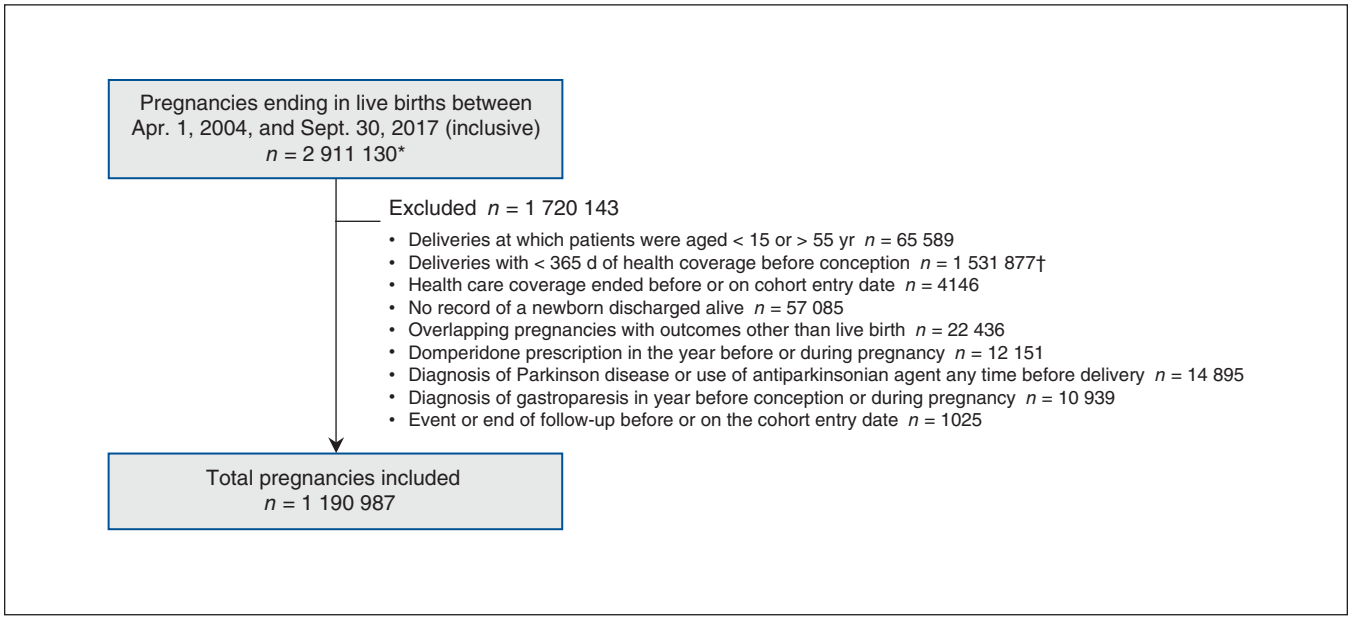


Figure 1: Flow diagram describing the construction of the study cohort across provinces, by pregnancy. *Patients were eligible to contribute multiple pregnancies to the study cohort. †The exclusion of observations with less than 365 days of health coverage was predominantly driven by Ontario, where the study population was restricted to patients receiving social assistance. Patients excluded in this step in Ontario included those who did not receive social assistance for at least 365 days before conception.

Table 1: Baseline characteristics of deliveries overall and by use of domperidone in the 6 months immediately postpartum*

Characteristic	No. (%) of deliveries†		
	Overall *n* = 1 190 987	Domperidone *n* = 137 401	No domperidone *n* = 1 053 586
Age, yr, mean ± SE	28.6 ± 0.6	29.6 ± 0.4	28.5 ± 0.6
Obesity‡	22 549 (1.9)	3221 (2.3)	19 328 (1.8)
Alcohol-related disorders	27 340 (2.3)	2266 (1.7)	25 074 (2.4)
Income quintile			
1 (lowest)	267 188 (22.4)	24 705 (18.0)	242 483 (23.0)
2	233 098 (19.6)	25 919 (18.9)	207 179 (19.7)
3	218 305 (18.3)	26 947 (19.6)	191 358 (18.2)
4	223 515 (18.8)	28 496 (20.7)	195 019 (18.5)
5 (highest)	177 454 (14.9)	23 423 (17.1)	154 031 (14.6)
Unknown	71 427 (6.0)	7911 (5.8)	63 516 (6.0)
Comorbidities			
Previous history of arrhythmia or conduction disorders	28 582 (2.4)	4047 (3.0)	24 535 (2.3)
Any insertion of a pacemaker or defibrillator	234 (< 0.1)	28 (< 0.1)	183 (< 0.1)
Hypertension	66 828 (5.6)	9658 (7.0)	57 170 (5.4)
Cardiomyopathy	1193 (0.1)	139 (0.1)	1054 (1.0)
Left ventricular hypertrophy	159 (< 0.1)	14 (< 0.1)	143 (0.0)
Heart failure	2435 (0.2)	330 (0.2)	2105 (0.2)
Ischemic heart disease	12 384 (1.0)	1956 (1.4)	10 428 (1.0)
Valvular heart disease	2620 (0.2)	327 (0.2)	2293 (0.2)
Diabetes	65 651 (5.5)	10 116 (7.4)	55 535 (5.3)
Depression	157 761 (13.3)	20 421 (14.9)	137 340 (13.0)
Pregnancy-related characteristics			
Multifetal gestation	22 008 (1.9)	5547 (4.0)	16 461 (1.6)
Parity ≥ 1			
No	579 511 (48.7)	87 614 (63.8)	491 897 (46.7)
Yes	611 025 (51.3)	49 773 (36.2)	561 252 (53.3)
Unknown	451 (0.0)	14 (0.0)	437 (0.0)
Cesarean delivery	332 987 (28.0)	49 579 (36.1)	283 408 (26.9)
Gestational age, wk, mean ± SE	39 ± 0.2	38.6 ± 0.3	39.1 ± 0.2
≤ 37	128 950 (10.8)	21 132 (15.4)	107 818 (10.2)
38–42 (inclusive)	1 061 930 (89.2)	116 262 (84.6)	945 668 (89.8)
≥ 43	107 (0.0)	6 (0.0)	100 (0.0)
Use of medications			
Antiarrhythmic drugs	26 731 (2.2)	4456 (3.2)	22 275 (2.1)
Statins	2286 (0.2)	366 (0.3)	1920 (0.2)
Antihypertensive medications	41 499 (3.5)	6915 (5.0)	34 584 (3.3)
Proton pump inhibitors	63 432 (5.3)	10 389 (7.6)	53 043 (5.0)
Antipsychotic medications	18 990 (1.6)	2486 (1.8)	16 504 (1.6)
Other medications with galactagogic effects	32 607 (2.7)	4652 (3.4)	27 955 (2.7)
Drugs with known risk of QT prolongation	294 860 (24.8)	42 866 (31.2)	251 994 (23.9)
Strong and moderate CYP3A4 inhibitors	130 647 (11.0)	18 051 (13.1)	112 596 (10.7)

Note: CYP3A4 = cytochrome P450 3A4, SE = standard error.
*Patients were permitted to contribute multiple observations to the study cohort.
†Unless stated otherwise.
‡Defined using diagnostic codes for obesity (*International Statistical Classification of Disease and Related Health Problems, 10th Revision* code E66.x and *International Classification of Diseases, 9th Revision* code 278.0).

summarize the characteristics of the cohort overall and by exposure status. Compared with patients not using domperidone, patients using domperidone were older, more likely to be obese, more likely to reside in higher socioeconomic areas and less likely to have alcohol-related disorders. Although the cohort was generally healthy, patients using domperidone had a higher prevalence of medication use and comorbidities, including risk factors for cardiac arrhythmias. Patients using

domperidone were also more likely to have had a multifetal gestation, cesarean delivery, premature birth and gestational complications during the cohort entry–defining pregnancy.

Drug utilization

Figure 2 and Appendix 1, Supplemental Figures 3–5 describe the prevalence of domperidone use in the 6 months postpartum between 2004 and 2017. Across provinces, postpartum use increased from 7% in 2003–2005 to 12% in 2009–2011, when it plateaued. Important interprovincial differences existed, with the greatest use observed in BC and Alberta and less frequent use in Saskatchewan, Manitoba and Ontario. The prevalence of use increased over time in most provinces, although small decreases were observed in later periods in BC and Alberta. The prevalence of use ranged from 2% in Saskatchewan to 10% in BC in 2003–2005 and from 6% in Manitoba to 14% in BC in 2015–2018. Similar patterns were observed when analyses were restricted to use of dosages greater than 30 mg/d and durations greater than 14 days (Appendix 1, Supplemental Figures 4 and 5).

Impact of Health Canada advisories

The results of our interrupted time series analyses are reported in Figures 3 and 4, and in Appendix 1, Supplemental Figures 6–15. After the 2012 advisory there was an immediate drop of 11.5 initiators per 100 000 person-days at the time of the advisory and a reduction in slope of initiation of 0.8 initiators per 100 000 person-days per quarter (Figure 3). Similar trends were observed for doses greater than 30 mg and durations greater than 14 days (Appendix 1, Supplemental Figures 6 and 7). Changes after the 2015 advisory were more modest (Figure 4; Appendix 1, Supplemental Figures 7 and 8).

Appendix 1, Supplemental Tables 5 and 6 summarize the dosage and duration of the first domperidone treatment episode among initiators by province and by period. Overall, among those dispensed domperidone, the dosage decreased across periods in each province. However, the median dosage remained greater than 30 mg/d in all provinces after the advisories. The median duration was 30 days in most provinces, which remained unchanged after the advisories.

The results of sensitivity analyses examining the relative reductions are found in Appendix 1, Supplemental Tables 7 and 8. This approach reduced the heterogeneity across sites and improved model fit relative to the primary analysis, but similar trends were observed as in our primary analysis. In addition, in all scenarios, the Akaike information criterion (AIC) for the interrupted time series analysis was smaller than the AIC for the linear model, indicating better model fit (Appendix 1, Supplemental Tables 9 and 10).

Cardiac events

Appendix 1, Supplemental Table 11 describes the overall incidence rates across the 5 provinces. Events were rare (22 composite events, 13 VTs, 10 sudden cardiac deaths and 168 all-cause deaths), with rates ranging from 0.18 (95% CI 0.09

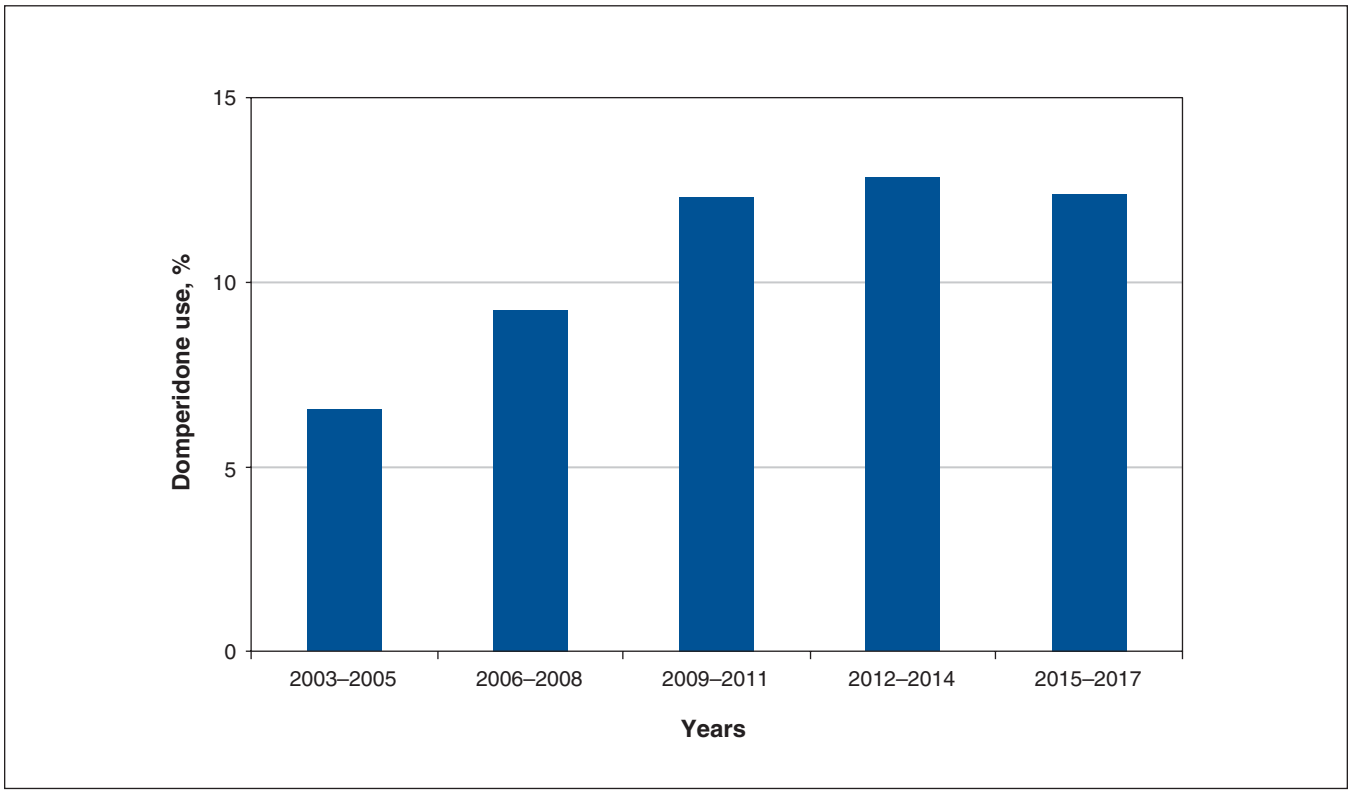
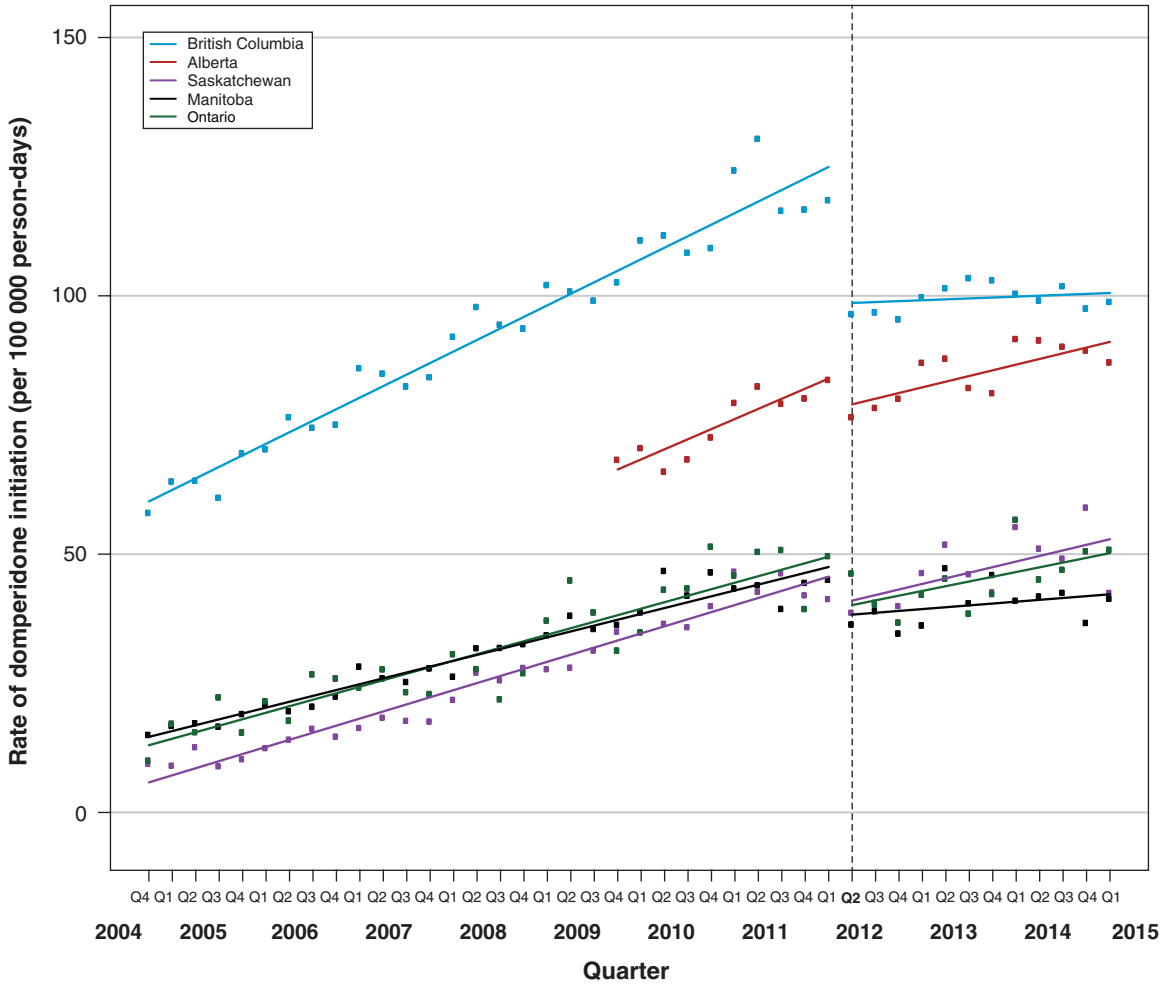


Figure 2: Prevalence of domperidone use in the 6 months after delivery among postpartum patients in 5 Canadian provinces. Health Canada advisories regarding domperidone were issued in March 2012 and January 2015.

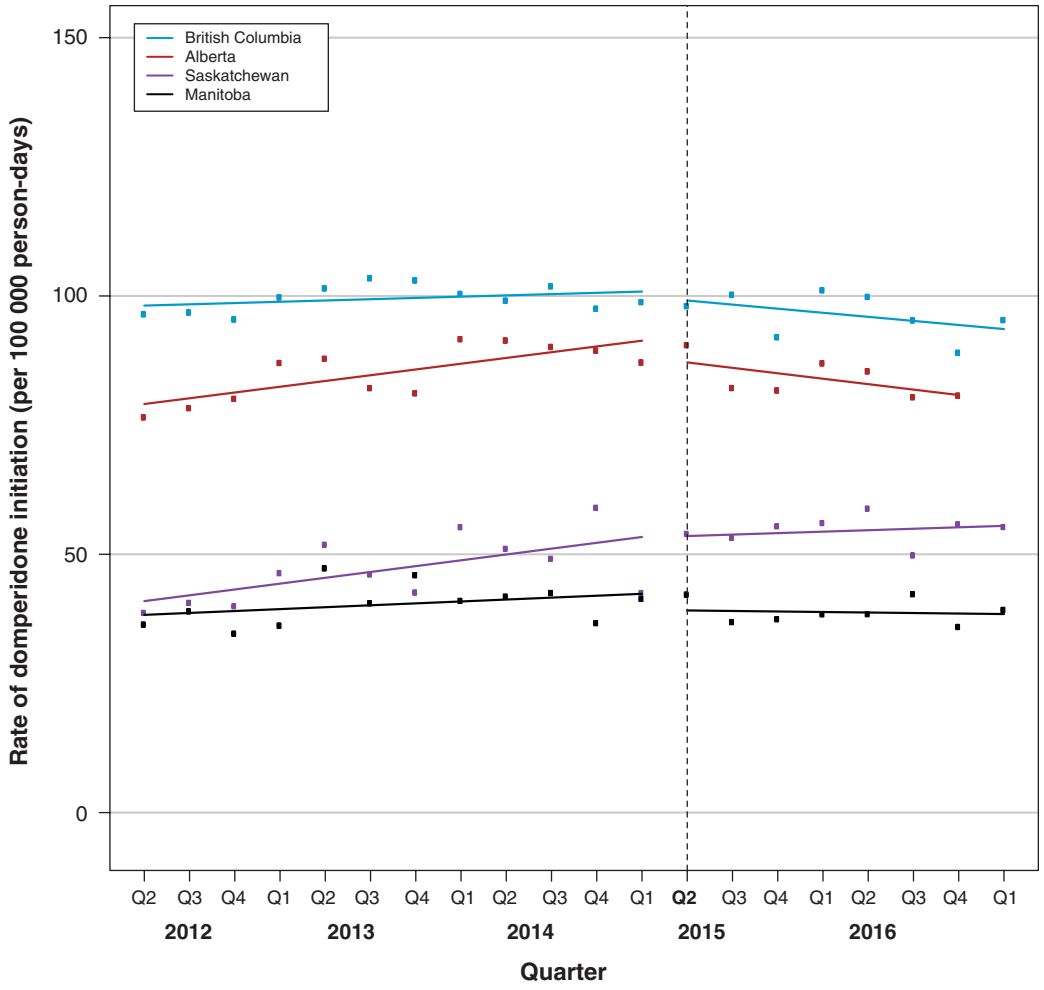


Province	Immediate impact (95% CI)*	Change in slope (95% CI)†
British Columbia	–26.5 (–33.0 to –20.0)	–2.1 (–2.9 to –1.3)
Alberta	–6.1 (–12.5 to 0.3)	–0.9 (–2.0 to 0.3)
Saskatchewan	–5.7 (–10.6 to –0.9)	–0.3 (–0.9 to 0.3)
Manitoba	–9.6 (–13.9 to –5.2)	–0.8 (–1.3 to –0.2)
Ontario	–10.3 (–17.3 to –3.2)	–0.3 (–1.2 to 0.5)
All provinces	–11.5 (–18.9 to –4.2) I^2= 88.2% Tau^2 = 61.8	–0.8 (–1.5 to –0.2) I^2 = 72.2% Tau^2 = 0.356

*Impact is measured in initiators per 100 000 person-days.
†Change in slope is measured in initiators per 100 000 person-days per quarter.

Figure 3: Interrupted time series analysis examining the impact of the 2012 Health Canada advisory on rates of initiation of domperidone in the 6 months immediately postpartum in 5 Canadian provinces. The dashed line represents the release of the 2012 Health Canada advisory. Note: CI = confidence interval.

to 0.33) per 10 000 person-years for sudden cardiac death to 2.95 (95% CI 2.54 to 3.44) per 10 000 person-years for all-cause mortality. Table 2 summarizes the rates of our safety end points by current domperidone use. Crude incidence rates for our composite end point of VT or sudden cardiac death were numerically higher with current use of domperidone than with no current use (crude rate ratio 2.01, 95% CI 0.47 to 8.60; crude rate difference 0.37, 95% CI –0.67 to 1.41 per 10 000 person-years). In contrast, all-cause mortality was lower with current domperidone use (crude rate ratio 0.37, 95% CI 0.12 to 1.15; rate difference –1.93, 95% CI –3.28 to –0.59 per 10 000 person-years).



Province	Immediate impact (95% CI)*	Change in slope (95% CI)†
British Columbia	–0.9 (–7.1 to 5.2)	–1.0 (–2.2 to 0.1)
Alberta	–3.2 (–10.1 to 3.8)	–2.2 (–3.6 to –0.7)
Saskatchewan	–0.1 (–6.8 to 6.6)	–0.8 (–2.0 to 0.3)
Manitoba	–3.1 (–9.0 to 2.8)	–0.5 (–1.5 to 0.6)
All provinces	–1.9 (–5.0 to 1.3) I^2 = 0.0% Tau^2 = 0.00	–1.0 (–1.6 to –0.4) I^2 = 0.33% Tau^2 = 0.001

*Impact is measured in initiators per 100 000 person-days.
†Change in slope is measured in initiators per 100 000 person-days per quarter.

Figure 4: Interrupted time series analysis examining the impact of the 2015 Health Canada advisory on rates of initiation of domperidone in the 6 months immediately postpartum in 4 Canadian provinces. Ontario was excluded from this analysis owing to insufficient data available post-advisory. The dashed line represents the release of the 2015 Health Canada advisory. Note: CI = confidence interval.

Interpretation

Our study was designed to assess off-label domperidone use among postpartum patients in Canada. We found that use was prevalent in this population, increasing substantially between 2004 and 2017 (7% in 2003–2005 until a plateau at 12% in 2009–2011 that persisted through 2015–2017). The 2012 Health Canada advisory[9] was associated with a reduction in prescribing overall and of dosages greater than 30 mg/d and durations greater than 14 days. The 2015 advisory[10] was associated with a more modest impact on prescribing. The safety analysis indicated a relatively higher risk of

Table 2: Rates of ventricular tachycardia, sudden cardiac death and all-cause mortality among postpartum patients in the 6 months immediately postpartum across the 5 participating provinces (2004–2017), by current use of domperidone

Variable	Incidence rate (95% CI)*	Crude rate ratio (95% CI)	Crude rate difference (95% CI)*
Composite of VT or sudden cardiac death			
Current domperidone use	0.74 (0.19 to 2.97)	2.01 (0.47 to 8.60)	0.37 (–0.67 to 1.41)
No current domperidone use	0.37 (0.24 to 0.57)	1.00 (Ref.)	0.00 (Ref.)
VT			
Current domperidone use	0.74 (0.19 to 2.97)	3.66 (0.81 to 16.49)	0.54 (–0.50 to 1.57)
No current domperidone use	0.20 (0.11 to 0.37)	1.00 (Ref.)	0.00 (Ref.)
Sudden cardiac death			
Current domperidone use	0.00 (0.00 to 0.00)	—	–0.18 (–0.30 to –0.07)
No current domperidone use	0.18 (0.10 to 0.34)	1.00 (Ref.)	0.00 (Ref.)
All-cause mortality			
Current domperidone use	1.11 (0.36 to 3.45)	0.37 (0.12 to 1.15)	–1.93 (–3.28 to –0.59)
No current domperidone use	3.05 (2.61 to 3.55)	1.00 (Ref.)	0.00 (Ref.)

Note: CI = confidence interval, Ref. = reference, VT = ventricular tachycardia.
*Incidence rate and rate difference are expressed as event per 10 000 person-years. Event totals by treatment group are not reported owing to the presence of small cells (counts < 6).

VT or sudden cardiac death among patients using domperidone than among those not using domperidone. However, the crude nature of these analyses and sparse data limit the conclusions that can be drawn from these findings.

We observed interprovincial variation in domperidone prescriptions. These differences approximate the prevalence of breastfeeding during the study period,[25,26] suggesting that differences in the prevalence of breastfeeding may be at least partially responsible for the observed interprovincial differences. Given our use of administrative data, we were unable to restrict inclusion to patients who were breastfeeding. Ultimately, the observed interprovincial differences are likely explained by a combination of differences in prescribing practices, health care access, patient preferences and breastfeeding practices.

The impact of regulatory warnings concerning domperidone has been examined previously outside of Canada.[27] Mehrabadi and colleagues found that the EMA advisory regarding domperidone was associated with decreased prescribing of dosages greater than 30 mg/d, a nonsignificant decrease in monthly prescriptions and no change in time trend in the United Kingdom.[27] Importantly, although the Health Canada advisories were followed by decreased rates of initiation at higher dosages and decreased median dosage in all provinces in our study, the median dosage in all provinces exceeded the recommended dosages of no more than 30 mg/d after the advisories.[9,10]

Mehrabadi and colleagues found that the rate of initiation of domperidone increased from 2002–2004 (0.56 per 100 person-years) to 2011–2013 (2.1 per 100 person-years), before dropping slightly in 2014–2015 (2.0 per 100 person-years) after the EMA advisory.[27] Domperidone use among postpartum patients was also assessed in an Australian tertiary teaching hospital, which reported that 5% of patients were dispensed domperidone, with use increasing during the 2004–2008 study period.[28]

Smolina and colleagues found that domperidone may increase the risk of ventricular arrhythmias or cardiac arrest (HR 2.25, 95% CI 0.84 to 6.01) using BC data.[11] Our utilization analyses described similar trends but included 4 additional provinces and up to 6 years of more contemporary data. Although we identified fewer events, this is likely the result of differences in event definitions, with Smolina and colleagues also including atrial arrhythmia codes and the present study restricting events to those considered sudden and unexpected, and using exposure grace periods. Despite these differences, the estimates reported by Smolina and colleagues are compatible with our estimates (crude rate ratio 2.01, 95% CI 0.47 to 8.60). The rates of VT and sudden cardiac death among patients using domperidone reported in the present study are higher than those reported by Mehrabadi and colleagues,[27] who reported no exposed ventricular arrhythmias, cardiac arrests or sudden cardiac deaths. Importantly, although our analysis suggests that domperidone may increase VT or sudden cardiac death risk, estimates are crude and imprecise. Although this analysis suggests a potential doubling of the risk, the absolute risk in this population remains very small. Our analyses also suggest a potential decreased risk of all-cause mortality, but this observation may be explained by confounding. Ultimately, given the unadjusted nature of these analyses, they should be interpreted very cautiously.

Limitations

Our study has several limitations. Data on prescription drug claims do not contain information regarding indication.

Although we excluded patients with approved indications for domperidone, it is possible that some patients were using it for indications other than lactation. Data regarding alcohol consumption and smoking status were not available. Also, data regarding breastfeeding were not systematically captured. Exposure misclassification is possible as data are not available regarding medication consumption. Assessment of VT and sudden cardiac death in administrative databases is challenging, and outcome misclassification is therefore possible. The limited number of events did not allow for formal safety analyses. Our interrupted time series analyses may also have been affected by unmeasured confounders (e.g., other changes in guidelines or clinical practice occurring around the time of the advisories). Finally, there were differences across sites in data availability. Ontario data were restricted to recipients of social assistance, and the generalizability of trends observed in this population to others is unknown. Vital statistics data were not available in Saskatchewan, and only partial emergency department data were available, potentially resulting in incomplete event capture.

Conclusion

The use of domperidone among postpartum patients increased substantially between 2004 and 2017, though variations existed across provinces. The 2012 Health Canada advisory was followed by important changes in prescribing practices across provinces, whereas the 2015 advisory had a more modest impact on prescribing. Our safety analysis showed a crude rate of VT or sudden cardiac death that was relatively higher among those using domperidone than among those not using domperidone. However, owing to sparse data and the lack of statistical adjustment, these results should be interpreted with caution. Nonetheless, the absolute rate of VT or sudden cardiac death is low in this population, and although a potential increased risk could not be confirmed in this large study, it should be discussed when considering treatment options for individual patients.

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SUPPLEMENTAL MATERIAL

Off-label Use of Domperidone Among Postpartum Women in Canada: A Multi-database Cohort Study

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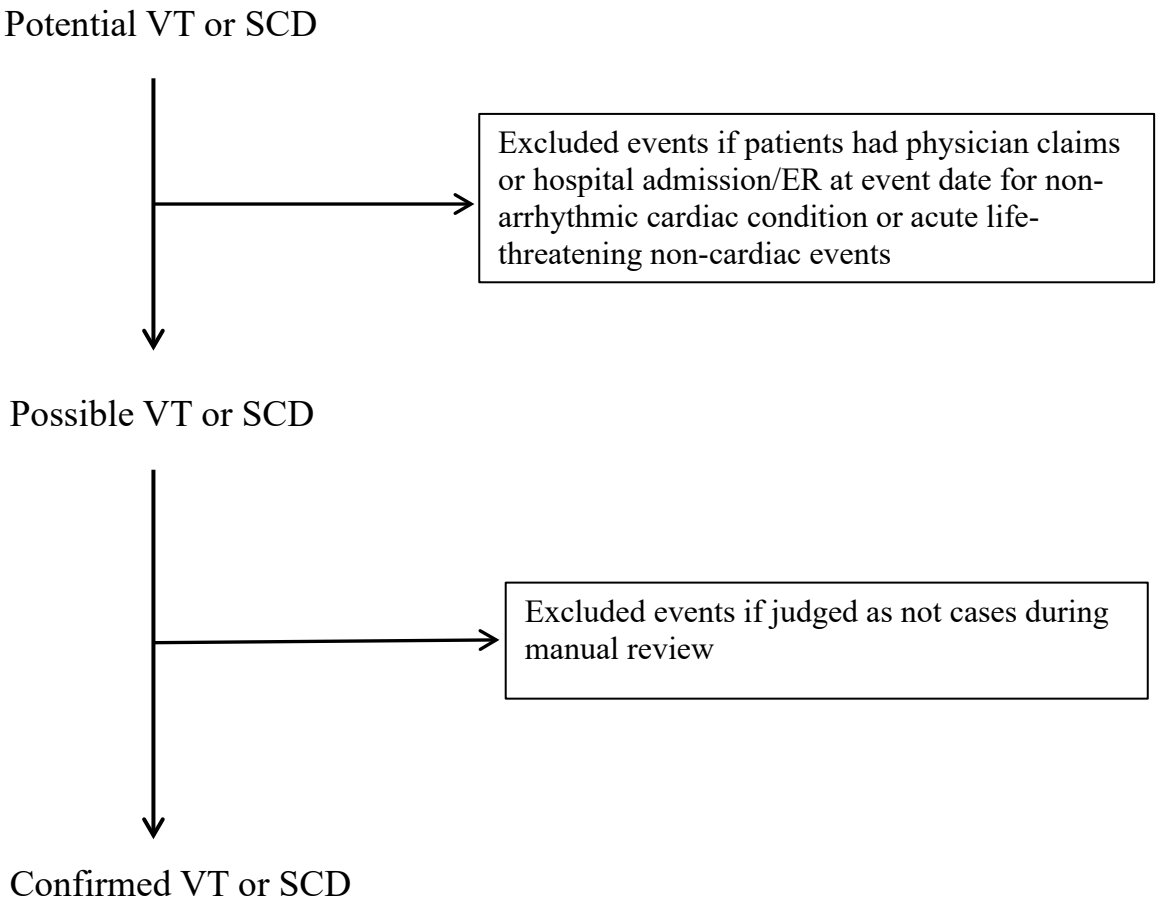
Appendix 1, as supplied by the authors. Appendix to: Moriello C, Paterson JM, Reynier P, et al; the Canadian Network for Observational Drug Effect Studies (CNODES) Investigators. Off-label postpartum use of domperidone in Canada: a multidatabase cohort study. *CMAJ Open* 2021. doi: 10.9778/cmajo.20200084.

Appendix 1, as supplied by the authors. Appendix to: Moriello C, Paterson JM, Reynier P, et al; the Canadian Network for Observational Drug Effect Studies (CNODES) Investigators. Off-label postpartum use of domperidone in Canada: a multidatabase cohort study. *CMAJ Open* 2021. doi: 10.9778/cmajo.20200084.

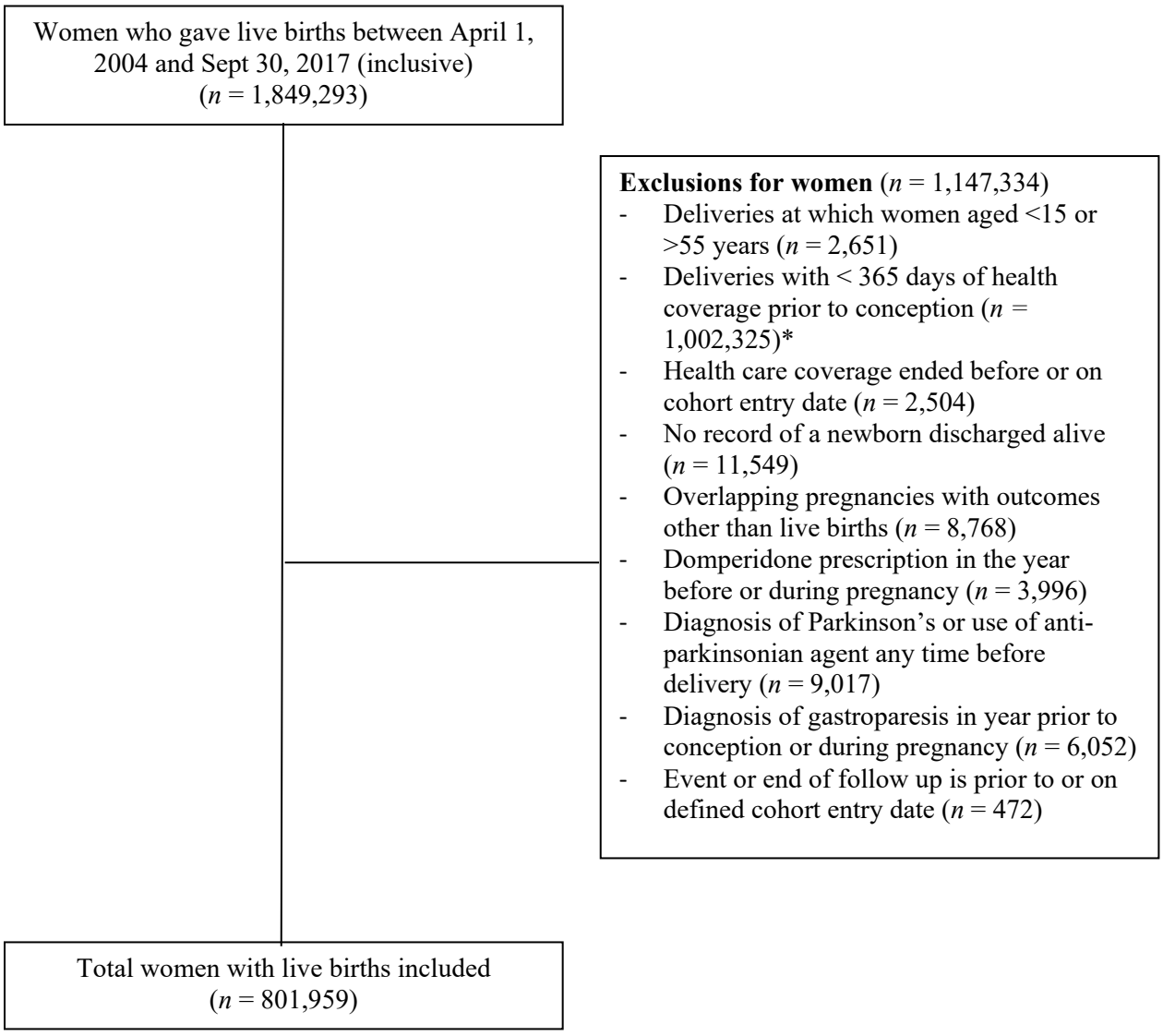
Supplemental Figure 1. Event adjudication process for SCD and VT.



We first identified all women with a first recorded diagnosis of VT or SCD (defined using Canadian version of International Statistical Classification of Disease and Related Health Problems, 10th Revision [ICD-10-CA] diagnostic codes) (1) in hospitalization, emergency room, or vital statistics data during the 180 days after cohort entry; these records represented *potential* VT/SCD events. From these potential events, we then used hospitalization, emergency room, vital statistics, and outpatient billing data to exclude records with diagnostic codes (International Classification 9th Revision [ICD-9-CM] or ICD-10-CA codes in all sites, with Ontario's outpatient billing data using modified ICD-8 codes) (1-3) indicating non-arrhythmic cardiac events or acute life-threatening non-cardiac events (Supplementary Table 2), with the remaining events

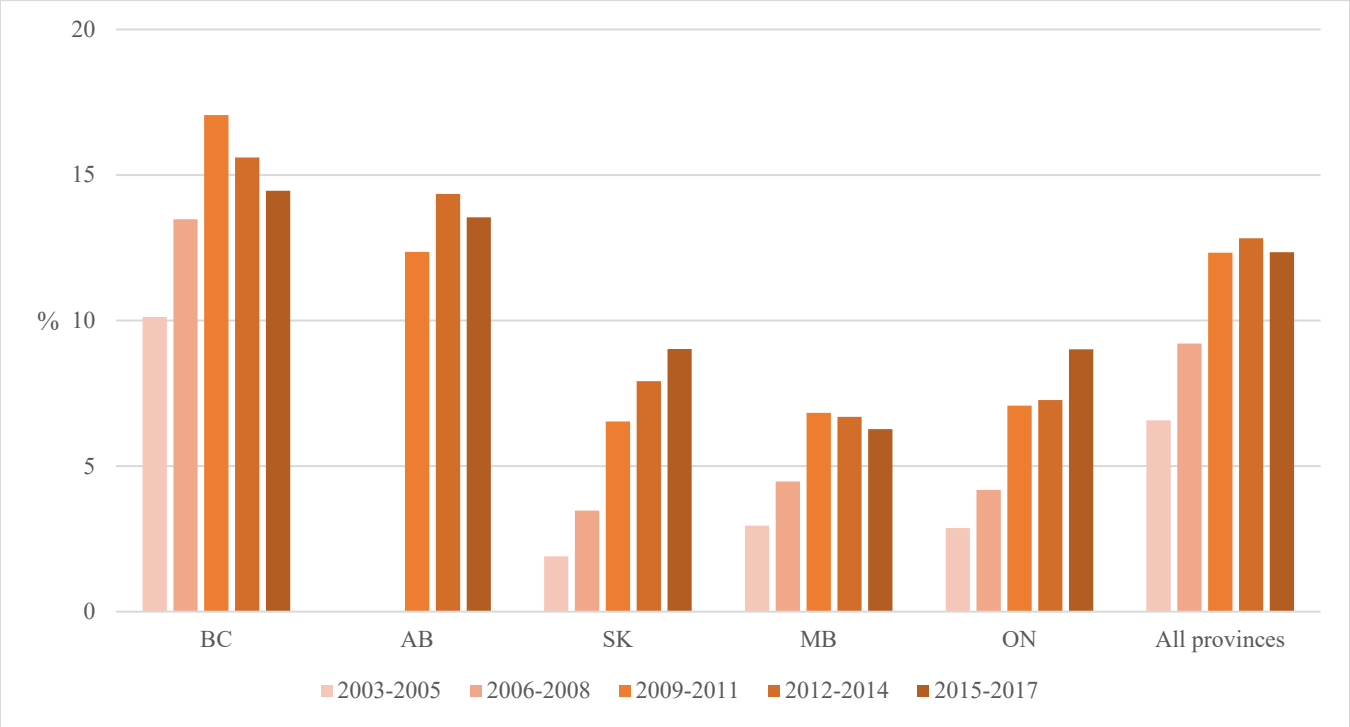
representing *possible* VT/SCD events. These remaining events then underwent manual review of their electronic administrative health records (including recorded diagnoses, procedures, and medication dispensing), blinded to exposure status, to further exclude events that did not meet the definition of SCD or VT.

Supplemental Figure 2. Flow diagram describing the construction of the study cohort across provinces, by woman.



* The exclusion of observations with <365 days of health coverage was predominantly driven by Ontario, which was restricted to social assistance data.

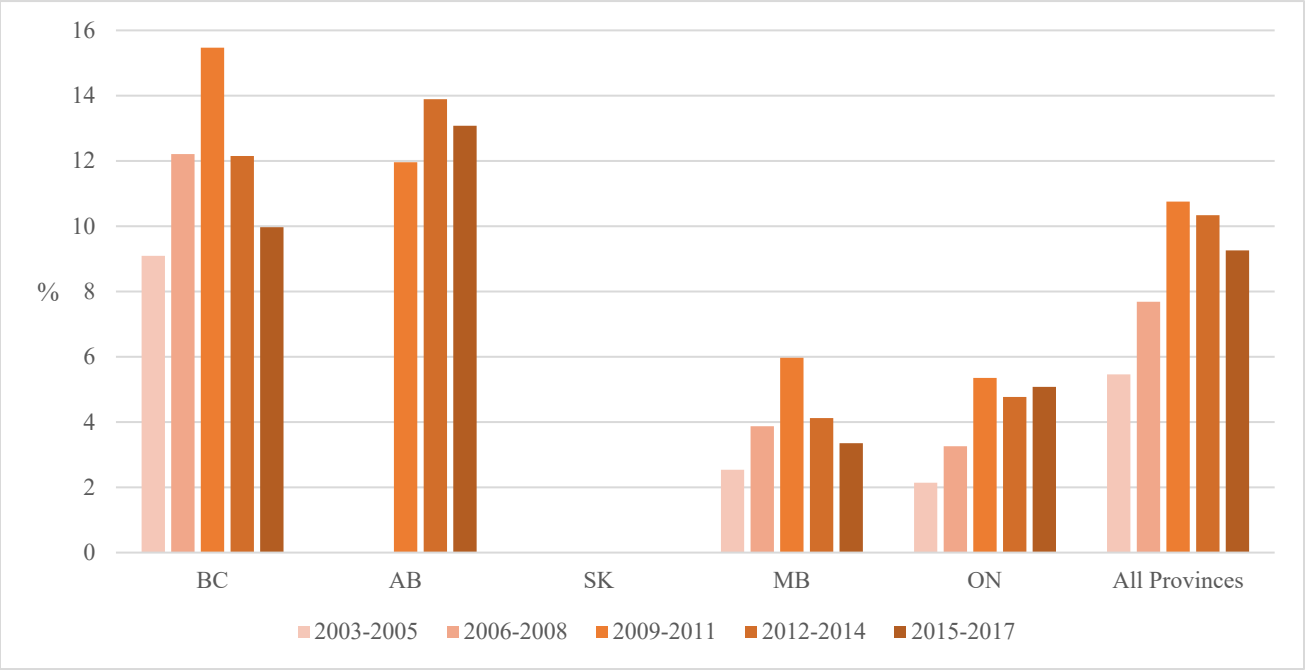
Supplemental Figure 3. Prevalence of domperidone use in the six months after delivery among postpartum women in five Canadian provinces, by province.



Abbreviations: BC: British Columbia; AB: Alberta; SK: Saskatchewan; MB: Manitoba; ON: Ontario.

Appendix 1, as supplied by the authors. Appendix to: Moriello C, Paterson JM, Reynier P, et al; the Canadian Network for Observational Drug Effect Studies (CNODES) Investigators. Off-label postpartum use of domperidone in Canada: a multidatabase cohort study. *CMAJ Open* 2021. doi: 10.9778/cmajo.20200084.

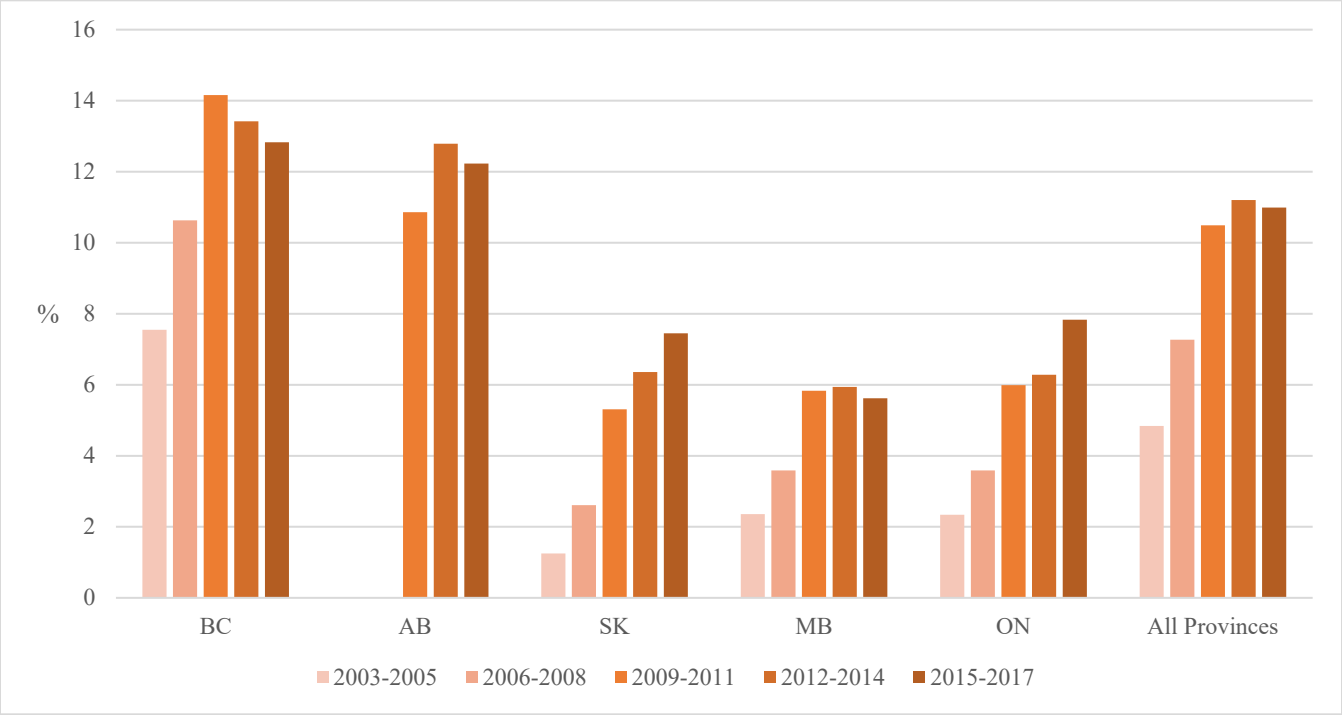
Supplemental Figure 4. Prevalence of domperidone use with a dose at first domperidone treatment episode >30 mg among postpartum women in four Canadian Provinces.



Note: Saskatchewan was excluded from the dose >30 mg analyses as data regarding dosage were not available**.**
Abbreviations: BC: British Columbia; AB: Alberta; SK: Saskatchewan; MB: Manitoba; ON: Ontario.

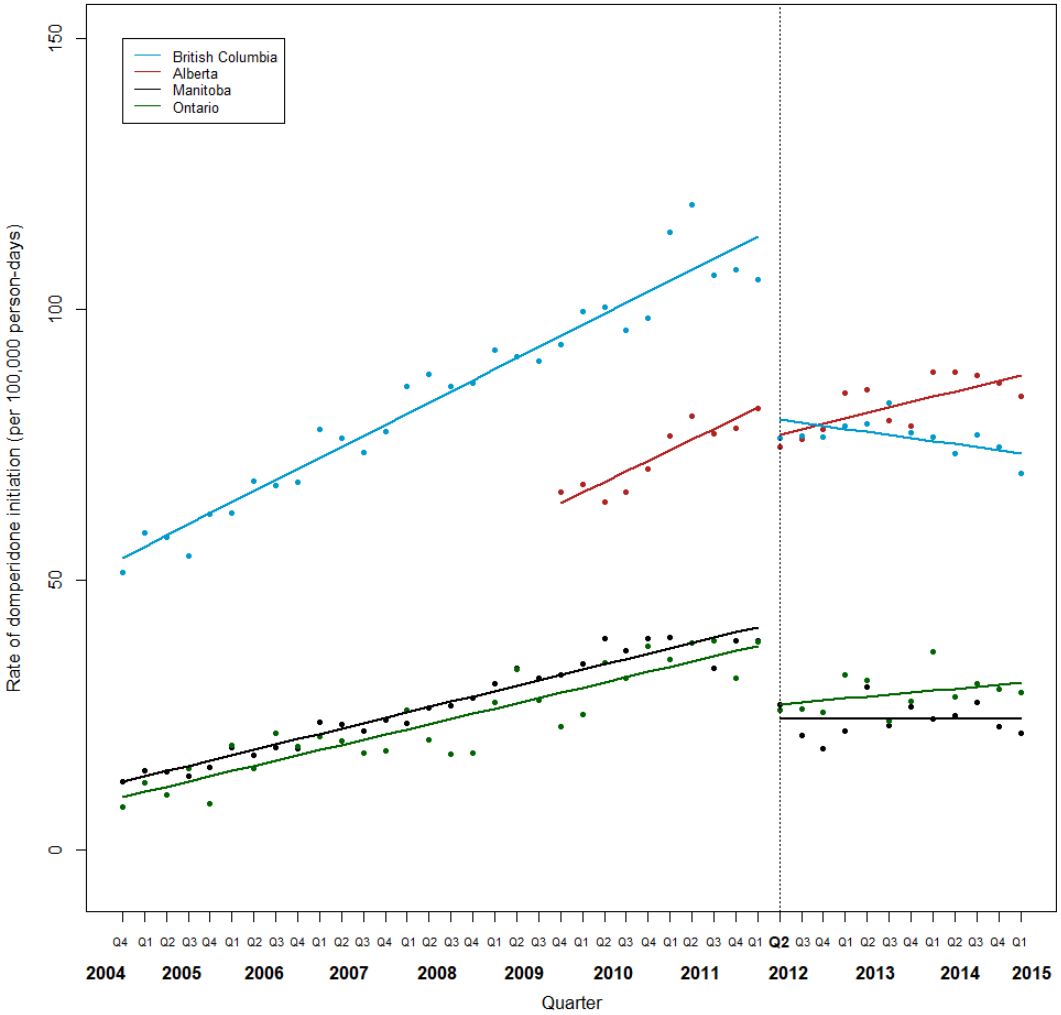
Appendix 1, as supplied by the authors. Appendix to: Moriello C, Paterson JM, Reynier P, et al; the Canadian Network for Observational Drug Effect Studies (CNODES) Investigators. Off-label postpartum use of domperidone in Canada: a multidatabase cohort study. *CMAJ Open* 2021. doi: 10.9778/cmajo.20200084.

Supplemental Figure 5. Prevalence of domperidone use with a duration of first domperidone treatment episode >14 days among postpartum women in five Canadian Provinces.



Abbreviations: BC: British Columbia; AB: Alberta; SK: Saskatchewan; MB: Manitoba; ON: Ontario.

Supplemental Figure 6. Interrupted time series analysis examining the impact of the 2012 Health Canada advisory on rates of initiation of domperidone at dose > 30 mg/day in the six months immediately postpartum in four Canadian provinces.



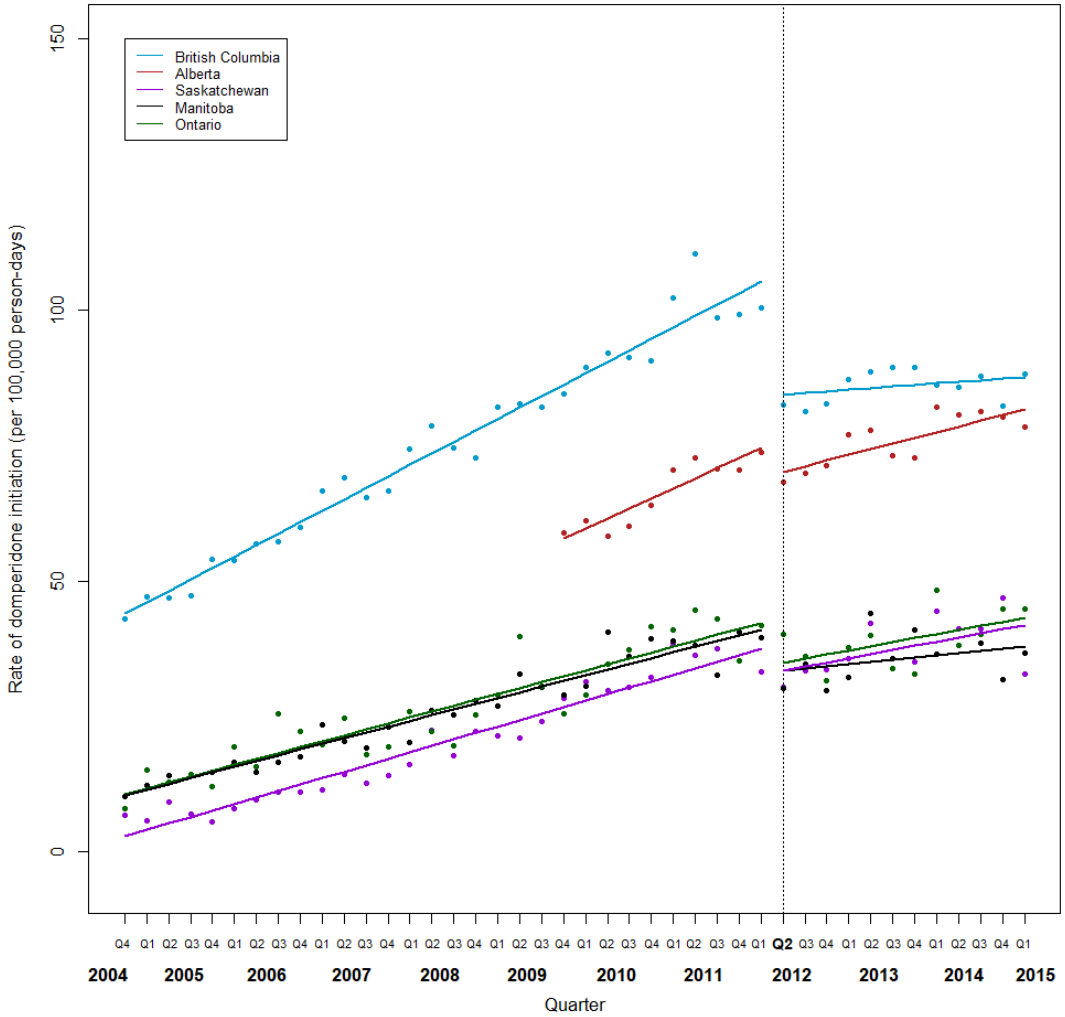
Province	Immediate Impact (95% CI)*	Change in Slope (95% CI)†
British Columbia	-33.3 (-39.9, -26.7)	-2.6 (-3.4, -1.8)
Alberta	-6.0 (-12.2, 0.2)	-0.9 (-2.1 0.2)
Manitoba	-17.1 (-20.8, -13.3)	-1.0 (-1.4, -0.5)
Ontario	-11.1 (-16.4, -5.9)	-0.6 (-1.2, 0.0)
All Provinces	-16.8 (-28.2, -5.4) I^2= 94.6% Tau^2= 127.22	-1.3 (-2.1, -0.4) I^2= 83.4% Tau^2= 0.639

Note: Saskatchewan does not have access to dosage data and was thus excluded from dosage analyses

* Impact is measured in initiators per 100,000 person-days.

† Change in slope is measured in initiators per 100,000 person-days per quarter.

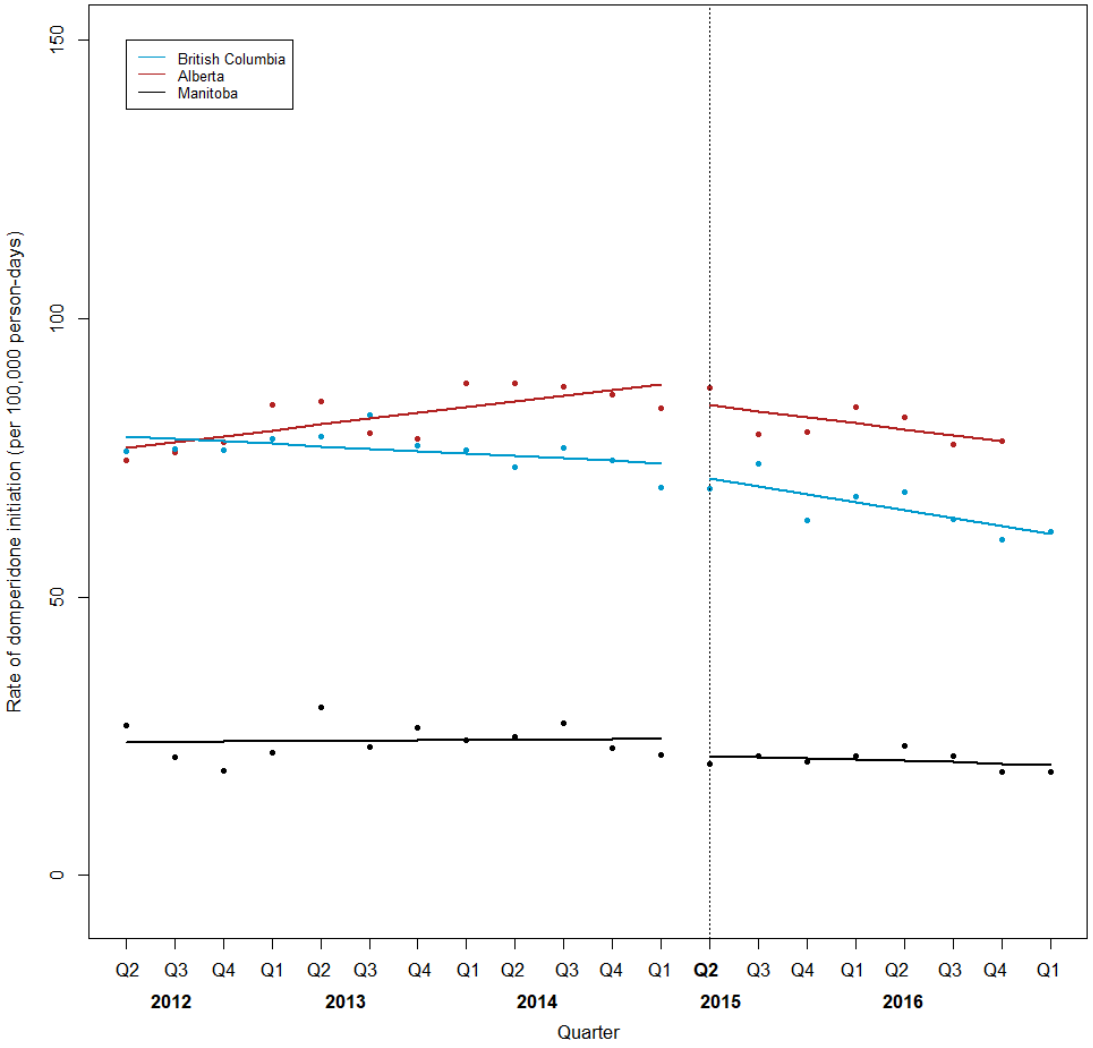
Supplemental Figure 7. Interrupted time series analysis examining the impact of the 2012 Health Canada advisory on rates of initiation of domperidone for duration > 14 days in the six months immediately postpartum in five Canadian provinces.



Province	Immediate Impact (95% CI)*	Change in Slope (95% CI)†
British Columbia	-21.1 (-26.5, -15.7	-1.8 (-2.5, -1.1)
Alberta	-5.4 (-10.7, -0.1)	-0.8 (-1.7, 0.1)
Saskatchewan	-4.8 (-9.5, -0.1)	-0.4 (-1.0, 0.2)
Manitoba	-7.9 (-12.1, -3.7)	-0.6 (-1.2, -0.1)
Ontario	-8.0 (-14.3, -1.8)	-0.3 (-1.1, 0.4)
All Provinces	-9.4 (-15.2, -3.6) I^2= 84.6% Tau^2= 37.12	-0.8 (-1.3, -0.3) I^2= 68.2% Tau^2= 0.243

* Impact is measured in initiators per 100,000 person-days.
† Change in slope is measured in initiators per 100,000 person-days per quarter.

Supplemental Figure 8. Interrupted time series analysis examining the impact of the 2015 Health Canada advisory on rates of initiation of domperidone at dose > 30 mg/day in the six months immediately postpartum in three Canadian provinces.



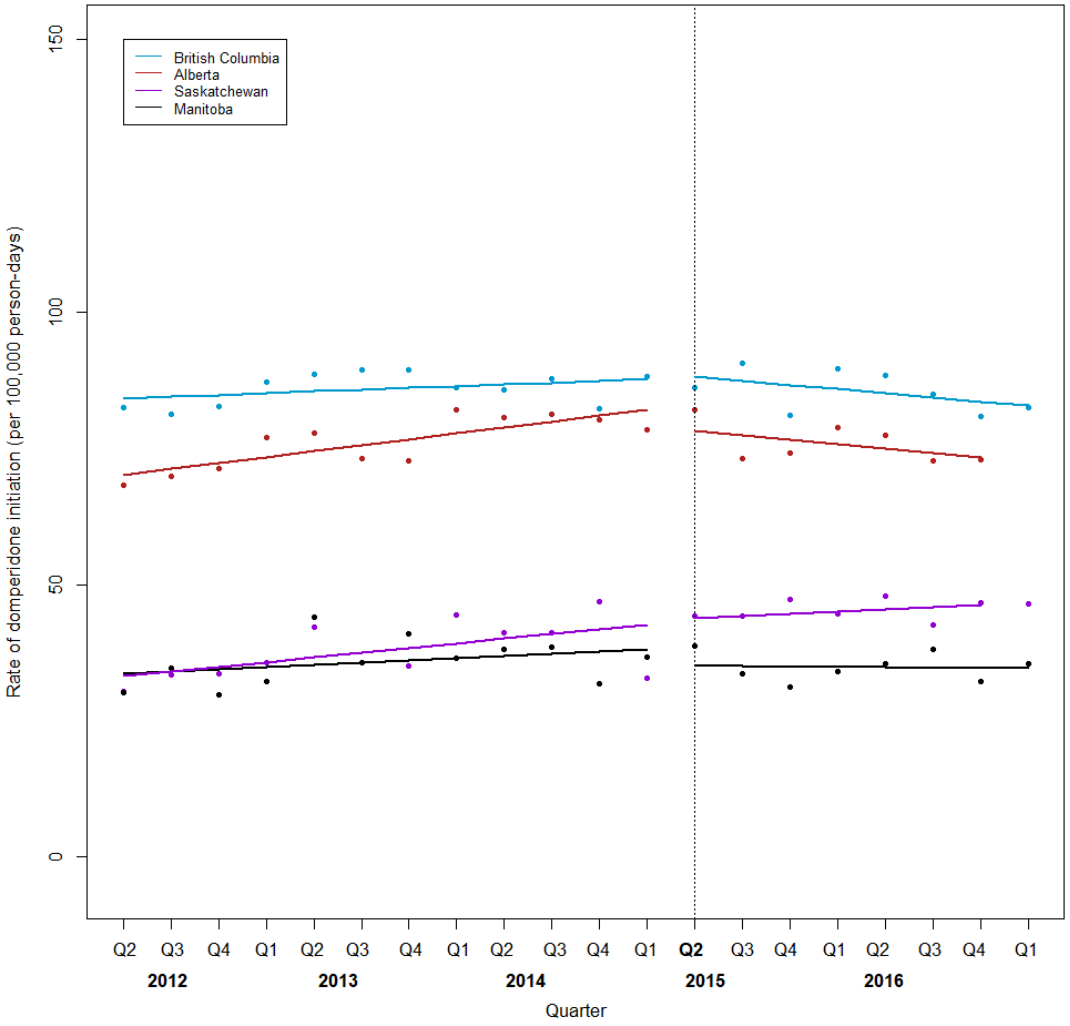
Province	Immediate Impact (95% CI)*	Change in Slope (95% CI)†
British Columbia	-1.2 (-6.7, 4.3)	-1.0 (-2.0, 0.01)
Alberta	-2.6 (-9.5, 4.3)	-2.1 (-3.5, -0.7)
Manitoba	-2.8 (-8.1, 2.6)	-0.3 (-1.3, 0.7)
All Provinces	-2.7 (-5.5, 1.2) I^2= 0.0% Tau^2= 0.00	-1.0 (-2.0, -0.1) I^2= 53.1% Tau^2= 0.373

Note: Saskatchewan does not have access to dosage data and was thus excluded from dosage analyses. Ontario was excluded from this analysis due to insufficient data available post-advisory.

* Impact is measured in initiators per 100,000 person-days.

† Change in slope is measured in initiators per 100,000 person-days per quarter.

Supplemental Figure 9. Interrupted time series analysis examining the impact of the 2015 Health Canada advisory on rates of initiation of domperidone for duration > 14 days in the six months immediately postpartum in four Canadian provinces.



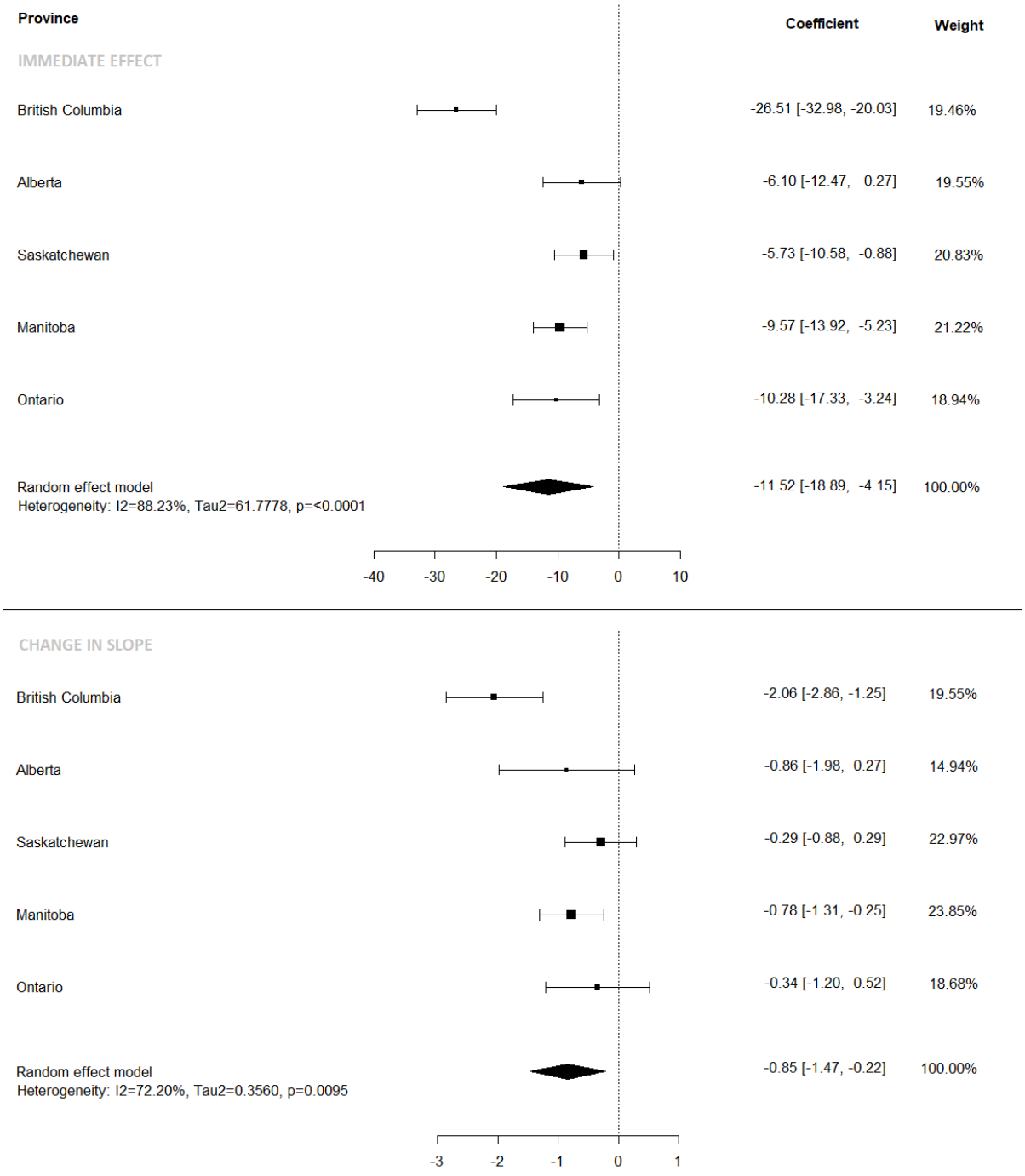
Province	Immediate Impact (95% CI)*	Change in Slope (95% CI)†
British Columbia	1.3 (-4.6, 7.1)	-1.1 (-2.2, -0.0)
Alberta	-2.9 (-8.7 2.9)	-1.9 (-3.1, -0.7)
Saskatchewan	0.8 (-4.6, 6.3)	-0.5 (-1.5, 0.5)
Manitoba	-3.0 (-9.6, 3.6)	-0.5 (-1.7, 0.7)
All Provinces	-0.8 (-3.7, 2.2) I^2= 0.0% Tau^2=0.00	-1.0 (-1.6, -0.3) I^2= 25.4% Tau^2= 0.108

Note: Ontario was excluded from this analysis due to insufficient data available post-advisory.

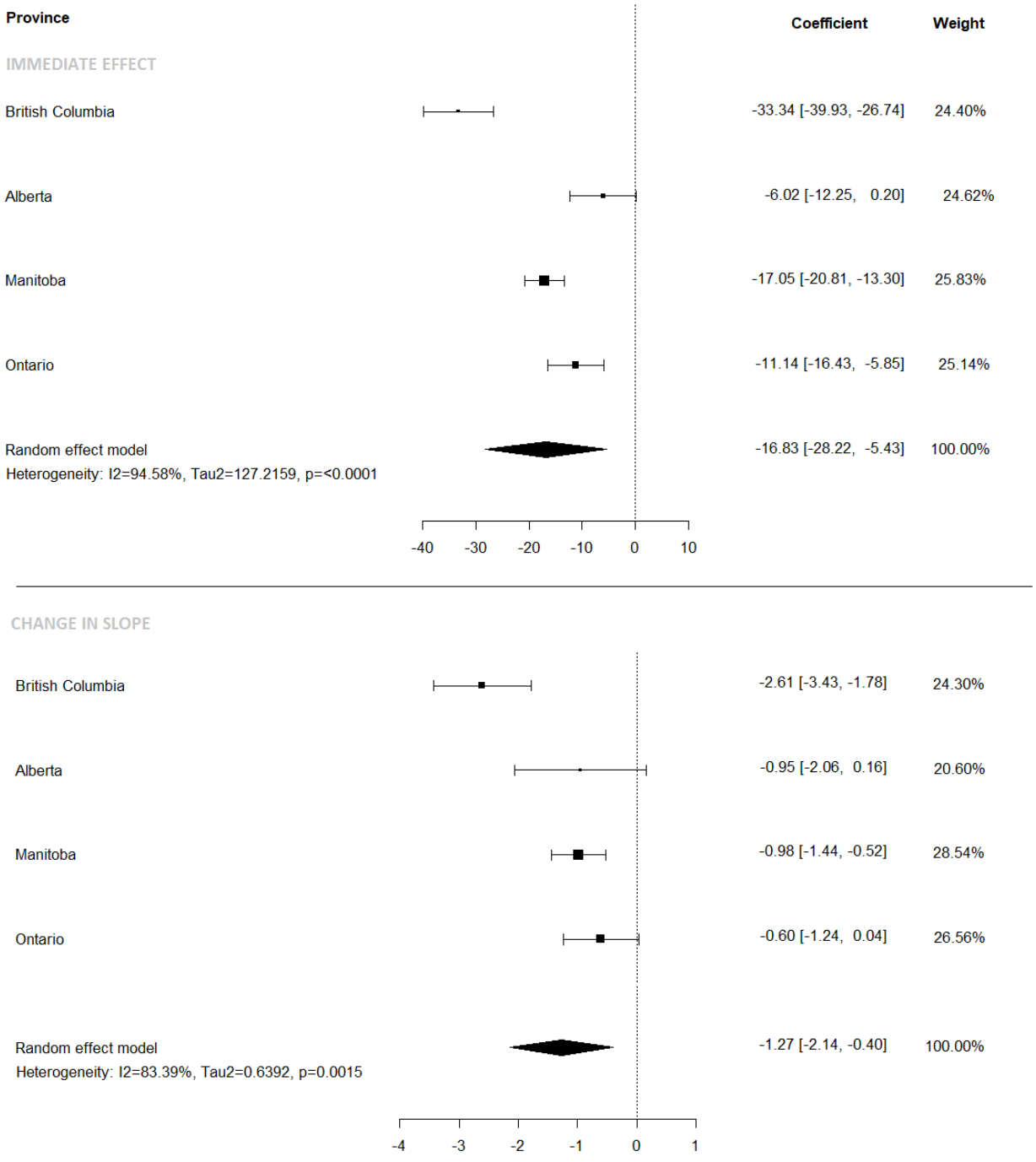
* Impact is measured in initiators per 100,000 person-days.

† Change in slope is measured in initiators per 100,000 person-days per quarter.

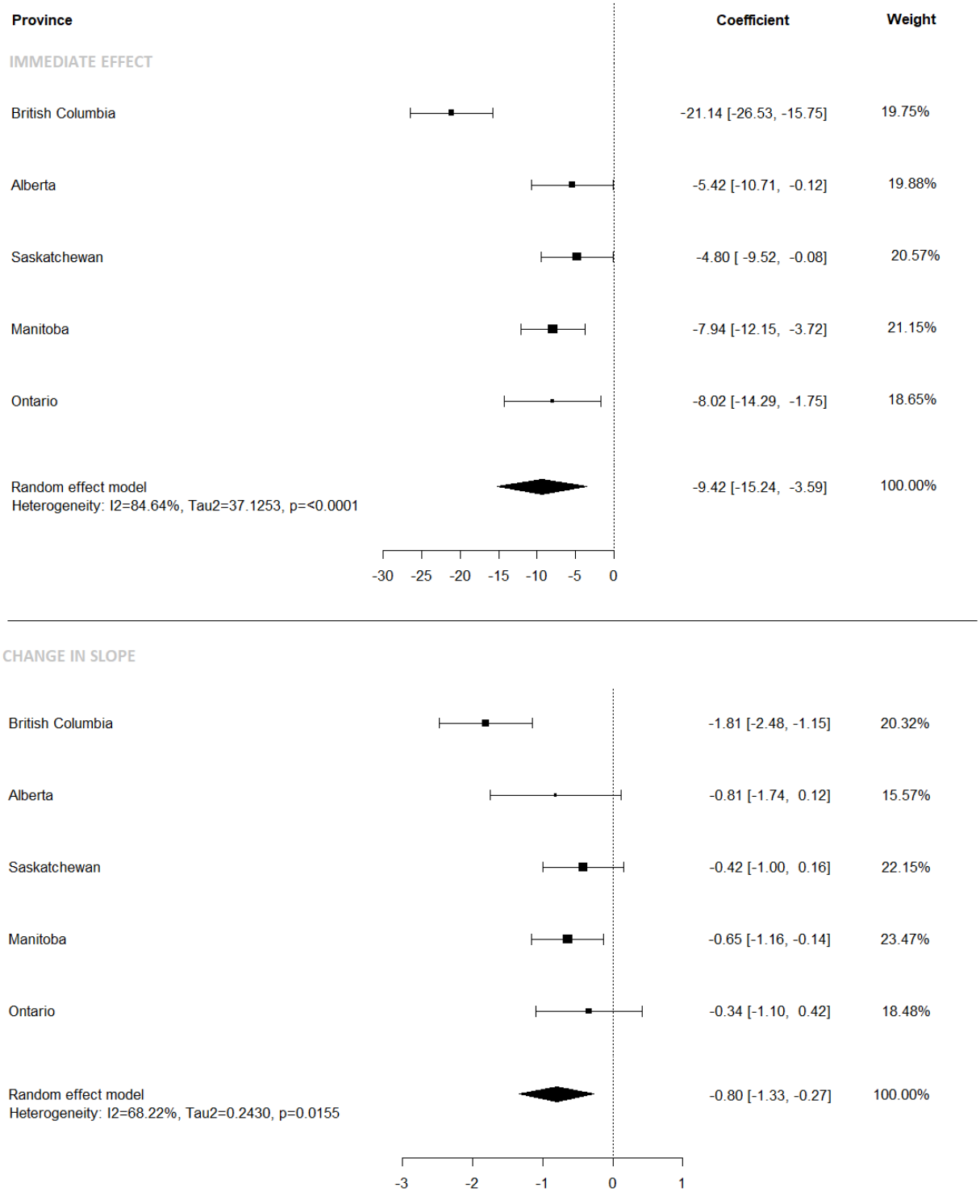
Supplemental Figure 10. Forest plot of interrupted time series analysis examining the impact of the 2012 Health Canada advisory on rates of initiation of domperidone in the six months immediately postpartum in five Canadian provinces.



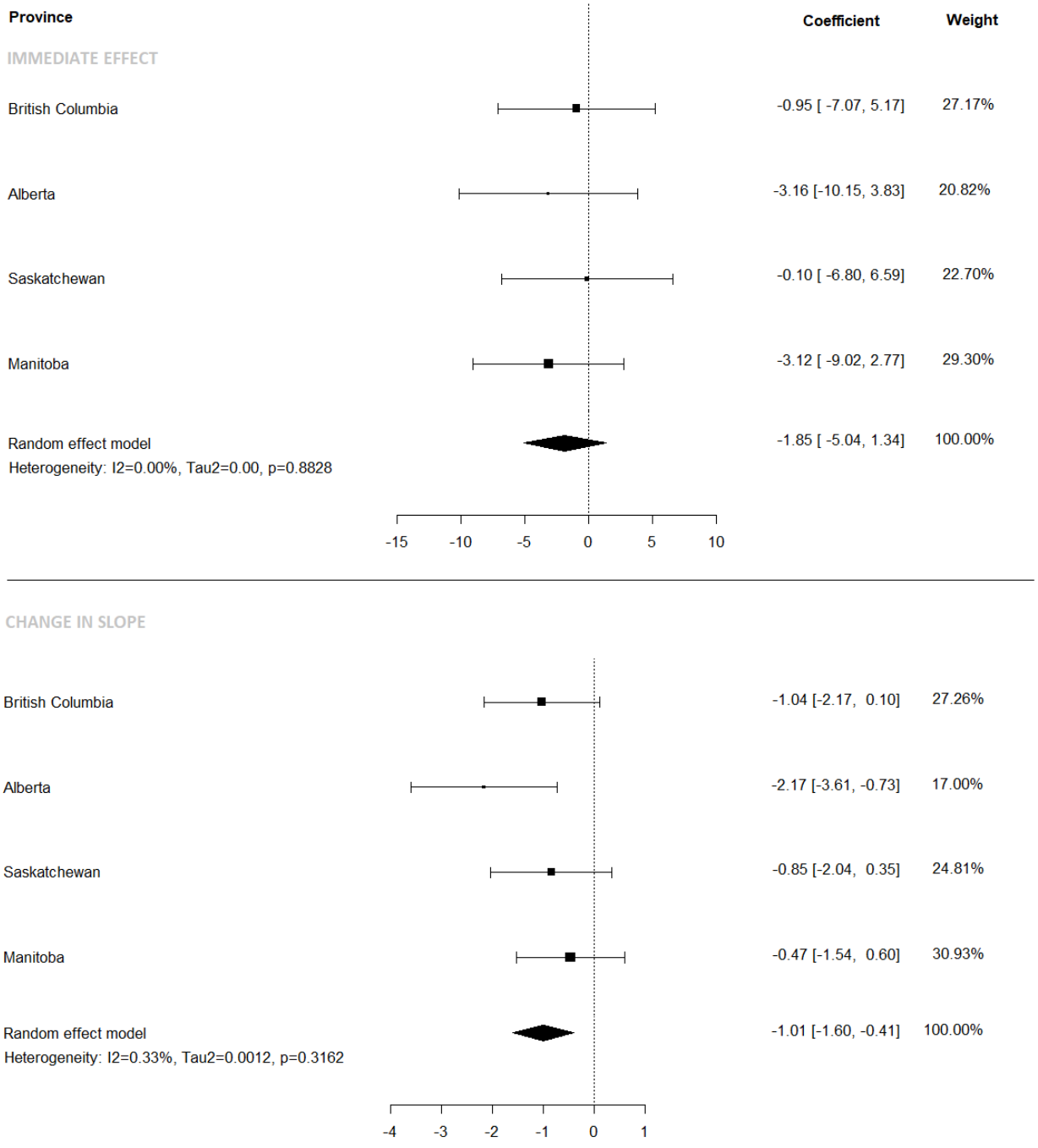
Supplemental Figure 11. Forest plot of interrupted time series analysis examining the impact of the 2012 Health Canada advisory on rates of initiation of domperidone at doses > 30 mg per day in the six months immediately postpartum in four Canadian provinces.



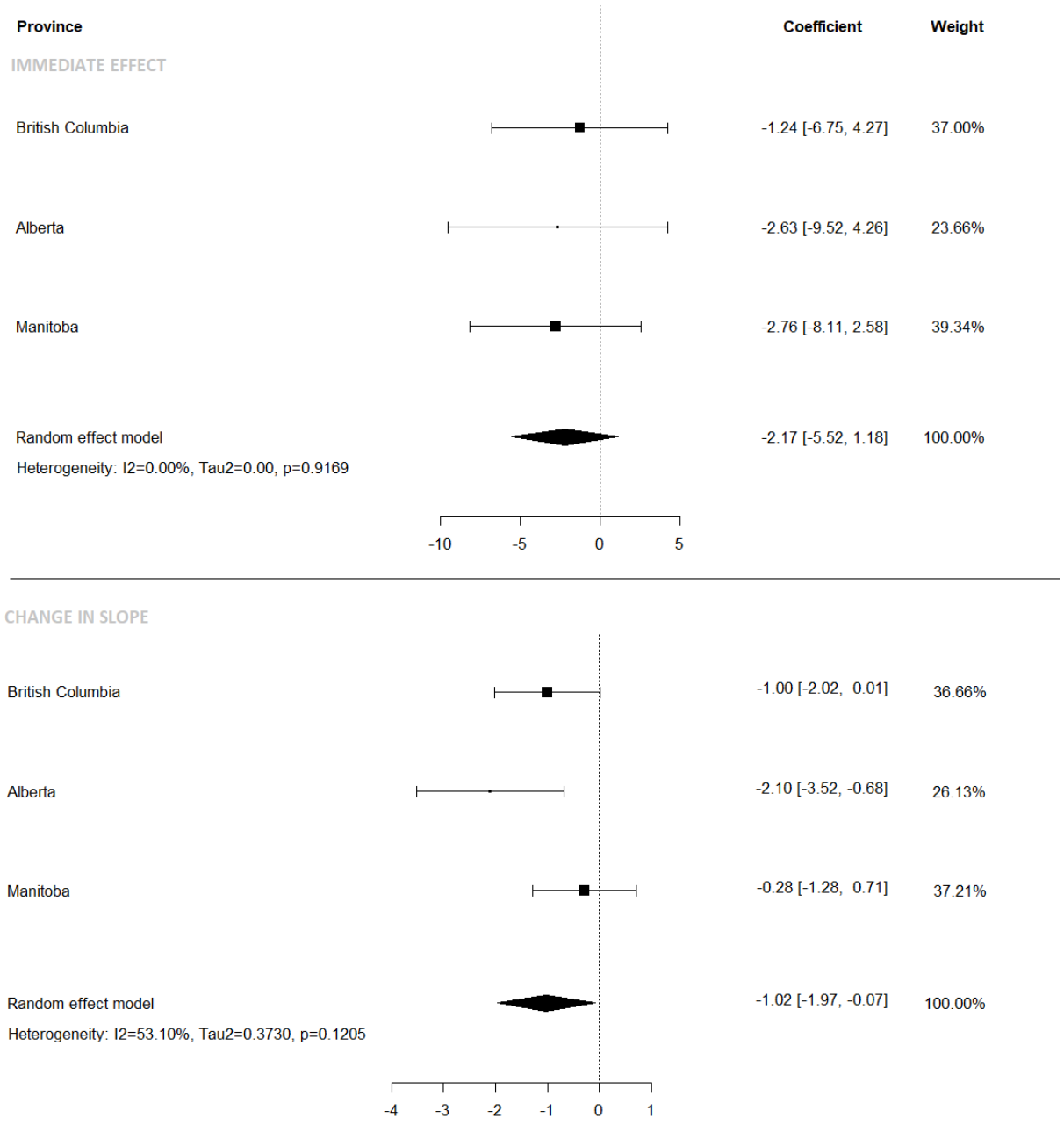
Supplemental Figure 12. Forest plot of interrupted time series analysis examining the impact of the 2012 Health Canada advisory on rates of initiation of domperidone with a duration >14 days in the six months immediately postpartum in five Canadian provinces.



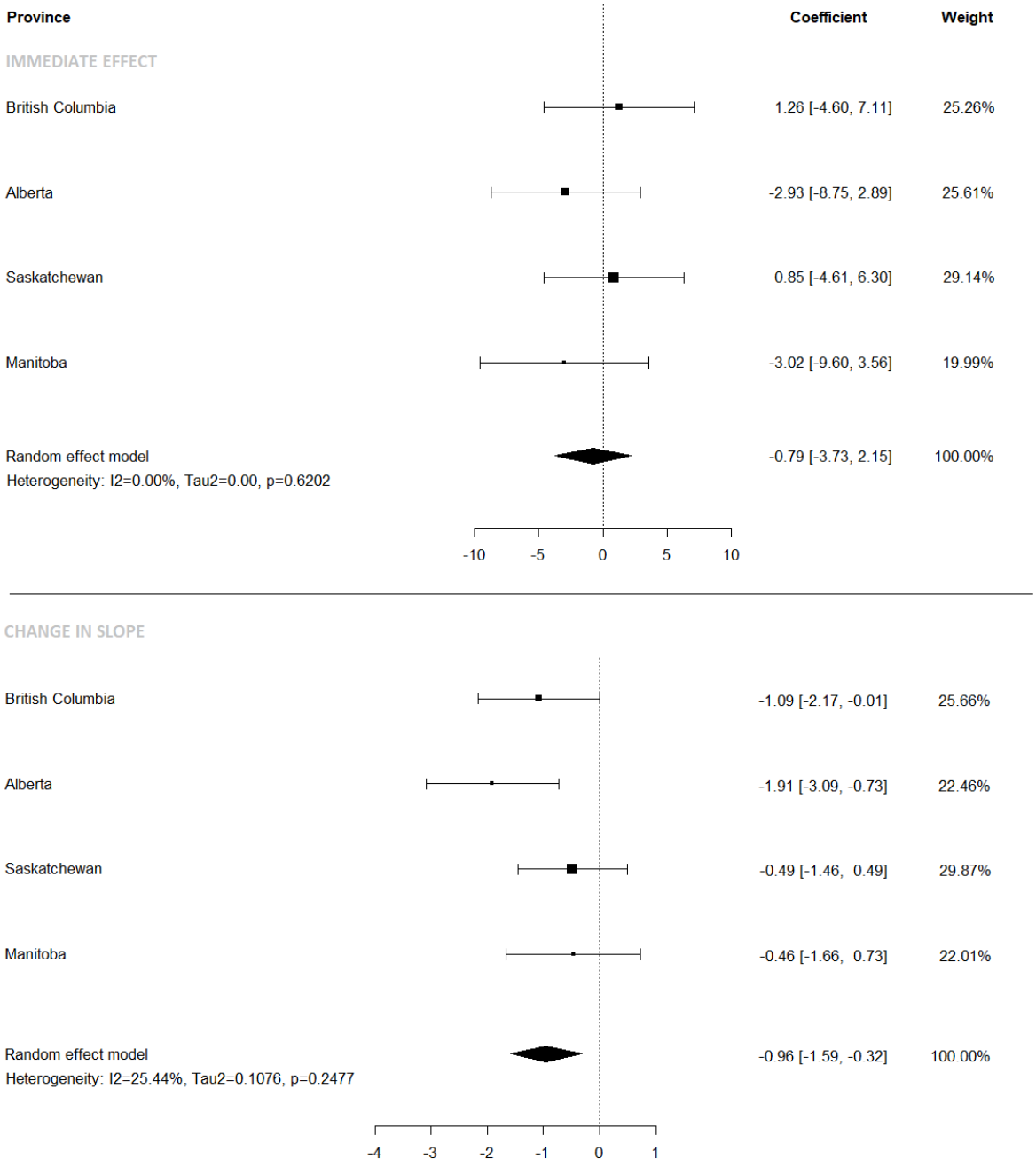
Supplemental Figure 13. Forest plot of interrupted time series analysis examining the impact of the 2015 Health Canada advisory on rates of initiation of domperidone in the six months immediately postpartum in four Canadian provinces.



Supplemental Figure 14. Forest plot of interrupted time series analysis examining the impact of the 2015 Health Canada advisory on rates of initiation of domperidone at a dose > 30 mg per day in the six months immediately postpartum in three Canadian provinces.



Supplemental Figure 15. Forest plot of interrupted time series analysis examining the impact of the 2015 Health Canada advisory on rates of initiation of domperidone with a duration >14 days in the six months immediately postpartum in four Canadian provinces.



Supplemental Table 1. List of databases used in each provinces.

Site	Start and end dates of data available per site	Databases				
		Population	Drug data and dispensing captured	Prescription drug claims	Hospitalization data	Outpatient billing data
British Columbia	April 1, 2004 – March 31, 2017	All	Dispensing (All)	PharmaNet	CIHI Discharge Abstract Database ICD-9: 1994-2002; ICD-10: Since 2002	Healthideas (ICD-9)
Alberta	April 1, 2009 – December 31, 2016	≥18 years	Dispensing (Public)	Pharmaceutical Information Network Dispenses	CIHI Discharge Abstract Database	Practitioner Claims (ICD-9)
Saskatchewan	April 1, 2004 – September 30, 2017	All	Dispensing (Public)	Prescription Drug Plan Historical Claims	CIHI Discharge Abstract Database ICD-9: Until Mar 2002; ICD-10 Since Apr 2002:	Medical Services Branch (ICD-9)
Manitoba	April 1, 2004 – March 31, 2017	All	Dispensing (All)	Drug Program Information Network	Hospital Abstracts User Manual Database (prior to April 1, 2004) Discharge abstract data/Manitoba Abstract Data Elements Database (since April 1, 2004) ICD-9: Apr 1979 to Mar 2004 ICD-10: Since Apr 2004	Manitoba Health Medical- Physician Services (ICD-9)
Ontario	April 1, 2004 – December 31, 2015	Social assistance recipients	Dispensing (Public)	Ontario Drug Benefit Plan Database	CIHI Discharge Abstract Database ICD-9: Until Mar 2002; ICD-10: Since Apr 2002	Ontario Health Insurance Plan (OHIP) Claims History Database (Modified ICD-8)

Abbreviations: CIHI: Canadian Institute for Health Information; ICD: International Classification of Disease (1-3)

Supplemental Table 2. Codes indicating non-arrhythmic cardiac event and acute life-threatening non-cardiac event.

	ICD 9	ICD 10
Non- arrhythmic cardiac causes		
Acute myocardial infarction	410.x	I21.x, I22.x
Acute ischemic heart disease	411.x, 413.x	I20.x, I23.x, I24.x
Myocarditis	422.x	I40.x, I41
Endocarditis	421.x	I33.x, I39
Aortic dissection/rupture	441.0, 441.1, 441.3, 441.5, 441.6	I71.0, I71.1, I71.3, I71.5, I71.8
Haemopericardium, cardiac tamponade	785.51, 423.0, 423.3	R57.0, I31.2
Acute life-threatening non-cardiac events		
Pulmonary Embolism	415.1	I26.x
Gastro-Intestinal Bleeding	530.21, 530.82, 531.0-531.2, 532.0-532.2, 533.0-533.2, 534.0-534.2, 456.0, 456.20, 578x	K22.8, K25.0-K25.2, K26.0-K26.2, K27.0-K27.2, K28.0-K28.2, I85.0, K92.0-K92.2
Peritonitis	567.x	K65.x
Stroke	430, 431, 433.x, 434.x	I60.x, I61.x, I62.x, I63.x
Metastatic cancer (1 month before)	196.x-198.x	C77.x-C79.x
Suicide	E950.x-E953.x, E954, E955.x, E956, E957.x, E958x	X60.x-X84.x
Pulmonary edema, distress syndrome, respiratory failure	518.4, 518.5x, 518.81, 518.82	J80, J96.0

Note: The conditions listed here are those for which events can be excluded without manual review. They are not meant to be an all-inclusive list of codes for the exclusion of potential events during manual review.
ICD: International Classification of Disease (1, 2)

Supplemental Table 3. Operational definitions of patient characteristics.

Covariate	ICD-9	ICD-10	ATC	Variable coding	Comments
Time interval between delivery and first domperidone prescription (days)	-	-	-	0-15 days 16-30 days 31-45 days > 45 days	-
Age	-	-	-	1: 15-19 2: 20-24 3: 25-29 4: 30-34 5: 35-39 6: 40-44 7: 45-55	Measured at cohort entry
	-	-	-	Continuous	Measured at cohort entry
Overweight or obese	278.0*	E66.x	-	0: No 1: Yes	Look back period is 5 years before index conception
Alcohol-related comorbidities	291.x* 303.x* 571.0* 571.1 571.2 571.3 535.3	F10x K70x K29.2 G31.2 G62.1 G72.1 I42.6 E24.4 K85.2 K86.0 Z50.2 Z71.4	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Income quintile	-	-	-	1st (highest) 2nd 3rd 4th 5th (lowest) Missing	Look back period is 5 years before cohort entry

Covariate	ICD-9	ICD-10	ATC	Variable coding	Comments
Previous history of arrhythmia or conductions disorders	426.x* 427.x*	I45.x I49.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Any insertion of a pacemaker or defibrillator	V45.01 V45.02	Z95.0 Z95.810	-	0: No 1: Yes	Look back period is 5 years before cohort entry Note: please also use the following CCI procedure codes to identify insertion of pacemaker: 1.HB.53.x 1.HD.53.x 1.HZ.53.x
Hypertension	401.x* 402.x* 403.x* 404.x 405.x	I10 I11.x I12.x I13.x I15.x I16.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Cardiomyopathy	425.x	I42.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Left ventricular hypertrophy	429.3	I51.7	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Heart failure	428.x*	I50.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Ischemic heart disease	410.x* 411.x 412* 413.x* 414.x	I20.x I21.x I22.x I23.x I24.x I25.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Valvular heart disease	394.x* 395.x 396.x 397.0 397.1	I07.1 I07.2 I07.8 I34.x I35.x I36.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry

Covariate	ICD-9	ICD-10	ATC	Variable coding	Comments
		I37.x I38 I39			
Asthma	493.x*	J45.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Diabetes	249.x 250.x*	E08.x E09.x E10.x E11.x E13.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Hyperlipidemia	272.0* 272.1 272.2 272.3 272.4	E78.0x E78.1 E78.2 E78.3 E78.4 E78.5	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Depression	292.84 296.2x 296.3x 296.5x 298.0 311*	F32.x F33.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Epilepsy	345.x*	G40.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Cerebrovascular disease	430 431 432.x* 433.x 434.x 435.x* 436* 437.x* 438.x	I60.x I61.x I62.x I63.x I65.x I66.x I67.x I68.x I69.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry

Covariate	ICD-9	ICD-10	ATC	Variable coding	Comments
		G45			
Peripheral vascular disease	440.x* 441.x 443.x 444.x 448.x	I70.x I71.x I73.x I74.x I78.x I79.x K55.1	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Hepatic diseases	070.x 570 571.x* 572.x 573.x*	B16.x B17.x B18.x B19.x K70.x K71.x K72.x K73.x K74.x K75.x K76.x K77	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Renal diseases	250.4 403.x* 404.x 580.x* 581.x* 582.x 583.x 584.x* 585.x* 586 587	E11.2 E13.2 I12.x I13.x N00.x N01.x N02.x N03.x N04.x N05.x N06.x N07.x N08 N10	-	0: No 1: Yes	Look back period is 5 years before cohort entry

Covariate	ICD-9	ICD-10	ATC	Variable coding	Comments
		N11.x N12 N15.x N16 N18.x N19.x			
Hypokalemia	276.8	E87.6	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Hypocalcemia	275.41	E83.51	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Hypomagnesemia	275.2	E83.42	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Schizophrenia	295.x*	F20.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Multi-fetal gestation	651.x*	O30.x	-	0: No 1: Yes	Measure during index pregnancy
Parity≥1	-	-	-	0: No 1: Yes 2: Unknown	Measure during index pregnancy Note: If this variable is not available in your dataset, please use the following DAD variables to define it: (1) Previous livebirths (2) Previous term deliveries (3) Previous pre-term deliveries
Gestational age	-	-	-	1. Continuous 2. Categorical as, <=37 weeks 38-42 weeks >=43 weeks	Measure at delivery
Caesarian section	669.7x	O82	-	0: No 1: Yes	Measure at delivery Please also use the following procedure codes to check for caesarean section,

Covariate	ICD-9	ICD-10	ATC	Variable coding	Comments
					CCI: 5MD60* CCP: 86* ICD9: 74* ICD-10-CA: 5.MD.60*
Gestational diabetes	648.0x 648.8x	O24.4	-	0: No 1: Yes	Measure during index pregnancy
Hypertensive disorders of pregnancy	642.x	O13.x	-	0: No 1: Yes	Measure during index pregnancy
Postpartum hemorrhage	666.x*	O72.x	-	0: No 1: Yes	Measure during the time interval between (and including) the day of delivery and 14 days after delivery
Complications of anesthesia during labour and delivery	668.x	O74.x	-	0: No 1: Yes	Measure at delivery
Antepartum hemorrhage	641.x	O46.x	-	0: No 1: Yes	Measure during index pregnancy
Infections or sepsis after childbirth	670.x	O85 O86.x	-	0: No 1: Yes	Measure during the time interval between delivery and 14 days after delivery
Anti-arrhythmic drugs	-	-	C01AA05 C01EB10 C01BA C01BB C01BC C01BD C01BG C07AA C07AB C07AG C08DA C08DB	0: No 1: Yes	Any use in the year before conception and during pregnancy
Statins	-	-	C10AA C10BA C10BX	0: No 1: Yes	Any use in the year before conception and during pregnancy
Antihypertensive medications	-	-	C02 C03	0: No 1: Yes	Any use in the year before conception and during pregnancy

Covariate	ICD-9	ICD-10	ATC	Variable coding	Comments
			C07 C08 C09		
Proton pump inhibitors	-	-	A02BC A02BD01 A02BD02 A02BD03 A02BD04 A02BD06 A02BD07 B01AC56 M01AE52	0: No 1: Yes	Any use in the year before conception and during pregnancy
Antipsychotic medications	-	-	N05A	0: No 1: Yes	Any use in the year before conception and during pregnancy
Hospitalized in the year before conception	-	-	-	0: No 1: Yes	Note: 1) Please extract this information from the Hospital Discharge Abstract Database (DAD). 2) The length of hospital stay should be at least 1 day
Number of clinic visit in the year before conception	-	-	-	Categorical as 0 1-3 4 and more	
Hospitalized during pregnancy	-	-	-	0: No 1: Yes	Note: 1) Please extract this information from the Hospital Discharge Abstract Database (DAD). 2) The length of hospital stay should be at least 1 day
Number of clinic visit during pregnancy	-	-	-	Categorical as 0 1-3	

Covariate	ICD-9	ICD-10	ATC	Variable coding	Comments
				4 and more	

* Denotes codes used for outpatient data by sites with only 3-digit physician billing data. ICD: International Classification of Disease (1, 2).

Supplemental Table 4. Baseline characteristics of deliveries overall and by use of domperidone in the six months immediately postpartum.

	Overall (n = 1,190,987)	Domperidone (n = 137,401)	No domperidone (n = 1,053,586)
Age (years), mean ± SE	28.6 ± 0.6	29.6 ± 0.4	28.5 ± 0.6
15-19, n (%)	54,061 (4.5)	2,811 (2.1)	51,250 (4.9)
20-24, n (%)	194,958 (16.4)	15,196 (11.1)	179,762 (17.1)
25-29, n (%)	352,403 (29.6)	37,625 (27.4)	314,778 (29.9)
30-34, n (%)	371,580 (31.2)	48,234 (35.1)	323,346 (30.7)
35-39, n (%)	179,903 (15.1)	26,979 (19.6)	152,924 (14.5)
40-44, n (%)	36,084 (3.0)	6,088 (4.4)	29,996 (2.9)
45-55, n (%)	1,998 (0.2)	468 (0.3)	1,530 (0.2)
Person days follow up (sum of person days for each outcome			
Composite of VT/SCD	207,301,730	24,138,820	183,162,910
VT	207,301,722	24,138,820	183,162,952
SCD	207,302,489	24,138,952	183,163,537
All-cause mortality	207,302,598	24,138,952	183,163,646
Comorbidities, n (%)			
Asthma	120,088 (10.1)	16,441 (12.0)	103,647 (9.5)
Hyperlipidemia	8,398 (0.7)	1,339 (1.0)	7,048 (0.7)
Epilepsy	1,1037 (0.9)	1,308 (1.0)	9,729 (0.9)
Cerebrovascular disease	5,176 (0.4)	736 (0.5)	4,440 (0.4)
Peripheral vascular disease	12,403 (1.0)	1,753 (1.3)	10,650 (1.0)
Hepatic disease	20,351 (1.7)	2,678 (2.0)	17,673 (1.7)
Renal disease	21,852 (1.8)	2,527 (1.8)	19,325 (1.8)
Schizophrenia	3,967 (0.3)	404 (0.3)	3,563 (0.3)
Hypokalemia	2,854 (0.2)	315 (0.2)	2,539 (0.2)
Hypocalcemia	63 (0.0)	*s*	60 (0.0)
Hypomagnesemia	85 (0.0)	10 (0.0)	75 (0.0)

	Overall (n = 1,190,987)	Domperidone (n = 137,401)	No domperidone (n = 1,053,586)
Complication of pregnancy or childbirth, n (%)			
Gestational diabetes	48,554 (4.1)	8,798 (6.4)	39,756 (3.8)
Hypertensive disorders of pregnancy	88,351 (7.4)	14,750 (10.7)	73,601 (7.0)
Postpartum hemorrhage	116,351 (9.8)	14,861 (10.8)	101,490 (9.6)
Complications of anesthesia during labor and delivery	10,633 (0.8)	1,675 (1.2)	8,958 (0.9)
Antepartum hemorrhage	55,560 (4.7)	8,491 (6.2)	47,069 (4.5)
Infections or sepsis after childbirth	15,289 (1.3)	2,450 (1.8)	12,839 (1.2)
Hospitalized year before conception, n (%)			
No	1,045,263 (87.8)	125,510 (91.4)	919,753 (87.3)
Yes	145,724 (12.2)	11,891 (8.7)	133,833 (12.7)
Number of physician visits in year before conception, n (%)			
0	109,466 (9.2)	8,777 (6.4)	100,689 (9.6)
1 to 3	248,062 (20.8)	22,885 (16.7)	225,177 (21.4)
4 and more	833,459 (70.0)	105,739 (77.0)	727,720 (69.1)
Hospitalized during pregnancy, n (%)			
No	744,178 (62.5)	77,846 (56.7)	666,332 (63.2)
Yes	446,809 (37.5)	59,555 (43.3)	387,254 (36.8)
Number of clinic visits during pregnancy, n (%)			
0	3,861 (0.3)	138 (0.1)	3,723 (0.4)
1 to 3	14,709 (1.2)	383 (0.3)	14,326 (1.4)
4 and more	1,172,417 (98.4)	136,880 (99.6)	1,035,537 (98.3)

Abbreviations: SCD: sudden cardiac death; SE: standard error; VT: ventricular tachyarrhythmia; s: Suppressed to protect patient privacy
Note: women were permitted to contribute multiple observations to the study cohort

Supplemental Table 5. Distribution of dosage of first domperidone treatment episode by province and calendar period.

	All	Pre-Advisory (April 1, 2004 to March 2, 2012)	Between Advisories (March 3, 2012 to January 20, 2015)	Post-Advisory (January 21, 2015 to September 20, 2017)
British Columbia				
N of observations	63,608	37,682	15,207	10,719
Mean ± SD, mg	60.9 ± 26.4	65.7 ± 26.0	55.8 ± 24.4	51.3 ± 26.8
Median, mg	61	80	57	40
First quartile, mg	40	40	30	30
Third quartile, mg	80	80	80	71
Frequency, n (%)				
0-10 mg	163 (0.3)	74 (0.2)	47 (0.3)	42 (0.4)
11-20 mg	982 (1.5)	474 (1.3)	272 (1.8)	236 (2.2)
21-30 mg	10,321 (16.2)	3,329 (8.8)	3,546 (23.3)	3,446 (32.1)
31-40 mg	10,903 (17.1)	6,087 (16.2)	2,932 (19.3)	1,884 (17.6)
41-50 mg	2,296 (3.6)	1,279 (3.4)	539 (3.5)	478 (4.5)
51-60 mg	6,789 (10.7)	3,323 (8.8)	1,946 (12.8)	1,520 (14.2)
61-70 mg	2,767 (4.4)	1,754 (4.7)	580 (3.8)	433 (4.0)
71-80 mg	21,798 (34.3)	16,510 (43.8)	3,752 (24.7)	1,536 (14.3)
≥81 mg	7,589 (11.9)	4,852 (12.9)	1,593 (10.5)	1,144 (10.7)
Alberta				
N of observations	51,953	17,275	20.960	13,718
Mean ± SD, mg	63.3 ± 41.5	65.4 ± 39.9	63.9 ± 42.0	59.8 ± 42.3
Median, mg	60	62	60	56
First quartile, mg	40	40	40	30
Third quartile, mg	80	80	80	80
Frequency, n (%)				
0-10 mg	291 (0.6)	60 (0.3)	126 (0.6)	105 (0.8)
11-20 mg	926 (1.8)	245 (1.4)	416 (2.0)	265 (1.9)
21-30 mg	10,209 (19.7)	2,643 (15.3)	4,151 (19.8)	3,415 (24.9)

	All	Pre-Advisory (April 1, 2004 to March 2, 2012)	Between Advisories (March 3, 2012 to January 20, 2015)	Post-Advisory (January 21, 2015 to September 20, 2017)
31-40 mg	10,871 (20.9)	3,837 (22.2)	4,394 (21.0)	2,640 (19.2)
41-50 mg	1,119 (2.2)	379 (2.2)	447 (2.1)	293 (2.1)
51-60 mg	4,659 (9.0)	1,455 (8.4)	1,810 (8.6)	1,394 (10.2)
61-70 mg	1,376 (2.6)	456 (2.6)	549 (2.6)	371 (2.7)
71-80 mg	14,357 (27.6)	5,464 (31.6)	5,576 (26.6)	3,317 (24.2)
≥81 mg	8,145 (15.7)	2,736 (15.8)	3,491 (16.7)	1,918 (14.0)
Manitoba				
N of observations	9,220	4,919	2,495	1,806
Mean ± SD, mg	57.9 ± 25.6	65.7 ± 25.2	50.1 ± 23.3	47.3 ± 22.4
Median, mg	60	80	40	38
First quartile, mg	30	40	30	30
Third quartile, mg	80	80	68	60
Frequency, n (%)				
0-10 mg	41 (0.4)	6 (0.1)	21 (0.8)	14 (0.8)
11-20 mg	177 (1.9)	51 (1.0)	68 (2.7)	58 (3.2)
21-30 mg	2,330 (25.3)	604 (12.3)	939 (37.6)	787 (43.6)
31-40 mg	1,191 (12.9)	697 (14.2)	303 (12.1)	191 (10.6)
41-50 mg	253 (2.7)	99 (2.0)	84 (3.4)	70 (3.9)
51-60 mg	1,231 (13.4)	571 (11.6)	385 (15.4)	275 (15.2)
61-70 mg	250 (2.7)	108 (2.2)	83 (3.3)	59 (3.3)
71-80 mg	2,744 (29.8)	2,189 (44.5)	370 (14.8)	185 (10.2)
≥81 mg	1,003 (10.9)	594 (12.1)	242 (9.7)	167 (9.2)
Ontario				
N of observations	3,110	1,781	1,126	203
Mean ± SD, mg	57.0 ± 28.7	59.1 ± 28.4	54.8 ± 29.0	51.0 ± 28.5
Median, mg	50	60	40	40
First quartile, mg	30	31	30	30
Third quartile, mg	80	80	80	69

	All	Pre-Advisory (April 1, 2004 to March 2, 2012)	Between Advisories (March 3, 2012 to January 20, 2015)	Post-Advisory (January 21, 2015 to September 20, 2017)
Frequency, n (%)				
0-10 mg	20 (0.6)	11 (0.6)	*s*	*s*
11-20 mg	115 (3.7)	63 (3.5)	43 (3.8)	9 (4.4)
21-30 mg	776 (25.0)	355 (19.9)	345 (30.6)	76 (37.4)
31-40 mg	562 (18.1)	354 (19.9)	181 (16.1)	27 (13.3)
41-50 mg	94 (3.0)	49 (2.8)	*s*	*s*
51-60 mg	380 (12.2)	213 (12.0)	144 (12.8)	23 (11.3)
61-70 mg	91 (2.9)	53 (3.0)	30 (2.7)	8 (3.9)
71-80 mg	422 (13.6)	310 (17.4)	97 (8.6)	15 (7.4)
≥81 mg	650 (20.9)	373 (20.9)	243 (21.6)	34 (16.8)

Abbreviation: SD: standard deviation, S: suppressed to protect patient privacy.

Note: Saskatchewan does not have access to dosage data and was thus excluded from dosage analyses.

Supplemental Table 6. Distribution of duration of first domperidone treatment episode by province and calendar period.

	All	Pre-Advisory (April 1, 2004 to March 2, 2012)	Between Advisories (March 3, 2012 to January 20, 2015)	Post-Advisory (January 21, 2015 to September 20, 2017)
British Columbia				
N of observations	63,608	37,682	15,207	10,719
Mean ± SD, days	44.2 ± 39.3	41.7 ± 38.0	47.8 ± 41.5	48.2 ± 39.9
Median, days	30	30	30	30
First quartile, days	21	17	25	28
Third quartile, days	56	50	60	60
Frequency, n (%)				
≤7 days	2,117 (3.3)	1,489 (4.0)	431 (2.8)	197 (1.8)
8-14 days	8,606 (13.5)	5,919 (15.7)	1,676 (11.0)	1,011 (9.4)
15-21 days	6,021 (9.5)	3,990 (10.6)	1,200 (7.9)	831 (7.8)
22-28 days	5,386 (8.5)	3,532 (9.4)	1,128 (7.4)	726 (6.8)
29-35 days	19,286 (30.3)	10,472 (27.8)	5,050 (33.2)	3,764 (35.1)
36-42 days	2,281 (3.6)	1,362 (3.6)	492 (3.2)	427 (4.0)
43+ days	19,911 (31.3)	10,918 (29.0)	5,230 (34.4)	3,763 (35.1)
Alberta				
N of observations	51,953	17,275	20.960	13,718
Mean ± SD, days	63.3 ± 41.5	65.4 ± 39.9	63.9 ± 42.0	59.8 ± 42.3
Median, days	30	30	30	30
First quartile, days	28	26	28	30
Third quartile, days	60	60	60	62
Frequency, n (%)				
≤7 days	1,236 (2.4)	446 (2.6)	483 (2.3)	307 (2.2)
8-14 days	4,452 (8.6)	1,649 (9.5)	1,776 (8.5)	1,027 (7.5)
15-21 days	3,660 (7.0)	1,190 (6.9)	1,536 (7.3)	934 (6.8)
22-28 days	3,712 (7.1)	1,361 (7.9)	1,485 ()7.1	866 (6.3)

	All	Pre-Advisory (April 1, 2004 to March 2, 2012)	Between Advisories (March 3, 2012 to January 20, 2015)	Post-Advisory (January 21, 2015 to September 20, 2017)
29-35 days	18,976 (36.5)	6,211 (36.0)	7,591 (36.2)	5,174 (37.7)
36-42 days	15,21 (2.9)	479 (2.8)	614 (2.9)	428 (3.1)
43+ days	18,396 (35.4)	5,939 (34.4)	7,475 (35.7)	4,982 (36.6)
Saskatchewan				
N of observations	9,510	4,023	2,918	2,569
Mean ± SD, days	26.2 ± 15.7	26.4 ± 16.2	25.9 ± 15.6	25.9 ± 15.1
Median, days	20	22	20	20
First quartile, days	18	18	18	18
Third quartile, days	35	35	35	35
Frequency, n (%)				
≤7 days	597 (6.3)	297 (7.4)	176 (6.0)	124 (4.8)
8-14 days	1,309 (13.8)	596 (14.8)	390 (13.4)	323 (12.6)
15-21 days	3,005 (31.6)	1,071 (26.6)	970 (33.2)	964 (37.5)
22-28 days	1,822 (19.2)	913 (22.7)	541 (18.5)	368 (14.3)
29-35 days	577 (6.1)	145 (3.6)	208 (7.1)	224 (8.7)
36-42 days	506 (5.3)	232 (5.8)	139 (4.8)	135 (5.3)
43+ days	1,694 (17.8)	769 (19.1)	494 (16.9)	431 (16.8)
Manitoba				
N of observations	9,220	4,919	2,495	1,806
Mean ± SD, days	46.2 ± 38.9	42.6 ± 36.8	50.4 ± 41.1	50.4 ± 39.9
Median, days	30	30	30	30
First quartile, days	21	21	30	30
Third quartile, days	60	55	62	63
Frequency, n (%)				
≤7 days	304 (3.3)	205 (4.2)	68 (2.7)	31 (1.7)
8-14 days	993 (10.8)	632 (12.8)	202 (8.1)	159 (8.8)
15-21 days	1,090 (11.8)	740 (15.0)	198 (7.9)	152 (8.4)
22-28 days	387 (4.2)	217 (4.4)	108 (4.3)	62 (3.4)

Appendix 1, as supplied by the authors. Appendix to: Moriello C, Paterson JM, Reynier P, et al; the Canadian Network for Observational Drug Effect Studies (CNODES) Investigators. Off-label postpartum use of domperidone in Canada: a multidatabase cohort study. *CMAJ Open* 2021. doi: 10.9778/cmajo.20200084.

	All	Pre-Advisory (April 1, 2004 to March 2, 2012)	Between Advisories (March 3, 2012 to January 20, 2015)	Post-Advisory (January 21, 2015 to September 20, 2017)
29-35 days	2,825 (30.6)	1,315 (26.7)	871 (34.9)	639 (35.4)
36-42 days	492 (5.3)	300 (6.1)	112 (4.5)	80 (4.4)
43+ days	3,129 (33.9)	1,510 (30.7)	936 (37.5)	683 (37.8)
Ontario				
N of observations	3,110	1,781	1,126	203
Mean ± SD, days	35.8 ± 27.7	34.8 ± 27.4	36.7 ± 27.7	40.0 ± 29.0
Median, days	30	30	30	30
First quartile, days	22	20	28	28
Third quartile, days	33	30	34	49
Frequency, n (%)				
≤7 days	75 (2.4)	55 (3.1)	*s**	*s*
8-14 days	377 (12.1)	217 (12.2)	134 (11.9)	26 (12.8)
15-21 days	325 (10.5)	217 (12.2)	92 (8.2)	16 (7.9)
22-28 days	203 (6.5)	136 (7.6)	58 (5.2)	9 (4.4)
29-35 days	1,442 (46.4)	792 (44.5)	560 (49.7)	90 (44.3)
36-42 days	66 (2.1)	36 (36)	*s*	*s*
43+ days	622 (20.0)	328 (18.4)	238 (21.1)	56 (27.6)

Abbreviation: SD: standard deviation, s: suppressed to protect patient privacy.

Supplemental Table 7. Interrupted time-series analyses modeling ln(prescription rate): Impact of 2012 Health Canada Advisory.

Province	Immediate Relative Change (95% CI)	Immediate Relative Decrease in Geometric Mean of Initiation Rate per Quarter	Relative Change in Slope (95% CI)	Relative Decrease in Slope of Geometric Mean of Initiation Rate per Quarter
All				
British Columbia	0.77 (0.71, 0.84)	30.0%	0.98 (0.97, 0.99)	2.5%
Alberta	0.93 (0.85, 1.001)	8.1%	0.99 (0.97, 1.001)	1.3%
Saskatchewan	0.78 (0.65, 0.94)	28.5%	0.96 (0.94, 0.98)	4.2%
Manitoba	0.74 (0.64, 0.86)	34.6%	0.97 (0.95, 0.99)	3.2%
Ontario	0.72 (0.58, 0.89)	38.9%	0.98 (0.95, 1.004)	2.3%
All Provinces	0.80 (0.72, 0.88) I^2= 67.8%	25.4%	0.98 (0.97, 0.98) I^2= 18.2%	2.5%
Dosage >30mg				
British Columbia	0.69 (0.63, 0.76)	45.1%	0.97 (0.95, 0.98)	3.5%
Alberta	0.92 (0.85, 1.001)	8.3%	0.99 (0.97, 1.0001)	1.5%
Manitoba	0.55 (0.46, 0.66)	80.7%	0.96 (0.94, 0.98)	4.3%
Ontario	0.64 (0.50, 0.81)	57.2%	0.97 (0.94, 0.99766)	3.2%
All Provinces	0.71 (0.53, 0.95) I^2= 93.2%	40.5%	0.97 (0.96, 0.98) I^2= 52.2%	3.0%
Duration >14 days				
British Columbia	0.78 (0.71, 0.85)	28.8%	0.97 (0.96, 0.98)	2.8%
Alberta	0.92 (0.86, 0.99675)	8.1%	0.99 (0.97, 0.999)	1.4%
Saskatchewan	0.75 (0.60, 0.93)	34.0%	0.95 (0.92, 0.98)	5.1%
Manitoba	0.72 (0.61, 0.85)	38.2%	0.97 (0.95, 0.99)	3.3%
Ontario	0.73 (0.58, 0.92)	36.6%	0.97 (0.95, 1.002)	2.6%
All Provinces	0.79 (0.71, 0.88) I^2= 68.8%	25.8%	0.97 (0.96, 0.98) I^2= 36.1%	2.7%

Supplemental Table 8. Interrupted time-series analyses modeling ln(prescription rate): Impact of 2015 Health Canada Advisory.

Province	Immediate Relative Change (95% CI)	Immediate Relative Decrease in Geometric Mean of Initiation Rate per Quarter	Relative Change in Slope (95% CI)	Immediate Relative Decrease in Geometric Mean of Initiation Rate per Quarter
All				
British Columbia	0.99 (0.93, 1.05)	0.9%	0.99 (0.98, 1.001)	1.1%
Alberta	0.96 (0.89, 1.05)	3.7%	0.97 (0.96, 0.99)	2.6%
Saskatchewan	1.00 (0.87, 1.15)	0.1%	0.98 (0.96, 1.01)	1.9%
Manitoba	0.93 (0.80, 1.07)	8.1%	0.99 (0.96, 1.01)	1.2%
All Provinces	0.98 (0.93, 1.02) I^2=0.0%	2.3%	0.98 (0.98, 0.99) I^2=8.1%	1.6%
Dosage >30mg				
British Columbia	0.99 (0.92, 1.06)	1.4%	0.98 (0.97, 0.9979)	1.6%
Alberta	0.97 (0.89, 1.05)	3.1%	0.97 (0.96, 0.99)	2.6%
Manitoba	0.89 (0.71, 1.13)	11.8%	0.99 (0.94, 1.03)	1.5%
All Provinces	0.97 (0.92, 1.03) I^2= 0.0%	2.7%	0.98 (0.97, 0.99) I^2= 0.0%	1.9%
Duration >14 days				
British Columbia	1.01 (0.95, 1.09)	1.4%*	0.99 (0.97, 1.08)	1.3%
Alberta	0.96 (0.89, 1.04)	3.9%	0.98 (0.96, 0.99)	2.6%
Saskatchewan	1.02 (0.88, 1.18)	2.1%*	0.99 (0.96, 1.01)	1.4%
Manitoba	0.92 (0.76, 1.10)	9.0%	0.99 (0.95, 1.10)	1.4%
All Provinces	0.99 (0.94, 1.04) I^2= 0.0%	1.1%	0.98 (0.97, 0.99) I^2= 0.0%	1.7%

*Immediate increase in geometric mean of initiation rate.

Appendix 1, as supplied by the authors. Appendix to: Moriello C, Paterson JM, Reynier P, et al; the Canadian Network for Observational Drug Effect Studies (CNODES) Investigators. Off-label postpartum use of domperidone in Canada: a multidatabase cohort study. *CMAJ Open* 2021. doi: 10.9778/cmajo.20200084.

Supplemental Table 9. AIC values for linear and interrupted time series analysis models of the 2012 Health Canada advisories overall, for domperidone dose > 30 mg/day, and for durations of >14 days in the six months immediately postpartum in five Canadian provinces.

	Outcome: Prescription Rate		Outcome: ln(Prescription Rate)	
	Linear	Interrupted Time Series	Linear	Interrupted Time Series
All				
British Columbia	332.7	243.0	-47.0	-132.5
Alberta	124.9	122.8	-66.5	-70.2
Saskatchewan	242.1	234.6	-15.9	-55.3
Manitoba	259.1	215.8	-25.0	-78.7
Ontario	272.1	258.6	-10.2	-28.1
Dose > 30 mg/day				
British Columbia	350.4	242.4	-20.7	-123.7
Alberta	124.5	121.2	-65.7	-70.9
Manitoba	288.0	201.6	14.2	-64.0
Ontario	268.2	238.3	8.8	-17.2
Duration > 14 days				
British Columbia	317.1	228.4	-43.0	-130.0
Alberta	118.4	114.9	-67.2	-73.1
Saskatchewan	235.0	224.4	0.06	-39.0
Manitoba	251.2	221.6	-18.0	-59.8
Ontario	260.1	249.3	-6.7	-22.8

Supplemental Table 10. AIC values for linear and interrupted time series analysis models of the 2015 Health Canada advisories overall, for domperidone dose > 30 mg/day, and for durations of >14 days in the six months immediately postpartum in four Canadian provinces.

	Outcome: Prescription Rate		Outcome: ln(Prescription Rate)	
	Linear	Interrupted Time Series	Linear	Interrupted Time Series
All				
British Columbia	110.5	111.3	-72.4	-71.6
Alberta	117.4	109.4	-51.2	-59.4
Saskatchewan	121.4	123.4	-33.8	-31.4
Manitoba	110.3	113.2	-37.6	-34.9
Dose > 30 mg/day				
British Columbia	107.9	108.0	-62.2	-63.1
Alberta	116.0	108.6	-51.4	-58.9
Manitoba	102.3	105.5	-23.9	-21.3
Duration >14 days				
British Columbia	108.9	110.4	-69.0	-67.5
Alberta	112.7	104.5	-51.8	-60.1
Saskatchewan	112.3	115.1	-33.9	-30.6
Manitoba	113.7	117.2	-29.5	-26.1

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Supplemental Table 11. Number of events and incidence rates of VT, SCD, and all-cause mortality in the six months immediately postpartum across the five participating provinces (2004-2017).

Endpoint	Number of events	Number of person-years of follow-up*	Incidence Rate (95% CI) †
Composite of VT/SCD	22	568,618.38	0.39 (0.25, 0.59)
VT	13	568,618.49	0.23 (0.13, 0.39)
SCD	10	568,620.46	0.18 (0.09, 0.33)
All-cause mortality	168	568,620.76	2.95 (2.54, 3.44)

Abbreviations: CI: confidence interval; SCD: sudden cardiac death; VT: ventricular tachyarrhythmia.
*Number of deliveries with livebirths: 1,190,987
†Incidence rates are expressed as event per 10,000 person-years.

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