Prescription of oxycodone versus codeine after childbirth and risk of persistent opioid use: a population-based cohort study

Jonathan S. Zipursky MD PhD, Karl Everett MSc, Tara Gomes MHSc PhD, J. Michael Paterson MSc, Ping Li PhD, Peter C. Austin PhD, Muhammad Mamdani MPH PharmD, Joel G. Ray MD MSc, David N. Juurlink MD PhD

Cite as: *CMAJ* 2023 July 31;195:E973-83. doi: 10.1503/cmaj.221351

Abstract

Background: Oxycodone is increasingly prescribed for postpartum analgesia in lieu of codeine owing to concerns regarding the neonatal safety of codeine during lactation. We examined whether initiation of oxycodone after delivery was associated with an increased risk of persistent opioid use relative to initiation of codeine.

Methods: We conducted a population-based cohort study of people who filled a prescription for either codeine or oxycodone within 7 days of discharge from hospital after delivery between Sept. 1, 2012, and June 30, 2020. The primary outcome was persistent opioid use, defined as 1 or more additional prescriptions for an opioid within 90 days of the first postpartum prescription and 1 or more additional prescriptions in the 91 to 365 days thereafter. We used inverse probability of treatment weighting to assess the risk of persistent postpartum opioid use, comparing people who initiated oxycodone with those who initiated codeine.

Results: Over the 8-year study period, we identified 70 607 people who filled an opioid prescription within 7 days of discharge from hospital: 21 308 (30.2%) received codeine and 49 299 (69.8%) oxycodone. Compared with people who filled a prescription for codeine, receipt of oxycodone was not associated with persistent opioid use (relative risk [RR] 1.04, 95% confidence interval [CI] 0.91–1.20). We found an association between a prescription for oxycodone and persistent use after vaginal delivery (RR 1.63, 95% CI 1.31–2.03), but not after cesarean delivery (RR 0.85, 95% CI 0.73–1.00).

Interpretation: Initiation of oxycodone (v. codeine) was not associated with an increased risk of persistent opioid use, except after vaginal delivery.

Opioids are commonly prescribed to treat pain after childbirth, but the amount prescribed often far exceeds what is taken.[1,2] In Ontario, about 40% of people who give birth fill a prescription for opioids after cesarean delivery, and less than 5% do so after vaginal delivery.[3] In some regions of the United States, those numbers are higher, with more than 80% and 50% filling prescriptions for opioids after cesarean and vaginal delivery, respectively.[1]

The last decade has seen a shift away from prescribing codeine to postpartum people, with corresponding increases in the prescribing of more potent opioids such as hydrocodone, hydromorphone and oxycodone.[3–6] In previous work, we found that during the last decade in Ontario, 13.7% of people filled an opioid prescription after delivery.[3] Most of these prescriptions were issued for oxycodone (42.0%), codeine (19.9%), morphine (19.3%) and hydromorphone (12.0%).[3] These changes coincided with a highly publicized 2006 case report attributing the death of a breastfeeding neonate to morphine toxicity resulting from maternal codeine use,[7] and subsequent warnings from regulatory agencies and professional organizations cautioning against the use of codeine by nursing parents.[6–11] However, the interpretation of the 2006 case report has been repeatedly questioned[12–16] and 2 related articles describing the case were recently retracted.[17]

The consequences to maternal health of the shift from codeine to other opioids have not been studied. In addition to often containing more morphine milligram equivalents (MMEs) at commonly prescribed doses, use of oxycodone has been associated with an increased risk of adverse effects, including a higher risk of opioid-related death.[18] Some evidence suggests that oxycodone is associated with a higher risk of addiction,[19,20] possibly related to increased dopaminergic signalling in the brain's reward circuitry.[21] These factors may, in turn, lead to higher rates of oxycodone abuse than with other opioids.[19,20,22]

Other studies have identified risk factors for persistent opioid use after childbirth, including illicit drug and tobacco use, diagnosis of chronic pain and concomitant use of benzodiazepines and antidepressants, and filling an opioid prescription before birth.[23,24] However, whether the type of opioid prescribed postpartum influences this risk is unknown. We examined whether postpartum treatment with oxycodone, as compared with codeine, was associated with an increased risk of persistent opioid use in people who gave birth in Ontario, Canada.

Methods

Study setting

We conducted a population-based retrospective cohort study of people prescribed either oxycodone or codeine from Sept. 1, 2012, to June 30, 2020, in Ontario, Canada (population 14.7 million in 2020). We selected Sept. 1, 2012, as the study start date because the Narcotics Monitoring System (NMS) database began collecting data in April 2012. We did not examine the first few months after implementation of the database (April–August 2012) to avoid concerns regarding accuracy and completeness of data early in its existence. Ontario residents have universal access to physician and hospital services, including prenatal and postpartum care. In addition, health care records and prescriptions for controlled medications can be tracked using established databases.

Data sources

We identified births using the ICES (formerly, the Institute for Clinical Evaluative Sciences) MOMBABY database, which identifies more than 98% of all Ontario births[25] and links the health care records of birthing parents and their babies. We identified postpartum opioid prescriptions using the NMS database, which contains detailed information on prescriptions for opioids and other controlled drugs, regardless of payer. The NMS database commenced in April 2012 and contains information on drug name, dispensing date, and quantity and days of medication supplied. It is regularly used in studies examining prescription opioid use in Ontario.[26–29] We obtained hospital admission data from the Canadian Institute for Health Information Discharge Abstract Database, which contains diagnostic and procedural information for all hospital admissions in Ontario.[30] We obtained basic demographic information from the Ontario Health Insurance Plan (OHIP) Registered Persons Database (RPDB), a registry of all people in Ontario eligible for health insurance.[31,32] We obtained details on mental health-related hospital admissions using the Ontario Mental Health Reporting System database, and used the OHIP Claims History Database to identify claims for outpatient physician services. These databases are linked in an anonymous fashion using encrypted health insurance numbers, and have been used extensively to study drug safety.[33–37] ICES is an independent, nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without patient consent, for health system evaluation and improvement. Similar coding has been used in studies by our group and others.[3,6]

Study population

The study design is outlined in Figure 1. We established a cohort of people aged 12–60 years who gave birth in hospital and filled a prescription for medications containing either oxycodone or codeine within 7 days of discharge. We chose a 7-day window after hospital discharge to allow enough time for patients to fill an outpatient opioid prescription. A shorter time period (used in some studies[23]) might exclude patients who filled a postpartum opioid prescription for pain, but a longer period (used in other studies[38]) would have risked including those who filled a prescription for an indication other than delivery pain. Studies by our group, and others, have used a similar time frame for ascertaining the first opioid prescription postpartum.[3,6,39]

We chose codeine as the comparator because it has historically been perceived as a "weak opioid" and, until recently, was the preferred opioid prescribed postpartum.[6] Owing in large part to concerns about neonatal safety with breastfeeding, codeine has been supplanted over the past decade by more potent opioids (including oxycodone).[3,6] In the last decade, in Ontario, oxycodone has become the most commonly prescribed opioid postpartum.[3]

We defined the index date as the date of maternal postpartum opioid prescription fill. We included only birthing parents who were discharged from hospital within 7 days of delivery, as extended hospital stays could reflect maternal illness or delivery complications that might influence prescribing decisions, and we limited the cohort to people who delivered between 20 and 42 weeks' gestation. To identify patients newly treated with

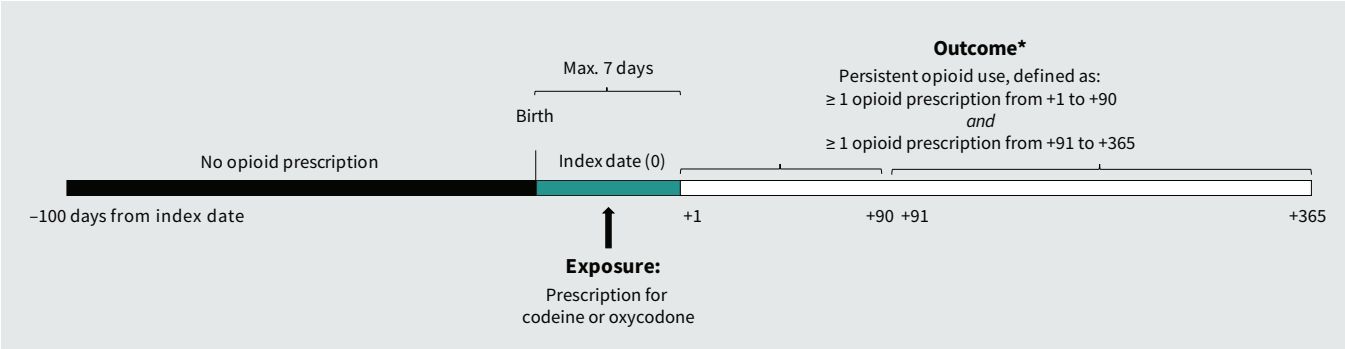

Figure 1: Schematic of study design. Note: *+1 to +365 days after the index date.

opioids postpartum, we excluded people who filled any opioid prescription, including buprenorphine or methadone, in the 100 days preceding the index date. Various definitions have been used in administrative data studies to classify people as opioid naive.[23,40–42] Although no standard definition exists, we have used the preceding definition previously.[3,6] For people with multiple deliveries during the study period, we included only the first.

Persistent opioid use

The primary outcome was persistent opioid use, defined as 1 or more additional opioid prescriptions in the 90 days after the index date and at least 1 additional prescription between 91 and 365 days after the index date (Figure 1). Subsequent opioid prescriptions could have been for any opioid, including oxycodone, codeine, hydromorphone, morphine, fentanyl or tramadol. Similar outcome definitions have been used in previous studies that examined persistent postpartum opioid use.[23] We excluded people who died during the follow-up period, although they were retained for analytical purposes if they met our definition of the primary outcome before death.

Statistical analysis

In the primary analysis, we conducted a complete case analysis and used inverse probability of treatment weighting to minimize potential confounders related to opioid selection.[43] To generate weights, we estimated a propensity score using a logistic regression model in which the choice of opioid (oxycodone or codeine) was regressed on measured baseline factors, including maternal characteristics (age, income quintile, rurality, gravidity [primigravid and number of live births], documented history of addiction, history of mental illness, derived maternal aggregated diagnosis groups [ADG] score from the Johns Hopkins ACG System version 10) and delivery characteristics (mode of delivery, neonatal birth weight, gestational age, severe maternal morbidity, episiotomy, perineal tear, maternal hospital length of stay, year of delivery and stillbirth). Sample codes are found in Appendix 1 (available at www.cmaj.ca/lookup/doi/10.1503/cmaj.221351/tab-related-content). Opioid prescriptions were converted to approximate MMEs using a standard opioid conversion algorithm[44] that has been used in other studies.[6,29]

We calculated stabilized weights by multiplying the inverse probability of treatment by the marginal probability of receiving the drug that was given.[45] We calculated standardized differences for baseline characteristics (both before and after weighting) to examine the balance between groups. Standardized differences less than 0.1 generally indicate good balance for a given covariate.[46] We estimated adjusted relative risks (RRs) using weighted modified Poisson regression and a robust variance estimator.[47] We also calculated weighted estimates of the absolute risk difference.

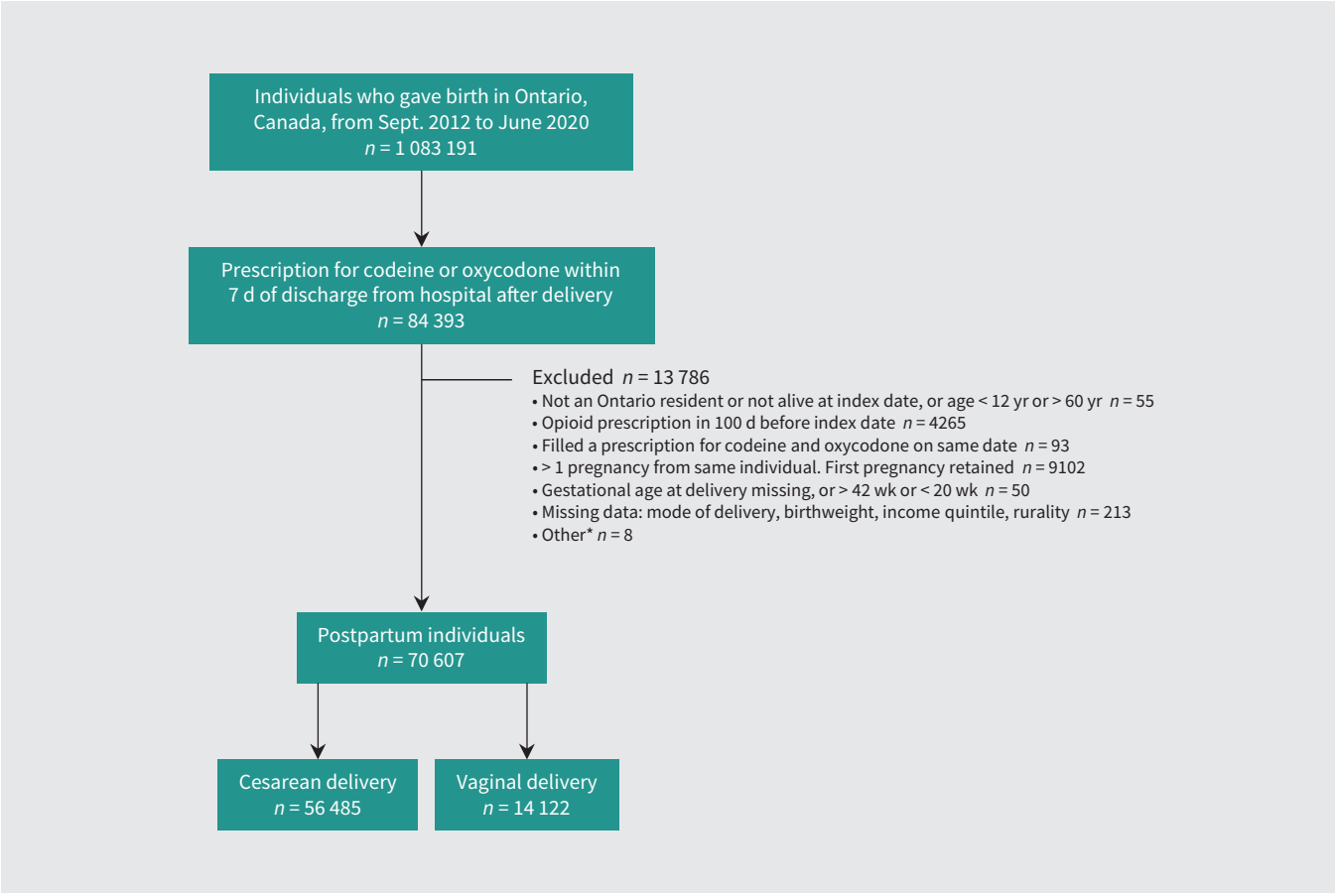

Figure 2: Study flow diagram. *Other includes death during study interval and opioid supply > 100 days. Exact numbers suppressed to adhere to institutional privacy regulations.

Table 1 (part 1 of 2): Characteristics of patients who filled prescriptions for either oxycodone or codeine within 7 days of discharge after delivery

Characteristic	No. (%)* of patients receiving oxycodone *n* = 49 299	No. (%)* of patients receiving codeine *n* = 21 308	Unweighted SD	IPTW SD†
Maternal				
Median (IQR) age, yr	32 (29–36)	30 (27–34)	0.399	0.018
Age group, yr				
< 25	3672 (7.4)	3423 (16.1)	0.039	–
25–35	32 466 (65.9)	14 428 (67.7)	0.257	–
> 35	13 161 (26.7)	3457 (16.2)	0.270	–
Income quintile				
1 (lowest)	10 009 (20.3)	4793 (22.5)	0.053	0.010
2	9384 (19.0)	4426 (20.8)	0.044	0.008
3	9568 (19.4)	4426 (20.8)	0.034	0.001
4	10 122 (20.5)	4370 (20.5)	0.001	0.005
5 (highest)	10 216 (20.7)	3293 (15.5)	0.137	0.013
Rural residence	4018 (8.2)	2672 (12.5)	0.145	0.004
Year of delivery				
2012	2264 (4.6)	2106 (9.9)	0.205	0.002
2013	7477 (15.2)	5083 (23.9)	0.221	0.006
2014	7481 (15.2)	4050 (19.0)	0.102	0.003
2015	7009 (14.2)	3237 (15.2)	0.028	0.002
2016	7152 (14.5)	2673 (12.5)	0.057	0.013
2017	6544 (13.3)	1757 (8.2)	0.163	0.011
2018	5255 (10.7)	1262 (5.9)	0.172	0.011
2019	4348 (8.8)	804 (3.8)	0.209	0.000
2020	1769 (3.6)	336 (1.6)	0.127	0.007
Median (IQR) no. of previous live births	0 (0–1)	0 (0–1)	0.144	0.005
Primigravid	27 625 (56.0)	10 678 (50.1)	0.119	0.014
Mental health diagnosis	5995 (12.2)	2390 (11.2)	0.029	0.004
Substance abuse diagnosis	636 (1.3)	369 (1.7)	0.036	0.002
Median (IQR) ADG	8 (5–10)	7 (4–9)	0.280	0.022
ADG score				
0–5	12 476 (25.3)	7986 (37.5)	0.265	–
6–10	27 020 (54.8)	10 115 (47.5)	0.147	–
> 10	9803 (19.9)	3207 (15.1)	0.128	–

We performed prespecified subgroup analyses by mode of delivery (cesarean v. vaginal). We created unique propensity scores for the 2 subgroups (excluding mode of delivery from the propensity scores) and, after reweighting, we reran the analyses in each subgroup. We used *z* tests to formally test whether the 2 subgroup-specific relative and absolute risks were equal. We also performed unweighted multivariable logistic regression to identify other possible independent risk factors for persistent opioid use, stratified by mode of delivery and adjusting for maternal, delivery and prescription characteristics, including the amount of opioid dispensed (in MMEs) and the duration of the initial prescription (in days). In these analyses, we used logistic regression models to generate odds ratios (ORs), because modified Poisson regression models failed to converge. We used the Wilcoxon rank sum test to compare the median MMEs prescribed to those who filled a prescription for oxycodone and codeine.

We represented relative and absolute risks and ORs with 95% CIs, and considered a 2-tailed type I error rate of 0.05 as the threshold for statistical significance. All analyses were performed at ICES, using SAS software (v. 9.4; SAS Institute, Cary, NC).

Table 1 (part 2 of 2): Characteristics of patients who filled prescriptions for either oxycodone or codeine within 7 days of discharge after delivery

Characteristic	No. (%)* of patients receiving oxycodone *n* = 49 299	No. (%)* of patients receiving codeine *n* = 21 308	Unweighted SD	IPTW SD†
Delivery				
Mode of delivery				
Vaginal				
Spontaneous	3027 (6.1)	7003 (32.9)	0.716	0.006
Operative	2158 (4.4)	1934 (9.1)	0.188	0.002
Cesarean	44 114 (89.5)	12 371 (58.1)	0.765	0.005
Median (IQR) gestational age, wk	39 (38–40)	39 (38–40)	0.209	0.000
≥ 37	43 551 (88.3)	19 892 (93.4)	0.175	–
34 to 36	3626 (7.4)	1052 (4.9)	0.101	–
< 34	2122 (4.3)	364 (1.7)	0.152	–
Episiotomy	2045 (4.1)	2657 (12.5)	0.305	0.003
1st- or 2nd-degree perineal tear	2335 (4.7)	4,654 (21.8)	0.521	0.004
3rd- or 4th-degree perineal tear	1204 (2.4)	696 (3.3)	0.050	0.006
Median (IQR) hospital length of stay, d	2 (2–3)	2 (1–2)	0.501	0.030
Severe maternal morbidity	1512 (3.1)	352 (1.7)	0.093	0.013
Median (IQR) birthweight, g	3360 (2975–3730)	3404 (3078–3746)	0.105	0.002
Stillbirth	69 (0.1)	12 (0.1)	0.027	0.005

Note: ADG = aggregated diagnosis groups defined using the Johns Hopkins ACG System version 10, IPTW = inverse probability of treatment weighting, IQR = interquartile range, SD = standardized difference.
*Unless otherwise specified.
†Weighted standardized differences are of the mean of continuous variables.

Ethics approval

The use of the data in this project was authorized under section 45 of Ontario's *Personal Health Information Protection Act* and does not require review by a research ethics board.

Results

Over the 8-year study period, we identified 70 607 opioid-naive people who filled prescriptions for either oxycodone or codeine within 7 days of delivery (Figure 2). Of these, 21 308 (30.2%) received codeine and 49 299 (69.8%) received oxycodone. Baseline characteristics are shown in Table 1. The median maternal age was 32 years (interquartile range [IQR] 28 to 35 yr), 63 917 (90.5%) lived in an urban setting, and 38 303 (54.2%) were primigravid. The median gestational age at delivery was 39.0 (IQR 38.0 to 40.0) weeks, and 56 485 (80.0%) had a cesarean delivery. The median opioid prescription duration was 3 (IQR 2 to 4) days, and the median opioid content per prescription was 150 (IQR 150 to 225) MMEs among people prescribed oxycodone and 135 (IQR 90 to 135) MMEs among people prescribed codeine ($p < 0.001$) (Table 2).

Association between opioid type and persistent use

Among people who initiated either oxycodone or codeine after delivery, 1460/70 607 (2.1%, 95% CI 2.0% to 2.2%) met our definition of persistent use in the subsequent year. In the primary analysis, 947/49 299 (1.92%) and 513/21 308 (2.41%) people who filled prescriptions for oxycodone and codeine, respectively, showed patterns of persistent opioid use in the year after delivery. After inverse probability of treatment weighting, receipt of oxycodone was not associated with a significantly increased risk of persistent opioid use relative to receipt of codeine (RR 1.04, 95% CI 0.91 to 1.20) (Table 3).

The risk of persistent use differed by mode of delivery (Appendix 1, Figure S1). Of the 14 122 opioid-naive people prescribed an opioid after vaginal delivery, 418 (2.96%) had evidence of new, persistent opioid use. The baseline characteristics of these people are provided in Appendix 1, Table S1. Among these people, an initial prescription for oxycodone was associated with an increased risk of persistent opioid use relative to codeine (RR 1.63, 95% CI 1.31 to 2.03). This corresponded to an absolute risk increase of 1.69% (95% CI 0.85% to 2.52%) associated with a new postpartum prescription for oxycodone after vaginal delivery.

Of the 56 485 people who filled an opioid prescription after cesarean delivery, 1042 (1.84%) had persistent opioid use. The baseline characteristics of these people are shown in Appendix 1, Table S2. Compared with people who filled an initial prescription for codeine, a prescription for oxycodone was associated with a slightly decreased risk of persistent opioid use (RR 0.85, 95% CI

Table 2: Characteristics of initial postpartum opioid prescriptions

Characteristic	No. (%)* of patients receiving oxycodone *n* = 49 299	No. (%)* of patients receiving codeine *n* = 21 308	SD
Median (IQR) MMEs	150 (150–225)	135 (90–135)	1.154
MME group			
< 112.5	7029 (14.3)	8186 (38.4)	0.570
112.5–225	38 738 (78.6)	12 501 (58.7)	0.439
> 225	3532 (7.2)	621 (2.9)	0.195
Median (IQR) days supply	3 (2–4)	3 (3–5)	0.284
Days' supply			
1–3	31 818 (64.5)	12 973 (60.9)	0.076
4–7	15 505 (31.5)	6515 (30.6)	0.019
> 7	1976 (4.0)	1820 (8.5)	0.188

Note: IQR = interquartile range, MME = morphine milligram equivalents, SD = standardized difference.
*Unless otherwise specified.

Table 3: Association between opioid type and persistent postpartum opioid use

	No. (%) of patients with outcome		RR (95% CI)		*p* value, IPTW
	Oxycodone	Codeine	Unweighted	IPTW*	
Full cohort, *n*	49 299	21 308			
	947 (1.92)	513 (2.41)	0.80 (0.72–0.89)	1.04 (0.91–1.20)	0.561
Vaginal delivery, *n*	5185	8937			
	178 (3.43)	240 (2.69)	1.28 (1.06–1.55)	1.63 (1.31–2.03)	< 0.0001
Cesarean delivery, *n*	44 114	12 371			
	769 (1.74)	273 (2.21)	0.79 (0.69–0.91)	0.85 (0.73–1.00)	0.045

Note: CI = confidence interval, IPTW = inverse probability of treatment weighting, RR = relative risk.
*Stabilized weights.

0.73 to 1.00). This corresponded to an absolute risk difference in persistent use of –0.32% (95% CI –0.64% to 0.007%). A *z* test was used to formally compare the relative and absolute risk estimates for the cesarean and vaginal delivery subgroups. The subgroup-specific effects were not equal: relative risks ($z = 4.71$; $p < 0.01$) and absolute risks ($z = 4.38$; $p < 0.01$).

Other risk factors for persistent opioid use

Persistent postpartum opioid use was associated with other maternal, delivery and prescription characteristics. A prescription containing more than 225 MMEs (equivalent to about 30 tablets of 5 mg oxycodone and to 50 tablets of 30 mg codeine) was associated with a roughly 2-fold increased risk of persistent use compared with less than 112.5 MMEs after both vaginal delivery (OR 2.51, 95% CI 1.70 to 3.71) and cesarean delivery (OR 1.78, 95% CI 1.36 to 2.33) (Figure 3 and Figure 4). In addition, a prescription duration of more than 7 days was also associated with a roughly 2-fold increased risk of persistent use compared with a duration of 1–3 days after both vaginal (OR 2.43, 95% CI 1.79 to 3.30) and cesarean delivery (OR 1.52, 95% CI 1.18 to 1.95). Most risk factors for persistent opioid use were consistent across modes of delivery. Specifically, a history of mental illness, substance use disorder and a greater number of maternal comorbidities (ADG > 10) were strongly associated with persistent use.

Interpretation

In this population-based study of about 70 000 opioid-naive postpartum people over an 8-year period, most of whom underwent cesarean delivery, we found that initiation of oxycodone after delivery was not associated with an increased risk of persistent opioid use relative to initiation of codeine. In secondary analyses, we found a 60% relative increase in the risk of persistent opioid use among people prescribed oxycodone relative to codeine after vaginal delivery, and a marginally lower risk among people who delivered by cesarean. Finally, we identified several other

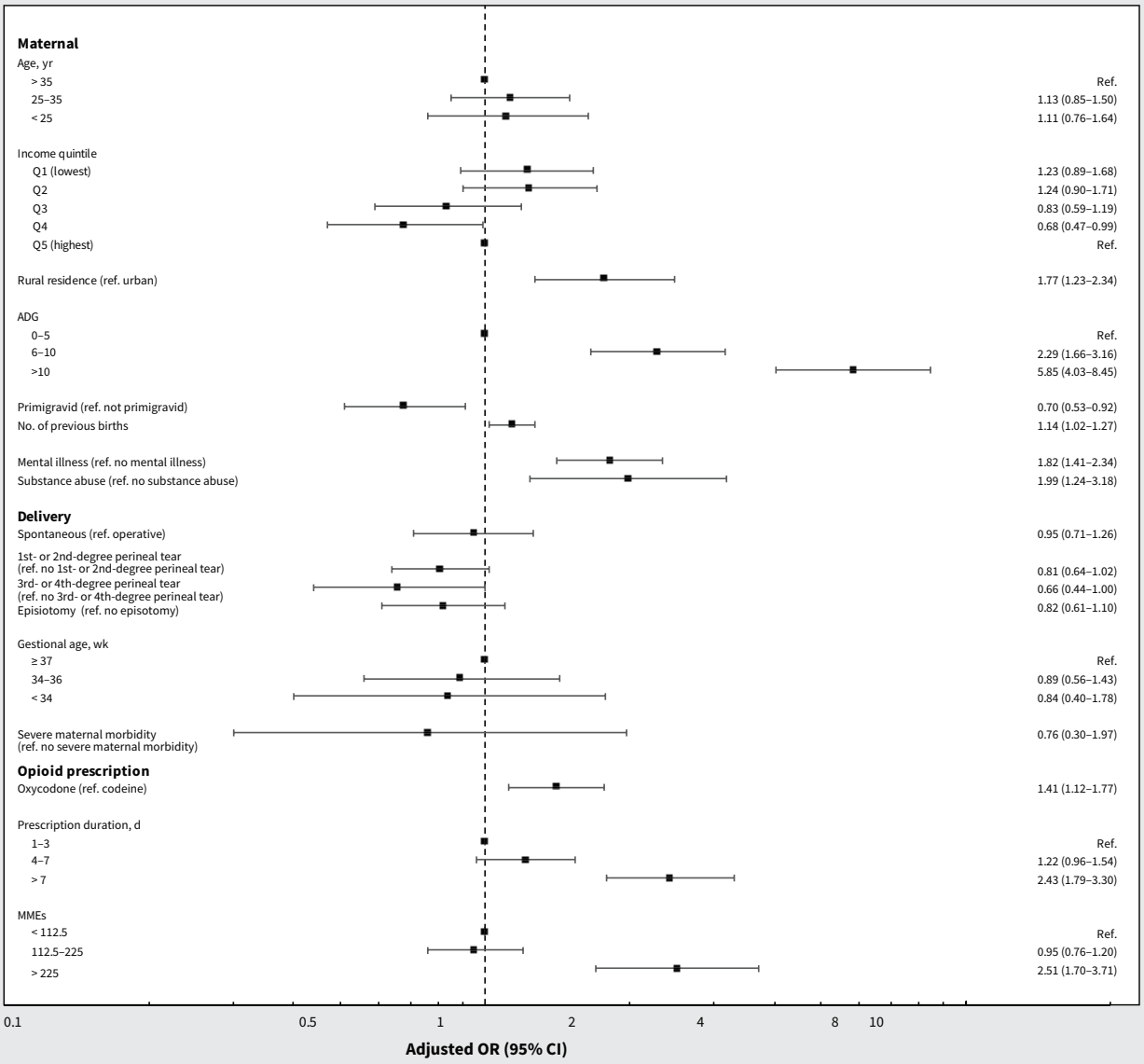

Figure 3: Factors associated with persistent opioid use after vaginal delivery. Note: ADG = aggregated diagnosis groups defined using the Johns Hopkins ACG System version 10, MMEs = morphine milligram equivalents, Ref. = reference category. Adjusted odds ratios (ORs) are presented with 95% confidence intervals (CIs).

factors associated with persistent opioid use, including a history of mental illness, substance use and a larger quantity of opioids in the initial postpartum prescription.

In recent years, oxycodone and morphine have largely supplanted codeine as the most commonly prescribed opioids after delivery in Ontario, Canada.[3,6] This occurred in part because of safety concerns related to the use of codeine while breastfeeding,[6–9,11,12] which have since been questioned.[12] The consequences of this trend on postpartum health have not been well characterized but are potentially concerning, for several reasons. Principally, patients have a strong expressed preference for oxycodone over other prescription opioids, which may impart a greater potential for nonmedical use.[19–22]

We observed an increased risk of persistent oxycodone use only among people who had a vaginal delivery. This observation warrants replication in additional studies. Receipt of an opioid prescription after a vaginal delivery is uncommon in Ontario (< 5%),[3,6] yet we identified that the risks of new persistent opioid use were greater after vaginal delivery than with cesarean delivery. Consequently, people who fill prescriptions for more potent opioids (such as oxycodone) after vaginal delivery may have underlying characteristics that predispose them to subsequent chronic opioid use, which we were unable to measure. A recent study by Zhu and colleagues found that rates of persistent opioid use after vaginal delivery were 4.10%.[39] In that study, people who filled an opioid prescription were more likely to be White and

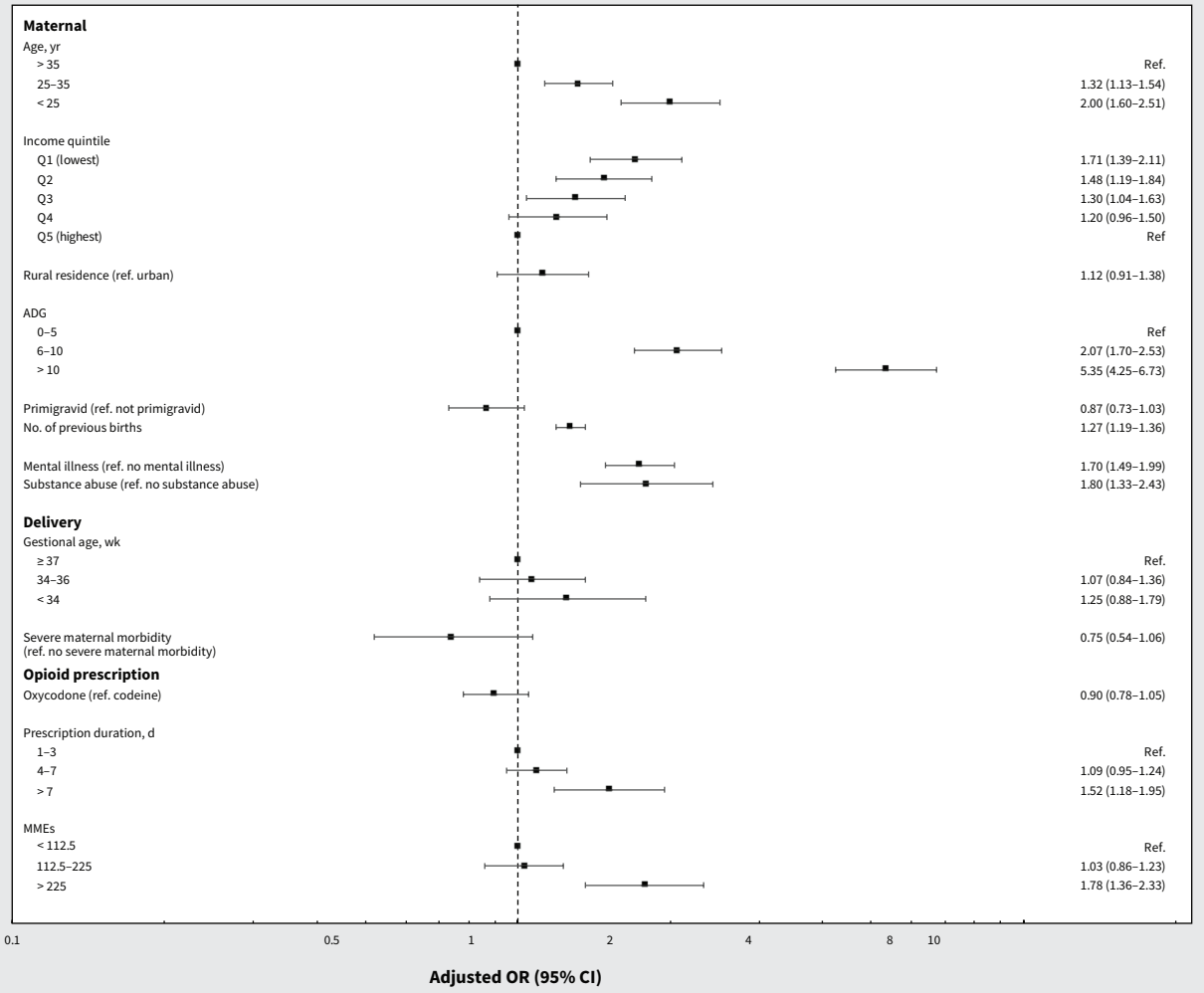

Figure 4: Factors associated with persistent opioid use after cesarean delivery. Note: ADG = aggregated diagnosis groups defined using the Johns Hopkins ACG System version 10, MMEs = morphine milligram equivalents, Ref. = reference category. Adjusted odds ratios (ORs) are presented with 95% confidence intervals (CIs).

smokers; reside in regions with high opioid-prescribing rates; undergo tubal ligation during hospital stay; have a diagnosis of depression, anxiety, back or neck pain, arthritis or migraine; and use other opioids and psychiatric medications in the 90 days before delivery.[39] We were unable to define some of these potential confounders in our study.

We also found that a prescription for oxycodone after cesarean delivery was associated with a marginally lower risk of new, persistent postpartum opioid use relative to codeine. The absolute risk decrease we detected was not statistically significant, and is unlikely to be clinically important. The finding was also not consistent in our multivariable analysis examining other possible factors associated with persistent opioid use, and thus might be explained by unmeasured confounding. Moreover, a study by Bateman and colleagues that examined risk factors for persistent opioid use after cesarean delivery found no association with the type of opioid prescribed.[24] However, in that study, codeine and oxycodone were not directly compared. The notion that different opioids might confer unique risks of persistent use specific to mode of delivery is hypothesis generating. Additional research is needed to validate these findings and examine the comparative safety of different opioid drugs in the postpartum period.

The observed differences among the cesarean and vaginal delivery subgroups suggest that these populations are different, including with respect to factors that might predict persistent opioid use. Most patients in our cohort (80%) underwent a cesarean delivery, and our findings are therefore most applicable to this group. Among people who had a cesarean delivery, we also identified a higher risk of new persistent use in those younger than 25 years and those of lower socioeconomic status. In a study by Bateman and colleagues, younger maternal age was also found to be a risk factor for new persistent opioid use after cesarean delivery.[24] Lower socioeconomic status has not been previously identified as a risk factor for persistent opioid use after childbirth, but has been shown to be a risk factor for persistent use after other surgical procedures.[48,49]

Current postpartum pain management guidelines suggest a stepwise multimodal approach to analgesia, including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids for breakthrough pain.[11,50] However, these guidelines lack specific recommendations on opioid selection, dosing and volume dispensed in the initial postpartum prescription.[11,50] In other patient populations, prescriptions for large quantities of opioids are clear risk factors for chronic opioid use.[38,51] This finding has been observed in patients after vaginal delivery,[23] but has yet to be documented widely in the obstetric literature. Our findings suggest that initial postpartum prescriptions containing large amounts of MMEs might represent an additional risk factor for persistent opioid use. Therefore, limiting the quantity of initial opioid prescriptions might be an additional strategy to reduce the risk of new, persistent opioid use after delivery. Others have suggested that, given the decreasing morbidity and mortality associated with elective surgical procedures, new persistent opioid use may represent one of the most common complications of perioperative care.[38] The same is likely true for postpartum care.

Limitations

Some limitations of our study merit emphasis. First, our findings may be influenced by unmeasured confounding, as we were unable to account for all potential factors that might be associated with both opioid selection postpartum and persistent use, such as patient race, use of tobacco and alcohol, use of illicit opioids, history of a pain syndrome, and use of other prescription drugs.[24] However, we used inverse probability of treatment weighting to minimize confounding related to the measured indication for each specific opioid. In addition, the calculated E-value associated with the RR in the vaginal delivery cohort was 2.64. This means that an unmeasured confounder associated with the outcome and exposure with a risk ratio of 2.64 would be necessary to explain the vaginal delivery findings.

Second, we acknowledge the possibility of outcome misclassification.[52] We chose a definition of new persistent opioid use that strikes a balance between sensitivity, specificity and face validity. Some studies of persistent opioid use after delivery have used a similar definition of new persistent use.[23,53] Although the definition of "persistent use" varies among studies, the positive predictive value and sensitivity of the persistent opioid use definition should be independent of the exposure strata, because all people who gave birth received either oxycodone or codeine.[54] Related, some people may have filled a subsequent opioid prescription for an indication materially unrelated to childbirth. Our administrative data cannot reliably determine the indication for or appropriateness of opioid prescriptions. However, this is equally true of oxycodone and codeine, and we strove to minimize this concern by defining persistent use as at least 1 prescription in the 90 days after the first, and a subsequent prescription between 91 and 365 days.

Third, we excluded some patients who filled an opioid prescription in the 100 days before the index date, multiple births by the same parent, and patients with missing data (Figure 2). Although exclusions can sometimes introduce selection bias, we think this is unlikely, given that our exclusions are not anticipated to be differentially affected by exposure status.

Fourth, we lacked information on use of other analgesics, including acetaminophen and NSAIDs, as well as nonprescription opioids. In addition, combination products of acetaminophen, codeine (8 mg) and caffeine are available over the counter in Canada.

Fifth, we have data only on filled prescriptions and cannot determine the extent to which patients took opioids prescribed to them.

Sixth, our study was performed in a single Canadian province where all patients have universal access to hospital and physician care, and our findings may not be generalizable to other regions. Still, our findings on risk factors for persistent opioid use are consistent with those of other studies using large insurance databases in the United States.[23,24]

Finally, we examined only oxycodone and codeine, and thus our findings might not be applicable to people prescribed other opioids postpartum.

Conclusion

Among postpartum people, we found that an initial prescription for oxycodone was not associated with a higher risk of persistent opioid use relative to codeine overall, although a disproportionately high risk of persistent use after initiation of oxycodone was seen after vaginal delivery. This finding has not been identified previously and warrants replication. Notably, a high volume of opioids dispensed in the initial postpartum prescription may also be a modifiable risk factor for persistent postpartum opioid use. Awareness of these factors and others related to persistent use may help clinicians tailor opioid prescribing while ensuring adequate analgesia after delivery.

References

1. Osmundson SS, Min JY, Grijalva CG. Opioid prescribing after childbirth: overprescribing and chronic use. *Curr Opin Obstet Gynecol* 2019;31:83-9.
2. Bateman BT, Cole NM, Maeda A, et al. Patterns of opioid prescription and use after cesarean delivery. *Obstet Gynecol* 2017;130:29-35.
3. Zipursky JS, Gomes T, Everett K, et al. Maternal opioid treatment after delivery and risk of adverse infant outcomes: population based cohort study. *BMJ* 2023;380:e074005.
4. Smolina K, Weymann D, Morgan S, et al. Association between regulatory advisories and codeine prescribing to postpartum women. *JAMA* 2015;313:1861-2.
5. Prabhu M, Garry EM, Hernandez-Diaz S, et al. Frequency of opioid dispensing after vaginal delivery. *Obstet Gynecol* 2018;132:459-65.
6. Zipursky JS, Pang A, Paterson JM, et al. Trends in postpartum opioid prescribing: a time series analysis. *Clin Pharmacol Ther* 2021;110:1004-10.
7. Koren G, Cairns J, Chitayat D, et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 2006;368:704.
8. Use of codeine and tramadol products in breastfeeding women: questions and answers. Silver Spring (MD): US Food and Drug Administration; updated 2019 Aug. 1. Available: https://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm118113.htm (accessed 2022 Sept. 12).
9. Codeine-containing medicines. Amsterdam (Netherlands): European Medicines Agency (EMA); updated 2013 Aug. 2. Available: https://www.ema.europa.eu/en/medicines/human/referrals/codeine-containing-medicines (accessed 2022 Sept. 12).

10. Important safety information on Tylenol with codeine in nursing mothers and ultra-rapid metabolizers of codeine: for health professionals. Ottawa: Health Canada; modified 2008 Oct. 8. Available: https://recalls-rappels.canada.ca/en/alert-recall/important-safety-information-tylenol-codeine-nursing-mothers-and-ultra-rapid (accessed 2023 July 4).
11. American College of Obstetricians and Gynecologists' Committee on Clinical Consensus–Obstetrics. Pharmacologic stepwise multimodal approach for postpartum pain management: ACOG Clinical Consensus No. 1. *Obstet Gynecol* 2021;138:507-17.
12. Zipursky J, Juurlink DN. The implausibility of neonatal opioid toxicity from breastfeeding. *Clin Pharmacol Ther* 2020;108:964-70.
13. Bateman DN, Eddleston M, Sandilands E. Codeine and breastfeeding. *Lancet* 2008;372:625, author reply 626.
14. Ferner RE. Did the drug cause death? Codeine and breastfeeding. *Lancet* 2008;372:606-8.
15. Young M. Morphine in breast milk. *Can Fam Physician* 2007;53:1005, author reply 1005-6.
16. Willmann S, Edginton AN, Coboeken K, et al. Risk to the breast-fed neonate from codeine treatment to the mother: a quantitative mechanistic modeling study. *Clin Pharmacol Ther* 2009;86:634-43.
17. Pimlott N, Tsuyuki RT. Risks of maternal codeine intake in breastfed infants: a joint statement of retraction from *Canadian Family Physician* and the *Canadian Pharmacists Journal* [published erratum in *Can Fam Physician* 2020;66:882]. *Can Fam Physician* 2020;66:793-6.
18. Dhalla IA, Mamdani MM, Sivilotti MLA, et al. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *CMAJ* 2009;181:891-6.
19. Wightman R, Perrone J, Portelli I, et al. Likeability and abuse liability of commonly prescribed opioids. *J Med Toxicol* 2012;8:335-40.
20. Remillard D, Kaye AD, McAnally H. Oxycodone's unparalleled addictive potential: Is it time for a moratorium? *Curr Pain Headache Rep* 2019;23:15.
21. Boström E, Hammarlund-Udenaes M, Simonsson USH. Blood-brain barrier transport helps to explain discrepancies in in vivo potency between oxycodone and morphine. *Anesthesiology* 2008;108:495-505.
22. Kibaly C, Alderete JA, Liu SH, et al. Oxycodone in the opioid epidemic: high 'liking', 'wanting', and abuse liability. *Cell Mol Neurobiol* 2021;41:899-926.
23. Peahl AF, Dalton VK, Montgomery JR, et al. Rates of new persistent opioid use after vaginal or cesarean birth among US women. *JAMA Netw Open* 2019;2:e197863.
24. Bateman BT, Franklin JM, Bykov K, et al. Persistent opioid use following cesarean delivery: patterns and predictors among opioid-naïve women. *Am J Obstet Gynecol* 2016;215:353.e1-18.
25. Fitzpatrick T, Wilton AS, Guttmann A. Development and validation of a simple algorithm to estimate common gestational age categories using standard administrative birth record data in Ontario, Canada. *J Obstet Gynaecol* 2021;41:207-11.
26. ICES Data Dictionary. Toronto: ICES. Available: https://datadictionary.ices.on.ca/Applications/DataDictionary/Default.aspx (accessed 2022 Mar. 7).
27. Campbell TJ, Martins D, Tadrous M, et al. Dental opioid prescription characteristics and the risk of new, persistent use. *Am J Prev Med* 2021;60:831-9.
28. Wunsch H, Hill AD, Fu L, et al. New opioid use after invasive mechanical ventilation and hospital discharge. *Am J Respir Crit Care Med* 2020;202:568-75.
29. Gomes T, Campbell T, Tadrous M, et al. Initial opioid prescription patterns and the risk of ongoing use and adverse outcomes. *Pharmacoepidemiol Drug Saf* 2021;30:379-89.
30. Juurlink D, Preyra C, Croxford R, et al. *Canadian Institute for Health Information Discharge Abstract Database: a validation study*. Toronto: ICES; 2006.
31. Wilkins R and Khan S. *Automated geographic coding based on the Statistics Canada postal code conversion files, including postal codes through October 2010.* Ottawa: Statistics Canada; 2011. Available: https://mdl.library.utoronto.ca/sites/default/public/mdldata/open/canada/national/statcan/postalcodes/pccfplus/2006/2010oct/MSWORD.PCCF5H.pdf (accessed 2023 July 4).
32. Iron K, Zagorski B, Sykora K, et al. *Living and dying in Ontario: an opportunity for improved health information: ICES investigative report.* Toronto: ICES; 2008.
33. Antoniou T, Gomes T, Mamdani MM, et al. Trimethoprim-sulfamethoxazole induced hyperkalaemia in elderly patients receiving spironolactone: nested case-control study. *BMJ* 2011;343:d5228.
34. Gomes T, Greaves S, van den Brink W, et al. Pregabalin and the risk for opioid-related death: a nested case-control study. *Ann Intern Med* 2018;169:732-4.
35. Finkelstein Y, Macdonald EM, Gonzalez A, et al.; Canadian Drug Safety And Effectiveness Research Network (CDSERN). Overdose risk in young children of women prescribed opioids. *Pediatrics* 2017;139:e20162887. doi: 10.1542/peds.2016-2887.
36. Turner SD, Gomes T, Camacho X, et al. Neonatal opioid withdrawal and antenatal opioid prescribing. *CMAJ Open* 2015;3:E55-61.
37. Zipursky J, Macdonald EM, Hollands S, et al. Proton pump inhibitors and hospitalization with hypomagnesemia: a population-based case-control study. *PLoS Med* 2014;11:e1001736.
38. Brummett CM, Waljee JF, Goesling J, et al. New persistent opioid use after minor and major surgical procedures in US adults. *JAMA Surg* 2017;152:e170504.
39. Zhu Y, Huybrechts KF, Desai RJ, et al. Prescription opioid use after vaginal delivery and subsequent persistent opioid use and misuse. *Am J Obstet Gynecol MFM* 2021;3:100304.
40. Lail S, Sequeira K, Lieu J, et al. Prescription of opioids for opioid-naive medical inpatients. *Can J Hosp Pharm* 2014;67:337-42.
41. Brat GA, Agniel D, Beam A, et al. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. *BMJ* 2018;360:j5790.
42. Brown CR, Chen Z, Khurshan F, et al. Development of persistent opioid use after cardiac surgery. *JAMA Cardiol* 2020;5:889-96.
43. Little RJA. Regression with missing X's: a review. *J Am Stat Assoc* 1992;87:1227-37.
44. Ontario Prescription Opioid Tool. Toronto: Ontario Drug Policy Research Network; 2018. doi: 10.31027/ODPRN.2018.01. Available: https://odprn.ca/ontario-opioid-drug-observatory/ontario-prescription-opioid-tool/ (accessed 2023 July 4).
45. Chesnaye NC, Stel VS, Tripepi G, et al. An introduction to inverse probability of treatment weighting in observational research. *Clin Kidney J* 2021;15:14-20.
46. Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. *Stat Med* 2007;26:734-53.
47. Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. *Stat Med* 2013;32:2837-49.
48. Johnson SP, Chung KC, Zhong L, et al. Risk of prolonged opioid use among opioid-naïve patients following common hand surgery procedures. *J Hand Surg Am* 2016;41:947-57.e3.
49. Clarke H, Soneji N, Ko DT, et al. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. *BMJ* 2014;348:g1251 10.1136/bmj.g1251.
50. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' committee on regional anesthesia, executive committee, and administrative council. *J Pain* 2016;17:131-57.
51. Shah A, Hayes CJ, Martin BC. Factors influencing long-term opioid use among opioid naive patients: an examination of initial prescription characteristics and pain etiologies. *J Pain* 2017;18:1374-83.
52. Jivraj NK, Raghavji F, Bethell J, et al. Persistent postoperative opioid use: a systematic literature search of definitions and population-based cohort study. *Anesthesiology* 2020;132:1528-39.
53. Peahl AF, Morgan DM, Dalton VK, et al. New persistent opioid use after acute opioid prescribing in pregnancy: a nationwide analysis. *Am J Obstet Gynecol* 2020;223:566.e1-13.
54. Hall GC, Lanes S, Bollaerts K, et al. Outcome misclassification: impact, usual practice in pharmacoepidemiology database studies and an online aid to correct biased estimates of risk ratio or cumulative incidence. *Pharmacoepidemiol Drug Saf* 2020;29:1450-5.

Competing interests: Jonathan Zipursky has received payments from private law firms for medicolegal opinions on the safety and effectiveness of analgesics, including opioids. Dr. Zipursky is supported by the University of Toronto Department of Medicine Clinician Scientist Training Program and a Canadian Institutes of Health Research (CIHR) Banting and Best Doctoral Award. David Juurlink reports receiving payment for expert testimony from multiple law firms related to analgesics, including opioids; an honorarium for a lecture on pain management from Texas Tech University Health Sciences Center; and reimbursement for travel costs for presentations and scientific meetings from CIHR, Stanford University and Texas Tech University Health Sciences Center. Dr. Juurlink is an unpaid member of Physicians for Responsible Opioid Prescribing (PROP), a nongovernmental organization with the goal of promoting opioid stewardship. Tara Gomes reports receiving grant and contract funding from the Ontario Ministry of Health, the Public Health Agency of Canada, the Ontario College of Pharmacists and the Government of Canada (paid to institution in support of Dr. Gomes' research program). A Tier 2 Canada Research Chair supports Dr. Gomes' salary. Dr. Gomes has also received payment for travel and a stipend for participating in the Drugs and Therapeutics Advisory Committee from Indigenous Services Canada. Muhammad Mamdani reports receiving grant funding from Roche, examining drug use for multiple sclerosis. Dr. Mamdani has also received honoraria as a member of the scientific advisory board of SaNotize. No other competing interests were declared.

This article has been peer reviewed.

Affiliations: Department of Medicine (Zipursky), Sunnybrook Health Sciences Centre; Institute of Health Policy, Management, and Evaluation (Zipursky, Gomes, Paterson, Austin, Mamdani, Ray), University of Toronto; ICES Central (Everett, Gomes, Paterson, Li, Austin, Mamdani, Ray, Zipursky); Keenan Research Centre of the Li Ka Shing Knowledge Institute (Gomes, Mamdani), St. Michael's Hospital; Leslie Dan Faculty of Pharmacy (Gomes, Mamdani), University of Toronto; Sunnybrook Research Institute (Austin, Juurlink, Zipursky); Department of Medicine (Ray), St. Michael's Hospital, Toronto, Ont.

Contributors: Jonathan Zipursky, Karl Everett, Tara Gomes, Ping Li, Peter Austin, Joel Ray and David Juurlink contributed to the conception and design of the work. All of the authors contributed to the acquisition, analysis and interpretation of data. All of the authors drafted the manuscript, revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Funding: This research was funded by a Canadian Institutes of Health Research project grant.

Data sharing: The data set from this study is held securely in coded form at ICES. Although legal data sharing agreements between ICES and data providers (e.g., health care organizations and governments) prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at https://www.ices.on.ca/DAS (das@ices.on.ca). The full data set creation plan and underlying analytical code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Disclaimer: This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care. Parts of this material are based on data and information compiled and provided by the Ontario MOH, the Canadian Institute for Health Information, and IQVIA Solutions Canada Inc. The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

Accepted: June 19, 2023

Correspondence to: Jonathan Zipursky,
Jonathan.Zipursky@sunnybrook.ca