

Overdose Risk in Young Children of Women Prescribed Opioids

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abstract

BACKGROUND AND OBJECTIVE: Over the past 20 years, the prescribing of opioids has increased dramatically in North America, with parallel increases in opioid addiction, overdose, and associated deaths. We examined whether young children of women prescribed opioids were at increased risk of opioid overdose.

METHODS: We conducted a population-based, nested case control study in Ontario, Canada, between 2002 and 2015. We identified children aged ≤ 10 years, whose mothers received publicly funded prescriptions for an opioid or a nonsteroidal antiinflammatory drug (comparator analgesic) in the preceding year. Cases were children who presented to hospital for or died of opioid overdose. Each case was matched with 4 controls with no opioid overdose. The primary outcome was the risk of opioid overdose.

RESULTS: We identified 103 children who presented to the hospital with opioid overdose and matched them with 412 controls. Half of the children with opioid overdose were < 2 years old. Compared with controls, children with an opioid overdose were far more likely to have a mother who received a prescription opioid (unadjusted odds ratio, 2.41; 95% confidence interval, 1.68–3.45) and who was prescribed antidepressants. The most commonly implicated overdose opioids were codeine (53.4%), oxycodone (32.0%), and methadone (15.5%).

CONCLUSIONS: Young children of mothers prescribed opioids are at a markedly increased risk of overdose. Physicians, pharmacists, and parents should take measures to mitigate the risk of opioid-related harm to children, such as prescribing smaller quantities, emphasizing the importance of secure medication storage, and the prompt disposal of unused opioids.

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Drs Finkelstein and Juurlink conceptualized and designed the study, obtained funding, drafted the manuscript; Ms Macdonald and Mr Gonzalez analyzed and interpreted the data and reviewed and revised the manuscript; Drs Sivilotti and Mamdani critically reviewed and revised the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: The increase in opioid prescribing in North America over the past 2 decades has led to the worst drug overdose epidemic in history. However, the impact of prescription opioids on young children in the home has not been well studied.

WHAT THIS STUDY ADDS: Young children of mothers prescribed opioids are at a markedly increased risk of overdose. Providers should take measures to mitigate the risk of pediatric opioid-related harm, such as prescribing smaller quantities, facilitating secure storage, and prompt disposal of unused opioids.

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The increased prescribing of opioids for chronic pain over the past 2 decades has led to dramatic parallel increases in opioid misuse, addiction, and opioid-related deaths in North America,^{1,2} resulting in what the Centers for Disease Control and Prevention have deemed the worst drug overdose epidemic in history.^{3,4} More than 250 000 Americans have died of opioids over the past 20 years, and roughly 7000 are treated each day in emergency departments across the United States for opioid misuse.⁴ Similar phenomena have been observed in Canada,⁵ the United Kingdom,⁶ and Australia.⁷

Although a great deal of harm associated with prescription opioids involves patients, misuse and overdose can also occur as the result of diversion, medication sharing, and other indirect mechanisms. However, the impact of prescription opioids on young children in the home has not been well studied.⁸ Scattered reports describe unintentional opioid exposures in children,⁸⁻¹⁰ but no reliable estimates exist regarding the specific risk to young children from opioids prescribed to family members. Young children are particularly prone to unintentional overdoses involving substances in their immediate environment and, less commonly, as victims of neglect or malice.¹¹

To determine the potential downstream impact of parental opioids prescribing on their young children, we explored whether maternal receipt of prescription opioids is associated with an increased risk of overdose harm to young children in the home.

METHODS

Setting and Data Sources

We conducted a population-based, nested case control study between April 1, 2002 and March 31, 2015 in Ontario, Canada. We identified

prescription claims using the publicly funded Ontario Public Drug Benefit Database. This database contains prescription information for all Ontario residents who receive social assistance. This is a subset of the Ontario population (~13.8 million): those receiving prescription medications subsidized by the province. All such residents receive all their medications, including over-the-counter medications, such as nonsteroidal antiinflammatory drugs (NSAIDs), free-of-charge, and all dispensed medications, including over-the-counter drugs, are captured in this database. Therefore, we identified all opioid and NSAID prescriptions reimbursed under this drug benefit plan during the study period. We used the Canadian Institute for Health Information Discharge Abstract Database, which contains detailed diagnostic information for all hospital admissions in Ontario, and we identified emergency department visits using the National Ambulatory Care Report System. We used the Ontario Health Insurance Plan database to identify claims for physician services, and obtained basic demographic data and dates of death from the Registered Persons Database, a registry of all Ontario residents eligible for health insurance. The Ontario Registrar General Death Database identified the cause of death reported on individual death certificates up to December 2012, the most recent data available. We identified mother-child pairs using birth records, as done previously.^{12,13} These databases were linked in an anonymous fashion using encrypted health card numbers and are routinely used to study drug safety.¹⁴⁻¹⁶

Study Subjects

We defined cases as children aged ≤ 10 years whose mothers received subsidized medications via Ontario's publicly funded drug plan and

who presented to the hospital for opioid toxicity. Opioid overdose was defined using the *International Classification of Diseases and Related Health Problems, Tenth Revision* codes T40.0, T40.1, T40.2, T40.3, T40.4, and T40.6. We also included children who died of opioid overdose in the prehospital setting, identified using the *International Classification of Diseases and Related Health Problems, Ninth Revision* codes X40-X49, X60-X69, X85-X90, Y10-Y19 and the Ontario Registrar General Death database, as validated previously.¹⁷ We excluded children >10 years of age to avoid inclusion of overdoses related to voluntary drug misuse, which is rare before adolescence. Only the first hospital presentation was considered for children with multiple episodes. The date of hospital presentation or death served as the index date for all analyses. For each case, we randomly selected 4 control children without an opioid overdose, matching on age (within 6 months) and sex. Each individual could serve as a control only once. To account for temporal changes in analgesic prescribing over the study period, each control subject was randomly assigned an index date within 6 months of his or her corresponding case.

Case and control children were linked to their mothers using birth records, as done previously.¹⁸ Among mothers of case and control children, we identified those who received either an opioid or an NSAID in the year preceding their child's opioid overdose. We chose NSAIDs as the reference exposure because, like opioids, they are primarily prescribed for analgesia and because individuals who receive analgesics for chronic pain are frequently inherently different from those who do not. Because those women's prescription costs are covered by the provincial government, they

TABLE 1 Characteristics of Cases and Controls

Characteristic	Cases (<i>n</i> = 103)	Controls (<i>n</i> = 412)	<i>P</i>
Children's characteristics			
Median (IQR) age, y	2 (1–3)	2 (1–3)	.996
Boy	53 (51.5)	212 (51.5)	.998
No. of siblings	1 (1–2)	1 (1–2)	.65
Maternal characteristics			
Median (IQR) age, y	28 (23–32)	28 (24–34)	.297
Rurality	12 (11.8)	36 (8.7)	.347
Income quintile			
1 (lowest)	47 (46.5)	222 (54.0)	.368
2	23 (22.8)	76 (18.5)	—
3	16 (15.8)	51 (12.4)	—
4	7 (6.9)	41 (10.0)	—
5	8 (7.9)	21 (5.1)	—
No. of prescription drugs (mean ± SD) ^a	1.55 ± 2.13	1.15 ± 2.44	.121
Alcohol use disorder ^b	≤5 ^c	11 (2.7)	.892
Affective disorder ^b	10 (9.7)	30 (7.3)	.41
Anxiety disorder ^b	67 (65.0)	232 (56.3)	.108
Depression ^b	20 (19.4)	60 (14.6)	.224
Schizophrenia ^b	≤5 ^c	7 (1.7)	.593
Prescription drugs ^d			
Antidepressant	47 (45.6)	120 (29.1)	<.001
Antipsychotic	8 (7.8)	26 (6.3)	.594
Benzodiazepines	25 (24.3)	67 (16.3)	.058
Anticonvulsants	6 (5.8)	14 (3.4)	.254

—, not applicable.

^a Number of distinct drugs is a validated marker of comorbidity.

^b In the 3 years preceding the index date.

^c Suppressed to reduce risk for reidentification.

^d In the year preceding the index date.

TABLE 2 Maternal Prescription and Child Opioid Overdose

Medication Use by Mother	No. (%) of Child Overdoses		OR (95% CI)
	Cases, <i>n</i> (%) (<i>n</i> = 103)	Controls, <i>n</i> (%) (<i>n</i> = 412)	Unadjusted
NSAID	13 (12.6)	111 (26.9)	1
Opioid	90 (87.4)	301 (73.1)	2.41 (1.68–3.45)

are unlikely to obtain NSAIDs without a prescription. Finally, to focus on maternal prescriptions, we also excluded children who were prescribed an opioid or NSAID for themselves in the 100 days before the index date.

Statistical Analysis

We compared the baseline characteristics of cases and controls using *P* values (Table 1). We used conditional logistic regression to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between pediatric

opioid overdose and maternal receipt of an opioid prescription. This is a specialized type of logistic regression used when cases with a specific outcome are matched with multiple controls; each case and his or her corresponding controls represent a stratum in the analysis. Other covariates were not included in the model to preserve model fit. In all analyses, maternal receipt of an NSAID prescription in the year preceding the index date constituted the reference exposure. We used SAS version 9.3 (SAS Institute, Inc., Cary, NC) for all

analyses, and a two-tailed type 1 error rate of .05 as the threshold for statistical significance. The study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre (Toronto, Ontario, Canada).

RESULTS

We identified 103 children aged ≤10 years with an opioid overdose, whose mothers received an opioid or NSAID under Ontario's publicly funded provincial drug plan in the previous year and matched them to 412 controls (Table 1). The median age was 2 years (interquartile range [IQR], 1–3 years), and 9 (8.7%) overdoses involved infants <12 months. Thirty-nine (37.9%) children were admitted to the hospital, including 13 to critical care units. No deaths were recorded in this cohort. The median ages of case and control mothers were 28 years (IQR, 23–32 years) and 28 years (IQR, 24–34 years), respectively. A larger proportion of case mothers had been prescribed antidepressants compared with control mothers (Table 1).

Overall, maternal receipt of an opioid prescription was associated with a substantially increased risk of pediatric opioid overdose (OR, 2.41; 95% CI, 1.68–3.45) (Table 2). Among cases, the most commonly implicated opioids were codeine (53.4%), oxycodone (32.0%), and methadone (15.5%).

DISCUSSION

In this population-based study, we found that young children of women prescribed an opioid were at a significantly higher risk of opioid overdose than children of women prescribed a NSAID. Half of children who presented to the hospital with opioid overdose were <2 years. The use of antidepressants by the mother

was associated with an increased risk for pediatric opioid overdose and may reflect the complex associations between chronic pain, addiction, and psychiatric comorbidities, such as depression. This study is the first to explore and contextualize the risk of overdose in young children of mothers prescribed opioids.

Our findings underscore the importance of secure storage of potentially toxic medications, such as opioids. Roughly 65% of all acute poison exposures reported to Poison Information Centers involve preschool children and are largely preventable. Rising rates of unintentional pediatric poisonings are strongly correlated with the increased use of adult drugs, dominated by prescription medications,¹⁹ and are associated with increased health care use, including emergency department visits²⁰ and hospitalizations.^{21,22} Campaigns, such as the Centers for Disease Control and Prevention's "Up and Away" initiative,²³ have the goal of reducing unintentional exposures among young children through parental education about safe medication handling and storage. Unused opioids may be subject to misuse or unintentional ingestion in the future.¹⁰ In light of the potentially fatal toxicity of opioids, parental awareness augmented by physician and pharmacist guidance should help reduce unintentional opioid exposures. Clinicians who provide care to young children should inquire specifically about prescription and nonprescription opioid use in the child's environment as part of the

ongoing effort to curb unintentional opioid overdose.

In our analysis, half of the children who presented to the hospital with an opioid overdose were <2 years, and 1 in 10 opioid overdoses occurred in infants <12 months. This observation is noteworthy because infants of this age rarely exhibit purposeful coordination and the necessary motor skills to independently access medications. This observation raises the possibility that some cases in our study may have involved caregiver neglect, error, or malice. We have previously reported that 1 in 8 children <2 years assessed by medical toxicology services in emergency departments in the United States had been exposed to illicit drugs or alcohol.¹¹

Some limitations of our work should be noted. Chief among these is that our database allows linkage of children with their mothers based on birth records, but does not allow identification of father-child nor sibling-child pairs. Consequently, we do not have data on opioid prescription claims for fathers or siblings. Our analyses are limited to children of mothers whose prescriptions are insured under the provincial publicly funded drug plan. This is a subpopulation at socioeconomic disadvantage, with potential implications on illicit drug use, child care, and parental access to health care. Finally, we had no information regarding illicit opioid use in the home, an important potential source of pediatric exposure.

CONCLUSIONS

Children of mothers prescribed opioids are at a substantially increased risk of opioid toxicity. Prescription of antidepressants to the mother was also associated with an increased risk for pediatric opioid overdose. Prescribers, pharmacists, and parents should be cognizant of the potentially fatal risk these drugs pose to young children in the home and take measures to mitigate it, such as dispensing smaller opioid quantities, considering alternatives to opioids, and emphasizing the importance of secure storage and prompt disposal of unused opioids.

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ABBREVIATIONS

CI: confidence interval
IQR: interquartile range
NSAID: nonsteroidal antiinflammatory drug
OR: odds ratio

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