

Overdose Risk in Young Children of Women Prescribed Opioids

Yaron Finkelstein, MD,^{a,b,c,d} Erin M. Macdonald, MSc,^d Alejandro Gonzalez, MSc,^d Marco L.A. Sivilotti, MD, MSc,^{e,f} Muhammad M. Mamdani, PharmD,^{d,g,h} David N. Juurlink, MD,^{d,i,j} Canadian Drug Safety And Effectiveness Research Network (CDSERN)

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.

FREE

Divisions of ^aEmergency Medicine, and ^bClinical Pharmacology and Toxicology, Hospital for Sick Children, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; ^cChild Health Evaluative Sciences, Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada; ^dThe Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada; ^eDepartment of Emergency Medicine, Queen's University, Kingston, Ontario, Canada; ^fDepartment of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada; ^gLi Ka Shing Centre for Healthcare Analytics Research and Training, St. Michael's Hospital, Toronto, Ontario, Canada; ^hDalla Lana School of Public Health, University of Toronto, Ontario, Canada; ⁱSunnybrook Research Institute, Sunnybrook Hospital, Toronto, Ontario, Canada; and Departments of ^jMedicine, Paediatrics and Health Policy, Management and Evaluation, University of Toronto, Ontario, Canada

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.

DOI: 10.1542/peds.2016-2887

Accepted for publication Dec 13, 2016

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.

To cite: Finkelstein Y, Macdonald EM, Gonzalez A, et al. Overdose Risk in Young Children of Women Prescribed Opioids. *Pediatrics*. 2017;139(3):e20162887

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.

ACKNOWLEDGMENTS

We thank Brogan, Inc (Ottawa, Ontario, Canada) for use of their Drug Product and Therapeutic Class Database. Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information. However, the analyses, conclusions, opinions and statements expressed herein are those of the authors, and not necessarily those of Canadian Institute for Health Information. We also thank Stephanie Cheng for her statistical input.

ABBREVIATIONS

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

Address correspondence to Yaron Finkelstein, MD, FACMT, Professor of Pediatrics, Pharmacology and Toxicology, University of Toronto, Divisions of Emergency Medicine and Clinical Pharmacology and Toxicology, 555 University Ave, Toronto, ON M5G 1X8, Canada. E-mail: yaron.finkelstein@sickkids.ca

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2017 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: Dr Juurlink is supported by the Eaton Scholar award (Department of Medicine, University of Toronto). The other authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: This study was supported by grants from the SickKids Research Institute, the SickKids Foundation, the Canadian Institutes of Health Research, and by the Institute for Clinical Evaluative Sciences, a nonprofit research institute sponsored by the Ontario Ministry of Health and Long-Term Care. The opinions, results, and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by the Institute for Clinical

Evaluative Sciences or the Ontario Ministry of Health and Long-Term Care is intended or should be inferred. Mr Gonzales had full access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

POTENTIAL CONFLICT OF INTEREST: Dr Mamdani has served on advisory boards and/or received honoraria from Astra Zeneca, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Hoffman La Roche, Novartis, Novo Nordisk, and Pfizer. The other authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Nelson LS, Juurlink DN, Perrone J. Addressing the opioid epidemic. *JAMA*. 2015;314(14):1453–1454
2. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths—United States, 2000–2014. *MMWR Morb Mortal Wkly Rep*. 2016;64(50–51):1378–1382
3. Paulozzi LJ. The epidemiology of drug overdoses in the United States. Paper presented at: Maimonides Medical Center Department of Psychiatry; December 2, 2010; Brooklyn, NY
4. Centers for Disease Control and Prevention. Understanding the epidemic. Available at: www.cdc.gov/drugoverdose/epidemic/index.html. Accessed January 6, 2016
5. Gomes T, Mamdani MM, Dhalla IA, Cornish S, Paterson JM, Juurlink DN. The burden of premature opioid-related mortality. *Addiction*. 2014;109(9):1482–1488
6. Handley SA, Flanagan RJ. Drugs and other chemicals involved in fatal poisoning in England and Wales during 2000–2011. *Clin Toxicol (Phila)*. 2014;52(1):1–12
7. Rintoul AC, Dobbin MD, Drummer OH, Ozanne-Smith J. Increasing deaths involving oxycodone, Victoria, Australia, 2000–09. *Inj Prev*. 2011;17(4):254–259
8. Bailey JE, Campagna E, Dart RC; RADARS System Poison Center Investigators. The underrecognized toll of prescription opioid abuse on young children. *Ann Emerg Med*. 2009;53(4):419–424
9. Glatstein M, Finkelstein Y, Scolnik D. Accidental methadone ingestion in an infant: case report and review of the literature. *Pediatr Emerg Care*. 2009;25(2):109–111
10. Voepel-Lewis T, Wagner D, Tait AR. Leftover prescription opioids after minor procedures: an unwitting source for accidental overdose in children. *JAMA Pediatr*. 2015;169(5):497–498
11. Finkelstein Y, Hutson JR, Wax PM, Brent J; Toxicology Investigators Consortium (ToxIC) Case Registry. Toxicosurveillance of infant and toddler poisonings in the United States. *J Med Toxicol*. 2012;8(3):263–266
12. Urquia ML, Frank JW, Glazier RH, Moineddin R. Birth outcomes by neighbourhood income and recent immigration in Toronto. *Health Rep*. 2007;18(4):21–30
13. Urquia ML, Frank JW, Moineddin R, Glazier RH. Immigrants' duration of residence and adverse birth outcomes: a population-based study. *BJOG*. 2010;117(5):591–601
14. Finkelstein Y, Macdonald EM, Li P, Hutson JR, Juurlink DN. Recurrence and mortality following severe cutaneous adverse reactions. *JAMA*. 2014;311(21):2231–2232
15. Juurlink DN, Gomes T, Lipscombe LL, Austin PC, Hux JE, Mamdani MM. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study. *BMJ*. 2009;339:b2942
16. Park-Wyllie LY, Juurlink DN, Kopp A, et al. Outpatient gatifloxacin therapy and dysglycemia in older adults. *N Engl J Med*. 2006;354(13):1352–1361
17. Gladstone E, Smolina K, Morgan SG, Fernandes KA, Martins D, Gomes T. Sensitivity and specificity of administrative mortality data for identifying prescription opioid-related deaths. *CMAJ*. 2016;188(4):E67–E72
18. Juurlink DN, Tenenbein M, Koren G, Redelmeier DA. Iron poisoning in young children: association with the birth of a sibling. *CMAJ*. 2003;168(12):1539–1542
19. Bond GR, Woodward RW, Ho M. The growing impact of pediatric pharmaceutical poisoning. *J Pediatr*. 2012;160(2):265–270.e1
20. Tadros A, Layman SM, Davis SM, Bozeman R, Davidov DM. Emergency department visits by pediatric patients for poisoning by prescription opioids. *Am J Drug Alcohol Abuse*. 2016;42(5):550–555
21. Burghardt LC, Ayers JW, Brownstein JS, Bronstein AC, Ewald MB, Bourgeois FT. Adult prescription drug use and pediatric medication exposures and poisonings. *Pediatrics*. 2013;132(1):18–27
22. Schillie SF, Shehab N, Thomas KE, Budnitz DS. Medication overdoses leading to emergency department visits among children. *Am J Prev Med*. 2009;37(3):181–187
23. Centers for Disease Control and Prevention. Put your medicines up and away and out of sight. Available at: www.cdc.gov/features/medicationstorage/. Accessed December 23, 2015

Overdose Risk in Young Children of Women Prescribed Opioids

Yaron Finkelstein, Erin M. Macdonald, Alejandro Gonzalez, Marco L.A. Sivilotti, Muhammad M. Mamdani, David N. Juurlink and Canadian Drug Safety And Effectiveness Research Network (CDSEEN)

Pediatrics 2017;139;

DOI: 10.1542/peds.2016-2887 originally published online February 20, 2017;

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/139/3/e20162887>

References

This article cites 20 articles, 5 of which you can access for free at:
<http://pediatrics.aappublications.org/content/139/3/e20162887#BIBL>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):
Injury, Violence & Poison Prevention
http://www.aappublications.org/cgi/collection/injury_violence_-_poison_prevention_sub
Pharmacology
http://www.aappublications.org/cgi/collection/pharmacology_sub
Toxicology
http://www.aappublications.org/cgi/collection/toxicology_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Overdose Risk in Young Children of Women Prescribed Opioids

Yaron Finkelstein, Erin M. Macdonald, Alejandro Gonzalez, Marco L.A. Sivilotti,
Muhammad M. Mamdani, David N. Juurlink and Canadian Drug Safety And
Effectiveness Research Network (CDSERN)

Pediatrics 2017;139;

DOI: 10.1542/peds.2016-2887 originally published online February 20, 2017;

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/139/3/e20162887>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2017 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

