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Trends in Routine Opioid Dispensing after Common Pediatric Surgeries in the United States: 2014–2019

Tori N. Sutherland, MD, MPH^{a,b,c}, Hannah Wunsch, MD, MSc^{d,e}, Craig Newcomb, MS^f, Scott Hadland, MD, MPH, MS^{g,h}, Lakisha Gaskins, MHS^{a,c}, Mark D. Neuman, MD, MSc^{a,b,c,i}

^aDepartment of Anesthesiology and Critical Care, Perelman School of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, USA

^bLeonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, USA

^cCenter for Perioperative Outcomes Research and Transformation, University of Pennsylvania Perelman School of Medicine Philadelphia, USA

^dDepartment of Critical Care Medicine, Sunnybrook Health Sciences Centre, Toronto, Canada

^eDepartment of Anesthesia and Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada

^fCenter for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine, Philadelphia, USA

^gDivision of Adolescent and Young Adult Medicine, MassGeneral Hospital for Children, Harvard Medical School, Boston, USA

^hDepartment of Pediatrics, Harvard Medical School, Boston, USA

ⁱCenter for Pharmacoepidemiology Research and Training, University of Pennsylvania Perelman School of Medicine, Philadelphia, USA

Abstract

BACKGROUND: Children who undergo common outpatient surgeries are routinely prescribed opioids, although available evidence suggests they should be used with discretion for procedures associated with mild to moderate pain. The study assessed trends in postoperative opioid prescribing over time to determine if prescribing declined.

Address correspondence to: Tori N. Sutherland, MD MPH, Department of Anesthesiology and Critical Care, Children's Hospital of Philadelphia, University of Pennsylvania, CHOP Research Institute, 2716 South Street, Suite 11.242, Philadelphia, PA 19146, Sutherland@chop.edu, Tel: 215-426-2122.

Contributor Statement Page

Dr. Neuman and Dr. Sutherland had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. They also obtained data, conceptualized and designed the study, acquired and analyzed data, drafted and critically reviewed the manuscript for important intellectual content.

Dr. Wunsch conceptualized and designed the study, obtained funding, performed data analysis and critically reviewed the manuscript for important intellectual content.

Mr. Newcomb participated in study design, statistical analysis and data interpretation and reviewed and revised the manuscript.

Ms. Gaskins participated in study design, coordinated data acquisition and management, reviewed and revised the manuscript.

Dr. Hadland participated in study design, data interpretation and critically reviewed the manuscript for important intellectual content.

Conflict of Interest Disclosures: No authors reported disclosures.

METHODS: We utilized a private insurance database to study opioid-naïve patients under age 18 who underwent one of 8 surgical procedures 2014–2019. The primary outcome was the likelihood of filling a prescription for opioids within 7 days of surgery and the secondary outcome was the total amount of opioid dispensed. We used Joinpoint regression analysis to identify temporal shifts in trends.

RESULTS: The study cohort included 124,249 opioid-naïve children. The percentage of children who filled an opioid prescription decreased from 78.2% (95% CI 76.3–80.1%) to 48.0% (95% CI 45.8–50.1%) among adolescents, from 53.9% (95% CI 51.6–56.2%) to 25.5% (95% CI 23.5–27.5%) among school-age children and 30.4% (95% CI 28.6–32.2%) to 11.5% (95% CI 10.1–12.9%) among preschool children. The average morphine milligram equivalent (MME) dispensed declined from 228.9 (95% CI 220.1–237.7) to 110.8 (95% CI 105.6–115.9) among adolescents, 121.3 (95% CI 116.7–125.9) to 65.9 (95% CI 61.1–70.7) among school-age children and 75.3 (95% CI 70.2–80.3) to 33.2 (95% CI 30.1–36.3) among preschool children. Using Joinpoint regression, we identified rapid opioid de-adoption beginning in late 2017, first in adolescents, followed by school-age and then preschool children.

CONCLUSION: Opioid prescribing after surgery decreased gradually from 2014 to 2017, with a more pronounced decrease seen beginning in late 2017.

INTRODUCTION

Opioids are routinely prescribed for common pediatric surgeries associated with mild to moderate pain; however, evidence suggests recovery is similar with either limited or no opioids.^{1–8} In children, excessive postoperative opioid exposure has been associated with adverse outcomes such as respiratory depression and new long-term use.^{6, 9–12}

Few data currently exist to characterize opioid prescribing trends for pediatric surgery, and it is unknown to what extent providers have moved away from routine opioid prescribing.^{2–4, 6, 7, 12, 13} Understanding patterns of opioid prescribing for children after surgery may facilitate policy efforts to address overuse moving forward. For example, opioid prescribing guidelines specific to pediatric surgical patients have recently been published and recommend limiting or avoiding opioid prescriptions for surgeries where pain is anticipated to be minimal.^{3, 4} These guidelines highlight the risks of opioid prescribing that are unique to pediatric patients.³ However, effective implementation of these evidence-based recommendations is limited by a lack of information on current opioid prescribing patterns and changes in prescribing over time for children undergoing surgery. The present study adds to the information available to policy makers and health systems to develop and target interventions intended to promote evidence-based prescribing.

To address this need, we designed this study to characterize trends in US prescribing practices for opioid-naïve children after surgery, including the percentage filling a prescription, the prescription quantity and refills dispensed. We selected 8 common pediatric surgeries considered to have a low likelihood of significant pain requiring opioids. Since adolescents, school-age and preschool children undergo different types of surgeries, we studied national trends among these three groups.^{12, 14} We examined if there was a change in study outcomes over time and then utilized Joinpoint regression to characterize changes

in slope of identified trends over time. We hypothesized that there would be a decrease in both the likelihood of filling an opioid prescription and prescription quantity consistent with de-adoption of routine opioid prescribing for children undergoing surgery during the study period.

METHODS

Study design and oversight

We conducted a retrospective cohort study using a national insurance database to determine baseline opioid dispensing trends and moments when trends changed between April 1, 2014 and March 31, 2019. Among children that received at least one opioid prescription within 7 days of surgery, we assessed the average amount of opioid dispensed in Morphine Milligram Equivalents (MME), the days supplied and the percentage of children that received more than one prescription (refill) within 30 days of surgery. We performed a visual comparison of trends and used Joinpoint regression analysis to identify points in time when rapid shifts in prescribing trends occurred. The purpose of this descriptive analysis was to characterize specific time points at which prescribing trends changed. As a result, we did not specify time points a priori at which we hypothesized a trend change would occur, and rather allowed the Joinpoint regression program to identify significant points at which change in trend were observed in the data.¹⁵ We used patient-level time series segmented regression to validate changes in prescribing likelihood identified by Joinpoint regression and control for potential confounders. This study was determined to be exempt from human subject research review by the University of Pennsylvania Institutional Review Board.

Data source

We used de-identified data from Optum's Clinformatics® Data Mart Database, a US health insurance database with over 15 million annual enrollees from all 50 states.¹⁶ The database contained both medical and pharmacy claims data.¹⁷ The study sample included all patients under age 18 with a submitted claim for surgery and continuous enrollment for the 90 days prior to the date of surgery during the study period. Demographic variables, such as race and ethnicity, were provided as recorded in the electronic medical record. Eight common pediatric surgeries were selected because severe postoperative pain requiring opioids was anticipated to be uncommon.^{6, 18, 19} 3, 4 These procedures were: tonsillectomy (with or without adenoidectomy), adenoidectomy only, laparoscopic appendectomy, cholecystectomy, dental surgery, knee arthroscopy, circumcision, and orchiopexy. Procedures were identified using Current Procedure Terminology (CPT) codes in physician claims (Appendix Table 1). For patients with more than one eligible surgery during the study period, we used the first procedure. Patients with claims for more than one eligible procedure on the same day, patients who required an inpatient stay and those that did not have 90 days of continuous enrollment prior to the procedure and 30 days after were excluded. We also excluded patients with a filled opioid prescription in the 90 days prior to surgery to capture new opioid prescriptions for opioid-naïve children, rather than refills for established chronic pain treatment.

Due to differences in development and anticipated procedure distribution by age, we analyzed data separately in 3 age groups: adolescents (11 through 17 years), school-age children (5 through 10 years) and infants to preschool-age (<5 years). Within a given age group, we limited our analyses to those procedures where we had an average of at least 100 observations per 12 months over the study period. Among adolescents, we studied knee arthroscopy, laparoscopic cholecystectomy, appendectomy, tonsillectomy, adenoidectomy only, dental surgery, orchiopexy and circumcision. Among school-age children, we studied laparoscopic appendectomy, tonsillectomy, adenoidectomy only, dental surgery, orchiopexy and circumcision. Among preschool-age children, we studied tonsillectomy, adenoidectomy only, dental surgery, orchiopexy and circumcision.

We defined baseline comorbidities in the 90 days prior to surgery using International Classification of Diseases (ICD) 9th and 10th revision diagnosis codes (Appendix Table 2) for obstructive sleep apnea (OSA), history of substance abuse, history of overdose, depression, and chronic conditions categorized into ten systems using the Pediatric Complex Chronic Conditions (CCC) classification, Version 2.²⁰

Outcome measures

Our primary outcome was the likelihood of filling an opioid prescription within 7 days of surgery. We included both liquid and tablet formulations, if applicable, of the following medications: codeine, hydrocodone, hydromorphone, morphine, oxycodone and tramadol. The secondary outcome was the total amount of opioid dispensed in the first prescription, measured in MME, which we calculated using standard tables.²¹ We also examined the average days supplied in the initial prescription and the percentage of patients who received more than one opioid prescription (refill) in the first 30 days after surgery.

Statistical analysis

We compared the distribution of procedures and patient characteristics over the study period and used descriptive statistics and simple hypothesis tests to characterize outcome distribution. By age group and surgery, we plotted the percentage of patients who filled a prescription, the average MME dispensed, days supplied and the percentage who filled more than one prescription to visually examine changes in prescribing outcomes.

We performed a Joinpoint regression analysis for prescription likelihood and MME dispensed to characterize changes over time in outcome trends. Joinpoint regression is a method to describe change in trends over time and to assess if a significant increase or decrease in rate occurred at a discrete moment in time.^{22, 23} The logistic-linear regression Joinpoint model evaluates a null hypothesis of no change in trend versus a pre-set maximum number of changes and displays the quarterly change that is specific to the trend after versus before a given moment in time where a change in trend is evaluated (i.e., the “Joinpoint”).²³ For scenarios where our initial model rejected the null hypothesis of no change (i.e. a change is identified), we assessed if the data were best described with one or two Joinpoints.²³

We subsequently performed a linear time series segmented regression analysis for each age group that examined the likelihood of receiving a prescription and included covariates for Joinpoint pre-post time intervals, the interaction between intervals and quarter, gender,

surgery type and obstructive sleep apnea diagnosis to verify that differences in trends before vs after identified Joinpoints persisted after controlling for potential confounders. A three-month calendar quarter was selected as the unit of time for these models. Analyses were conducted in SAS (version 9.4, SAS Institute, Cary, NC) and the Joinpoint Trend Analysis Software (Version 4.8.0.1, National Cancer Institute, Bethesda, MD). All tests were two-sided and significance was set at the 5% level.

RESULTS

Overview

The study cohort included 124,249 patients; 45.0% were female, and the median age was 7.0 years (interquartile ratio (IQR) 4.0–14.0 years) (Table 1). There were 43,487 adolescents (35.1% of the sample), 40,221 (32.5%) school-age children and 40,541 (32.7%) children under age 5. Overall, the most common comorbidities were obstructive sleep apnea (N=18,891; 15.2%, $p<0.001$), history of congenital defect (N=2,103; 1.7%, $p<0.001$) and history of cardiovascular diagnosis (N=1,615; 1.3%, $p<0.001$). 66.4% (N=82,445) of children were White, 9.6% (N=11,989) identified as Hispanic/Latino, 5.7% (N=7,190) were Black or African American and 3.0% (N=3,681) were Asian.

Among all children, the three most commonly performed surgeries were tonsillectomy with or without adenoidectomy (N=46,461; 37.4%, $p<0.001$), dental surgery (N=22,267; 17.9%, $p<0.001$) and adenoidectomy only (N=21,167; 17.1%, $p<0.001$). Among adolescents, the three most common procedures were knee arthroscopy (N=11,816, 27.2%), dental surgery (N=10,320, 23.7%) and tonsillectomy (N=9,823, 22.6%). School-age children most commonly underwent tonsillectomy (N=23,098, 57.8%) followed by adenoidectomy only (N=6,048, 15.1%) and dental surgery (N=5,747, 14.4%). Among preschool children, tonsillectomy was the most common surgery (N=13,540, 33.5%), followed by adenoidectomy only (N=13,515, 33.5%) and dental surgery (N=6,200, 15.4%).

Prescription likelihood, average MME, days supplied and refill trends over time

Comparing the first quarter of the five-year study period to the last quarter, the percentage filling an opioid prescription after surgery decreased from 78.2% (95% CI 76.3–80.1%) to 48.0% (95% CI 45.8–50.1%) among adolescents, from 53.9% (95% CI 51.6–56.2%) to 25.5% (95% CI 23.5–27.5%) among school-age children and from 30.4% (95% CI 28.6–32.2%) to 11.5% (95% CI 10.1–12.9%) among preschool children ($p<0.001$ for all groups; Figure 1). The likelihood of receiving a prescription varied across procedures; among adolescents, opioids were most common after knee arthroscopy, tonsillectomy, orchiopexy and laparoscopic cholecystectomy, while in preschool and school-age children, opioids were most commonly prescribed after orchiopexy, tonsillectomy and circumcision.

The average MME dispensed in the first prescription declined over the study period from 228.9 (95% CI 220.1–237.7) to 110.8 (95% CI 105.6–115.9) among adolescents, from 121.3 (95% CI 116.7–125.9) to 65.9 (95% CI 61.1–70.7) among school-age children and from 75.3 (95% CI 70.2–80.3) to 33.2 (95% CI 30.1–36.3) among preschool children. ($p<0.001$ for all groups; Figure 2). The average days' supply in the first prescription declined over

the study period from 5.2 days (95% CI 5.1–5.4) to 3.0 days (95% CI 2.9–3.1) among adolescents, 7.7 days (95% CI 7.4–7.9) to 3.4 days (95% CI 3.2–3.6) among school-age children and 8.0 days (95% CI 7.6–8.3) to 3.3 days (95% CI 3.1–3.6) among preschool children (Appendix Figure 2). The likelihood of receiving an opioid refill decreased from 12.7% (95% CI 11.1–14.3%) to 5.4% (95% CI 4.4–6.3%) among adolescents, 5.1% (95% CI 4.1–6.1%) to 3.1% (95% CI 2.3–3.8%) among school-age children and 1.6% (95% CI 1.1–2.1%) to 0.51% (95% CI 0.21–0.81%) among preschool-age children ($p < 0.001$ for all comparisons; Appendix Figure 1). Hydrocodone was the most commonly prescribed opioid among all three groups over the study period, followed by oxycodone; while the likelihood of filling a hydrocodone prescription reflected overall trends, oxycodone prescribing remained static overall in the two younger age groups until a modest decline was noted beginning in 2018 (Appendix Figure 3).

Joinpoint regression

Our Joinpoint analysis of temporal trends in the likelihood of filling an opioid prescription revealed an initial period of gradual change, followed by a period of more rapid decline (Figure 3; Table 2). While this pattern occurred in all age groups, the timing of the trend change differed by age. Adolescents were the first to demonstrate a sharp change in the likelihood of filling a prescription. The quarterly decrease in prescribing was 0.47%/quarter ($p = 0.04$ for trend) until Quarter 4 of 2017, when it decreased to 8.3%/quarter ($p < 0.001$) between Quarter 4 of 2017 and Quarter 1 of 2019. School-age children followed a similar trajectory with a decrease of 1.4%/quarter ($p < 0.001$) from the beginning of the study period until Quarter 2 of 2018; after this point, prescribing decreased by 17.6%/quarter ($p < 0.001$) until the end of the study period. Among preschool children, prescribing decreased slightly until Quarter 3 of 2018 (2.6%/quarter, $p < 0.001$) when it began to decline rapidly (27.5%/quarter, $p = 0.09$). Similar patterns were observed in Joinpoint regressions examining trends in average MME dispensed over time. We also confirmed the changes in trends identified by Joinpoint regression for odds of receiving a prescription in a segmented regression analysis that controlled for potential confounders (Appendix Table 3).

DISCUSSION

Among 124,249 opioid-naïve children undergoing 8 common pediatric surgeries between 2014 to 2019, opioid prescribing declined substantially over time; prescribing first decreased gradually from 2014 through late 2017, followed by a more rapid period of decline from 2017 through 2019. Both the onset and the magnitude of decrease in the likelihood of filling an opioid prescription differed for adolescents, school-age and preschool children. Overall, prescribing was more common as age increased. We noted that the rate of decline in prescribing likelihood was steeper among younger children and that they received an increased days' supply compared to adolescents. With regard to the average MME dispensed, we noted similar trends in the rate of decline that began first among adolescents. As an example of change in prescribing trends, the average preschool-age child who filled an opioid prescription at the beginning of the study period received 75.3 MME, approximately 15 5mg hydrocodone tablets, and 33.2 MME, approximately 6.5 5mg tablets,

at the end of the study period. The latter amount is equivalent to a 7-day supply for an average 4-year-old.

Our Joinpoint analyses characterized specific moments in time when rapid de-escalation of routine opioid prescribing began. The drop in prescribing occurred first among adolescents in Quarter 4 of 2017. School-age children followed a similar pattern in Quarter 2 of 2018. Preschool-age children were noted to begin to exhibit this decrease three months later in Quarter 3 of 2018. The results do not identify the specific events that caused these declines, however, there are several possible explanations. First, the declines in prescribing may have been a delayed response to the Food and Drug Administration (FDA) April 2017 restriction on use of tramadol and codeine in children and to increased attention placed on risks of opioid prescribing after pediatric surgery when they were not needed.²⁴ However, these recommendations focused on children under age 12, while changes were first seen among adolescents. Second, a series of studies that discussed the risks of opioid prescribing after pediatric surgery, including potential risks of new chronic use with excessive prescribing,^{9, 10} were published in early 2018. It is possible that increasing general awareness of these risks prior to study publication may have contributed to prescribing decline when it was not indicated. Third, in a previous study, our group identified decreases in opioid prescribing after surgery associated with release of a guideline on opioid prescribing for chronic pain by the US Centers for Disease Control and Prevention in March 2016.²⁵ It is possible that decreases observed in children could reflect a ‘spillover effect’ of these guidelines from adult to pediatric prescribers. Of note, Renny et al. utilized pharmacy claims data to identify an overall downtrend in all-cause pediatric opioid prescriptions between 2006–2018, suggesting that the declines observed here may be reflective of broader trends away from opioids for pain management in children that were not limited to the context of surgery.¹³ It is also possible that local or state policy changes, health system initiatives, or insurer policies for coverage of pain treatments may have contributed to changes over time in opioid dispensing trends after surgery in children

Our findings have helped to fill significant gaps in knowledge with regard to opioid dispensing and pain management in pediatrics. The trend towards de-adoption identified by our group is supported by a growing body of evidence suggesting that opioids can be discretionary after common pediatric surgeries associated with mild to moderate pain.^{12, 26 27} For example, society guidelines for the most common surgery studied, tonsillectomy, first recommended non-opioid analgesics as first line therapy in February 2019 after data demonstrated equivalent pain control for most children.²⁸ Increasing knowledge prompted publication of Michigan OPEN’s first national pediatric opioid prescribing range recommendations in May 2020 and the first comprehensive expert consensus guidelines specific to pediatric surgery for discretionary opioid use in January 2021.^{3, 28} With increasing awareness of multi-modal pain management and new knowledge of prescribing trends specific to each age group and surgery, we recommend use of our results to inform targeted guideline implementation efforts.

LIMITATIONS

This study has limitations. Our patient population was from a private insurance claims database, and it is possible that findings may not be broadly applicable to patients covered by public insurance programs or patients without insurance. We cannot rule out that disparities in pain management did not increase during the study period, and further research is indicated to characterize these disparities. In addition, although we were able to document prescribing trends after surgery, we were unable to characterize the opioid quantity consumed by individual children and their family's unique perception of post-operative pain management, and additional research is indicated. While we noted that opioid refills decreased over the study period, we were not able to definitively measure pain experience, including pain scores and patient satisfaction. Finally, at the societal level, patient-level variables may have changed over the study period with possible implications for influence on prescribing, but it is reassuring that our study cohort remained demographically similar over time.

CONCLUSIONS

We identified that de-adoption of routine opioid prescribing after common pediatric surgeries occurred during the study period. This trend was first noted in adolescents in late 2017, and it was then identified among school-age and preschool-age children over time. Additional research is indicated to better understand the reasons underlying changes in patterns of opioid prescribing for children of different ages after surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Role of Funder:

Neither funding source had any role in the design or conduct of the study.

Abbreviations:

MME	Morphine Milligram Equivalents
CPT	Current Procedure Terminology
ICD	International Classification of Diseases
OSA	obstructive sleep apnea

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Table of Contents Summary

Using Joinpoint regression, our study identified substantial decreases in postoperative opioid dispensing after outpatient pediatric surgeries beginning in 2017.

What's Known on This Subject

Children who undergo common outpatient surgeries are routinely prescribed opioids, although available evidence suggests they should be used with discretion for procedures associated with mild to moderate pain.

What This Study Adds

Between 2014–2019, study results identified a substantial decrease in both the percentage of children filling an opioid prescription and the opioid quantity dispensed that began in 2017. The onset of this decline differed by age group and surgery.

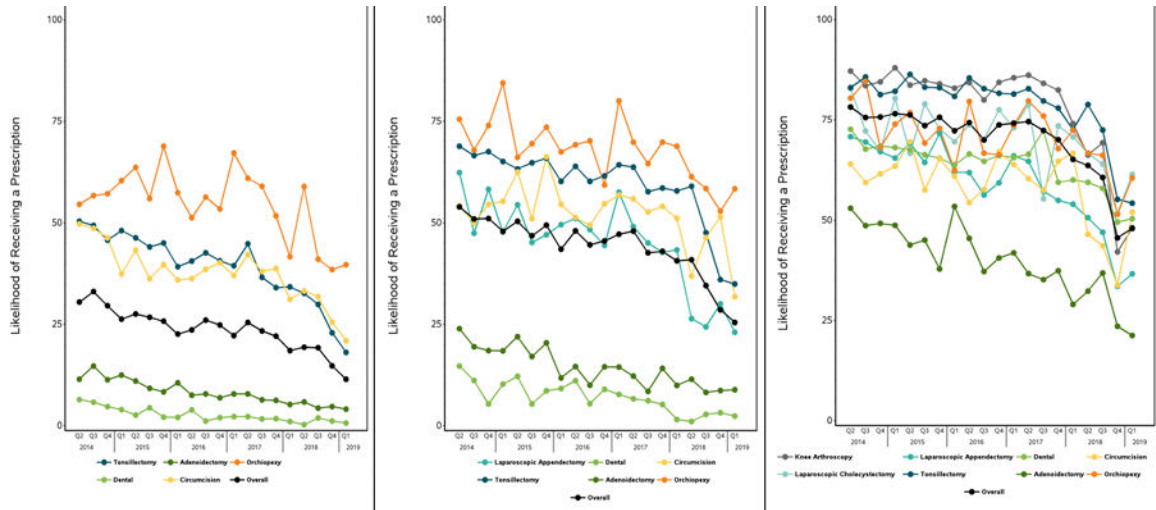


Figure 1. Percentage of Children Who Received a Prescription for Opioids After Surgery, Overall and by Procedure, 2014–2019.

Each figure displays, by year, the percentage of children undergoing a given surgery who did not receive a prescription for opioids when an equivalent recovery without opioids was considered possible. Panels show data for the relevant procedures specific to the three age groups: (A) Infant to 4 years (B) 5 to 10 years (C) 11 to 17 years

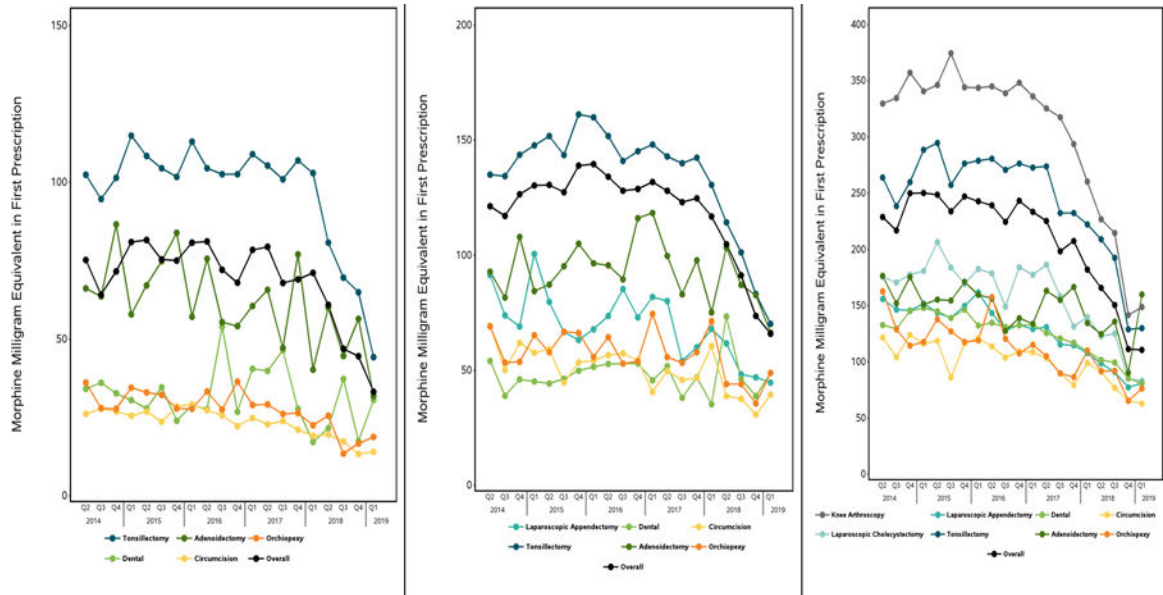


Figure 2. Postoperative Opioid Prescription Quantity, Among Children Who Received an Opioid Prescription, Overall and by Procedure, 2014–2019.

Panels show total amount of opioid in Morphine Milligram Equivalents (MME) dispensed in the first opioid prescription filled within 7 days after surgeries specific to the three age groups: (A) Infant to 4 years (B) 5 to 10 years (C) 11 to 17 years

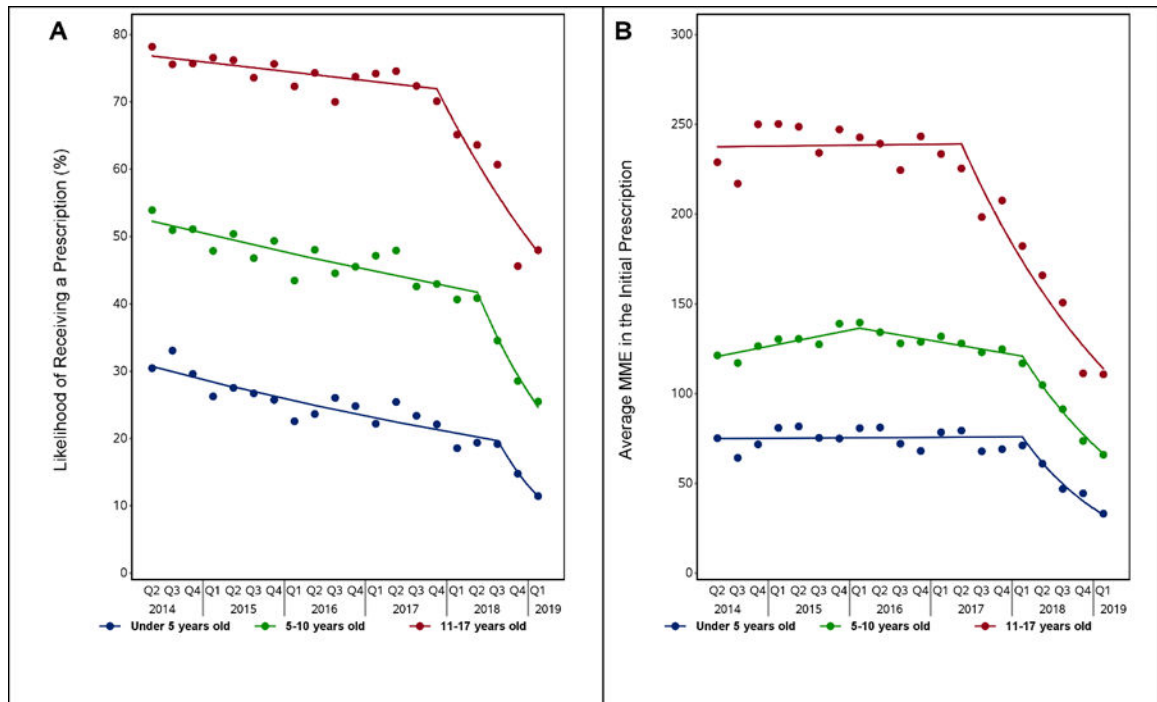


Figure 3. Jointpoint Regression Models, by Age Group, 2014–2019.

Panels show (A) the likelihood of receiving an opioid prescription after surgery and (B) the total amount of opioid in Morphine Milligram Equivalents (MME) dispensed in the first opioid prescription filled within 7 days after surgery, specific to the three age groups

Table 1.

Surgical patient and procedure characteristics, by age group

Variable/Age group	Infant to preschool-age, 0 to 4 years, N=40,541(32.6%)	School-aged children, 5 to 10 years, N=40,221(32.4%)	Adolescents, 11 to 17 years, N=43,487(35.0%)	Overall (N=124,249)
Patient characteristics				
Age, median (IQR)	3.0 (1.0–4.0)	7.0 (5.0–8.0)	15.0 (13.0–16.0)	7.0 (4.0–14.0)
Female gender, N(%)	15,345 (38.0%)	18,191 (45.5%)	22,124 (50.9%)	55,880 (45.0%)
Surgical procedures				
Adenoidectomy	13,515 (33.5%)	6,048 (15.1%)	1,604 (3.7%)	21,167 (17.1%)
Appendectomy ^a		2,285 (5.7%)	6,143 (14.1%)	8,565 (6.9%)
Arthroscopic knee surgery			11,816 (27.2%)	12,093 (9.7%)
Cholecystectomy			1,165 (2.7%)	1,239 (1.0%)
Circumcision	5,747 (14.2%)	1,450 (3.6%)	1,249 (2.9%)	8,446 (6.8%)
Dental surgery	6,200 (15.4%)	5,747 (14.4%)	10,320 (23.7%)	22,267 (17.9%)
Orchiopexy	1,388 (3.4%)	1,319 (3.3%)	1,367 (3.1%)	4,074 (3.3%)
Tonsillectomy +/- Adenoidectomy	13,540 (33.5%)	23,098 (57.8%)	9,823 (22.6%)	46,461 (37.4%)
Common comorbidities				
Obstructive sleep apnea history, N(%)	7,575 (18.8%)	8,974 (22.5%)	2,339 (5.4%)	18,891 (15.2%)
Congenital defect diagnosis, N(%)	794 (2.0%)	590 (1.5%)	709 (1.6%)	2,103 (1.7%)
Cardiovascular diagnosis, N(%)	626 (1.5%)	492 (1.2%)	490 (1.1%)	1,615 (1.3%)
Neurologic/neuromuscular diagnosis N(%)	428 (1.1%)	449 (1.1%)	385 (0.9%)	1,262 (1.0%)
Race/Ethnicity				
White, non-Hispanic	24,950 (61.8%)	26,872 (67.3%)	30,348 (69.8%)	82,445 (66.4%)
Black or African American	2,412 (6.0%)	2,182 (5.5%)	2,493 (5.7%)	7,190 (5.7%)
Asian, non-Hispanic	1,244 (3.1%)	1,267 (3.2%)	1,162 (2.7%)	3,681 (3.0%)
Hispanic/Latino	3,487 (8.6%)	4,227 (10.6%)	4,219 (9.7%)	11,989 (9.6%)
Other/Unknown	8,297 (20.5%)	5,399 (13.5%)	5,265 (12.1%)	19,025 (15.3%)

^a Procedures with less than 100 occurrences across 12 calendar months were not included in age brackets

^b Comorbidities with <1% prevalence were not included.

Table 2.

Joinpoint regression analysis for likelihood of receiving an opioid prescription and average MME, if issued, by age group

	Likelihood of receiving a prescription				Average MME dispensed in initial prescription					
	Trend 1		Trend 2		Trend 1		Trend 2		Trend 3	
	Quarter percentage change (SE)	p-value	Quarter percentage change (SE)	p-value	Quarter percentage change (SE)	p-value	Quarter percentage change (SE)	p-value	Quarter percentage change (SE)	p-value
0–4 years	–2.6% (0.003)	<0.001	–27.5% (0.15)	0.09	0.09% (0.005)	0.85	–21.2% (0.04)	<0.001		
5–10 years	–1.4% (0.002)	<0.001	–17.6% (0.04)	<0.001	1.8% (0.004)	0.002	–1.5% (0.005)	0.007	–14.9% (0.02)	<0.001
11–17 years	–0.4% (0.002)	0.04	–8.3% (0.02)	<0.001	0.06% (0.006)	0.92	–10.6% (0.01)	<0.001		

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