Effects of the FDA Codeine Safety Investigation on Racial and Geographic Disparities in Opioid Prescribing after Pediatric Tonsillectomy and/or Adenoidectomy

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Abstract

Objective. Our objective was to examine the impact of the U.S. FDA's 2013 black box warning against codeine on codeine and other opioid prescription filling after pediatric tonsillectomy and/or adenoidectomy (T/A) overall and by child race and provider urbanity/rurality. *Methods.* Patients ≤ 18 who underwent T/A in 8/2011 to 8/2016 were identified in Ohio Medicaid claims. Interrupted time series analyses were used to evaluate the impact of the FDA warning on codeine or other opioid prescription filling post-T/A. *Results.* In August 2011, codeine prescription filling was lower among black than white children ($P < .001$) and among children treated at institutions in metropolitan counties than less populous counties ($P < .001$). The FDA warning was associated with a 24.0% drop in codeine prescription filling ($P < .001$) and 5.5% increase in alternative opioid prescription filling ($P = .046$). At conclusion, there remained geographic but no longer racial disparities in codeine prescribing. *Conclusion.* Codeine prescribing after pediatric T/A decreased after the FDA's black box warning. However, geographic disparities in codeine prescribing remain.

Keywords

black box warning, opiates, codeine, pediatrics, disparities

Highlights

What do we already know about this topic?

Codeine prescribing after tonsillectomy and adenoidectomy decreased nationwide after the FDA's black box warning against this practice was issued in February 2013, but whether racial and geographic disparities in such prescribing were impacted by the black box warning is not clear.

How does your research contribute to the field?

We found that in Ohio, there are no longer racial disparities in codeine prescribing after tonsillectomy and adenoidectomy. However, geographic disparities in such prescribing remain, and the prescribing of more potent opioids after tonsillectomy and adenoidectomy has increased slightly.

What are your research's implications toward theory, practice, or policy?

Efforts to eliminate codeine prescribing after tonsillectomy and adenoidectomy are still needed in some

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hospitals and surgery centers, particularly those outside of large and moderate-sized urban areas.

Introduction

Codeine was at one time a commonly-used analgesic in pediatric patients in the United States both for pain control and as an antitussive. It was known to have a slower onset than morphine and had a similar duration of symptom relief, seemingly ideal for safe post-surgical dosing, particularly after routine surgery such as tonsillectomy and/or adenoidectomy.[1] However, more recent pharmacokinetic research has shown that codeine's efficacy is reliant on its metabolism to morphine by the enzyme CYP2D6, activity rates of which are highly variable.[2] The majority of the population has a normal range of CYP2D6 activity, but a small proportion of the population has overactive enzymes that rapidly convert codeine to high amounts of morphine in the body. There is significant variability in the frequency of the ultra-rapid metabolizer genotype by race, with only 1% of Chinese or Japanese patients noted as being ultrametabolizers, but potentially greater than 15% of Middle Eastern and North African patients classified as ultrametabolizers.[3]

Safety concerns began to be raised around use of codeine in children in the U.S. in the late 1990s and early 2000s. The variable metabolism of the drug was cited as the cause of life-threatening overdoses among adults, but initially only isolated events were documented.[4] In 2012 a case series was published in which codeine was implicated in the deaths of multiple children who used it after undergoing tonsillectomy.[5] In August of 2012, this series prompted a U.S. Food and Drug Administration (FDA) investigation into the rates of respiratory depression and death associated with codeine use, particularly after tonsillectomy or adenoidectomy. In February 2013, the FDA implemented a black box warning, the FDA's strongest safety statement, describing the risk and contraindication of codeine usage in children undergoing tonsillectomy and/or adenoidectomy.[6]

Across the U.S., prescriptions of codeine after tonsillectomy and adenoidectomy decreased significantly after this black box warning was issued.[7] However, it is likely that such decreases were not uniform across demographic groups. There have been many studies demonstrating racial disparities and geographic variation in opioid prescribing.[8-11] Racial disparities in pain management in adults exist across a variety of settings.[12-16] In the pediatric population, racial disparities have been reported in the treatment of acute pain when children present to the emergency department with long bone fractures or appendicitis.[17,18] In addition, differences in children's receipt of opioids after some surgical procedures by race/ethnicity and urbanicity/rurality have been reported, though this finding has not been consistent across all studies.[19-22] Racial and geographic differences in pediatric postoperative opioid prescribing may arise from a variety of causes, including clinicians' implicit racial biases.[23,24] Alternately, racial and geographic differences in postoperative opioid prescribing at the population-level may arise from differences in standards of care and protocols across, rather than within, institutions. Regardless of their cause, rates of codeine and alternate opioid prescribing after tonsillectomy and/or adenoidectomy that differ by child race or provider location and that are not driven by clinical factors are concerning. We therefore sought to examine whether the U.S. FDA's black box warning had differential effects on codeine and alternate opioid prescribing after tonsillectomy and/or adenoidectomy by patient race or provider urban/rural location.

Methods

Data Source and Study Population

We analyzed Ohio Medicaid claims data from August 2011-August 2016. This included health care claims and enrollment data on all children who were enrolled in Ohio Medicaid anytime during this period. Data was available on all Ohio Medicaid/Children's Health Insurance Program (CHIP) enrollees under 19 years of age. During the study period, children in families with incomes up to 206% of the federal poverty level were eligible for Medicaid/CHIP in Ohio.[25] A total of 2 028 130 unique children aged 0 to 18 years were represented in the database. We identified children who underwent tonsillectomy and/or adenoidectomy by searching for professional (surgeon) claims containing *Current Procedural Terminology* (CPT®) codes 42820, 42821, 42825, 42826, 42830, 42831, 42835, or 42836. The first such procedure of each child during the study period was included. In order to include a relatively consistent set of surgeons and other postsurgical opioid prescribers throughout the entire study period, we excluded children who underwent surgery out of state. Because an objective of the study was to examine disparities in the receipt of postsurgical opioids between black and white children, we also excluded children with missing race or a race other than black or white. Finally, in order to capture all opioid prescription fills within 14 days of surgery in all patients, we excluded children not enrolled in Ohio Medicaid during the month after surgery and children whose surgery occurred after August 17th, 2016.

Study Design

To examine the effect of the FDA codeine investigation on opioid prescription filling after tonsillectomy and/or adenoidectomy (T/A), we used an interrupted time series design. This is a quasi-experimental design that is frequently used to evaluate the impact of policy changes or system-level interventions that occur at particular points in time.[26,27] We did not include a control group because of the potential spillover effects of the FDA codeine investigation on other surgical populations.[7]

All patient-level observations were aggregated at the month level based on the date of surgery. The unit of analysis in this study was therefore the monthly proportion of children who filled a prescription for codeine or an alternate opioid after undergoing tonsillectomy and/or adenoidectomy. Months were classified into 3 periods: pre-FDA investigation August 2011 to July 2012 (12 months), FDA investigation period August 2012 to February 2013 (7 months); and post-FDA warning March 2013 to August 2016 (41 months). Data from the 7-month investigation period were excluded from statistical analyses. For analyses of racial disparities, observations were further aggregated within groups defined by patient race (black/white). For analyses of geographic disparities, observations were aggregated within groups defined by the National Center for Health Statistics 2013 county-level rural/urban classification of the location of the institution where surgery was performed.[28] Rural/urban classification was dichotomized as "Large central metro/Medium metro," which included large central metro and medium metro counties versus "other," which included small metro, micropolitan, and noncore counties. Institutions were identified from facility claims. The institution-level characteristics examined in descriptive analyses were urban/rural location (classified as described above), children's hospital status, and teaching hospital status. Members of the Children's Hospital Association were considered children's hospitals. The 2015 American Hospital Association Annual Survey of Hospitals was used to identify teaching hospitals. Hospital-owned ambulatory surgery centers were classified based on the characteristics of their owning hospital. Patient level factors evaluated included age, sex, race, and urban/rural location of residence.

Finally, this study examined tonsillectomy and adenoidectomy because the FDA's 2013 black box warning specifically targeted these procedures. However, the FDA in April 2017 announced a contraindication against the use of codeine-containing medications for any pain in children under 12 years of age.[29] We did not have access to statewide claims data for any time period after April 2017. However, in order to discern the extent to which opioids were being prescribed after other common pediatric surgical procedures prior to this date and thus the potential impact of this more recent FDA contraindication on postoperative codeine prescribing, we examined the proportion of children aged 1 to 11 years who filled a codeine prescription after several other common pediatric surgical procedures during the last 3 months of our study period. These procedures included inguinal hernia repair (CPT 49491, 49492, 49495, 49496, 49500, 49501, 49505, 49507, 49520, 49521, 49525, 49650), appendectomy (CPT 44950, 44960, 44970), circumcision (CPT 54150, 54161), and supracondylar humeral fracture fixation (CPT 24538, 24545, 24546).

Outcome Definition

The outcomes of interest in this study were: (1) the proportion of patients with at least 1 prescription fill for codeine after surgery and (2) the proportion of patients with at least 1 prescription fill for an alternative opioid after surgery. Prescription fills on the day of surgery through 14 days after surgery were included. To identify opioid prescription fills, we searched the outpatient pharmacy claims database for opioid national drug codes (NDCs) identified by the Centers for Disease Control and Prevention.[30] Using a substring search of the drug name, we categorized opioids as codeine products or alternative opioid medications (e.g. oxycodone, hydrocodone, etc.).

Statistical Analysis

For analyses of racial disparities in postsurgical opioid prescription filling, we fit linear segmented regression models for the 2 outcomes of interest as a function of patient race, month of surgery, an interaction between race and month, an indicator for pre-investigation versus post-FDA warning period, an interaction between race and the post-warning period indicator, the number of months after the investigation ended, and an interaction between race and the number of months after the investigation ended. In order to adjust for confounding by patient demographic characteristics and procedure type, models also included mean age, the percentage of patients who were male, and the percentage of cases that were adenoidectomy without tonsillectomy in each racial group. These models enabled the estimation of adjusted absolute average monthly changes in outcomes both before and after the FDA investigation and the estimation of absolute changes in the outcomes from the beginning to end of the investigation in black and white children. In addition, these models enabled the statistical testing of racial differences in these parameters. We used

the SAS AUTOREG procedure to account for first-order autocorrelation in the outcomes. Finally, we performed a sensitivity analysis in which we excluded patients who underwent adenoidectomy without tonsillectomy, as these patients were less likely to receive an opioid prescription than tonsillectomy patients.

Analyses evaluating geographic disparities in post-surgical opioid prescription filling were analogous to those described above. The examination of geographic disparities compared patients treated at hospitals and ambulatory surgery centers in large central metropolitan counties and medium sized metropolitan counties, where all children's hospitals and the majority of teaching hospitals in Ohio are located, versus other counties. Additional information on these 2 groups of Ohio counties is available in Supplemental Material.

Patient and institution (hospital or ambulatory surgery center) level characteristics associated with the filling of a codeine prescription, an alternative opioid, or neither during the 3 months preceding the FDA investigation (May-July 2012) and during the last 3 months of our study period (June-August 2016) were examined using chi square tests. Finally, the proportions of children who underwent tonsillectomy, adenoidectomy without tonsillectomy, or one of several other common pediatric surgical procedures and who filled a prescription for codeine, an alternative opioid, or neither during the last 3 months of our study period were compared using Fisher exact tests. SAS Enterprise Guide 7.15 (SAS Institute Inc., Cary, NC) was used for all statistical analyses. Two-sided P values less than .05 were considered statistically significant.

Ethical Approval and Informed Consent

Ethical approval and informed consent were not needed for the scope of this study.

Results

Codeine Prescription Filling

We identified 57 639 Ohio children less than or equal to 18 years of age who underwent a tonsillectomy and/or adenoidectomy in August 2011 to August 2016. After excluding patients who were treated out of state (n = 2209), lacked data on race (n = 2948), identified as a race other than black or white (n = 1544), or were not enrolled in Ohio Medicaid in the month after surgery (n = 304), our final study cohort consisted of 50 634 patients. The majority of children were white (n = 39 502; 78%) and aged 1 to 6 years (n = 30 334; 60%). Tables 1 and 2 describe the demographics of the

studied population by patient race and geographic location of the treating institution.

During the first month of the study period (August 2011), prior to the FDA investigation, white children were significantly more likely than black children to fill a prescription for codeine (48.0% vs 33.8%, $P < .001$) (Figure 1a). From the month prior to the start of the investigation (July 2012) to the month after the black box warning was issued (March 2013), there was a decrease of 24% in the filling of codeine prescriptions after tonsillectomy and adenoidectomy among all children (95% CI: 20.4 to 27.7%, $P < .001$). However, that decrease was greater among white children than black children (28.3% vs 23.7%, $P < .001$). At the end of the study period (June-August 2016), there was no longer a racial disparity in rates of codeine prescription filling after T/A (4.9% in white children vs 4.1% in black children; $P = .43$).

When similar comparative analyses were performed to examine geographic disparities in codeine prescription filling after T/A, we found that, at the beginning of the study period, children undergoing T/A at facilities in large central metro counties or medium metro counties were significantly less likely than children undergoing T/A in other counties to fill a prescription for codeine (41.4% vs 55.1%, $P < .001$) (Figure 1b). However, the FDA investigation and black box warning were associated with similar decreases in codeine prescription filling in both types of geographic areas (26.5% decrease in large or medium metro counties vs 30.0% decrease in all other counties, $P = .21$). At the end of the study period, there was still a significant difference in rates of codeine prescription filling by the location of the institution in which surgery was performed, with children undergoing T/A in hospitals or surgery centers in large or medium sized metro counties less likely to fill a codeine prescription when compared to children who underwent their operation in other Ohio counties (2.0% vs 14.1%, $P < .001$). All results were similar when only the 38 485 children who underwent tonsillectomy (not adenoidectomy alone) were examined (data not shown).

Alternate Opioid Prescription Filling

At the beginning of the study period, 29.4% of all children filled a prescription for an opioid other than codeine after their T/A. However, there was a racial disparity in the filling of alternate opioid prescriptions, with black children significantly more likely to fill a prescription when compared to white children (32.8% vs 27.5%, $P = .04$) (Figure 2a). When prescription filling rates were compared from the month before the investigation started to the month after the black box warning was

Table 1. Characteristics of Children Enrolled in Ohio Medicaid Who Underwent Tonsillectomy and/or Adenoidectomy in August 2011 to August 2016, Overall and by Race.

	All included children (N = 50 634)	White children (N = 39 502)	Black children (N = 11 132)	P
Adenoidectomy without tonsillectomy	12 149 (24.0)	9092 (23.0)	3057 (27.5)	<.001
Female (%)	25 467 (50.3)	20 038 (50.7)	5429 (48.8)	<.001
White race (%)	39 502 (78.0)	–	–	
Age in years (%)				<.001
<1	308 (0.6)	175 (0.4)	133 (1.2)	
1 to 2	7861 (15.5)	5500 (13.9)	2361 (21.2)	
3 to 4	11 638 (23.0)	9000 (22.8)	2638 (23.7)	
5 to 6	10 835 (21.4)	8748 (22.2)	2087 (18.8)	
7 to 8	6953 (13.7)	5651 (14.3)	1302 (11.7)	
9 to 10	4417 (8.7)	3541 (9.0)	876 (7.9)	
11 to 12	3160 (6.2)	2497 (6.3)	663 (6.0)	
13 to 14	2216 (4.4)	1790 (4.5)	426 (3.8)	
15 to 16	1914 (3.8)	1532 (3.9)	382 (3.4)	
17 to 18	1332 (2.6)	1068 (2.7)	264 (2.4)	
Rural/urban location of residence (%)				<.001
Large central metro	12 841 (25.4)	6337 (16.1)	6504 (58.4)	
Large fringe metro	8053 (15.9)	7437 (18.8)	616 (5.5)	
Medium metro	13 846 (27.4)	10 654 (27.0)	3192 (28.7)	
Small metro	2863 (5.7)	2438 (6.2)	425 (3.8)	
Micropolitan	10 608 (21.0)	10 245 (26.0)	363 (3.3)	
Noncore	2405 (4.8)	2376 (6.0)	29 (0.3)	
Rural/urban location of institution (%)				<.001
Large central metro	21 479 (42.6)	14 387 (36.6)	7092 (63.8)	
Large fringe metro	2276 (4.5)	2068 (5.3)	208 (1.9)	
Medium metro	17 037 (33.8)	13 754 (35.0)	3283 (29.5)	
Small metro	2262 (4.5)	1993 (5.1)	269 (2.4)	
Micropolitan	6943 (13.8)	6686 (17.0)	257 (2.3)	
Noncore	446 (0.9)	441 (1.1)	5 (0.04)	
Type of institution				<.001
Children's hospital or affiliated ASC	27 013 (53.6)	18 827 (47.9)	8186 (73.7)	
Other teaching hospital or teaching hospital-affiliated ASC	11 278 (22.4)	9691 (24.6)	1587 (14.3)	
Non-teaching hospital, non-teaching hospital affiliated ASC, or independent ASC	12 152 (24.1)	10 811 (27.5)	1341 (12.1)	

Abbreviation: ASC, ambulatory surgery center.

issued, there was an absolute increase of 5.5% in the proportion of all children filling of an alternate opioid prescription (*P* = .04). An upward trend in alternate opioid prescription filling continued throughout the duration of the study period at a rate of 0.25% per month (*P* = .02). At the end of the study period, 45.5% of all patients filled a prescription for an alternate opioid, and there was no longer a racial disparity in alternate opioid prescription filling, with 46.8% of black children filling such a prescription and 45.2% of white children filling such a prescription (*P* = .53).

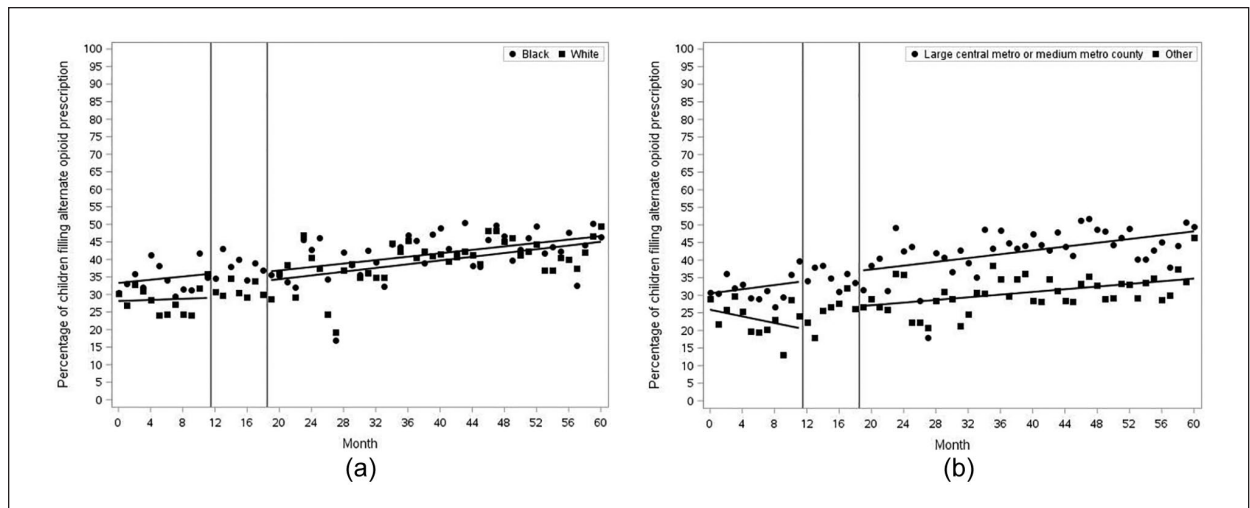When looking at alternate opioid prescription filling by location of the hospital or ambulatory care center, there was no significant difference at the beginning of the study period (29.1% among patients treated in large or medium metro counties versus 25.1% in all other counties, *P* = .07) (Figure 2b). After the release of the black box warning, there were similar increases in the rate of alternate opioid prescription filling across provider locations. However, at the end of the study period, the proportion of children filling an alternate opioid prescription was higher among patients treated by providers in large or medium metro counties (47.7% vs 38.0%, *P* < .001). All results were similar when only patients undergoing tonsillectomy (not adenoidectomy alone) were included (data not shown).

Table 2. Characteristics of Children Enrolled in Ohio Medicaid Who Underwent Tonsillectomy and/or Adenoidectomy in August 2011 to August 2016, by Rural/Urban Location of Institution.

	Large central metro (N=21 479)	Large fringe metro (N=2276)	Medium metro (N=17 037)	Small metro (N=2262)	Micropolitan or noncore (N=7389)	P
Adenoidectomy without tonsillectomy	6100 (28.4)	613 (26.9)	3731 (21.9)	358 (15.8)	1303 (17.6)	<.001
Female (%)	10409 (48.5)	1207 (53.0)	8556 (50.2)	1203 (53.2)	3982 (53.9)	<.001
White race (%)	14387 (67.0)	2068 (91.0)	13754 (80.7)	1993 (88.1)	7127 (96.5)	<.001
Age in years (%)						<.001
<1	219 (1.0)	1 (0.04)	79 (0.5)	4 (0.2)	4 (0.1)	
1 to 2	4064 (18.9)	208 (9.1)	2731 (16.0)	200 (8.8)	629 (8.5)	
3 to 4	5035 (23.4)	483 (21.2)	4070 (23.9)	454 (20.1)	1554 (21.0)	
5 to 6	4529 (21.1)	498 (21.9)	3572 (21.0)	540 (23.9)	1653 (22.4)	
7 to 8	2827 (13.2)	339 (14.9)	2265 (13.3)	369 (16.3)	1131 (15.3)	
9 to 10	1720 (8.0)	215 (9.5)	1471 (8.6)	227 (10.0)	764 (10.3)	
11 to 12	1194 (5.6)	176 (7.7)	1018 (6.0)	169 (7.5)	596 (8.1)	
13 to 14	798 (3.7)	139 (6.1)	743 (4.4)	129 (5.7)	399 (5.4)	
15 to 16	629 (2.9)	122 (5.4)	680 (4.0)	97 (4.3)	370 (5.0)	
17 to 18	464 (2.2)	95 (4.2)	408 (2.4)	73 (3.2)	289 (3.9)	
Rural/urban location of residence (%)						<.001
Large central metro	12581 (58.6)	92 (4.0)	106 (0.6)	13 (0.6)	35 (0.5)	
Large fringe metro	5450 (25.4)	1778 (78.1)	496 (2.9)	12 (0.5)	293 (4.0)	
Medium metro	301 (1.4)	23 (1.0)	13303 (78.1)	22 (1.0)	159 (2.2)	
Small metro	331 (1.5)	2 (0.1)	600 (3.5)	1470 (65.0)	404 (5.5)	
Micropolitan	2194 (10.2)	359 (15.8)	2067 (12.1)	543 (24.0)	5417 (73.3)	
Noncore	614 (2.9)	22 (1.0)	459 (2.7)	200 (8.9)	1079 (14.6)	
Type of institution						<.001
Children's hospital or affiliated ASC	17228 (80.2)	0 (0)	9785 (57.4)	0 (0)	0 (0)	
Other teaching hospital or teaching hospital-affiliated ASC	2544 (11.8)	1108 (48.7)	3650 (21.4)	305 (13.5)	3671 (49.7)	
Non-teaching hospital, non-teaching hospital affiliated ASC, or independent ASC	1707 (8.0)	1168 (51.3)	3602 (21.1)	1957 (86.5)	3718 (50.3)	
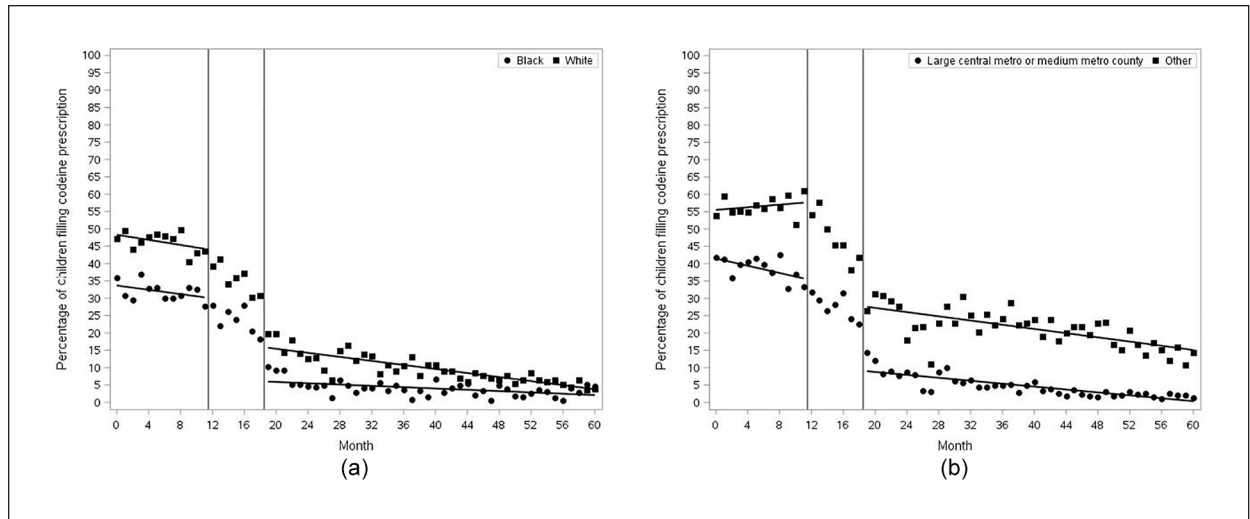
Figure 1. (a) Proportions of white and black children filling a codeine prescription within 14 days after tonsillectomy and/or adenoidectomy. The lines show the predicted probabilities from the segmented regression model. The period of the FDA investigation (August 2012-Feb 2013) is shown between the 2 vertical lines. (b) Proportions of children filling a codeine prescription within 14 days after tonsillectomy and/or adenoidectomy, by location of institution.

Figure 2. (a) Proportions of white and black children filling an alternate opioid prescription within 14 days after tonsillectomy and/or adenoidectomy. The lines show the predicted probabilities from the segmented regression model. The period of the FDA investigation (August 2012-Feb 2013) is shown between the 2 vertical lines. (b) Proportions of children filling an alternate opioid prescription within 14 days after tonsillectomy and/or adenoidectomy, by location of institution.

Overall Opioid Prescribing After Tonsillectomy and/or Adenoidectomy and Codeine Prescribing After Other Common Surgical Procedures

With regard to overall rates of opioid prescription filling after tonsillectomy and/or adenoidectomy, at the beginning of the study period, only 25.0% of all patients did not fill any prescription for an opioid (codeine or otherwise). At the end of the study period, that number had increased to 49.8% of patients ($P < .001$). Among patients undergoing tonsillectomy, this rate increased from 15.9% to 41.5% ($P < .001$). However, among patients undergoing adenoidectomy without tonsillectomy, this rate decreased from 87.2% to 70.6% ($P < .001$). When other common pediatric surgical procedures performed in children aged 1 to 11 during the

last 3 months of the study period were examined, we found that rates of codeine prescription filling after appendectomy (4.7%), circumcision (5.3%), and supracondylar humeral fracture fixation (7.1%) were similar to tonsillectomy (5.7%) ($P > .05$ for all). However, the rate of codeine prescription filling after inguinal hernia repair (1.6%) was significantly lower than after tonsillectomy ($P = .049$).

Discussion

This study demonstrates that while differences between black and white children existed in both codeine and alternate opioid prescription filling after T/A prior to the FDA codeine safety investigation, the FDA's black box warning on codeine for T/A patients has been associated with the elimination of these differences. The racial disparity was in the expected direction for codeine, with white children filling codeine prescriptions more frequently than black children prior to the FDA's investigation. This aligns with previous studies reporting that white children are more likely than black children to receive opioids for the same conditions and after the same procedures.[17-19,21] This disparity is concerning not only because of codeine's known safety risks in children with high enzyme CYP2D6 function, but also because many patients experience poor analgesia from codeine as a result of low enzyme function. Therefore, the prescribing of codeine to more white children than black children may have in fact disproportionate placed white children at undue risk of both respiratory depression and poor pain control. The racial disparity in alternate opioid prescription filling was in the opposite direction as we expected prior to the FDA's investigation, with black children filing prescriptions for alternate opioids more frequently than white children. Notably, this difference was smaller than the difference in codeine prescription filling. Thus, there was an overall lower rate of opioid prescription filling in black as compared to white children prior to the FDA's codeine investigation, which was not present at the end of the study period. Throughout the entire study period, geographic differences in opioid prescription filling after T/A were present, with patients who underwent surgery outside of large and medium sized metro counties being more likely to fill a codeine prescription. More than 2 years after the issuance of the FDA black box warning, this finding persisted and was accompanied by a higher rate of alternate opioid prescription filling among children who underwent surgery in large and medium sized metro counties.

Previous studies have shown a significant racial disparity between black and white patients in opioid use for acute pain treatment, even while controlling for factors such as severity of injury, insurance status, and history of substance abuse.[10,11] Our results showing racial differences in rates of codeine prescription filling at the beginning of the study period corroborate these findings, with white children significantly more likely than black children to fill a codeine prescription after T/A. Among tonsillectomy patients specifically, a study by Sadhasivam et al. found that black children experienced higher levels of pain post-tonsillectomy and yet still received less opioid treatment in the hospital.[21] Prior to the FDA's investigation and widespread concerns about codeine, studies demonstrated that Tylenol with codeine was more effective at controlling post-tonsillectomy pain in children than ibuprofen, and codeine was considered standard post-operative care for a long period of time.[31,32] In our study, even when accounting for alternate opioid prescriptions, black children were overall less likely to fill any type of opioid analgesic prescription in the postoperative period at the beginning of the study period, indicating a racial disparity in overall post-operative pain management after tonsillectomy.

The FDA investigation and resultant black box warning led to a decrease in codeine prescribing among both white and black children. The overall decrease immediately after the warning was issued was greater among white children, possibly indicating that the FDA warning was heeded more often when surgeons cared for white patients. Over the course of the remaining 16 days of the study period, codeine prescription filling decreased gradually among both white and black children, ending with similar rates of codeine prescription filling in both races (4.9% in white children vs 4.1% in black children). There was no significant racial difference in alternate opioid prescription filling at the end of the study period, thus indicating that 1 consequence of the FDA warning was the elimination of racial disparities in the receipt of opioid pain medication post T/A.

One of the persistent disparities we identified in prescription patterns was by geographic location of the facility in which the patient had their operation. Patients whose operation occurred in a hospital or ambulatory surgery center outside of a large central urban county or medium-sized urban county were significantly more likely to fill a prescription for codeine throughout the study period. At the end of the study period in August 2016, 14% of these patients were still filling prescriptions for codeine. Previous research by Boss et al. utilizing the National Survey of Ambulatory surgery identified higher rates of complications in children undergoing tonsillectomy in small/medium metropolitan areas, but no previous research has identified geographic disparities in

post-tonsillectomy pain management.[33] It is unclear where the source of this disparity lies, but it is unlikely that codeine prescriptions are being written at equal rates in rural and urban centers with patients in rural areas more likely to fill the prescription. Previous research has shown that the impacts of other FDA black box warnings on prescribing have also not been even across the country.[34] It may be that such geographic differences are explained by geographic variation in the distribution and influence of pharmaceutical marketing or key opinion leaders. Alternately, it may be that formulary policies or other pharmacy practices play a key role, as not all pharmacies are able to fill prescriptions for hydrocodone or oxycodone in liquid form for young children. It is possible that further education or outreach may reduce codeine prescribing by providers practicing in rural areas. Single institutions have shown the importance of identifying barriers to change, and formal and informal education as important components of gradually decreasing and eventually eliminating codeine from children's hospitals.[35] It may be, however, that greater availability of non-codeine liquid pain medications for children at pharmacies outside of larger urban areas may also be needed.

Given the nature of the patient population and clinical scenario, it is possible that liquid formulations of other opioids are more difficult to acquire due to pharmacy options, and that codeine is the only available option. Alternatively, despite recommendations against the use of codeine by organizations such as the American Academy of Pediatrics, it is possible that some providers still prefer to use codeine and continue to do so with an understanding of its risks.[36] Further efforts at an institutional level may be required, such as complete elimination of codeine from the hospital pharmacy. Our large, tertiary pediatric hospital removed codeine from its formulary in 2012, and other children's hospitals that have done the same have reported rapid adaptation to alternative analgesics.[37]

While our study did find that racial disparities in codeine prescription filling no longer existed at the end of the study period, we acknowledge that our findings in Ohio may not necessarily apply to other states. Importantly, racial disparities in pediatric outpatient opioid prescribing have been noted in a recent national study, indicating that there is still work to be done to identify drivers of and implement interventions to reduce this disparity.[8] In general, racial disparities in health care are typically driven by factors acting at multiple levels and across multiple domains.[38] However, provider biases driven by systemic and institutional racism certainly play a role, and these biases must be targeted for racial disparities to be eliminated.[39] With regard to overall opioid use in the setting of the opioid epidemic, at the beginning of the study period, the vast majority (84.1%) of patients filled some type of opioid prescription. By the end of the study period, only 58.5% of patients filled any opioid prescription. In addition to addressing disparities in care, it is important for future research to assess the appropriate role and choice of narcotics and other analgesics after procedures such as tonsillectomy.

There are several limitations to our study. This study was conducted using Ohio Medicaid claims, so results may not be generalizable to the rest of the country. The nature of the administrative claims database used for this study limited the number of patient and provider level characteristics we could incorporate into our analysis, such as comorbid conditions, complications, and provider race. Due to limited sample sizes we also could not include results from patients of races other than black or white. Additionally, our results indicate prescription filling rates, and we were unable to ascertain the rate at which prescriptions were written that may not have been filled.

Conclusion

The FDA black box warning on codeine resulted in the elimination of racial disparities in codeine prescription filling after tonsillectomy or adenoidectomy in the state of Ohio. However, patients who undergo these procedures in hospitals and ambulatory surgery centers outside of large and medium metro areas are still significantly more likely to fill a prescription for codeine. Rates of alternate opioid prescription filling increased in response to decreases in codeine prescriptions, but overall levels of postoperative opioid prescriptions after T/A have decreased since the FDA black box warning in 2013.

Author Contributions

AL drafted the initial version of the manuscript. JNC led the statistical analyses and interpretation of results. KJD, PCM and SKW provided clinical insight. DJC obtained research funding and provided disparities research support. All authors provided substantial review and approval of the final document.

Declaration of Conflicting Interests

Funding

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Supplemental Material

Supplemental material for this article is available online.

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