Effect of FDA Investigation on Opioid Prescribing to Children After Tonsillectomy/Adenoidectomy

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abstract

BACKGROUND: In August 2012, the Food and Drug Administration investigated the safety of codeine use by children after tonsillectomy and/or adenoidectomy, culminating in a black box warning in February 2013. The objective of this study was to evaluate the association between the investigation and opioid prescribing to children undergoing these surgeries.

METHODS: We identified 362 992 privately insured children in the 2010–2015 Truven MarketScan Commercial Claims and Encounters database who underwent tonsillectomy and/or adenoidectomy. Using an interrupted time series design, we estimated level and slope changes in the proportion of children with ≥1 prescription fills for codeine and ≥1 fills for an alternative opioid, such as hydrocodone, within 7 days of surgery.

RESULTS: The investigation was associated with a significant −13.3 (95% confidence interval: −14.5 to −12.1) percentage point level change in the proportion of children with ≥1 prescription fills for codeine after tonsillectomy and/or adenoidectomy. Despite this drop, 5.1% of children had ≥1 prescription fills for codeine in December 2015. The investigation was not associated with significant level changes in alternative opioid prescribing, although the proportion of children receiving alternative opioids increased during the study period because of other factors.

CONCLUSIONS: The Food and Drug Administration investigation substantially decreased codeine prescribing to children after tonsillectomy and/or adenoidectomy. However, 1 in 20 children undergoing these surgeries were still prescribed codeine in December 2015 despite its well-documented safety and efficacy issues.

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WHAT'S KNOWN ON THIS SUBJECT: Between August 2012 and February 2013, the Food and Drug Administration investigated the safety of codeine use by children after tonsillectomy and/or adenoidectomy, culminating in a black box warning. The association between this investigation and opioid prescribing is unknown.

WHAT THIS STUDY ADDS: Using a national sample of commercial claims, we found the investigation was associated with substantial decreases in codeine prescribing to children after tonsillectomy and/or adenoidectomy. However, 1 in 20 children were still prescribed codeine in December 2015.

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Historically, codeine has been 1 of the most commonly prescribed analgesics to children after tonsillectomy and/or adenoidectomy in part because of its perceived favorable safety profile compared with higher-potency alternative opioids, such as oxycodone and hydrocodone.[1] However, between 1969 and 2012, the US Food and Drug Administration (FDA) received 13 reports of children who died or overdosed after taking codeine, including 8 who had recently undergone these surgeries.[2] Many of these adverse events were associated with genetic polymorphisms resulting in high function of the enzyme that metabolizes codeine to morphine, leading to dangerously elevated blood morphine levels.[2–4] On August 1, 2012, the FDA responded to these reports by announcing an investigation into the safety of codeine use by children after tonsillectomy and/or adenoidectomy. On February 20, 2013, this investigation culminated in a black box warning.[2] Notably, the warning recommended against codeine use in all children undergoing these surgeries and not just children with obstructive sleep apnea (OSA), which is a risk factor for opioid-induced respiratory depression.[5]

To date, the association between this investigation and changes in codeine prescribing to children after tonsillectomy and/or adenoidectomy is unknown. Previous FDA safety investigations have been associated with sizable but incomplete changes in provider practice.[6,7] For example, the FDA issued several warnings between 2003 and 2004 on the increased risk of suicidal ideation among children taking antidepressants. These warnings were associated with a 20% to 30% reduction in antidepressant prescribing to children but no significant changes in recommended patient monitoring after antidepressant initiation.[6,7] As another example, the FDA issued a warning in January 2008 against the use of cough and cold medicines in children <2 years of age. This warning, along with concomitant labeling and marketing changes by the pharmaceutical industry, decreased but did not eliminate prescriptions for cough and cold medicines in this age group.[8]

Similarly, the association between the FDA investigation and prescribing of alternative noncodeine opioids to children after tonsillectomy and/or adenoidectomy is unknown. In theory, providers could have responded to the investigation by relying on nonopioid agents, such as ibuprofen,[9] resulting in decreased overall opioid prescribing to children after tonsillectomy and/or adenoidectomy. However, they could also have responded by substituting codeine with higher-potency opioids, such as hydrocodone. Documenting any substitutions is crucial because some noncodeine opioids may also be unsafe for children after tonsillectomy and/or adenoidectomy. For example, in April 2017, the FDA announced a contraindication against the use of tramadol by children after these surgeries, citing similar concerns about genetic variability in tramadol metabolism.[10]

In this study, we used a quasi-experimental approach and 2010–2015 commercial claims data to examine the association between the FDA safety investigation and opioid prescribing to children after tonsillectomy and/or adenoidectomy. We conducted a subgroup analysis to examine whether this association varied among children with and without OSA.

METHODS

Data Source

We analyzed data from the 2010–2015 Truven MarketScan Commercial Claims and Encounters database, which is a convenience sample of claims from individuals aged 0 to 64 years with employer-sponsored insurance. MarketScan enrollees receive insurance from 1 of >100 employers across the United States.[11] Annual sample sizes in the 2010–2014 MarketScan database range from 45.2 million to 53.1 million. In 2015, the sample size decreased to 28.3 million because of changes in data contributors; however, results were similar when we excluded data from this year (Supplemental Table 4).

Study Population

Among 72 million children aged 0 to 18 years in the 2010–2015 MarketScan database, we initially included 469 647 who underwent tonsillectomy and/or adenoidectomy. To identify these surgeries, we searched the MarketScan inpatient, outpatient, and facility files for procedure codes corresponding to tonsillectomy, adenoidectomy, or both (*Current Procedural Terminology* codes 42820, 42821, 42825, 42826, 42830, 42831, 42835, and 42836; *International Classification of Diseases, Ninth Revision* and *International Classification of Diseases, 10th Revision* procedure codes 28.2, 28.3, 28.6, 0CTP0ZZ, 0CTPXZZ, 0CTQXZZ, and 0CTQ0ZZ). We defined the index date as the first instance of 1 of these codes.

We made 2 sample exclusions. First, we excluded 95 901 children whose prescription drug claims data were not included in MarketScan (ie, the employer only contributed medical but not pharmacy claims). Second, because we searched for opioid prescription fills within 7 days of surgery as described below, we eliminated 10 754 children whose health care utilization could not be observed for this time period (eg, children undergoing surgery on the last 7 days of 2010–2015). In a sensitivity analysis, results were similar when including these children

(Supplemental Table 5). Our final sample included 362 992 children.

Study Measures

We created 2 dichotomous dependent variables: the occurrence of ≥1 prescription fills for codeine after tonsillectomy and/or adenoidectomy, and the occurrence of ≥1 prescription fills for an opioid other than codeine (alternative opioids). We included prescription fills that occurred on the index date and within 7 days. This interval is consistent with previous research on opioid use[12] and reflects the period in which many patients experience the most intense pain after tonsillectomy and/or adenoidectomy. Estimates changed minimally when we searched for prescription fills occurring within 3 or 14 days of the index date instead of 7 (Supplemental Table 6).

To identify opioid prescription fills, we searched the MarketScan prescription drug files for specific opioid national drug codes (NDCs) by using a slightly modified version of the list of opioid NDCs compiled by the Centers for Disease Control and Prevention.[13] We excluded cough and cold preparations containing opioids, both because these were unlikely to be prescribed after tonsillectomy and/or tonsillectomy and because the FDA announced an investigation into the safety of codeine cough and cold preparations for children during the study period (July 2015).[14] Based on a substring search of the medication name, we classified opioids as codeine products and alternative opioid products (oxycodone, hydrocodone, butorphanol, fentanyl, hydromorphone, levorphanol, meperidine, morphine, oxymorphone, pentazocine, propoxyphene, tapentadol, and tramadol). The list of NDCs used in our search was identical across data years.

Study Design

To quantify the impact of the FDA investigation on opioid prescribing, we used an interrupted time series design, which is a strong, quasi-experimental approach that is frequently used to estimate the effects of interventions on prescription drug fills.[15] Following previous research on FDA safety investigations, we did not include a control group because the national nature of the investigations may have caused spillover effects on codeine prescribing in other populations (eg, adults undergoing tonsillectomy and/or adenoidectomy) and in other clinical scenarios (eg, children undergoing other types of outpatient surgery).[6]

We assigned children to 1 of 72 months on the basis of their index dates and defined the investigation as the 7-month period between August 2012 and February 2013. Thus, the preinvestigation period included the 31 months between January 2010 and July 2012, whereas the postinvestigation period included the 34 months between March 2013 and December 2015; data from the 7-month investigation period were excluded in the analyses. We chose not to model the effects of the announcement and the black box warning separately because the net effect of the entire investigation may be of more policy relevance than the effect of individual components. We provide results from an analysis that models the effects separately in Supplemental Table 7.

Statistical Analysis

We fit linear segmented regression models predicting the 2 dependent variables as a function of month, an indicator of postinvestigation period status (post), and the number of months after the investigation ended (monthsafter). The coefficient for month represented the absolute percentage point change per month in prescribing outcomes over the study period, the coefficient for post represented the level change in the fitted line between the beginning and end of the investigation, and the coefficient for monthsafter represented the slope change in the fitted line after the investigation ended.[15,16] We used the SAS AUTOREG procedure to account for first-order autocorrelation.

We also conducted a descriptive analysis to examine changes in the types of opioids prescribed to children after tonsillectomy and/or adenoidectomy. Among all opioid prescription fills occurring within 7 days of these surgeries, we calculated the monthly proportion that fell into the following 4 categories: (1) products containing codeine, (2–3) products containing the 2 most commonly prescribed alternative opioids (hydrocodone and oxycodone), and (4) products containing other opioids.

In a subgroup analysis, we analyzed whether associations varied among children with and without OSA. Following previous research, we defined OSA as the presence of any of the following *International Classification of Diseases, Ninth Revision* or *International Classification of Diseases, 10th Revision* diagnosis codes on a claim occurring on the index date: 327.23, OSA; 780.57, unspecified sleep apnea; 780.51, insomnia with sleep apnea (unspecified); 780.53, hypersomnia with sleep apnea (unspecified); G47.33, OSA; and G47.30, unspecified sleep apnea.[17–19] In a sensitivity analysis, results were similar when we defined OSA as the presence of these codes on a claim occurring on the index date or in the previous 90 days (Supplemental Table 8).

To evaluate the possibility of selection bias from abrupt changes in the case mix during the investigation, we determined whether our estimates changed substantially when controlling for demographic characteristics in regressions (mean

TABLE 1 Characteristics of Children Undergoing Tonsillectomy and/or Adenoidectomy, MarketScan 2010–2015

Characteristics	2010	2011	2012	2013	2014	2015	All Years
Sample size[a]	69 547	75 454	71 664	54 712	49 712	41 903	362 992
Girls (%)	48.8	48.9	48.7	48.8	48.4	48.9	48.7
Age, y (%)							
0–5	49.0	48.0	49.6	51.4	51.4	51.4	49.9
6–12	35.8	37.3	35.4	33.9	34.7	34.2	35.4
3–18	15.2	14.7	15.0	14.6	13.8	14.4	14.7
Region (%)							
Northeast	10.5	13.6	14.6	13.4	15.6	12.6	13.3
Midwest	29.5	28.3	28.4	24.9	23.4	22.0	26.6
South	45.0	42.6	41.3	42.1	43.6	50.4	43.8
West	14.3	13.3	14.0	16.7	14.8	14.6	14.5
Unknown	0.7	2.2	1.6	3.0	2.7	0.3	1.8

[a] The number of children undergoing tonsillectomy and/or adenoidectomy fluctuates from year to year largely because of differences in the number of children in each year of the MarketScan: 12 557 596 (2010), 14 266 215 (2011), 11 533 618 (2012), 14 237 823 (2013), 12 168 782 (2014), and 7 255 815 (2015).

monthly age, percentage girls, and percentage in each US census region). To evaluate whether our estimates could be biased by other events occurring at the same time as the investigation, we searched for opioid shortages by using the drug shortage lists maintained by the FDA and the American Society of Health-System Pharmacists.[20,21] Furthermore, we used the search terms "opioids," "codeine," "oxycodone," and "hydrocodone" in LexisNexis Academic to examine opioid-related North American news articles published between August 1, 2012, and February 28, 2013.

All analyses used SAS 9.4 (SAS Institute, Inc, Cary, NC). Two-sided *P* values <.05 were considered significant. The Institutional Review Board of the University of Chicago deemed that this study was not human subjects research.

RESULTS

Sample Characteristics

Among the 362 992 children in our sample, 48.7% were girls, 49.9% were aged 0 to 5 years, 35.4% were aged 6 to 12 years, and 14.7% were aged 13 to 18 years (Table 1). Overall, 13.3% were from the Northeast census region compared with 26.6% from the Midwest, 43.8% from the South, and 14.5% from the West. Children in the sample lived in all 50 states and the District of Columbia. According to our definition, 60 535 children (16.7% of the sample) had OSA, whereas 302 457 (83.3%) did not.

Main Results

Figure 1 displays trends in the 2 dependent variables during the study period. In January 2010, 31.0% of children had ≥1 prescription fills for codeine within 7 days of tonsillectomy and/or adenoidectomy. This percentage declined −0.3 (95% confidence interval [CI]: −0.3 to −0.2) percentage points per month between January 2010 and July 2012, which was the month before the investigation started (Table 2). The investigation was associated with a significant −13.3 (95% CI: −14.5 to −12.1) percentage point level change and a significant 0.1 (95% CI: 0.1 to 0.2) percentage point slope change in codeine prescription fills, indicating that the monthly rate of change in the postinvestigation period was slower but still negative. In December 2015, 5.1% of children had ≥1 prescription fills for codeine within 7 days of surgery.

Similarly, in January 2010, 31.7% of children had ≥1 prescription fills for an alternative opioid within 7 days of tonsillectomy and/or adenoidectomy. This percentage increased 0.2 (95% CI: 0.1 to 0.3) percentage points per month between January 2010 and July 2012 (Table 2). The investigation was associated with a nonsignificant −1.2 (95% CI: −3.5 to 1.0) percentage point level change and a significant −0.2 (95% CI: −0.3 to −0.1) percentage point slope change in alternative opioid prescription fills, indicating that the monthly rate of change in the postinvestigation period was close to 0. In December 2015, 46.1% of children had ≥1 prescription fills for an alternative opioid within 7 days of surgery.

During the overall study period, an average of 1.1% of the children had prescription fills for both codeine and an alternative opioid within 7 days of tonsillectomy and/or adenoidectomy. In January 2010, 38.8% of children had no prescription fills for any opioid within 7 days of surgery compared with 50.4% of children in December 2015.

Changes in Type of Opioid Prescribed

During the study period, children in the sample had a total of 246 459 opioid prescription fills within 7 days of tonsillectomy and/or adenoidectomy. Figure 2 displays trends in the proportion of these fills in which the active ingredient was codeine, hydrocodone, oxycodone, or another opioid. In January 2010, codeine products constituted 46.8% of fills compared with 48.4% for hydrocodone products, 3.8% for oxycodone products, and 0.1% for other opioid products. In December

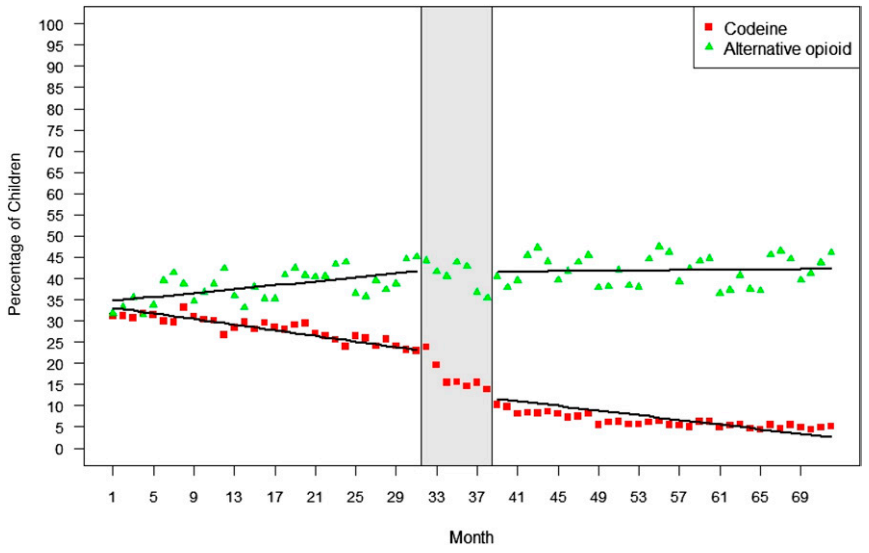

FIGURE 1
Opioid prescribing to children after tonsillectomy and/or adenoidectomy. The graph displays the percentage of children with ≥1 prescription fills for codeine and ≥1 prescription fills for an alternative opioid within 7 days of tonsillectomy and/or adenoidectomy (MarketScan 2010–2015). Month 1 corresponds to January 2010, and month 72 corresponds to December 2015. The investigation period (shaded in gray) includes month 32 (the announcement of the FDA safety investigation in August 2012) through month 38 (the FDA black box warning in February 2013). The lines represent the predicted values from segmented regressions. Squares represent codeine, and triangles represent alternative opioids, such as hydrocodone or oxycodone.

TABLE 2 Results From Segmented Regression Analyses

Dependent Variable	Coefficient	Estimate (95% CI)[a]
≥1 prescription fills for codeine after tonsillectomy	Intercept	32.3 (31.6 to 33.0)
	Month[b]	−0.3 (−0.3 to −0.2)
	Post[b]	−13.3 (−14.5 to −12.1)
	Monthsafter[b]	0.1 (0.1 to 0.2)
≥1 prescription fills for an alternative opioid after tonsillectomy	Intercept	35.1 (33.2 to 37.0)
	Month[b]	0.2 (0.1 to 0.3)
	Post[b]	−1.2 (−3.5 to 1.0)
	Monthsafter[b]	−0.2 (−0.3 to −0.1)

[a] Coefficients from regressions were multiplied by 100 and are expressed as percentage point changes.
[b] The coefficient for month represents the absolute percentage point change per month over the study period; the coefficient for post represents the immediate level change after the investigation ended; and the coefficient for monthsafter represents the slope change after the investigation ended.

2015, codeine products constituted 9.1% of fills compared with 72.7% for hydrocodone products, 17.4% for oxycodone products, and 0.8% for other opioid products. Thus, providers who chose to prescribe opioids to children increasingly relied on high-potency agents, such as hydrocodone and oxycodone, over time.

Subgroup Analysis

In the subgroup analysis, 38.0% of children with OSA and 30.0% of children without OSA had ≥1 prescription fills for codeine within 7 days of tonsillectomy and/or adenoidectomy in January 2010, compared with 3.0% and 5.6% in December 2015, respectively. The investigation was associated with a −16.2 (95% CI: −18.2 to −14.3) percentage point level change in the proportion of children with OSA who had ≥1 prescription fills for codeine after surgery, compared with a −12.6 (95% CI: −13.9 to −11.4) percentage point level change among children without OSA (Table 3). As indicated by the nonoverlapping confidence intervals, the magnitude of these level changes was significantly different between subgroups. Similar to the main analysis, the investigation was not associated with significant level changes in alternative opioid prescription fills in either subgroup.

Conclusions were unchanged when additionally controlling for demographic characteristics in regressions (Supplemental Table 9). We did not find evidence that any opioid drug shortages occurred at the same time as the investigation. Among 484 opioid-related news articles in LexisNexis Academic that were published while the investigation was underway, many reported on the toll of the opioid epidemic generally, whereas a handful reported on the January 24, 2013, FDA hearing on tightening restrictions for hydrocodone prescribing.[22] None reported the occurrence of events other than the investigation that specifically pertained to opioid prescribing to children after tonsillectomy and/or adenoidectomy.

DISCUSSION

The 2012–2013 FDA investigation into the safety of codeine use by children after tonsillectomy and/or adenoidectomy was associated with a significant 13.3 percentage point drop in codeine prescribing to these children. Despite this, 5.1% of all children and 3.0% of children with OSA were still prescribed codeine after tonsillectomy and/or adenoidectomy in December 2015. The existence of residual inappropriate codeine prescribing is concerning not just because of codeine's safety risks but also because many patients receive poor analgesia from codeine because of low function of the enzyme that metabolizes codeine to morphine.[9] Thus, the decision to prescribe codeine may increase the risk of either respiratory depression

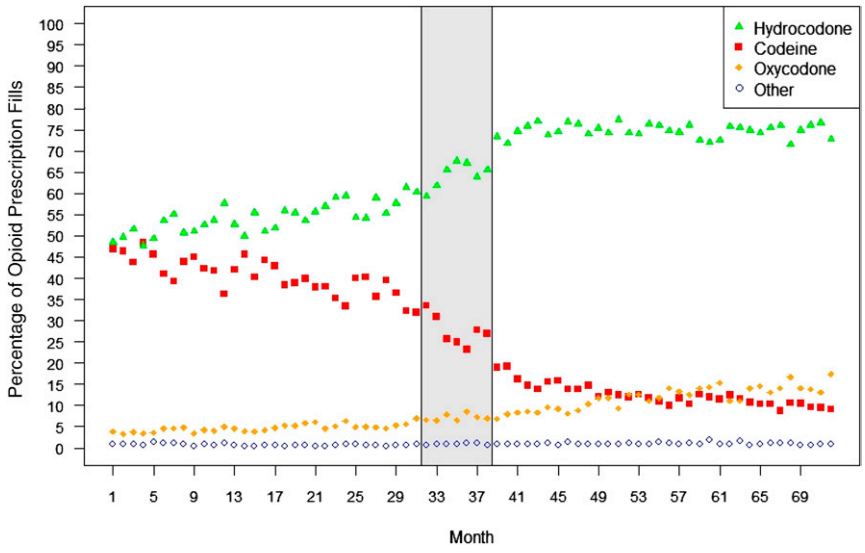

FIGURE 2

Change in type of opioid prescribed to children after tonsillectomy and/or adenoidectomy (MarketScan 2010–2015). Month 1 corresponds to January 2010, and month 72 corresponds to December 2015. The investigation period (shaded in gray) is defined by month 32 (the FDA announcement of the safety investigation in August 2012) and month 38 (the FDA black box warning in February 2013). The y-axis represents the percentage of opioid prescription fills after tonsillectomy and/or adenoidectomy that were comprised of products containing hydrocodone, codeine, oxycodone, or other opioids. Triangles represent hydrocodone, squares represent codeine, diamonds represent oxycodone, and empty circles represent other opioids.

TABLE 3 Results From Subgroup Analysis of Children With and Without OSA

Dependent Variable	Coefficient	Children With OSA (n = 60 535)	Children Without OSA (n = 302 457)
		Estimate (95% CI)[a]	Estimate (95% CI)[a]
≥1 prescription fills for codeine after tonsillectomy	Intercept	39.6 (38.4 to 40.8)	31.0 (30.3 to 31.8)
	Month[b]	−0.4 (−0.4 to −0.3)	−0.3 (−0.3 to −0.2)
	Post[b]	−16.2 (−18.2 to −14.3)	−12.6 (−13.9 to −11.4)
	Monthsafter[b]	0.2 (0.1 to 0.3)	0.1 (0.1 to 0.2)
≥1 prescription fills for an alternative opioid after tonsillectomy	Intercept	35.6 (34.4 to 36.7)	35.0 (32.9 to 37.2)
	Month[b]	0.3 (0.2 to 0.4)	0.2 (0.1 to 0.3)
	Post[b]	−0.8 (−2.8 to 1.2)	−1.3 (−3.8 to 1.1)
	Monthsafter[b]	−0.3 (−0.4 to −0.2)	−0.2 (−0.4 to −0.1)

[a] Coefficients from regressions were multiplied by 100 and are expressed as percentage point changes.

[b] The coefficient for month represents the absolute percentage point change per month over the study period; the coefficient for post represents the immediate level change after the investigation ended; and the coefficient for monthsafter represents the slope change after the investigation ended.

(for patients with high enzyme function) or ineffective pain control (for patients with low enzyme function). Given the typical lack of access to genotype information in clinical settings and the availability of effective alternative pain-control strategies (eg, ibuprofen),[9] this decision may be viewed as an unnecessary gamble, particularly for children with OSA, who are at a higher risk for opioid-related respiratory depression.

Our finding of residual inappropriate codeine prescribing is consistent with previous policy literature suggesting that FDA safety investigations can alter provider behavior but only to a certain degree.[6,23] It is likely that the reductions in codeine prescribing occurred among providers who are amenable to change. Therefore, further reductions may be difficult without concerted quality-improvement efforts aimed at overcoming potential barriers among providers who are resistant to change, including clinical inertia, a lack of agreement, or a lack of experience with alternative options.[24]

The FDA investigation was not associated with significant level changes in the proportion of children with prescription fills for alternative opioids after tonsillectomy and/or adenoidectomy. However, the unadjusted proportion of children receiving alternative opioids rose substantially during the study period, presumably because of factors other than the investigation itself. This increase deserves further examination given the abuse liability associated with higher-potency opioids[25] as well as the growing evidence of genetic variability in the metabolism of many alternative opioids, including oxycodone and tramadol.[9,10]

Our study has a number of strengths, including its large sample size and use of a strong quasi-experimental design. We found little evidence that results were biased by changes in the case mix at the time of the intervention. Furthermore, we negated the possibility of bias from changes in our measurement instrument by using an identical strategy to identify opioid prescription fills across the study period.

Our study also has limitations. First, because we relied on a convenience sample of commercial claims, the

generalizability of the results to other commercially insured children and to publicly insured children is unclear. Second, we assessed prescription fills for opioids, which may be lower than the number of actual opioid prescriptions (eg, if parents choose not to fill an opioid prescription). Third, although adjusting for available demographic information did not substantially change results, we cannot exclude the possibility that our results might be biased by abrupt changes in unmeasured demographic factors during the investigation. Fourth, because of data limitations, we could not ascertain the characteristics of providers who were still prescribing codeine to children after tonsillectomy and/or adenoidectomy in 2015. Fifth, we could not assess the use of over-the-counter agents such as ibuprofen because we relied on claims data.

Finally, there was not a plausible control group because of the national nature of the investigation and the resulting potential for spillover effects. Therefore, we cannot completely rule out the possibility that our results could be biased by the occurrence of other events that affected opioid prescribing. However, our review of drug shortages and opioid-related news articles did not support this possibility. Although several recent events have focused on codeine prescribing to children, including the September 2016 American Academy of Pediatrics recommendation that providers stop prescribing codeine to children for any indication,[26] the timing of these events was too late to bias our findings.

CONCLUSIONS

The FDA safety investigation was associated with large reductions in codeine prescribing to children after tonsillectomy and/or adenoidectomy. However, ~1 in 20 children were still prescribed codeine in December 2015 despite its well-documented safety and efficacy issues. Future quality-improvement efforts should focus on eliminating this residual inappropriate codeine prescribing and on encouraging the use of effective nonopioid medications such as ibuprofen.[9]

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ABBREVIATIONS

CI: confidence interval
FDA: Food and Drug Administration
NDC: national drug code
OSA: obstructive sleep apnea

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