Opioid Analgesic Utilization in Pediatric Population with Acute Pain

by
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Dedicated to

My family

For their everlasting support and unwavering belief in me

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ABSTRACT

Background:

Opioid epidemic is a long-standing challenge faced by the United States with millions of children and adolescents being exposed to opioids and its harmful effects. Statewide opioid prescribing policies, pediatric opioid analgesic guidelines and FDA warnings have been implemented in an effort to minimize opioid utilization in the pediatric population as well as recommending other analgesic alternatives to manage pain. However, guidelines and policies have an intended and an unintended effect.

Objective.

The overarching goal of the dissertation project was to examine the intended and unintended consequences of guidelines and policies that were instituted to reduce opioid use in children in the light of the opioid epidemic To achieve the goal, the following three aims were investigated: Aim 1: To evaluate the association between initial opioid analgesic prescription duration and receipt of repeat opioid prescription in children and adolescents; Aim 2: To examine the association between outpatient post-surgical analgesic prescription and risk of insufficiently managed pain such as additional analgesic dispensing and pain-associated hospital admission and ER visit; and Aim 3: To determine the change in repeat opioid analgesic prescription trend in children and adolescents experiencing acute pain.

Methods.

The study included children and adolescents 1–17 years of age who were enrolled in a large Medicaid Managed Care plan and filled an incident opioid analgesic prescription (Aims 1, 2 and 3) or an incident non-opioid analgesic prescription (Aim 2) during 2013–2018. A hierarchical multivariable logistic regression model with patients nested under prescribers was fitted to test that

(i) the association of initial opioid analgesic prescription duration and the likelihood of receiving a repeat prescription (Aim 1) and (ii) the risk of having additional pain-related service utilization associated with analgesic modality (Aim 2). A generalized linear regression analysis was conducted to examine changes in repeat opioid analgesic dispensing over time at quarterly intervals (Aim 3).

Results.

Of 17,086 incident opioid recipients 10.4% received a repeat opioid analgesic. The multilevel model indicated that after controlling for patient characteristics, diagnoses and procedures associated with initial opioid prescription, children receiving 4–7 days' supply [aOR: 0.98(0.9–1.1)], 8–10 days' supply [aOR: 1.03(0.8–1.3)], and >10 days' supply [aOR: 0.85(0.7–1.1)] had comparable likelihoods of receiving a repeat opioid analgesic prescription as those receiving 1–3 days' supply

(Aim 1). Of the children undergoing outpatient procedures, 42.3% received incident opioid and 57.7% received incident non-opioid. Around 15% patients in opioid and non-opioid groups had pain-related service utilization. The multilevel model indicated that initial opioid analgesic recipients were two times more likely than non-opioid analgesic recipients to receive an additional analgesic dispensing [aOR: 2.33(95%CI: 2.0–2.8)] and 60% less likely of having a pain-associated hospital admission or ER visit [aOR: 0.41(95%CI: 0.3–0.5)] (Aim 2). There was a significant decline in repeat opioid trend from 11.5% in Q1, 2013 to 9.6% in Q4, 2018 with a quarterly percentage change (QPC) of 6.8% decline (95%CI: 0.6%–12.6%).

Conclusion.

Initial opioid analgesic duration was not associated with the risk of receiving a repeat opioid analgesic prescription (Aim 1). In 15% of patients who required additional pain management

beyond the initial analgesic prescription following an outpatient procedure, those initiated on opioid analgesics are more likely to receive additional analgesics, while those initiated on non-opioid analgesics are more likely to have pain-associated ER visits and hospital admissions (Aim 2). There has been a steady decline (~7% per quarter) in repeat opioid analgesic dispensing between 2013 to 2018 (Aim 3).

EXECUTIVE SUMMARY

Acute pain is defined as, "the normal predicted physiological response to a noxious chemical, thermal or mechanical stimulus and is typically associated with invasive procedures, trauma and disease which is generally time-limited."[1] Children and adolescents are often prescribed either opioid or non-opioid analgesics for the management of their acute pain.[2-4]

Studies have indicated that early opioid use in children is associated with increased risk of persistent use[5-7] and future misuse.[8, 9] In the light of the opioid epidemic, expert-opinion driven, and policy driven measures were implemented to minimize the use of opioid analgesics in the pediatric population. The first policy driven measure instituted were the state laws passed in over 35 states to limit the prescribing duration of opioid analgesics.[10] However, previous studies have pointed out that insufficient pain management is a potential unintended consequence of restrictive prescribing limits.[11-14] With this mandated limit in place, experts anticipate an increase in the number of patients requesting repeat opioid prescriptions or refills.[12] Our first study aimed at determining the association between initial opioid prescription duration and the likelihood of receiving a repeat opioid prescription in opioid-naïve children experiencing acute pain. The study found that 17,086 children and adolescents received an incident opioid analgesic and of these 1,780 (10.4%) received a repeat opioid analgesic. The study concluded that initial opioid analgesic duration was not associated with the risk of receiving a repeat opioid analgesic prescription.

The second expert-opinion driven measure was a new set of guidelines that were published in February 2021 recommending the use of non-opioid combination therapies for pediatric surgical procedures.[15] There was empirical evidence supporting that acetaminophen plus ibuprofen was as effective as acetaminophen plus tramadol in reducing post-operative pain

in children undergoing tonsillectomy.[16] Similarly, empirical data supported the possibility of an opioid-free recovery for surgical procedures such as appendectomy[17], orthopedic procedures[18] and inguinal hernia repair.[19, 20] However, most of the trials included route of administration as either intravenous (IV), intramuscular (IM) and subcutaneous (SC). These routes of analgesic admiration are used much less frequent than the oral opioid and non-opioid analgesics. Secondly, most existing pediatric trials followed patients for very brief durations ranging from 24-hrs to a few days following an analgesic administration. These follow-up periods may not be sufficiently long to capture consequences associated with unmanaged pain. Literature has reported that if acute pain is not controlled effectively, it may lead to chronic post-surgical pain (CPSP) that could last longer than 2 months post-procedure.[21-25] Our second study aimed at examining the association between receipt of incident opioid vs. non-opioid analgesic following an outpatient surgical procedure and the risk of having additional pain related service utilization such as additional analgesic dispensing, hospital admission or an emergency room (ER) visit associated with pain. Our study found that of the 13,678 children who underwent an outpatient procedure 5783 (42.3%) received an incident opioid and 7,895 (57.7%) received an incident non-opioid analgesic prescription. Our study concluded that there were 15% patients in both the opioid and non-opioid groups that had additional pain-related service encounters. In the 15% of patients with insufficiently managed pain, those initiated on opioid analgesic were more likely to receive additional analgesics while those initiated on non-opioid analgesics were more likely to have pain-associated ER visits and hospital admissions.

The third policy-driven initiative was the issuance of an array of warnings and contraindications for opioid use in children and adolescents since 2012.[26-28] Recent studies have pointed to a decreasing opioid dispensing trend in children and adolescents.[29, 30] However, most

of these trend studies are derived from incident opioid exposures or overall prescription counts.[29-31] Repeat opioid prescription is the gateway to persistent use and chronic opioid use in patients receiving opioids for acute pain. The impact of policy change on the utilization of repeated opioid prescription remained unknown. Our third study aimed at determining whether the consistent decline in trend as seen in previous studies and as a consequence of FDA warnings is observed for overall utilization of repeat opioid in children receiving incident opioid prescription for acute pain in the outpatient setting. The variation of repeat opioid utilization trend across age and racial/ethnic groups was also investigated in a sub-cohort of children undergoing outpatient surgical procedures. Of the 17,086 children receiving an incident opioid, 1,780 (10.4%) filled a repeat opioid analgesic. There was a significant decline in the repeat opioid trend from 11.5% in the first quarter of 2013 to 9.6% in the last quarter of 2018 with an approximate quarterly percentage change (QPC) of ~7%. Additionally, a significant decline in trend was observed among all subgroups of patients undergoing outpatient surgical procedures across all age, gender and racial/ethnic groups.

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DISSERTATION AIM 1. Association between the initial opioid prescription duration and the risk of receiving a repeat opioid prescription among children with acute pain

Abstract

Objectives:

Thirty-five states in the US have instituted various prescribing limits to restrict the duration of opioid prescription for the management of acute pain. A potential consequence of restrictive prescribing is insufficiently managed pain. Our study evaluated the association between initial opioid analgesic prescription duration and receipt of a repeat opioid prescription in children and adolescents.

Methods:

Eligible individuals were children and adolescents between 1 – 17 years of age who enrolled in a large Medicaid Managed Care plan and filled an incident opioid prescription during 2013 to 2018. An incident opioid prescription was defined as receipt of an opioid analgesic with no prior use of any opioid for a period of 12 months. A repeat opioid prescription was defined as the receipt of a subsequent opioid analgesic prescription within 30 days since the end of the incident opioid prescription. A hierarchical multivariable logistic regression model with patients nested under prescribers was fitted to test the association between incident opioid prescription duration and the likelihood of receiving a repeat opioid prescription.

Results:

The study included 17,086 children who received an incident opioid prescription. The cohort consisted of 6,272 (36.7%) individuals who received a 1 – 3 days' supply, 8,442 (49.4%) received a 4 – 7 days' supply, 1,434 (8.4%) received an 8 – 10 days' supply and 938 (5.5%) received a >10 days' supply. Of these incident opioid recipients, 1,780 (10.4%) filled a repeat opioid prescription. The multilevel model results indicated that, after controlling for patient

characteristics, diagnoses and procedures associated with the initial opioid prescription, children receiving 4 – 7 days' supply [aOR: 0.98 (0.9 – 1.1)], 8 – 10 days' supply [aOR: 1.03 (0.8 – 1.3)], and >10 days' supply [aOR: 0.85 (0.7 – 1.1)] had comparable likelihoods of receiving a repeat opioid analgesic prescription as those receiving 1 – 3 days' supply.

Conclusion:

Nearly 10% of children who filled an opioid analgesic prescription for acute pain received a repeat opioid prescription within a month since the end of the initial prescription. Initial opioid analgesic duration was not associated with the risk of receiving a repeat opioid analgesic prescription.

1. Introduction.

In the recent four years, 35 states have passed laws to limit the prescribing duration of opioid analgesics.[10] The prescribing limits varied significantly across states with the limits ranging from 3 days to 31 days[11] probably because the optimal opioid prescription duration for acute pain for different scenarios remains unknown.

Previous studies have pointed out that insufficient pain management is a potential unintended consequence of restrictive prescribing limits[11-14] which poses a challenge not only to prescribers but also increases the disease burden on patients. With a mandated prescribing limit implemented in various states, experts anticipate that an increased number of patients will be requesting repeat prescriptions or refills.[12]

Our study aimed at determining the association between initial opioid prescription duration and the likelihood of receiving a repeat opioid analgesic prescription in opioid-naïve children and adolescents experiencing acute pain. We hypothesized that children and adolescents receiving an initial opioid prescription with a relatively shorter days' supply were more likely to have a repeat prescription compared to those receiving the initial prescription with a relatively longer duration after controlling for patient characteristics and diagnoses and procedures associated with the initial opioid prescription.

2. Methods.

2.1. Data Sources:

The Texas Children's Health Plan (TCHP) is a Medicaid Managed Care plan founded by the Texas Children's Hospital. It offers managed Medicaid and CHIP benefits to children in over 20 counties in southeast Texas. Our study extracted the de-identified TCHP data between January 1, 2013 and December 31, 2018 that included patient demographics (age, gender, race,

Medicaid eligibility and member enrollment information), medical claims (outpatient service utilizations such as diagnoses and procedures), and pharmacy claims (outpatient prescription utilization with duration and prescriber specialty).

2.2. Patient Cohort Development:

2.2.1. Inclusion and Exclusion Criteria:

The study cohort included children 1 to 17 years of age who filled an incident opioid analgesic prescription. An incident use was defined as the receipt of an opioid prescription without prior use of any opioid for a period of at least 12 months. Generic Product Identifier (GPI) medication codes were utilized to identify the prescription opioid analgesics such as codeine, hydrocodone and tramadol. Patients that did not fulfill the continuous enrollment criteria of 12-month period (baseline) before and 30-day period (follow-up) after the end of incident opioid analgesic prescription were excluded from the study sample. Additionally, children and adolescents with a diagnosis of malignancy or sickle-cell disease (SCD) during the study period were excluded from the cohort.

2.2.2. Outcome Assessment:

A repeat opioid analgesic prescription was defined as the receipt of a subsequent opioid prescription within 30 days since the end of the incident opioid prescription (fill date + days' supply). To further understand the impact of the follow-up duration on study findings, we conducted sensitivity analyses by reducing the follow-up duration between the end of the initial opioid prescription and the dispensing for a subsequent opioid prescription to 20 days and 10 days respectively.

2.2.3. Primary Exposure:

The primary exposure was the duration of initial opioid analgesic prescription measured as days' supply. Initial opioid analgesic days' supply was categorized based on previous studies[35] and state limits[10]. We constructed four categories namely (1) very low initial duration (1 – 3-day supply); (2) low initial duration (4 – 7-day supply); (3) moderate initial duration (8 – 10-day supply) and (4) high initial duration (> 10-day supply).

2.2.4. Covariates:

The study controlled for patient and prescriber characteristics (**Table S1**) that could potentially confound the association between incident opioid prescription duration and the receipt of repeat opioid analgesic prescription. These factors were identified based on the conceptual framework of the Andersen Behavioral Model.[36, 37] Predisposing factors such as age, gender, race/ethnicity and Medicaid eligibility are present prior to the treatment. Enabling factors such as prescriber specialty constitute an individual's ability to secure health services. Need factors such as potential indications for receipt of opioids (pain diagnoses and outpatient procedures) provide insight into the individual's health status.

To identify the diagnoses and procedures associated with the incident analgesic prescription, a previously published algorithm[38] was utilized to assign priority scores to the procedures and diagnoses (**Supplement 1, Table S2**).

2.3. Statistical Analysis:

A hierarchical multivariable logistic regression model was fitted to test the association between duration of incident opioid analgesic and likelihood of receiving a repeat opioid analgesic prescription. Accounting for the hierarchical structure of the data with patients nested within prescribers, a random intercept fixed effects multilevel modeling approach[39-41] was utilized to account for the inter-cluster (between prescriber) variation and intra-cluster (within

prescriber) correlation in the multivariable model.[42-44] An Intraclass Correlation Coefficient (ICC) was calculated to ascertain the need for using a multilevel model.[42, 45] Adjusted Odds Ratios (aORs) and 95% Confidence Intervals (CIs) were estimated at a statistical significance of $\alpha = 0.05$. All the statistical analyses were conducted using SAS Enterprise Guide 8.1 (SAS Institute, Cary, NC) statistical software.

2.4. Subgroup analysis:

For a subgroup of patients who underwent outpatient surgical procedures, traumatic injury and orthopedic surgeries, three separate hierarchical multivariable logistic regression models were fitted to test the association between duration of incident opioid analgesic and likelihood of receiving a repeat opioid analgesic prescription.

2.5. Ethic Statement:

The University of Houston and Baylor College of Medicine's Institutional Review Board (IRB) approved the study and granted a waived informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

3. Results.

3.1. Distribution of opioid prescription duration

There were 37,119 TCHP enrollees who received an opioid analgesic during the study period. After excluding individuals 18 years of age or older, those diagnosed with malignancy and sickle-cell disease, and those who did not have continuous enrollment 1 year prior to and 30 days after the end of incident opioid analgesic prescription, the final cohort comprised of 17,086 incident opioid analgesic recipients (**Figure 1**). The duration of the index opioid prescription had a mean (SD) of 5.2 (3.8) days and a median (IQR) of 5 (3) days. Of the 17,086 incident opioid

prescriptions filled for children and adolescents, 6,272 (36.1%) had the very low initial duration (1 – 3 days), 8,442 (49.4%) had the low initial duration (4 – 7 days), 1,434 (8.4%) had the moderate initial duration (8 – 10 days) and 938 (5.5%) had the high initial duration (>10 days).

3.2. Patient sociodemographic, clinical characteristics, and prescriber specialty by initial opioid analgesic duration categories

Descriptive statistics by incident opioid prescription durations showed that children receiving more than 10 days initial opioid prescription (high initial opioid duration) were relatively younger compared to all the other three relatively shorter duration categories ($p<0.001$) (**Table 1**).

Approximately 56% high initial duration (>10 days) and 50% of the moderate initial duration (8 – 10 days) opioid prescriptions filled by the study cohort were prescribed by surgical specialists. Dentists and Emergency Room (ER) physicians also prescribed a large quantity of opioid prescriptions filled by the cohort (42.8%), however, the majority of opioid prescriptions prescribed by dentists and ER physicians were less than 7 days. Dentists prescribed 16% of opioid prescriptions in the moderate initial duration category and 17% in the high initial duration category, while ER physicians prescribed 11% of opioid prescriptions in the moderate initial duration and 6% in the high initial duration categories. (**Table 1**).

Consistent with prescriber specialties, outpatient surgical procedures, dental procedures and traumatic injury were the most prevalent diagnoses and procedures observed in all opioid prescription duration groups. Children who underwent an outpatient surgery/procedure composed 50% of the high initial opioid duration recipients, 45% of moderate initial opioid duration recipients, 34% of low initial opioid duration recipients and 29% of very low initial opioid duration recipients ($p<0.001$). In contrast, a relatively higher proportion of children in the

very low and low initial opioid groups underwent a dental procedure or had a traumatic injury. There were 27% of recipients in the very low initial opioid duration, 25% in the low initial opioid duration, 25% in the moderate initial opioid duration and 20% of the high initial opioid duration categories that had a traumatic injury related diagnosis respectively. Similarly, around 27% of the recipients in very low opioid duration and 27% of recipients in low initial opioid duration categories underwent a dental procedure whilst only 15% of moderate initial opioid duration recipients and 17% of high initial opioid duration recipients underwent a dental procedure($p<0.001$). (**Table 1**).

3.3. Proportion of patients receiving repeat opioid prescription by initial opioid prescribing duration

There were 10.4% (N = 1,780) of the incident opioid analgesic recipients who filled a repeat opioid analgesic (**Figure 1**) with an average time (SD) to repeat prescription of 11.9 (9.3) days and a median (IQR) of 9 (12) days since the end of the incident opioid analgesic prescription. Bivariate analyses showed that the proportion of incident opioid analgesic recipients receiving a repeat prescription was slightly higher for the very low initial duration group (11.3%), followed by the low initial duration group (10.0%), the moderate initial duration group (10.8%), and lastly the high initial duration group (8.1%) (p-value = 0.005) (**Figure 2**).

3.4. Multilevel model analysis on the association between initial opioid analgesic duration and likelihood of receiving repeat opioid prescription

3.4.1. Intraclass Correlation Coefficient Estimation:

The Intraclass Correlation Coefficient (ICC) for the unconditional model was 20.1% (ICC = 0.201, p-value <.0001) which indicated that approximately 20% of the variance in the

receipt of repeat prescription (outcome) was explained by variations across prescribers and therefore the study warranted the utilization of a multilevel model.

3.4.2. Multivariable Analysis on the entire study cohort:

The findings from the multilevel logistic regression model indicate that likelihood of receiving a repeat opioid prescription was not significantly lower in patients receiving higher initial durations compared to those receiving a very low initial duration as indicated in **Table 2**. [Low initial opioid duration vs. Very low initial opioid duration: aOR: 0.98 (0.9 – 1.1)], [Moderate initial opioid duration vs. Very low initial opioid duration: aOR: 1.03 (0.8 – 1.3)], [High initial opioid duration vs. Very low initial opioid duration: aOR: 0.85 (0.7 – 1.1)].

Children and adolescents with a diagnosis of traumatic injury were 2.5 times more likely to receive a repeat opioid analgesic prescription [aOR: 2.52 (95%CI: 1.1 – 6.2)] compared to those without (**Table 2**). All other covariates were not statistically significantly associated with receipt of a repeat prescription. The findings were consistent in all sensitivity analyses.

3.4.3. Sensitivity Analysis on follow-up duration:

After reducing the time period for repeat opioid prescription identification from 30 days since the end of the incident opioid analgesic prescription to 20 days and 10 days, the total number of repeat opioid prescription recipients reduced to 1,570 (9.2%) and 1,270 (7.4%) respectively. However, the likelihood of receiving a repeat opioid analgesic prescription remained comparable across children with various initial opioid prescription durations **(Table 3)**.

3.4.4. Subgroup analyses on, children undergoing outpatient surgical procedures, children experiencing traumatic injury and children undergoing orthopedic surgeries:

Consistent with the findings obtained in the main analysis, the duration of initial opioid analgesic was not statistically significantly associated with the receipt of a repeat opioid in the

subgroup of children undergoing outpatient surgical procedures, traumatic injury and orthopedic surgeries (**Table 2)**.

3.4.5. Covariates:

In the main as well as the subgroup analyses, older children were slightly more likely to receive a repeat prescription compared to their younger counterparts [aOR range: 1.08 – 1.16]. Children and adolescents belonging to Asian [aOR range: 0.26 – 0.79], Hispanic [aOR range: 0.28 – 0.58], Non-Hispanic Black [aOR range: 0.56 – 0.84] and Unknown race/ethnicity [aOR range: 0.35 – 0.61] had a lower likelihood of receiving a repeat prescription compared to Non-Hispanic Whites **(Table 2)**.

4. Discussion.

Our study findings suggest that one opioid prescription may have provided sufficient analgesia for vast majority (90%) of children and adolescents who have experienced acute pain. Only ~10% of the study cohort filled a repeat opioid prescription. The duration of initial opioid analgesic prescribed was not associated with the receipt of a repeat opioid analgesic prescription. Specifically, children who received an incident opioid analgesic prescription with very short initial duration (1 to 3 days' supply), did not have a higher risk of receiving a repeat prescription as compared to those who received an initial prescription with short, moderate, and long initial durations.

A potential explanation for the finding could be that, regardless of the duration of initial opioid prescription, for most patients, sufficient analgesia may be achieved by an opioid prescription not exceeding 3 days and the leftover opioid prescriptions could potentially remain unused. In fact, several published studies, including one conducted within the Texas Children's Health Care system, have shown that opioid analgesics prescribed for a longer duration (in the

excess of 15 – 20 pills or >3 – 4-day supply) remain unused in a majority of patients with acute pain or those undergoing outpatient surgical procedures.[46-50] Based on the National Survey on Drug Use and Health (NSDUH) as well as previous studies, it was identified that these unused leftover opioid analgesics could be used for other non-pharmacological purposes leading to misuse and abuse as well as pose a potential for diversion.[49, 51-54]

Consistent with the findings of the main analysis conducted on all children receiving an incident opioid prescription, we have also found that the initial prescribing duration was also not associated with the receipt of a repeat opioid analgesic prescription among sub-cohorts of children who underwent outpatient surgical procedures, orthopedic surgery and traumatic injury respectively. These patient subgroups were selected because they were either the subgroups that are perceived to have more severe pain and require longer pain management than other acute pain conditions (e.g., back pain, musculoskeletal pain, generalized pain), or were identified in the main analysis as the diagnoses associated with higher risk of repeat opioid prescription. The finding could be explained by the fact that the exact intensity of pain and the concurrent duration of opioid analgesic prescribing are difficult to predict. Pain varies from individual-to-individual based on nociceptive stimulus, age and previous pain experience.[21] The study by Ferland et al., (2018) acknowledges the challenge that as a result of interpatient variability in pain intensity in pediatric population, clinicians are constantly faced with the challenge of determining the optimal duration of analgesic treatment.[21]

In the main, sensitivity, and subgroup analyses, the factor most significantly associated with patient likelihood of receiving a repeat opioid prescription was patients' race/ ethnicity. Children belonging to Asian, Hispanic, Non-Hispanic Black and Unknown race were ~50% less likely to receive a repeat opioid compared to their Non-Hispanic White counterparts. Previous

studies have indicated that the differential prescribing of opioid analgesics in children could be multi-factual. One of the potential reasons is the caregivers' influence on the prescribing physician in prescribing controlled substances such as opioid analgesics since different caregivers from different racial/ethnic backgrounds view their child's pain differently.[55-59] Another reason indicated in previous studies is the differential prescribing of opioid analgesic by physicians for non-white populations compared to white populations for similar pain profiles because the physicians react differently to the pain in Black and Hispanic population compared to White population indicative of physicians' implicit bias.[33, 34, 60] Further studies are required to assess the physician perception on prescribing of opioids to children of various racial/ethnic backgrounds.

Our results have also confirmed the findings from previous studies that physician experience, education, age as well as the years in practice[61-63], and the age of patient significantly influence opioid prescribing behavior of physicians.[63] The multilevel models showed that more than 20% of variances in receiving a repeat opioid prescription in the study cohort were explained by various characteristics and prescribing behaviors across prescribers, and older children were more likely to receive of a repeat opioid analgesic than the younger ones across the main as well as the subgroup analyses.

Our study findings are significant because it provides evidence to support the opioid prescribing limits currently implemented in Texas[64] and more than 35 other states.[65] It suggests that the opioid prescribing limits, even the most strict ones, are unlikely to cause an increasing number of pediatric patients requiring a repeat opioid prescription. Instead, the state prescribing limits could reduce the unnecessary pediatric exposure to opioids as has been found in adults.[10, 11, 14, 64]

Our study has several limitations. First, by utilizing a claims database, our study does not include a direct measure for pain intensity that could potentially confound the association between the duration of the initial prescription and the risk of receiving a repeat prescription. We believe this potential unmeasured confounding is unlikely to change our conclusion given that, patient diagnoses and procedures can be seen as a surrogate for the measurement of pain intensity. As we observed in the data, majority of children who underwent outpatient surgical procedures received high and moderate duration of opioid prescriptions than those who received any other diagnoses and procedures. Furthermore, we have conducted an e-value estimation which is used to assess the *"minimum strength of association that an unmeasured confounder would need to have with both the exposure and the outcome to fully explain away a specific exposure-outcome association conditional on the measured covariates."*[66] A large e-value would imply considerable unmeasured confounding exists and the unmeasured confounder would be needed to explain away the current effect estimate. A small e-value implies little unmeasured confounding and thus the model is relatively robust even without the presence of the unmeasured confounder to explain away the current effect estimate. An e-value of 1 indicates no unmeasured confounding. The possibility that presence of pain severity (unmeasured confounder) could have potentially shifted the odds ratios for the low, moderate and high initial opioid durations to below 1 with respect to very low initial opioid duration as the reference are highly unlikely because the e-value estimate for each of these three groups was 1.32, 1.72 and 1.40 respectively. Our e-value calculation suggests that the effect of the unmeasured confounder is weak and that the covariates controlled for in our model were robust enough to explain the exposure-outcome effect estimates. Therefore, in conclusion, absence of pain severity does not have a significant impact on our study findings, and they are relatively accurate. Secondly, by utilizing a Medicaid

Managed Care database, the generalizability of our findings are restricted to children from a less affluent socioeconomic background and are not translatable to children enrolled in commercial insurance.

5. Conclusion.

Nearly 10% of the children receiving an incident opioid prescription for acute pain received a repeat opioid prescription within a month since the initial opioid prescription. Initial opioid prescription duration was not associated with the likelihood of receiving a repeat opioid prescription. The receipt of a repeat opioid prescription is associated with children age, race/ethnicity, and variations in prescribers' prescribing behaviors. Future studies are needed to specifically understand the appropriate initial opioid duration for these patient subgroups.

6. References

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7. Tables.

Table 1. *Sociodemographic, clinical and prescriber characteristics for opioid analgesic recipients stratified by duration of initial opioid analgesic prescription categories.*

	Very low initial duration (1 – 3 days) N = 6,272	**Low initial duration (4 – 7 days) N = 8,442**	**Moderate initial duration (8 – 10 days) N = 1,434**	**High initial duration (> 10 days) N = 938**	
Characteristics	**n (n/N%)**	**n (n/N%)**	**n (n/N%)**	**n (n/N%)**	**p-value**
Demographics					
Age (Mean ± SD)	11.7 ± 4.7	10.8 ± 4.9	9.8 ± 4.9	8.2 ± 4.9	<0.001*
Gender					
Female vs. Male	3,110 (49.6)	4,232 (50.2)	717 (50.0)	440 (46.9)	0.30
Race					
Alaskan American	25 (0.4)	33 (0.4)	3 (0.2)	1 (0.1)	0.39
Asian	100 (1.6)	160 (1.9)	16 (1.1)	13 (1.4)	0.12
Non-Hispanic Black	1,043 (16.6)	1,278 (15.1)	193 (13.4)	131 (13.9)	0.004*
Non-Hispanic White	1,024 (16.3)	1,291 (15.3)	247 (17.2)	139 (14.8)	0.12
Hispanic	3,612 (57.6)	4,959 (58.7)	840 (58.6)	538 (57.4)	0.51
Unknown	468 (7.5)	721 (8.5)	135 (9.4)	116 (12.4)	<0.001*
Medicaid Eligibility					
Medicaid vs. CHIP[a]	5,544 (88.4)	7,390 (87.5)	1,264 (88.2)	829 (88.4)	0.44
Prescriber Specialty					
Dentists	1,738 (27.7)	2,263 (26.8)	227 (15.8)	164 (17.5)	<0.001*
Emergency Room (ER) Physicians	1,361 (21.7)	1,339 (15.9)	169 (11.8)	59 (6.3)	<0.001*
Obstetricians and Gynecologists	100 (1.6)	188 (2.2)	18 (1.3)	7 (0.8)	<0.001*
Other Specialists	177 (2.8)	243 (2.9)	56 (3.9)	31 (3.3)	0.14
Physician Assistant	163 (2.6)	163 (1.9)	43 (3.0)	10 (1.1)	0.001*
Primary Care Physicians (PCP)	954 (15.2)	1,047 (12.4)	192 (13.3)	140 (14.9)	<0.001*
Surgical Specialists (Surgeons)	1,779 (28.4)	3,199 (37.9)	729 (50.8)	527 (56.2)	<0.001*
Procedures and Diagnoses					
Abdominal Pain	213 (3.4)	270 (3.2)	33 (2.3)	18 (1.9)	0.025*
Back pain and/or back disorders	73 (1.2)	83 (1.0)	12 (0.8)	16 (1.7)	0.15
Dental Surgery/Procedure	1,738 (27.7)	2,263 (26.8)	227 (15.8)	164 (17.5)	<0.001*
General infections	153 (2.4)	177 (2.1)	27 (1.9)	17 (1.8)	0.33
Generalized Pain	68 (1.1)	61 (0.7)	9 (0.6)	4 (0.4)	0.034*
Headache and Migraines	76 (1.2)	100 (1.2)	23 (1.6)	9 (1.0)	0.50
Musculoskeletal pain	151 (2.4)	142 (1.7)	36 (2.5)	23 (2.5)	0.008*
Outpatient Surgery/Procedure	1,795 (28.6)	2,864 (33.9)	649 (45.3)	475 (50.6)	<0.001*
Respiratory infections	254 (4.1)	313 (3.7)	52 (3.6)	24 (2.6)	0.15
Traumatic injury	1,720 (27.4)	2,136 (25.3)	361 (25.2)	185 (19.7)	<0.001*

*indicates statistically significant difference at $p < 0.05$ [a]CHIP: Children's Health Insurance Program

Table 2. *Adjusted association between initial opioid analgesic duration and likelihood of receiving repeat opioid analgesic prescription (Main Findings and Subgroup Findings).*

	Main Analysis		**Subgroup Analysis - Outpatient procedure**		**Subgroup Analysis - Traumatic injury**		**Subgroup Analysis - Outpatient procedure (Orthopedic Surgery)**	
Primary Exposure	Adjusted Odds Ratio*	95% Confidence Intervals	Adjusted Odds Ratio†	95% Confidence Intervals	Adjusted Odds Ratio††	95% Confidence Intervals	Adjusted Odds Ratio††	95% Confidence Intervals
Initial Opioid Analgesic Duration[a]								
Very low initial duration (1 – 3 days' supply)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Low initial duration (4 – 7 days' supply)	0.98	0.87 – 1.11	0.97	0.75 – 1.24	0.94	0.77 – 1.15	0.81	0.39 – 1.67
Moderate initial duration (8 – 10 days' supply)	1.03	0.83 – 1.27	0.93	0.64 – 1.35	0.85	0.58 – 1.24	1.12	0.39 – 3.15
High initial duration (> 10 days' supply)	0.85	0.65 – 1.13	0.89	0.61 – 1.27	1.13	0.71 – 1.79	0.62	0.14 – 2.78
Age	1.11**	1.10 – 1.13	1.09**	1.07 – 1.13	1.08**	1.06 – 1.11	1.16**	1.06 – 1.28
Race								
Non-Hispanic White	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Asian	0.52**	0.34 – 0.80	0.26**	0.11 – 0.61	0.79**	0.38 – 0.89	0.11	0.09 – 1.29
Hispanic	0.44**	0.39 – 0.51	0.29**	0.22 – 0.38	0.58**	0.38 – 0.74	0.28**	0.12 – 0.67
Non-Hispanic Black	0.75**	0.64 – 0.88	0.65**	0.47 – 0.90	0.84**	0.64 – 0.93	0.56**	0.21 – 0.97
Unknown	0.59**	0.47 – 0.74	0.35**	0.23 – 0.53	0.61**	0.40 – 0.94	0.31	0.09 – 1.06
Traumatic injury (yes vs. no)	2.52**	1.04 – 6.15	N/A	N/A	N/A	N/A	N/A	N/A
Outpatient Procedure Type								
Adenotonsillectomy	N/A	N/A	Ref.	Ref.	N/A	N/A	N/A	N/A
Appendectomy	N/A	N/A	0.51	0.21 – 1.26	N/A	N/A	N/A	N/A
Circumcision	N/A	N/A	0.98	0.87 – 2.43	N/A	N/A	N/A	N/A
Inguinal Hernia Repair	N/A	N/A	1.28	0.73 – 3.29	N/A	N/A	N/A	N/A
Orthopedic Surgeries	N/A	N/A	2.91**	1.25 – 6.73	N/A	N/A	N/A	N/A
Other surgery/procedures	N/A	N/A	1.54	0.69 – 3.45	N/A	N/A	N/A	N/A
Wound Repair	N/A	N/A	2.29	0.90 – 5.85	N/A	N/A	N/A	N/A

*Adjusted for age, gender, race/ethnicity, Medicaid eligibility, and procedures and diagnoses.

**Indicates statistical significance at $p < 0.05$

[a] Duration of outcome identification period: 30 days from the end of index opioid analgesic fill.

†Adjusted for age, gender, race/ethnicity, Medicaid eligibility, and type of outpatient procedures

††Adjusted for age, gender, race/ethnicity, and Medicaid eligibility

‡All other covariates are not statistically significantly associated with the receipt of repeat opioid prescription (outcome).

Table 3. *Adjusted association between initial opioid analgesic duration and likelihood of receiving repeat opioid analgesic prescription (Sensitivity Analysis).*

Primary Exposure	Adjusted Odds Ratio*	95% Confidence Intervals
Initial Opioid Analgesic Duration[a]		
Very low initial duration (1 – 3 days' supply)	Ref.	Ref.
Low initial duration (4 – 7 days' supply)	0.99	0.87 – 1.12
Moderate initial duration (8 – 10 days' supply)	1.05	0.85 – 1.31
High initial duration (> 10 days' supply)	0.77	0.57 – 1.05
Initial Opioid Analgesic Duration[b]		
Very low initial duration (1 – 3 days' supply)	Ref.	Ref.
Low initial duration (4 – 7 days' supply)	0.98	0.85 – 1.12
Moderate initial duration (8 – 10 days' supply)	1.07	0.85 – 1.35
High initial duration (> 10 days' supply)	0.77	0.56 – 1.07

[a] Duration of outcome identification period: 20 days from the end of index opioid analgesic fill.

[b] Duration of outcome identification period: 10 days from the end of index opioid analgesic fill.

*Covariates: Older age and traumatic injury diagnosis are positively associated with receipt of repeat opioid analgesic whereas female gender, and persons belonging to Asian, Hispanic, Non-Hispanic Black and Unknown race/ethnicity are negatively associated with receipt of repeat opioid analgesics. All other covariates are not statistically significantly associated with the outcome.

8. Figures

Figure 1. Consort diagram representing cohort development and outcome identification.

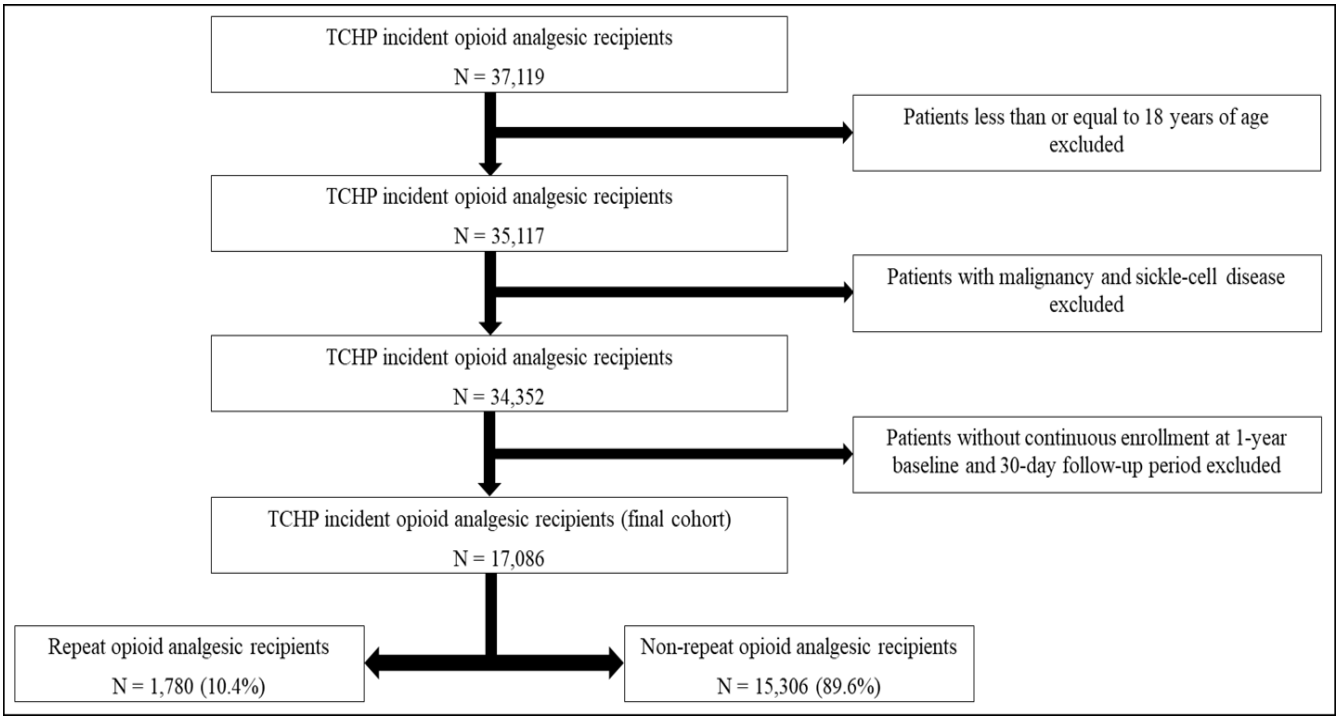

Figure 2. Distribution of initial opioid analgesic duration for repeat opioid prescription recipients.

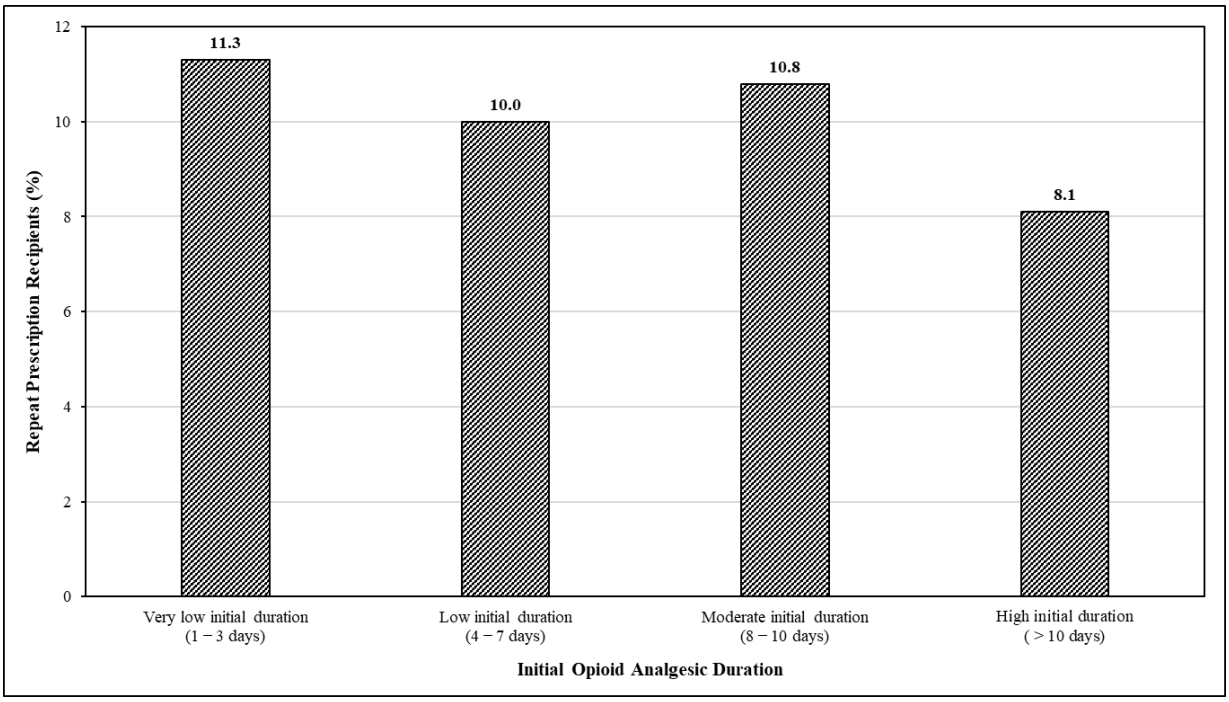

Figure Legend.
The above figure represents the repeat opioid prescription recipients as a proportion of individuals receiving initial opioid analgesic in each opioid analgesic duration category.

Appendix

Appendix Table 1. Risk factors for repeat opioid analgesics in children based on the Andersen Behavioral Model[36, 37].

Type of external factors	Covariates in the study
Predisposing factors (Exist prior to treatment)	Patient demographics (age, gender, race/ethnicity)
	Medicaid eligibility categories (Medicaid and CHIP)
Enabling factors (Constitute an individual's ability to secure health services)	Prescriber specialty
Need factors (Explain an individual's health status or diagnosis that necessitates healthcare intervention)	Medical diagnoses and outpatient procedures as indications leading to receipt of pain medications

9. Appendix.

Scoring Algorithm[38].

According to the algorithm, the priority was given to procedures and diagnoses closest to the index opioid prescription (temporal proximity) as well as to indications with stronger association with the analgesic prescription (procedure over diagnosis). For instance, during this identification process, if a patient received two diagnosis/ procedures on the same day, one for a surgical procedure and another for respiratory infection, the surgical procedure was considered as the more probable indication for the receipt of an analgesic prescription based on the pre-determined indication priority (**eTable 2**). An additional correction was applied to a small number of records (less than 5%) wherein if the high-priority indication was immediately preceding the low-priority indication (within a span of less than a week) then the high-priority indication was considered the more probable indication. For example, consider the index prescription date as day 0 and respiratory infection diagnosis (low-priority indication) on day 4 preceding the index date and trauma diagnosis (high-priority indication) on day 6 preceding the index date, then based on the correction the trauma diagnosis was the attributable indication for the analgesic prescription.

Appendix Table 2. Priority rating for medical diagnoses and outpatient procedures.

Indication	Priority
Outpatient surgery/procedure	1
Trauma	2
Dental surgery/procedure	3
Back pain	4
Musculoskeletal pain	5

Abdominal pain	6
Headache and Migraines	7
Generalized pain	8
Respiratory infections	9
Other infections	10

Appendix References.

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DISSERTATION AIM 2. Pain associated service utilization following the initial analgesic prescription in children and adolescents undergoing outpatient surgical procedures

Abstract

Objectives:

Our study examined the association between outpatient post-surgical analgesic prescription and risk of insufficiently managed pain such as additional analgesic dispensing and pain-associated hospital admission and ER visit.

Methods:

Eligible individuals were children and adolescents between 1 – 17 years of age who were enrolled in a large Medicaid Managed Care plan and filled an incident analgesic following an outpatient surgery during 2013 to 2018. An incident analgesic prescription was defined as receipt of an opioid or non-opioid analgesic with no prior use of the medication for a period of 12 months. Pain associated service utilizations from the dispensing of incident analgesic prescription to 30 days following the end of the prescription were measured as (1) additional analgesic dispensing, and (2) pain-associated hospital admission or ER visit. A hierarchical multivariable logistic regression model with patients nested under prescribers was fitted to test the association between incident analgesic prescription and risk of having additional pain-related service utilization.

Results:

Of 13,678 children meeting the inclusion criteria, 5,783 (42.3%) received an incident opioid and 7,895 (57.7%) received an incident non-opioid analgesic prescription respectively. There were15% patients in both opioid and non-opioid groups had additional pain-related service encounters. The multilevel model indicated that initial opioid analgesic recipients were two times

more likely than non-opioid analgesic recipients to receive an additional analgesic dispensing [aOR: 2.33 (95% CI: 2.0 – 2.8)] and 60% less likely of having a pain-associated hospital admission or ER visit [aOR: 0.41 (95% CI: 0.3 – 0.5)].

Conclusion:

Majority (85%) of post-surgical patients have their pain sufficient managed by initial analgesic. In the 15% of patients with insufficiently managed pain, those initiated on opioid analgesics are more likely to receive additional analgesics, while those initiated on non-opioid analgesics are more likely to have pain-associated ER visits and hospital admissions.

1. Introduction.

Children and adolescents frequently receive opioid analgesics for post-surgical pain in the outpatient setting. It is often the first occasion for opioid-naïve children to get exposed to opioids. Early opioid use in children has been found to be associated with increased risk of future misuse.[8, 9]

To reduce pediatric opioid exposure as a postoperative analgesic, a new set of guidelines were published in February 2021 recommending the use of non-opioid combination therapies for some commonly conducted pediatric surgical procedures.[15]

Among pediatric surgical procedures for which the opioid-free recovery is recommended, the evidence supporting the use of non-opioid analgesics as the first-line treatment for post-operative pain is the strongest for adenotonsillectomy. A randomized controlled trial by Kelly et al., (2015) on 91 children found that acetaminophen plus ibuprofen led to similar reduction in pain scores as acetaminophen plus morphine on Day 1 and Day 5 after the surgery.[67] A single-center prospective observational study by Walrave et al. (2018) has also reported that the combination of acetaminophen plus ibuprofen was as effective as acetaminophen plus tramadol in reducing post-operative pain scores in children undergoing tonsillectomy.[16]

Empirical data are also available to support the possibility of opioid-free recovery for appendectomy[17], orthopedic procedures[18] and inguinal hernia repair.[19, 20] These evidences, however, are not head-to-head trials involving a direct comparison between opioid and non-opioid analgesics. Instead, the comparisons were made between non-opioids (e.g., NSAIDs) vs. placebo (e.g., saline) on the future risk of requiring rescue opioids during the 24 – 48 hours post-surgery.

It is important to note that nearly all existing trials were conducted on inpatients, and the intravenous (IV), intramuscular (IM) and subcutaneous (SC) opioid or non-opioid analgesics were used in these studies.[17-20] In real world practice, however, most pediatric surgical procedures are provided in outpatient setting. The most used pain management modalities are oral opioid and non-opioid analgesics.

Moreover, the existing pediatric trials followed patients ranging from 24-hrs to a few days since the surgery, which may not be sufficiently long to capture the consequences of unmanaged pain. Literature has reported that if acute pain is not controlled effectively, it may lead to unmanaged pain and further to chronic post-surgical pain (CPSP) that could last longer than 2 months post-procedure.[21-25] This would not only require longer term exposure to analgesics but may also result into additional pain related service utilizations including ER visits and hospital admissions. The only pediatric study examining these outcomes was a retrospective case series study by Bedwell et al. (2014) which inferred that for children undergoing tonsillectomy, there was no difference in the risk of pain associated ER visit when comparing the recipients of acetaminophen plus ibuprofen vs. acetaminophen plus codeine.[68]

Our study aimed at examining the association between receipt of incident opioid vs. non-opioid analgesic following an outpatient surgical procedure and the risk of having additional pain related service utilization by the initial analgesic modality. We hypothesized that the likelihood of having a service utilization such as additional analgesic dispensing, hospital admission, or Emergency Room (ER) visit associated with pain is comparable among children and adolescents initiated on opioid vs. non-opioid analgesic following an outpatient surgery.

2. Methods.

2.1. Data Sources.

The study utilized the claims data of Texas Children's Health Plan (TCHP), a Medicaid Managed Care founded by Texas Children's Hospital. The health plan offers Medicaid and CHIP to over 20 counties across Southeast Texas. We extracted the de-identified data between January 1, 2013 and December 31, 2018 comprising of patient sociodemographic (age, gender, race/ethnicity, Medicaid eligibility and member enrollment information), medical claims (outpatient service utilizations such as diagnoses and procedures), and pharmacy claims (outpatient prescription dispensing and prescriber specialty).

2.2. Study design

2.2.1. Design, and follow-up period

The study utilized a retrospective cohort design to assess the risk of having pain-associated service utilizations such as additional analgesic dispensing and hospital admission and Emergency Room (ER) visits in patients who received an opioid or a non-opioid analgesic for pain management after an outpatient surgical procedure. The study design included a 12-month baseline period prior to the incident analgesic dispensing, and an outcome identification period starting from the incident analgesic dispensing to 30 days after the end of the incident analgesic (days' supply of the index analgesic prescription + 30 days) (**Figure 1**). The 12-month baseline period was imposed to ensure that an incident analgesic cohort was captured. The follow up period ranging from 31 days to up to two months which was determined based on 1) previous reports on the time to chronic post-surgical pain (CPSP) that could last 2 to 3 months post-procedure;[21-25] and 2) the maximum day supply of the incident analgesic prescription (30-day supply) plus an additional 30 days of allowable period for the identification of additional pain-related service utilization.

1.3. Patient Cohort Development.

1.3.1. Inclusion and Exclusion Criteria:

The study included children 1 to 17 years of age enrolled in the TCHP between January 1, 2013 to December 31, 2018 with receipt of an incident opioid or non-opioid analgesic prescription within 10 days following an outpatient surgical procedure based on a previous study.[38] Incident use was defined as receipt of an opioid or non-opioid analgesic with no prior use of this medication for a period of 12 months. Generic Product Identifier (GPI) codes were used to identify prescription opioids such as codeine, hydrocodone and tramadol; and non-opioid analgesics such as acetaminophen, aspirin, ibuprofen, ketoprofen, naproxen, ketorolac, indomethacin, etodolac and meloxicam.

Patients who did not fulfil the continuous enrollment criteria of 12-month period (baseline) before and 30-day period (follow-up) after the end of the incident opioid or non-opioid analgesic (index date + days' supply) were excluded from the study sample. Furthermore, children and adolescents with a diagnosis of malignancy and sickle-cell disease (SCD) during the study period were excluded from the cohort.

1.3.2. Outcome Assessment:

Pain associated service utilizations anytime during the outcome identification period (index date + days' supply + 30 days) were measured as (1) *Additional analgesic dispensing* defined as receipt of an additional opioid or a non-opioid analgesic, and (2) *Hospital admission or ER visit associated with pain indications* such as post-procedural pain, abdominal pain, back pain, limb & joint pain and pelvic pain. This outcome measure was defined as a hospital

admission or an Emergency Room (ER) visit with a primary pain diagnosis medical claim as identified using ICD-9-CM, ICD-10 codes.

1.3.3. Primary Exposure:

The primary exposure of interest was the receipt of an incident opioid or a non-opioid analgesic.

1.3.4. Covariates:

The study controlled for patient and prescriber characteristics that could potentially confound the association between incident analgesic receipt and risk of insufficiently managed pain. These factors were identified based on the conceptual framework of the Andersen Behavioral Model.[36, 37] Predisposing factors such as age, gender, race/ethnicity and Medicaid eligibility are present prior to the treatment. Enabling factors such as provider specialty constitute an individual's ability to secure health services. Need factors such as type of outpatient surgical procedure provide insight into the individual's health status.

2.4. Statistical Analysis.

Accounting for the hierarchical structure of the data with patients nested within providers, a random intercept fixed effects multilevel modeling approach[39-41] was utilized to account for the inter-cluster (between provider) variation and intra-cluster (within provider) correlation in the multivariable model.[42-44] An Intraclass Correlation Coefficient (ICC) was calculated to ascertain the need for using a multilevel model.[42, 45]

A hierarchical multivariable logistic regression model was fitted to test the association between receipt of incident opioid or non-opioid analgesic and (1) Additional analgesic dispensing (2) Hospital admission or ER visit associated with pain. Adjusted Odds Ratios (aORs)

and 95% Confidence Intervals (CIs) were estimated at a statistical significance of $\alpha = 0.05$. All statistical analyses were conducted using SAS Enterprise Guide 8.1 (SAS Institute, Cary, NC) statistical software.

2.5. Sensitivity Analysis:

For sensitivity analysis, we tested the robustness of the findings by reducing the follow up period to 20 days and 10 days respectively.

2.6. Ethic Statement:

The University of Houston and Baylor College of Medicine's Institutional Review Board (IRB) approved the study and granted a waived informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

3. Results.

3.1. Cohort Characteristics.

We identified 29,384 TCHP enrollees undergoing an outpatient surgery/procedure and receiving an incident opioid or non-opioid analgesic dispensing during 2013 to 2018. After excluding individuals 18 years of age or older (N = 26,217), those diagnosed with malignancy and sickle-cell disease (N = 25,561), and those who did not have continuous enrollment 12 months prior to and 30 days after the end of incident opioid or non-opioid analgesic dispensing, the final cohort comprised of 13,678 incident opioid or non-opioid analgesic recipients who underwent an outpatient surgical procedure. Of these 5,783 (42.3%) received an incident opioid analgesic and 7,895 (57.7%) received an incident non-opioid analgesic (**Figure 2**). The average duration (SD) of the incident opioid analgesic prescription was 5.7 (4.0) days with a median

(IQR) of 5 (4) days and average duration (SD) of incident non-opioid analgesic was 7.7 (6.0) days with a median (IQR) of 6 (5) days.

3.2. Descriptive statistics by incident analgesics (Table 1).

Majority of the study cohort were males (55.0%), Hispanics (61.3%), and enrolled in Medicaid (88.1%). As compared to non-opioid analgesic recipients, opioid recipients were relatively older (mean (SD): 10.5 (10.3) years vs. 8.5 (4.9) years, p <0.001), and had a slightly lower proportion of Non-Hispanic White recipients (N = 885; 11.2%) compared to the opioid group (N = 816; 14.1%) (p<0.001). The duration of incident opioid prescriptions [mean (SD): 5.7 (4.0) days] were shorter compared to the incident non-opioid analgesic prescription [mean (SD): 7.7 (6.0) days] (p<0.001).

There were 88% of the incident opioid and 81% of incident non-opioid analgesic prescriptions prescribed by surgical specialists (p<0.001). Opioid analgesics were used more frequently than non-opioid analgesics among children who underwent adenotonsillectomy (30% vs. 24.5%; p<0.001) and orthopedic surgeries (11% vs. 6%; p<0.001)

3.3. Additional analgesic dispensing (Outcome 1) **(Table 2).**

Within the outcome identification period (**Figure 1**), 689 (11.9%) of the 5,783 incident opioid analgesic recipients and 529 (6.7%) of the 7,895 incident non-opioid analgesic recipients filled an additional analgesic prescription. Among those who filled an additional analgesic prescription, 510 (74%) of incident opioid recipients and 347 (68%) of the incident non-opioid analgesic recipients continued their initial analgesic medications, while the others changed their analgesic modality either from opioids to non-opioids or vice versa.

After reducing the outcome identification period for additional analgesic dispensing from 30 days from the end of incident analgesic dispensing to 20 days and 10 days, the total

number of additional analgesic recipients reduced slightly to 606 (10.5%) in the initial opioid group and 446 (5.7%) in the initial non-opioid group at 20 days and to 498 (8.6%) in the initial opioid group and 342 (4.3%) in the initial non-opioid group at 10 days respectively.

3.4. Hospital admission and Emergency Room (ER) visit patients (Outcome 2) **(Table 2).**

Other than the individuals filling a subsequent analgesic prescription, 197 (3.4%) of the incident opioid analgesic recipients and 645 (8.2%) of the incident non-opioid analgesic recipients had either a hospital admission or an ER visit associated with pain. Of these 197 patients, 144 (2.4%) had an ER visit and 53 (0.9%) had a hospital admission. Of the 645 patients, 507 (6.4%) had an ER visit and 138 (1.8%) had a hospital admission. (Refer to Appendix Tables 1 and 2 for pain indications)

The total number of hospital admissions or ER visit recipients reduced to 168 (2.9%) in the initial opioid group and 520 (6.6%) in the initial non-opioid group at 20 days and to 122 (2.1%) in the initial opioid group and 381 (4.8%) in the initial non-opioid group at 10 days respectively.

3.5. Multilevel model analysis on the association between initial opioid vs. non-opioid analgesic and receipt of an additional analgesic dispensing (Outcome 1) or hospital admission or an ER visit associated with pain (Outcome 2)

3.5.1. Intraclass Correlation Coefficient (ICC) Estimation.

The Intraclass Correlation Coefficient (ICC) for the unconditional model was 17.0% (ICC = 0.170, p-value < 0.001) for the comparison on additional analgesic dispensing (outcome 1) and 9.4% (ICC = 0.094, p-value < 0.001) on hospital admission or ER visit (outcome 2) which indicated that approximately 17% of the variance in the receipt of an additional analgesic dispensing (outcome 1) and approximately 9% of the variance in hospital admission or ER visit

(outcome 2) were explained by variations across providers and therefore the study warranted the utilization of a multilevel model.

3.5.2. Multivariable Analyses.

Findings of the two multivariable logistic regression models indicate that initial opioid analgesic recipients were over two times more likely than non-opioid analgesic recipients to receive an additional analgesic dispensing [aOR: 2.33 (95% CI: 2.0 – 2.8)] (**Table 3**), and 60% less likely of having a hospital admission or ER visit associated with pain [aOR: 0.41 (95% CI: 0.3 – 0.5)] (**Table 4**) during an up to two months period since the index analgesic dispensing.

3.5.3. Sensitivity Analysis:

After reducing the outcome identification period, the likelihood of receiving an additional analgesic remained significantly higher for patients initiated on opioid vs. non-opioid analgesic [aOR: 2.52 (95% CI: 2.1 – 3.0)] at 20 days, [aOR: 2.89 (95% CI: 2.4 – 3.6)] and at 10 days respectively (**Table 3**), and the likelihood of a hospital admission or ER visit was significantly lower for patients initiated on opioid vs. non-opioid analgesic [aOR: 0.44 (95% CI: 0.4 – 0.5)] at 20 days and [aOR: 0.43 (95% CI: 0.3 – 0.5)] at 10 days respectively. (**Table 4**)

3.5.4. Covariates:

In the main analysis, children belonging to Non-Hispanic Black race [aOR: 0.72 (95% CI: 0.6 – 0.9)], Hispanic race [aOR: 0.60 (95% CI: 0.5 – 0.7)] and other race/ethnicity [aOR: 0.65 (95% CI: 0.5 – 0.8)] were significantly less likely to receive an additional analgesic dispensing compared to their Non-Hispanic White counterparts. Similarly, children belonging to Non-Hispanic Black race [aOR: 0.74 (95% CI: 0.6 – 0.9)] and Hispanic race [aOR: 0.61 (95% CI: 0.5 – 0.8)] were significantly less likely to have a hospital admission or an ER visit associated with pain compared to their Non-Hispanic White counterparts.

The risk of having additional pain associated service utilization varied significantly across procedures. As compared to children having other procedures, those undergoing inguinal hernia repair and orthopedic surgeries had 36% and 71% higher risk of requiring an additional analgesic prescription respectively, and those undergoing adenotonsillectomy had 71% higher risk of pain related hospital admission or an ER visit (**Tables 3 and 4**).

4. Discussion.

Our study findings suggest that for majority (85%) of the patients undergoing surgical procedures, additional service associated with pain was not required beyond the initial analgesic prescription regardless of the analgesic modality. The finding is consistent with the existing clinical trial results regarding the equal analgesic effects between opioid and non-opioid analgesics[16, 67, 68] and supporting the new guideline recommendations of an opioid-free recovery (recommendation 8) and use of enteral (including oral) non-opioid analgesics such as NSAIDs (recommendation 11) for children underwent outpatient surgical procedures.[15]

Our study findings also indicate that, despite 15% children in both opioid and non-opioid groups requiring additional service associated with pain, the type of service encounter varied significantly between study groups, with a higher proportion of the opioid group (12%) receiving an additional analgesic prescription than the non-opioid group (7%), and a much larger percentage of the non-opioid group (8%) having a pain-related hospital admission or ER visit than the opioid group (3%).

Improving the detection of early sign of unmanaged pain among non-opioid analgesic recipients and providing timely intervention to prevent pain-related hospitalization and ER visit is of vital important in promoting the opioid-free recovery for pediatric procedures. Post-surgery hospital admissions and ER visits pose a significant burden to patients, caregivers, physicians,

and the health care system. Pain-related hospital admission and ER visit impairs the physical functioning as well as the quality of life of the patients,[69-71] increases patient and caregiver anxiety that could lead to pain catastrophizing,[72, 73] and poses additional financial burden to payers.

Previous studies showed that early detection of unmanaged pain following surgery could be achieved by dynamic post-surgical monitoring of pediatric patients. The study by Touyz and Marchand found in children receiving periodontal surgical procedures found that those who received a follow-up phone call required a lower number of subsequent analgesic pills compared to those who did not receive the phone call (4.7 pills per week vs. 15.7 pills per week). The study by Jones et al. focusing on adenotonsillectomy patients found that only 15.4% of all the patients receiving a post-operative follow-up call required a subsequent physician visit. These studies have indicated that post-procedure follow-up telephone calls to patients not only helps reduce pain but also reduces pain-related follow-up visits.[74, 75]

Our findings further suggest that timely augmentation using opioid analgesics is also important in preventing pain-related ER visit and hospital admission observed among non-opioid recipients. We found pain-related hospital admission or ER visit usually happened within a few days (range: -29 days – 7 days) following the completion of the index non-opioid analgesic prescription, and when a repeat analgesic prescription was prescribed, most non-opioid analgesic recipients continuously received the same non-opioid prescription (~4%), with only ~2% receiving an augmentation with opioid analgesics.

The importance of our study lies in the fact that it not only generates evidence to support the implementation new practice guideline, but also points out the potential unintended consequence of shifting the practice paradigm. Further research is warranted to identify and

implement optimal patient-focused pain management strategies in high-risk post-surgical patients initiated on non-opioid analgesics to reduce the unintended consequences.

Our study has a few limitations, firstly, our study population comprises of patients enrolled in Medicaid in the Southeast of Texas and since opioid analgesic prescribing trends vary across different regions[76], our findings may not be generalizable to other regions of United States. Secondly, receipt of an opioid or a non-opioid does not necessarily equate to consumption. Previous studies have indicated that parents' perception strongly influence receipt of opioids in children and many parents withhold use of opioids in children especially with the ongoing opioid epidemic.[56-58, 77] This may lead to pain remaining insufficiently managed in the patients initiated on an opioid analgesic. Future research is warranted to comprehensively measure pain scores in the post-procedural period that can help accurately guide the analgesic therapy in pediatric patients undergoing surgical procedures.

5. Conclusion.

Majority of the pediatric patients undergoing surgical procedures have their pain sufficiently managed, however, a small proportion (~15%) of patients require additional analgesic management. Patients initiated on opioid analgesics are more likely to receive additional analgesics, while those initiated on non-opioid analgesics are more likely to have pain associated ER visits and hospital admissions.

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7. Tables.

Table 1. Sociodemographic, clinical and prescriber characteristics for outpatient surgical procedure recipients stratified by incident opioid and non-opioid analgesic recipients.

	Incident Opioid recipients (N = 5,783)	**Incident Non-opioid recipients (N = 7,895)**	
Characteristics	**n (n/N%)**	**n (n/N%)**	**p-value**
Incident analgesic duration (mean ± SD)	5.7 ± 4.0	7.7 ± 6.0	<0.001*
Age (mean ± SD)	10.5 ± 10.3	8.5 ± 4.9	<0.001*
Gender			
Female	2,635 (45.5)	3,521 (44.6)	0.26
Male	3,148 (54.4)	4,374 (55.4)	
Race			
Hispanic	3,491 (60.4)	4,890 (61.9)	0.06
Non-Hispanic Black	732 (12.7)	936 (11.9)	0.16
Non-Hispanic White	816 (14.1)	885 (11.2)	<0.001*
Other races/ethnicities*	744 (12.9)	1,184 (15.0)	<0.001*
Medicaid Eligibility			
Medicaid	5,038 (87.1)	7,014 (88.8)	0.01*
CHIP	745 (12.9)	881 (11.2)	
Prescriber Specialty			
Emergency Room (ER) Prescriber	657 (11.4)	1,437 (18.2)	<0.001*
Surgical Specialist	5,126 (88.6)	6,458 (81.8)	<0.001*
Type of Procedure			
Adenotonsillectomy	1,744 (30.2)	1,933 (24.5)	<0.001*
Appendectomy	840 (14.5)	940 (12.0)	<0.001*
Circumcision	783 (13.5)	887 (11.2)	0.01*
Inguinal Hernia Repair	245 (4.2)	744 (9.4)	<0.001*
Orthopedic Surgeries	632 (10.9)	440 (5.6)	<0.001*
Other Surgery/Procedure**	1,054 (18.2)	1,861 (23.6)	<0.001*
Procedure on nail	132 (2.3)	281 (3.6)	0.01*
Wound Repair	191 (3.3)	270 (3.4)	0.08

*Other races/ethnicities include: Asian, Alaskan American and Unknown

**Other surgery/procedures include orchiopexy, myringotomy, burns

†CHIP: Children's Health Insurance Program

Table 2. Outcome distribution across opioid and non-opioid analgesic recipients

Outcome Measures	Opioid Recipients (N = 5,783)	Non-opioid Recipients (N = 7,895)
Main Findings[a]		
Additional analgesic recipients (Outcome 1)	689 (11.9%)	529 (6.7%)
Hospital Admission and ER visit recipients (Outcome 2)	197 (3.4%)	645 (8.2%)
Sensitivity Findings[b]		
Additional analgesic recipients (Outcome 1)	606 (10.5%)	446 (5.7%)
Hospital Admission and ER visit recipients (Outcome 2)	168 (2.9%)	520 (6.6%)
Sensitivity Findings[c]		
Additional analgesic recipients (Outcome 1)	498 (8.6%)	342 (4.3%)
Hospital Admission and ER visit recipients (Outcome 2)	122 (2.1%)	381 (4.8%)

[a] Duration of outcome identification period: 30 days from the end of incident analgesic fill (Main findings)
[b] Duration of outcome identification period: 20 days from end of incident analgesic fill (Sensitivity findings)
[c] Duration of outcome identification period: 10 days from the end of incident analgesic fill (Sensitivity findings)

Table 3. Adjusted association between incident opioid vs. non-opioid dispensing and additional analgesic dispensing (Main and Sensitivity Findings).

	Main Findings[a]	***Sensitivity Findings[b]***	***Sensitivity Findings[c]***
Predictor Characteristics	**Adjusted Odds Ratios (95% CI)**	**Adjusted Odds Ratios (95% CI)**	**Adjusted Odds Ratios (95% CI)**
Incident Analgesic Dispensed			
Opioid	2.33* (2.0 – 2.8)	2.52* (2.1 – 3.0)	2.89* (2.4 – 3.6)
Non-opioid	Ref.	Ref.	Ref.
Days' supply of incident analgesic prescriptions	0.99 (0.9 – 1.1)	1.00 (0.9 – 1.1)	1.01 (0.9 – 1.1)
Age	1.03* (1.0 – 1.1)	1.03* (1.0 – 1.1)	1.05* (1.0 – 1.1)
Gender			
Female	0.94 (0.8 – 1.1)	0.88 (0.7 – 1.1)	0.79 (0.7 – 1.1)
Male	Ref.	Ref.	Ref.
Race/ethnicity			
Hispanic	0.60* (0.5 – 0.7)	0.56* (0.5 – 0.7)	0.54* (0.4 – 0.7)
Non-Hispanic Black	0.72* (0.6 – 0.9)	0.66* (0.5 – 0.8)	0.72* (0.6 – 0.9)
Non-Hispanic White	Ref.	Ref.	Ref.
Other races/ethnicities[‡]	0.65* (0.5 – 0.8)	0.62* (0.5 – 0.8)	0.66* (0.5 – 0.9)
Medicaid Eligibility			
Medicaid	0.90 (0.8 – 1.1)	0.92 (0.8 – 1.1)	0.91 (0.7 – 1.1)
*CHIP***	Ref.	Ref.	Ref.
Type of outpatient procedure			
Adenotonsillectomy	1.03* (1.0 – 1.4)	1.14* (1.1 – 1.8)	1.18* (1.1 – 2.2)
Appendectomy	0.62* (0.5 – 0.8)	0.59* (0.4 – 0.8)	0.52 (0.4 – 0.7)
Circumcision	1.08* (1.0 – 1.4)	1.17* (1.1 – 1.5)	1.22* (1.1 – 2.1)
Inguinal Hernia Repair	1.36* (1.2 – 1.9)	1.40* (1.2 – 1.8)	1.58* (1.4 – 2.3)
Orthopedic Surgery	1.68* (1.3 – 2.1)	1.76* (1.4 – 2.2)	1.70* (1.3 – 2.2)
Other surgery/procedure[†]	Ref.	Ref.	Ref.
Procedure on nail	1.34 (0.9 – 1.7)	1.27 (0.9 – 1.9)	1.41 (0.9 – 2.2)
Wound Repair	1.30 (0.9 – 1.9)	1.32 (0.9 – 1.9)	1.53 (0.9 – 2.3)

*indicates statistical significance

**CHIP: Children's Health Insurance Program

‡Other races/ethnicities include: Asian, Alaskan American and Unknown

†Other surgery/procedures include orchiopexy, myringotomy, burns

[a] Duration of outcome identification period: 30 days from the end of incident analgesic fill (Main findings)

[b] Duration of outcome identification period: 20 days from end of incident analgesic fill (Sensitivity findings)

[c] Duration of outcome identification period: 10 days from the end of incident analgesic fill (Sensitivity findings)

Table 4. Adjusted association between incident opioid vs. non-opioid dispensing and hospital admission and ER visit (Main and Sensitivity Findings).

	Main Findings[a]	***Sensitivity Findings***[b]	***Sensitivity Findings***[c]
Predictor Characteristics	**Adjusted Odds Ratios (95% CI)**	**Adjusted Odds Ratios (95% CI)**	**Adjusted Odds Ratios (95% CI)**
Incident Analgesic Dispensed			
Opioid	0.41* (0.3 – 0.5)	0.44* (0.4 – 0.5)	0.43* (0.3 – 0.5)
Non-opioid	Ref.	Ref.	Ref.
Days' supply of incident analgesic prescriptions	1.10 (0.9 – 1.1)	1.00 (0.9 – 1.1)	0.99 (0.9 – 1.1)
Age	1.01 (0.9 – 1.1)	1.00 (0.9 – 1.1)	0.97 (0.9 – 1.1)
Gender			
Female	0.97 (0.9 – 1.1)	0.98 (0.8 – 1.2)	1.04 (0.8 – 1.2)
Male	Ref.	Ref.	Ref.
Race/ethnicity			
Hispanic	0.61* (0.5 – 0.8)	0.63* (0.5 – 0.8)	0.58* (0.5 – 0.7)
Non-Hispanic Black	0.74* (0.6 – 0.9)	0.80* (0.6 – 0.9)	0.62* (0.4 – 0.9)
Non-Hispanic White	Ref.	Ref.	Ref.
Other races/ethnicities‡	0.89 (0.7 – 1.1)	0.91 (0.7 – 1.2)	0.71 (0.5 – 1.2)
Medicaid Eligibility			
Medicaid	1.20 (0.9 – 1.5)	1.16 (0.9 – 1.5)	1.12 (0.8 – 1.5)
*CHIP***	Ref.	Ref.	Ref.
Type of outpatient procedure			
Adenotonsillectomy	1.71* (1.1 – 2.7)	2.02* (1.3 – 3.2)	1.81* (1.1 – 3.1)
Appendectomy	1.18 (0.9 – 1.5)	1.13 (0.9 – 1.5)	1.06 (0.8 – 1.5)
Circumcision	1.47 (0.9 – 1.5)	1.39 (0.9 – 1.7)	1.32 (0.8 – 1.4)
Inguinal Hernia Repair	1.34* (0.9 – 1.6)	1.28 (0.9 – 1.6)	1.25 (0.7 – 1.7)
Orthopedic Surgery	1.09 (0.8 – 1.6)	1.14 (0.8 – 1.7)	1.40 (0.9 – 2.2)
Other surgery/procedure†	Ref.	Ref.	Ref.
Procedure on nail	0.70 (0.4 – 1.3)	0.64 (0.3 – 1.3)	0.68 (0.6 – 1.4)
Wound Repair	0.89 (0.4 – 1.6)	0.76 (0.6 – 1.3)	0.60 (0.3 – 1.4)

*indicates statistical significance

**CHIP: Children's Health Insurance Program

‡Other races/ethnicities include: Asian, Alaskan American and Unknown

†Other surgery/procedures include orchiopexy, myringotomy, burns

[a] Duration of outcome identification period: 30 days from the end of incident analgesic fill (Main findings)

[b] Duration of outcome identification period: 20 days from end of incident analgesic fill (Sensitivity findings)

[c] Duration of outcome identification period: 10 days from the end of incident analgesic fill (Sensitivity findings)

8. Figures.

Figure 1. Study design diagram representing cohort development.

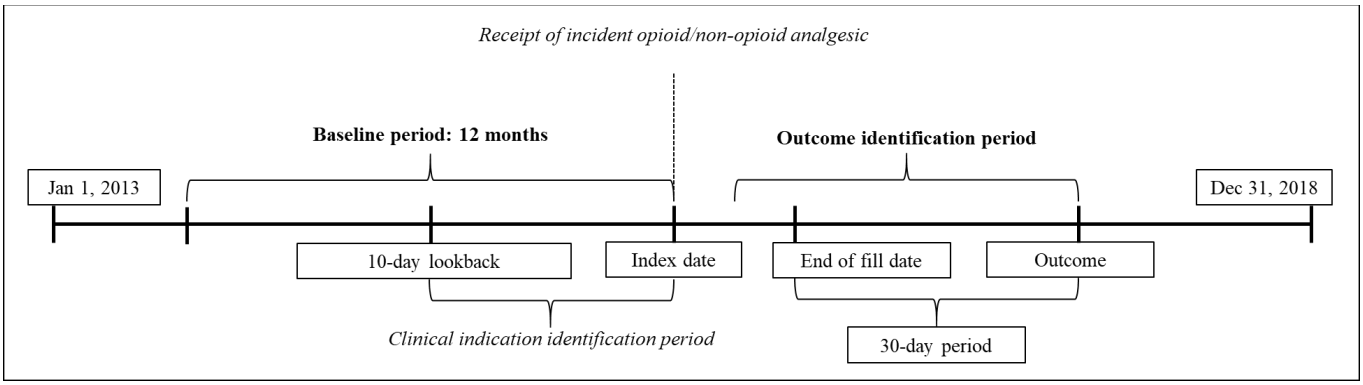
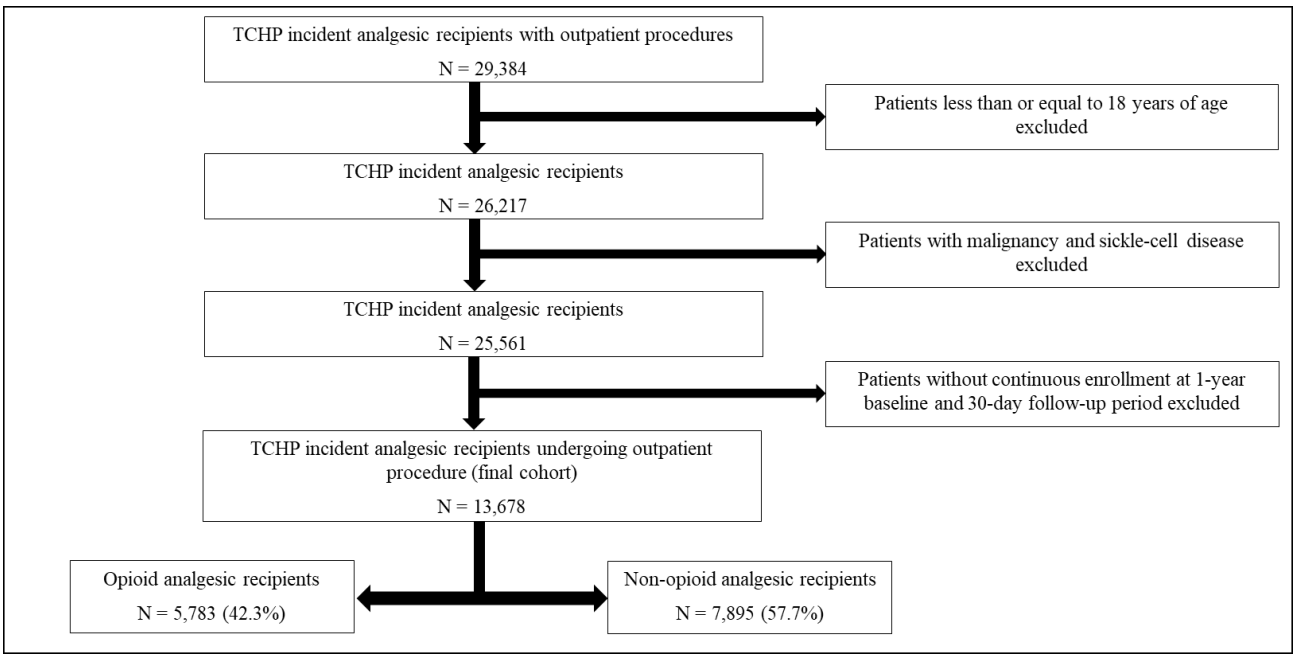


Figure 2. Consort diagram representing cohort development and outcome identification.



9. Appendix.

Appendix Table 1. ER visit and hospital admission associated with pain diagnosis

Pain Diagnoses	ER visit (N = 651)	Hospital Admission (N = 191)
Abdominal pain	87	15
Acute postprocedural pain	341	79
Back pain/lumbar pain	8	7
Limb and joint pain	56	26
Other unspecified pain	101	63
Pelvic pain and pain associated with micturition	58	1

DISSERTATION AIM 3. Trends in repeat opioid analgesic prescription utilization for acute pain in children: 2013 – 2018

Abstract

Objectives:

Our study examined the change in repeat opioid analgesic prescription trend in children and adolescents experiencing acute pain between 2013 to 2018.

Methods:

Eligible individuals were children and adolescents between 1 – 17 years of age who were enrolled in a large Medicaid Managed Care plan and filled an incident opioid analgesic prescription during 2013 to 2018. An incident prescription was defined as receipt of an opioid analgesic with no prior use for 12 months. A repeat opioid prescription was defined as receipt of a subsequent opioid prescription within 30 days since the end of incident opioid prescription. A generalized linear regression analysis was conducted to examine changes in repeat opioid analgesic dispensing over time at quarterly intervals from January 1, 2013 to December 31, 2018.

Results:

The cohort comprised of 17,086 children and adolescents receiving an incident opioid analgesic. Of these, 1,780 (10.4%) filled a repeat opioid analgesic prescription. There was a significant decline in the repeat opioid analgesic trend from 11.5% in the first quarter of 2013 to 9.6% in the last quarter of 2018. The average quarterly percentage change (QPC) was 6.8% decline (95% CI: 0.6% – 12.6%) based on the generalized linear regression. A significant decline in trend was also observed in a subgroup of patients undergoing outpatient surgical procedures across all age, gender and racial/ethnic groups.

Conclusion:

Approximately 10% of incident opioid analgesic recipients received a repeat opioid for management of their acute pain. There has been a steady decline (~7% per quarter) in repeat opioid analgesic dispensing between 2013 to 2018.

1. Introduction.

Children and adolescents frequently receive opioid analgesics for the management of acute pain.[2-4] Exposing opioid-naïve children and adolescents to opioids is associated with increased risk of persistent opioid use as well as long-term use in the future.[5-7] The 2016 Center for Disease Control and Prevention (CDC) guidelines also stated that *"long-term opioid use begins with treatment of acute pain."*[78]

In the wake of the opioid epidemic, the U.S. FDA issued an array of warnings and contraindications for opioid use in children and adolescents since 2012.[26-28] Recent studies point to a decreasing opioid dispensing trend in children and adolescents with an average annual decline ranging from 15% to 35% from 2006 – 2018.[29, 30] Another trend study indicates a decline in opioid prescriptions from 74.9% in 2010 to 66.9% in 2017 as a proportion of overall analgesics prescribed for pediatric postoperative pain management in an ambulatory care setting.[31]

Repeat opioid prescription following the initial analgesic prescription is the gateway to persistent use and chronic opioid use in patients who received an opioid for acute pain. These recently published opioid utilization trends, however, are generally derived from incident opioid exposures or overall prescription counts.[29-31] The trend associated with the important intermediate step between acute opioid use and persistent use, repeat opioid prescription for acute pain, has yet to be investigated.

Common acute pain diagnoses in pediatric population include abdominal pain, back pain, pain associated with traumatic injury and pain associated with outpatient surgical or dental procedures.[5-7, 29-31] Of these indications, surgical procedures is the one associated most frequent dispensing of repeat opioid prescription.[5-7] The study by Rizeq et. al (2019) has found consistent

decline in incident opioid analgesic use after ambulatory surgery in children.[31] It remains unknown whether repeat opioid analgesic trend for children undergoing outpatient surgical procedures has decreased in a similar pattern.

Additionally, a prominent racial/ethnic disparity in opioid utilization has been frequently reported in literature, with significantly lower utilization in Hispanic and Black children than their White couterparts.[32-34] A recent study by Basco et. al (2021) has found differential changes in incident opioid trends in children across different age groups and across various racial/ethnic groups.[29] It is important to know whether the change in utilization of repeat opioid prescription has disproportionally affected the minority children.

Our study aims at determining whether the consistent decline in trend as seen in previous studies and as a consequence of FDA warnings is observed for overall utilization of repeat opioid in children receiving incident opioid prescription for acute pain in the outpatient setting. The variation of repeat opioid utilization trend across age and racial/ethnic groups was also investigated in a sub-cohort of children undergoing outpatient surgical procedures.

2. Methods.

2.1. Data Source.

The study utilized the claims data of Texas Children's Health Plan (TCHP), a Medicaid Managed Care founded by Texas Children's Hospital. The health plan offers Medicaid and CHIP to over 20 counties across Southeast Texas. We extracted the de-identified data between January 1, 2013 and December 31, 2018. The data provides comprehensive sociodemographic (age, gender, race, Medicaid eligibility, member enrollment), medical claims (outpatient service

utilizations such as diagnoses and procedures), and pharmacy claims (outpatient prescription utilization with duration and prescriber specialty) information.

2.2. Study Design.

2.2.1. Study cohort & design.

The study included children and adolescents 1 to 17 years of age enrolled in TCHP between January 1, 2013 and December 31, 2018 with receipt of an incident opioid analgesic following an acute pain diagnosis or an outpatient surgical procedure based on a previous study.[38]

An incident opioid analgesic use was defined as receipt of an opioid analgesic with no prior use of the mediation for a period of 12-months. The diagnosis or procedure associated with the incident opioid prescription was identified during a 30-day lookback period. Individuals having a diagnosis associated with chronic opioid use such as malignancy and sickle-cell disease (SCD) were excluded from the cohort.

To accurately identify the incident opioid recipients and capture the subsequent opioid prescription, children are required to be continuously enrolled in the health plan from 12 months prior to the incident opioid analgesic dispensing to 30 days after the end of the incident opioid analgesic (incident opioid prescription days' supply + 30 days).

2.2.2. Outcome Assessment.

Repeat opioid prescription: A repeat opioid prescription was defined as the receipt of a subsequent opioid prescription within 30 days since the end of the incident opioid analgesic dispensing since (1) the maximum duration of incident opioid analgesic prescriptions was 30

days and (2) previous studies indicate that opioid use >90 days post-surgery or pain diagnosis qualifies as persistent opioid use.[5, 7, 79, 80]

Quarterly utilization of repeat opioid prescription: The 6-year timeframe from January 1, 2013 to December 31, 2018 were divided among 24 discrete quarters (4 per year). The quarterly estimates of repeat opioid utilization was presented as a proportion of total incident analgesic recipients in the same quarter. The estimate ratio was expressed per 100 incident opioid analgesic recipients. For example, in the quarterly timeframe from January 1, 2015 to March 31, 2015, the total number of repeat opioid analgesic recipients was 59 and the total number of incident opioid analgesic recipients was 596. The quarterly estimate of repeat opioid recipients per 100 incident opioid recipients was expressed as (59/637)*100 = 9.26 repeat opioid recipients per 100 incident opioid recipients in that specific quarter.

2.3. Statistical Analysis.

2.3.1. Overall Trend Analysis:

The proportions of repeat opioid analgesic recipients per 100 incident opioid analgesic recipients were identified for each quarter. (**Figure 1**). For the overall population trend estimation, the Cochran-Armitage trend test was performed to assess the directionality of the trend as well as the corresponding statistical significance. Additionally, a generalized linear regression was conducted to calculate the Quarterly Percentage Change (QPC) in trend across the 24 quarters from January 2013 to December 2018.

2.3.2. Stratified Trend Analysis in children undergoing outpatient surgery:

For the subgroup of Medicaid enrolled patients who underwent an outpatient surgical procedure, an age-sex-race based stratified trend analysis was performed. The sub-cohort was

selected because outpatient procedures is the most common indication for which opioid were prescribed. It is also the acute pain indication associated with the highest use of repeat opioid prescriptions.

Firstly, the patients were stratified into 4 groups (strata) based on their age (children vs. adolescents) and gender (male vs. female). Secondly, three separate regression analyses were conducted within each stratum for each racial/ethnic group (Non-Hispanic White, Non-Hispanic Black and Hispanics) with time (quarter) as the only independent variable. Lastly, the stratified trend analysis compared the relative change in the use of repeat opioid prescription over time within each stratum.

Linear and Logistic regression estimates and corresponding 95% confidence intervals were calculated at a statistical significance of $\alpha = 0.05$. All statistical analyses were conducted in SAS Enterprise Guide 8.1 (SAS Institute, Cary, NC) statistical software.

2.4. Ethic Statement.

The University of Houston and Baylor College of Medicine's Institutional Review Board (IRB) approved the study and granted a waived informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

3. Results.

3.1. Cohort distributions for opioid recipients:

There were 37,119 TCHP enrollees who received an incident opioid analgesic. After excluding individuals 18 years or older (n=6,681), those diagnosed with malignancy and sickle-cell disease (n=2,435) and those who did not have a continuous enrollment 1 year prior and 30

days after the end of the incident analgesic dispensed (n=10,917), the final incident opioid recipient cohort comprised of 17,086 individuals. (**Figure 2**).

Of the 17,086 incident opioid analgesic recipients, 1,780 received a repeat opioid analgesic between January 1, 2013 – December 31, 2018. The distribution of the repeat opioid analgesic recipients per quarter is listed in **Table 1**.

3.2. Overall quarterly trend estimates:

The overall proportion of patients receiving a repeat opioid analgesic dispensing decreased from 11.5% in 2013 Q1 to 9.6% in 2018 Q4. The Cochran-Armitage trend test indicated a test statistic of 2.55 ($p < 0.001$) indicating a statistically significantly declining trend. The average quarterly percentage change (QPC) was 6.8% decline (95% CI: 0.6% – 12.6%) based on the generalized linear regression. (**Figure 3**).

3.3. Stratum-specific quarterly trend estimates for repeat opioid analgesic recipients with an outpatient surgical procedure indication:

The repeat opioid analgesic trend was also compared across race/ethnicity (Hispanic, Non-Hispanic Black and Non-Hispanic White) within 4 stratums categorized by gender (males, females) and age (children, adolescents) among Medicaid enrolled children who underwent an outpatient surgical procedure.

As presented in **Table 2** and **Figures 4a-4c**, Non-Hispanic Whites had the highest repeat opioid utilization within all 4 stratums at Q1, 2013, followed by non-Hispanic Blacks and Hispanics in stratum 1 (male, children), 2 (female, children), and 4 (female, adolescents). The only stratum in which Hispanics had a higher utilization rate than their black counterparts at the beginning of the follow-up was the stratum 3 (male, adolescents).

Significant decline in repeat opioid utilization overtime has been observed in all racial/ethnic groups within each stratum. The greatest absolute reduction in children (stratum 1 and 2) was observed in non-Hispanic Whites, followed by non-Hispanic Blacks, and Hispanics. However, the racial/ethnic group experienced most significant decrease in repeated opioid utilization among adolescents (stratum 3 and 4) was Hispanics, followed by non-Hispanic Whites and Blacks.

At the end of the 6-year follow up, the racial/ethnic variations in repeat opioid utilization associated with surgical procedures have significantly reduced in children (stratum 1 and 2) yet persisted among adolescents (stratum 3 and 4). In Q1, 2013, the absolute differences in repeat opioid utilization between Non-Hispanic White and Hispanic children were 18.8% for stratum 1 and 22.1% for stratum 2 respectively. In Q4, 2018, the differences dropped to 2.7% in stratum 1 and to 2.6% in stratum 2 respectively. In contrast, the absolute difference observed between Non-Hispanic White and Hispanic adolescents had increased from 6.0% to 11.0% in stratum 3, and from 12.7% to 14.7% in stratum 4 during the 6-year study period.

4. Discussion.

Our study findings indicate that, consistent with the overall opioid utilization trend,[29, 30] the utilization of repeat opioid analgesics in children and adolescents with acute pain has steadily declined from 11.5% to 9.6% at a quarterly rate of ~7% per quarter from 2013 to 2018. The finding indicates that the array of FDA warnings and contraindications for the use of opioids in children[26-28, 81], along with the public campaign of addressing the opioid epidemic, have not only affected the chance of receiving an incident opioid prescription in opioid-naïve pediatric patients but also for pediatric patients who initially received an opioid analgesic.

The subgroup analysis in Medicaid enrolled pediatric patients who underwent an outpatient surgical procedure has also shown consistent decline of repeat opioid prescription utilization in all racial/ethnic groups across all age and gender specific stratums.

Despite a reduction in repeat opioid utilization was observed in all patient subgroups during the 6-year study period, the change of racial/ethnic variation in repeat opioid utilization overtime is different in children and adolescents. In younger age groups (stratum 1 and stratum 2), a greater reduction of repeat opioid utilization in the racial/ethnic group with relatively higher initial utilization rate resulted into reduced racial/ethnic variations toward the end of the follow up period. Among adolescents (stratum 3 and stratum 4), Hispanics who had relatively lower utilization than Non-Hispanic Whites at the beginning of the follow-up appeared being disproportionally affected by the policy change and public campaign and had a steeper reduction trend than their Non-Hispanic White and especially Non-Hispanic Black counterparts. Significant utilization gaps between Hispanics and Non-Hispanic White in repeat opioid utilization persist toward the end of the follow up period. A potential explanation for this could be that caregivers from various racial/ethnic groups specifically Hispanics have a distinctively lower preference to provide opioid analgesics to their children.[56-58]

Another finding from our study is that in contrast to Non-Hispanic White and Hispanic adolescents, the change in repeat opioid trend over time is relatively lower in Non-Hispanic Black adolescents and they were the least affected group as result of the policy changes in the light of the opioid epidemic. A potential explanation for this could be that the perception of pain varies widely among Non-Hispanic Blacks compared to Non-Hispanic Whites.[82] Studies have indicated that Non-Hispanic Black individuals experience a higher degree of pain compared to Non-Hispanic White individuals for a range of clinical conditions including post-surgical pain.[82-

[84] Due to a higher pain perception in the Non-Hispanic Black individuals, the physicians may continue to prescribe repeat opioid analgesics to these individuals for management of their acute post-surgical pain.

One potential limitation of our study is that it since it was carried out in a Texas Medicaid Managed Care pediatric population, the trend findings may not be generalizable to commercially insured pediatric populations and future studies may want to expand their populations based on type of insurance coverage.

5. Conclusion.

Our findings suggest that repeat opioid analgesic utilization for management of acute pain in children and adolescents of all sociodemographic groups is on a decline from the first quarter of 2013 to the last quarter of 2018 indicating that FDA warnings and contraindications for minimizing opioid exposure in pediatric populations are being potentially followed by physicians and there is an increased awareness among parents.

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7. Tables

Table 1. Calendar-time specific estimates of repeat opioid analgesic recipients per quarter.

Year	Quarter	Repeat opioid analgesic recipients (Numerator)	Incident opioid analgesic recipients (Denominator)	Proportion of repeat opioid recipients per 100 incident opioid recipients
2013	Q1	116	1012	11.46
	Q2	109	1093	9.97
	Q3	126	1029	12.24
	Q4	107	939	11.40
2014	Q1	90	799	11.26
	Q2	104	864	12.04
	Q3	98	796	12.31
	Q4	60	589	10.19
2015	Q1	59	637	9.26
	Q2	67	736	9.10
	Q3	79	801	9.86
	Q4	73	773	9.44
2016	Q1	81	832	9.74
	Q2	63	685	9.20
	Q3	89	785	11.34
	Q4	57	633	9.00
2017	Q1	66	709	9.31
	Q2	60	665	9.02
	Q3	45	549	8.20
	Q4	58	491	11.81
2018	Q1	55	476	11.55
	Q2	48	436	11.01
	Q3	42	465	9.03
	Q4	28	292	9.59

Table 2. Stratum-specific quarterly percentage change (QPC) in repeat opioid analgesic trends in Medicaid enrolled children and adolescents with an outpatient surgical procedure indication.

Stratum and Covariate Patterns	**Quarterly Percentage Change (%)**	**95% Confidence Intervals**	**Change**	**p-value**
Stratum 1, Covariate Pattern 1[a]	7.5	7.4 – 7.7	Decreasing	<0.001
Stratum 1, Covariate Pattern 2[b]	45.3	45.1 – 49.5	Decreasing	<0.001
Stratum 1, Covariate Pattern 3[c]	53.5	51.2 – 55.7	Decreasing	<0.001
Stratum 2, Covariate Pattern 1[d]	26.6	23.5 – 29.6	Decreasing	<0.001
Stratum 2, Covariate Pattern 2[e]	60.3	56.9 – 63.4	Decreasing	<0.001
Stratum 2, Covariate Pattern 3[f]	68.3	64.4 – 71.7	Decreasing	<0.001
Stratum 3, Covariate Pattern 1[g]	63.5	59.2 – 67.4	Decreasing	<0.001
Stratum 3, Covariate Pattern 2[h]	29.4	28.9 – 29.9	Decreasing	<0.001
Stratum 3, Covariate Pattern 3[i]	56.7	55.4 – 57.9	Decreasing	<0.001
Stratum 4, Covariate Pattern 1[j]	50.3	47.4 – 53.0	Decreasing	<0.001
Stratum 4, Covariate Pattern 2[k]	31.4	30.8 – 32.0	Decreasing	<0.001
Stratum 4, Covariate Pattern 3[l]	46.8	46.1 – 47.5	Decreasing	<0.001

[a] Stratum 1, Covariate Pattern 1: Children (1 – 12 years), Male, Hispanic
[b] Stratum 1, Covariate Pattern 2: Children (1 – 12 years), Male, Non-Hispanic Black
[c] Stratum 1, Covariate Pattern 3: Children (1 – 12 years), Male, Non-Hispanic White
[d] Stratum 2, Covariate Pattern 1: Children (1 – 12 years), Female, Hispanic
[e] Stratum 2, Covariate Pattern 2: Children (1 – 12 years), Female, Non-Hispanic Black
[f] Stratum 2, Covariate Pattern 3: Children (1 – 12 years), Female, Non-Hispanic White
[g] Stratum 3, Covariate Pattern 1: Adolescents (13 – 17 years), Male, Hispanic
[h] Stratum 3, Covariate Pattern 2: Adolescents (13 – 17 years), Male, Non-Hispanic Black
[i] Stratum 3, Covariate Pattern 3: Adolescents (13 – 17 years), Male, Non-Hispanic White
[j] Stratum 4, Covariate Pattern 1: Adolescents (13 – 17 years), Female, Hispanic
[k] Stratum 4, Covariate Pattern 2: Adolescents (13 – 17 years), Female, Non-Hispanic Black
[l] Stratum 4, Covariate Pattern 3: Adolescents (13 – 17 years), Female, Non-Hispanic White

8. Figures.

Figure 1. Study design diagram representing cohort development

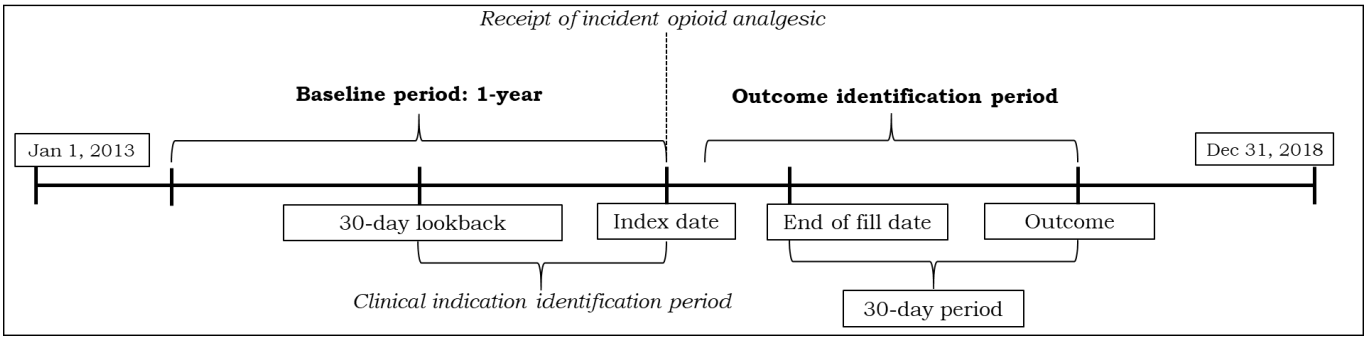


Figure 2. Consort diagram representing cohort development.

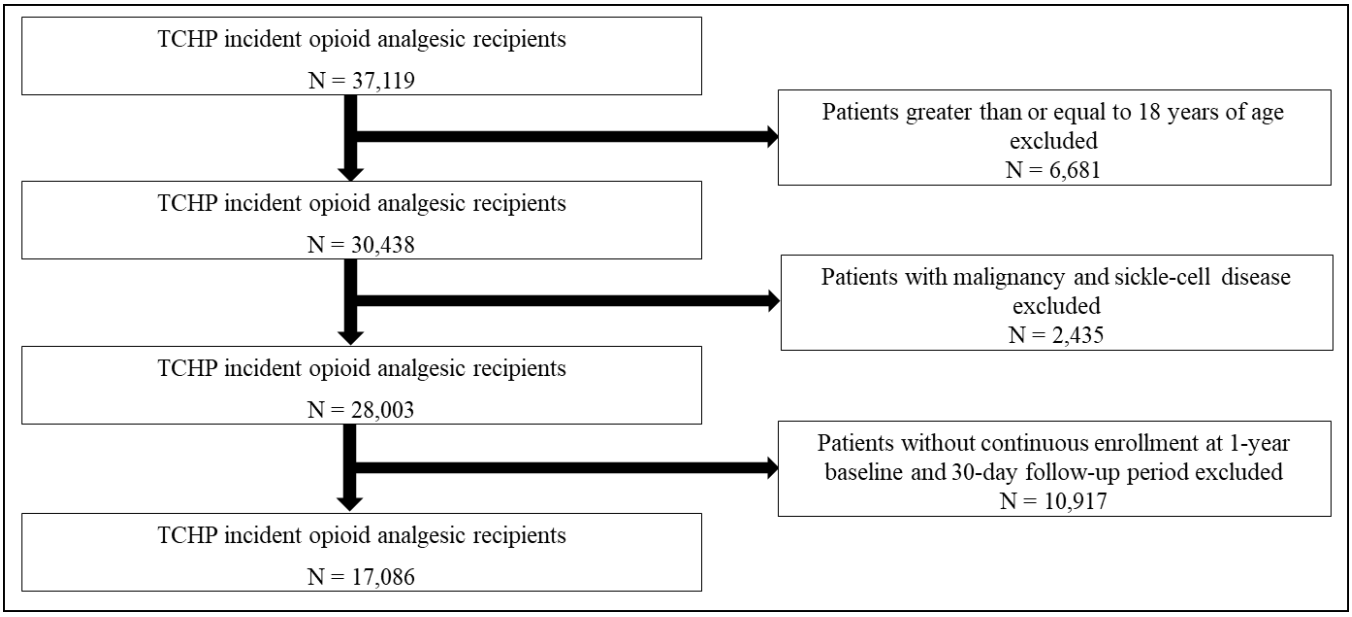


Figure 3. Quarterly trend for proportion of repeat opioid analgesic recipients per 100 incident opioid analgesic recipients.

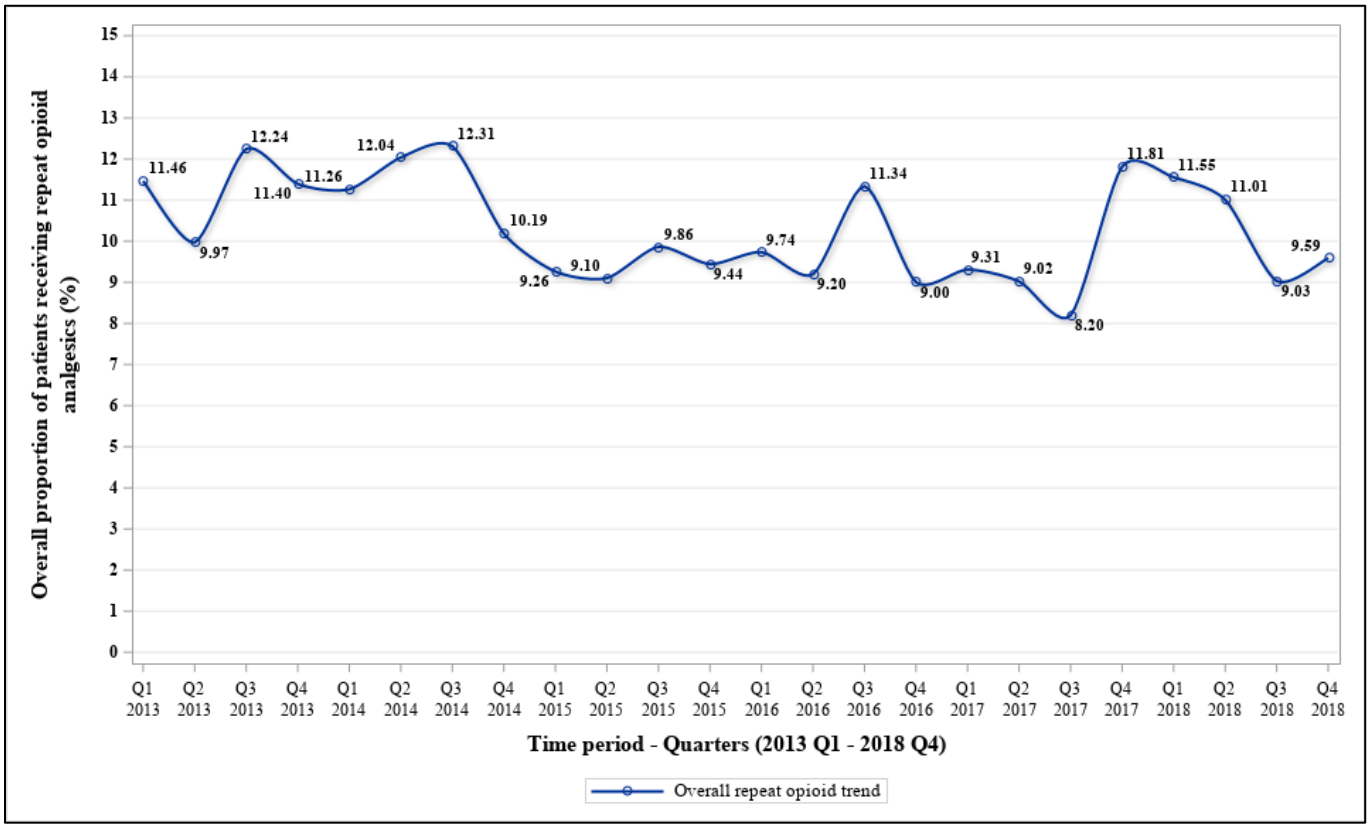


Figure 4a. Adjusted quarterly repeat opioid analgesic trend for Medicaid enrolled, male children (1 – 12 years) with an outpatient procedure stratified by race/ethnicity.

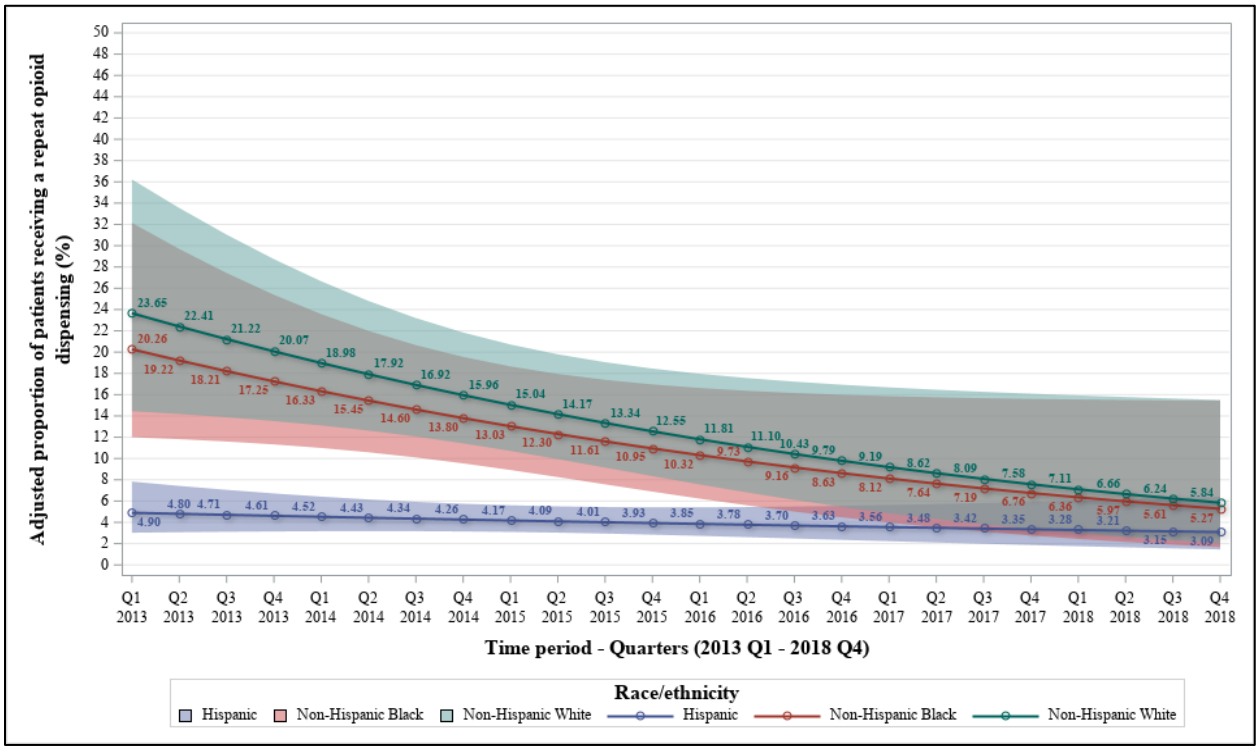


Figure 4b. Adjusted quarterly repeat opioid analgesic trend for Medicaid enrolled, female children (1 – 12 years) with an outpatient procedure stratified by race/ethnicity.

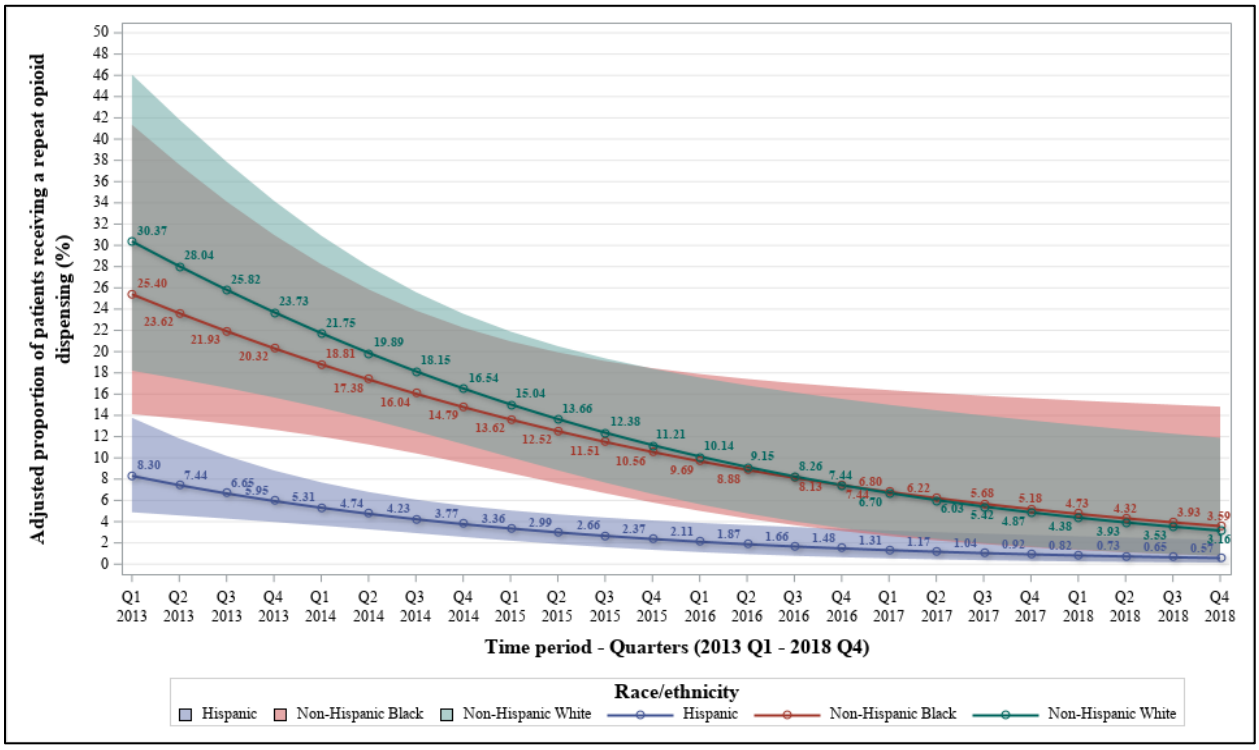


Figure 4c. Adjusted quarterly repeat opioid analgesic trend for Medicaid enrolled, male adolescents (13 – 17 years) with an outpatient procedure stratified by race/ethnicity.

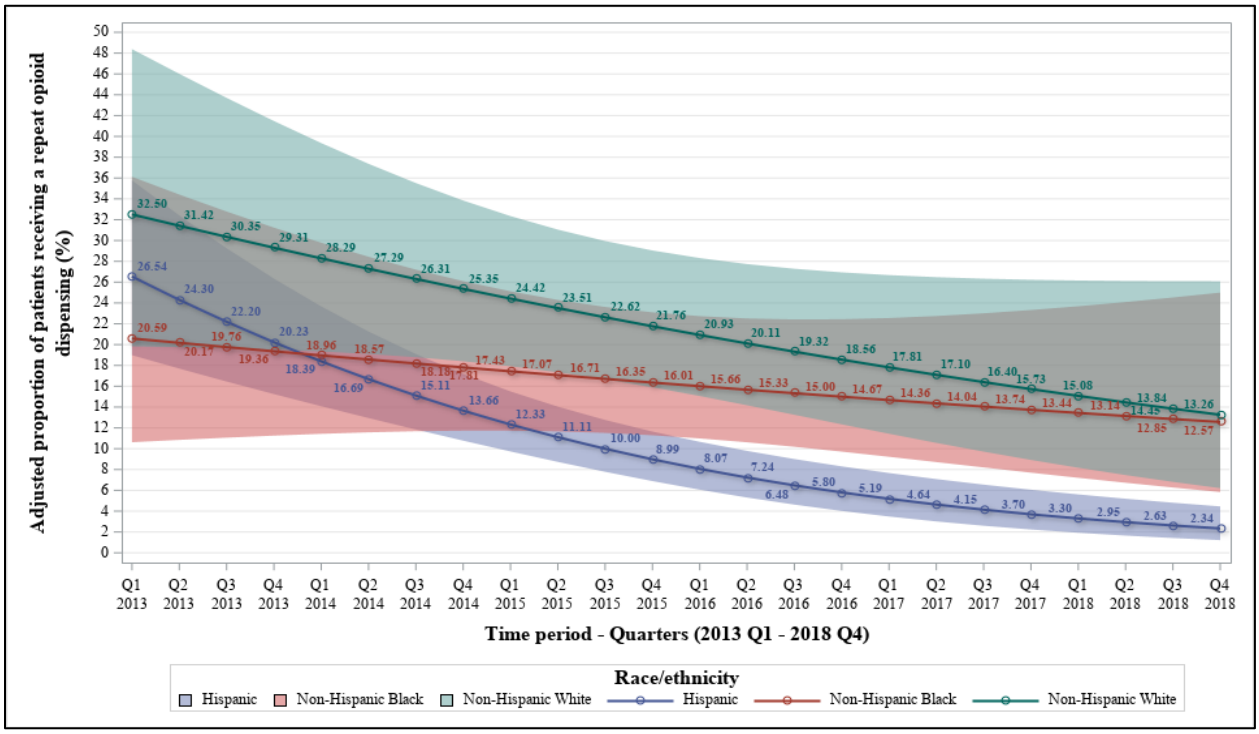
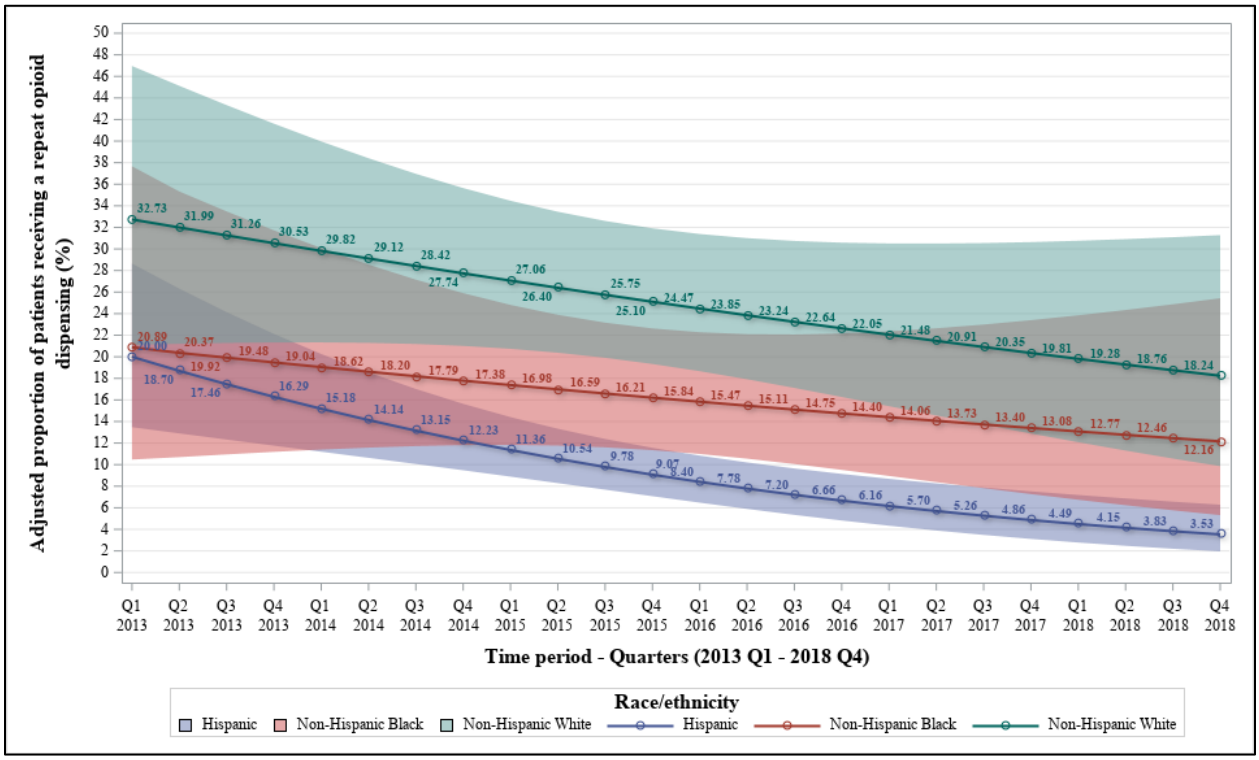


Figure 4d. Adjusted quarterly repeat opioid analgesic trend for Medicaid enrolled, female adolescents (13 – 17 years) with an outpatient procedure stratified by race/ethnicity.



9. Appendix.

Appendix 1

Stratum-specific covariate patterns.

Covariate Patterns as represented in Figure 2a

Covariate Pattern 1: **Children** (1 – 12 years of age), **male**, Hispanics, Medicaid eligible and outpatient procedure recipients.

Covariate Pattern 2: **Children** (1 – 12 years of age), **male**, Non-Hispanic Black, Medicaid eligible and outpatient procedure recipients.

Covariate Pattern 3: **Children** (1 – 12 years of age), **male**, Non-Hispanic White, Medicaid eligible and outpatient procedure recipients.

Covariate Patterns as represented in Figure 2b

Covariate Pattern 4: **Children** (1 – 12 years of age), **female**, Hispanics, Medicaid eligible and outpatient procedure recipients.

Covariate Pattern 5: **Children** (1 – 12 years of age), **female**, Non-Hispanic Black, Medicaid eligible and outpatient procedure recipients.

Covariate Pattern 6: **Children** (1 – 12 years of age), **female**, Non-Hispanic White, Medicaid eligible and outpatient procedure recipients.

Covariate Patterns as represented in Figure 2c

Covariate Pattern 7: **Adolescents** (13 – 17 years of age), **male**, Hispanics, Medicaid eligible and outpatient procedure recipients.

Covariate Pattern 8: **Adolescents** (13 – 17 years of age), **male**, Non-Hispanic Black, Medicaid eligible and outpatient procedure recipients.

Covariate Pattern 9: **Adolescents** (13 – 17 years of age), **male**, Non-Hispanic White, Medicaid eligible and outpatient procedure recipients.

Covariate Patterns as represented in Figure 2d

Covariate Pattern 7: **Adolescents** (13 – 17 years of age), **female**, Hispanics, Medicaid eligible and outpatient procedure recipients.

Covariate Pattern 8: **Adolescents** (13 – 17 years of age), **female**, Non-Hispanic Black, Medicaid eligible and outpatient procedure recipients.

Covariate Pattern 9: **Adolescents** (13 – 17 years of age), **female**, Non-Hispanic White, Medicaid eligible and outpatient procedure recipients.

POLICY and PRACTICE IMPLICATIONS.

Opioid epidemic is a major concern in the United States with millions of children and adolescents affected annually. To mitigate the opioid crises and to reduce opioid use in children and adolescents, expert-opinion based guidelines, state opioid prescribing policies and FDA warnings and contraindications for opioid use were employed.

Our study findings demonstrated that the current changes made to opioid policies and guidelines are likely to achieve their intended goal of reducing the use of prescription opioid analgesics in opioid-naïve children and adolescents. In majority of the children and adolescents the migration of pain management modality from opioid to non-opioid analgesics, and the reduction in opioid prescription duration will not affect their pain management outcomes.

However, policies and guidelines often have unintended consequences. Our study also demonstrated that, the change in postoperative pain management paradigm from opioid to non-opioid analgesics may increase the risk of unmanaged pain and lead to increased ER visits and hospital admissions in a small proportion of children. Our study also pointed that Hispanic adolescents may have been disproportionally affected by the policy change which has led to a widened disparity between non-Hispanic White and Hispanic adolescents in postoperative opioid analgesic utilization in 2018 as compared to the difference observed in 2012.

In summary, our study findings provide support to the existing policies and guidelines that have been installed to minimize the use of opioid analgesics in children, but it also highlights key risk areas wherein unintended consequences of these guidelines and policies may impact the child. Our findings imply further studies to assess the long-term effect of the policy change and indicate the need of future interventions and policy adjustment to address the unintended consequences.