FINAL PROGRESS REPORT

Risk of Acute Asthma Associated with the Pediatric Use of Opioids

Principal Investigator: Hua Chen, MD, PhD[1]

Co-Investigator: Harold J. Farber, MD, MSPH[2,3]

Organization

[1]Department of Pharmaceutical Health Outcomes and Policy,

University of Houston College of Pharmacy, Houston, Texas

[2]Department of Pediatrics, Section of Pulmonology,

Baylor College of Medicine and Texas Children's Hospital, Houston, Texas

[3]Medical Affairs

Texas Children's Health Plan, Houston, Texas

Date of the Project

8/8/2019 – 1/31/2021

Federal Project Officer

Eileen M. Hogan, MPA

Patient Safety Organizations (PSO) Division & General Patient Safety Division

Center for Quality Improvement and Patient Safety (CQuIPS), Agency for Healthcare Research and Quality (AHRQ)

Acknowledgement of Agency Support

This project was supported by the Agency for Health Care Research and Quality (AHRQ)

Grant Number

R03HS026790-01A1

2. STRUCTURED ABSTRACT:

Purpose: The proposed research examined factors associated with receipt of opioid versus non-opioid analgesics in children with current asthma and evaluated the risk of asthma exacerbation associated with opioid analgesics in the population.

Scope: The study utilized data provided by a large pediatric Medicaid Managed Care Plan in Texas and focused on an AHRQ priority population (children in low-income households).

Methods: Eligible individuals include those 1 to 17 years of age with current asthma and received an incident analgesic prescription. Current asthma was defined as receipt of both an asthma diagnosis and an anti-asthmatic medication in the 12-month period prior to analgesic medication initiation. Asthma exacerbation was defined as hospitalization or ER visit within 3 days since the receipt of analgesic prescription and with asthma being the primary or secondary diagnosis. A weighted multivariable logistic regression using Inverse Probability Treatment Weight (IPTW) was performed to test the association between analgesic medication exposure and the risk of asthma exacerbation.

Results: The utilization of opioid analgesics was most common among children undergoing outpatient procedures, dental procedures, having traumatic injuries, or respiratory infections. Asthma exacerbation was observed in 24 (0.5%) opioid and 22 (0.3%) non-opioid analgesic recipients within 3 days of analgesic initiation. Weighted logistic regression results showed that children receiving opioid analgesics [aOR: 1.6 (0.9-2.9)] did not have a higher risk of asthma exacerbation compared with their counterparts who received non-opioid analgesics.

Conclusion: Opioid analgesics has been frequently used in children with asthma; however, asthma exacerbation associated with analgesic use in children is an uncommon event, and the risk is comparable among children receiving opioid versus non-opioid analgesics.

Key Words: Children, Adolescents, Opioid, Asthma, Asthma Exacerbation, Analgesics, Medicaid

3. PURPOSE

Aim 1: To assess the sociodemographic, clinical, and provider characteristics for opioid and non-opioid analgesic utilization in children with current asthma

Aim 2: To examine the risk of asthma exacerbation associated with the utilization of opioid analgesics in children with current asthma

4. SCOPE

Introduction (Aim 1)

Asthma is one of the most common chronic diseases in the pediatric population, affecting 8.7% of the children under 18 years of age and 10.2% of the older teens aged 15-19 years.[1,2] Of those with an asthma diagnosis and receiving anti-asthmatic treatment during the year 2018, 53.8% experienced an asthma exacerbation in the 12 months prior to the survey.[1] Asthma exacerbations are acute episodic events typically characterized by difficulty in breathing (dyspnea), chest tightness, coughing, or wheezing. Severe asthma exacerbations can be potentially life threatening and may warrant an emergency room (ER) visit or hospitalization.[3,4]

Case reports of asthma exacerbations after recreational drug abuse continue to increase. Abuse of cocaine and the opioid heroin have the richest literature supporting an interaction between opioids and asthma and offer possible pathophysiological mechanisms.[5] Opioids might worsen asthma through two potential mechanisms. One mechanism is the activation of the microglia by the opioid analgesics through the toll-like receptors 4 (TLR4), resulting in release of proinflammatory mediators such as cytokines, interleukins, and prostaglandins as well as release of histamine from mast cells.[4,6-8] This can potentially cause a pseudoallergic reaction leading to flushing, hives, airway hyperresponsiveness, airflow obstruction, and exacerbation of asthma. Another more well-known mechanism is that opioids could depress the respiration by their action on the respiratory center at the base of the brain, resulting in decreased central respiratory drive, respiratory rate, and tidal volume. [6,8-10] It can exacerbate pooling of secretions, airway obstruction, and hypoxemia in patients, causing severe asthma exacerbations.

Package inserts of hydrocodone, codeine, and tramadol include a contraindication warning for patients *"with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment"*[11-14] Opioids could potentially trigger asthma exacerbation through two pharmacological mechanisms: one mechanism involves microglial activation via TLR4 releasing pro-inflammatory mediators, like cytokines, interleukins, prostaglandins, and histamine from mast cells[4,6-8]. This can precipitate a pseudoallergic reaction causing airway hyperresponsiveness, flushing, and hives, thus exacerbating asthma. Another mechanism involves opioids depressing respiration through their activity on the respiratory center at the base of the brain, causing a fall in the respiratory drive, respiratory rate, and tidal volume[6,8-10]; this could result in respiratory failure in the event of a severe asthma exacerbation.

Despite the potential mechanisms and the US Food and Drug Administration (FDA) warnings, there is a lack of data about how prescription opioids have been used in children with asthma, and the risk of asthma exacerbation associated with opioid analgesics has yet to be assessed by empirical or epidemiological studies. To bridge the knowledge gap, our study aimed

(1) To describe the utilization pattern of opioid analgesics in children and adolescents with current asthma and to identify patient and prescriber characteristics associated with the use of opioid analgesics versus alternative pharmacotherapies (non-opioid analgesics).

(2) To quantify the risk of asthma exacerbation associated with opioid analgesics versus alternative pharmacotherapies (non-opioid analgesics) in children with current asthma.

5. METHODS

Data.

De-identified patient-level data from January 1, 2013, to June 30, 2018, were extracted from the computerized claims datasets of Texas Children's Health Plan (TCHP). TCHP, founded by Texas Children's

Hospital, offers managed Medicaid (STAR) and CHIP for more than 20 counties in eastern Texas.[15] The data included patient demographics (age, gender, race/ethnicity, Medicaid eligibility categories, and monthly enrollment), medical claims (inpatient and outpatient service utilizations, and location of service), and pharmacy claims (outpatient prescription utilizations including dosage). The data also included the filling record of non-opioid pain relievers, such as acetaminophen, ibuprofen, naproxen, and indomethacin. Non-opioid pain relievers are covered under Texas Medicaid, which made the comparison between prescription opioids and their alternatives possible.

Methods (Aim 1)

Sample.

The study sample consisted of all children and adolescents 1 to 17 years of age enrolled in TCHP with current asthma and receipt of an incident opioid or non-opioid analgesic prescription during the study period. Current asthma was defined as having both asthma diagnosis and receiving anti-asthmatic medication during 1-year period before the index analgesic prescription. Asthma diagnosis was identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision (ICD-10), medical diagnoses codes [ICD-9-CM: 493; ICD-10: J45, J46].[3,16-19]

Asthma treatments identified in the study cohort were inhaled and oral corticosteroids, beta-adrenergic agonists and their combinations, leukotriene modifiers, methylxanthines, and bronchodilators. Individuals who did not have 1 year of continuous TCHP enrollment prior to the index analgesic prescription and those who had a malignancy or sickle-cell disease (SCD) were excluded from the analyses. Prescriptions were captured using the Generic Product Identifier (GPI) codes. Prescription opioid analgesics include medications such as codeine, hydrocodone, tramadol, etc., whereas the non-opioid analgesics include nonsteroidal anti-inflammatory drugs (NSAIDS) as well as other analgesics. Incident use was defined as receipt of an opioid or a non-opioid analgesic prescription with no prior use of these medications for a period of 1 year.

Factors associated with the utilization of opioids versus alternative analgesics.

Potential predictors for the receipt of prescription opioid analgesics and alternative pharmacotherapies (**Table 1**) were identified during the 1-year periods prior (pre-index period) to the incident analgesic dispensing based on the conceptual framework of Andersen Behavioral Model.[20,21] Predisposing factors are the factors that are present prior to the treatment. Enabling factors constitute an individual's ability to secure health services. Need factors provide insight into the individual's health status and diagnoses that warrant healthcare interventions.

Table 1. *Risk factors for the use of opioid analgesics in children based on the Andersen Behavioral Model.*

Type of external factors	Covariates in the study
Predisposing factors (Exist prior to treatment)	Patient demographics (age, gender, race/ethnicity)
	Medicaid eligibility categories (Medicaid STAR and CHIP)
Enabling factors (Constitute an individual's ability to secure health services)	Geographic location of patients' residence (urban/rural)
	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
	Asthma-related ER visit and hospitalization, short-acting beta agonist (SABA) overuse

To ascertain analgesic indications, all medical diagnoses and outpatient procedures patients received during a 30-day period prior to the index analgesic prescription were identified. These procedures and diagnoses were assigned a priority score according to a published algorithm.[22] The algorithm gave priority to procedure and diagnosis that are closest to the index date and having the strongest association with the analgesic prescription. For instance, during this identification process, if a patient received two diagnoses/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 **(Table 2)**. An additional correction was applied to a small number of records (less than 5%) wherein 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, when considering the index prescription date as day 0 and respiratory infection diagnosis (low-priority indication) on day 4 preceding the index date and traumatic injury diagnosis (high-priority indication) on day 6 preceding the index date, based on the correction, the traumatic injury was the attributable indication for the analgesic prescription.

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

Indication	Priority
Outpatient Surgery/Procedure	1
Trauma: Fracture, sprain, contusion, wound, other and/or unspecified trauma	2
Dental Surgery/Procedure	3
Back pain and/or degenerative back disorders	4
Other musculoskeletal or soft tissue pain and/or disorders	5
Abdominal pain	6
Headache and migraines	7
Generalized pain	8
Respiratory infections	9
Psychiatric disorders and/or neurologic conditions	10
Other infections	11

Uncontrolled asthma was measured by asthma-related hospitalization, ER visit, and SABA overuse during the 1 year prior index period. Asthma-related hospitalization and ER visit were defined as correspondent service utilizations with asthma as the primary or the secondary diagnosis.[25] SABA overuse was defined as filling six or more prescriptions during a 1-year period.[22-24]

Statistical Analyses.

The bivariate statistics for sociodemographic, clinical, and provider characteristics were compared between opioid and non-opioid analgesic recipients using chi-square tests for categorical variables and t-tests for continuous variables.

A multivariable logistic regression model was fitted to assess the association of receiving prescription opioid versus alternative analgesics (dependent variable) with patient and provider characteristics (independent variables). Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated at a statistical significance level of α=0.05. All the statistical analyses were conducted using SAS Enterprise Guide 8.1 (SAS Institute, Cary, NC) statistical software.[26]

Methods (Aim 2)

Sample:

Inclusion Criteria

Individuals enrolled in TCHP between January 1, 2013, and December 31, 2018, were included if they had current asthma, received an incident prescription of opioid or non-opioid analgesics, and were age 1-17 years on the date that the incident analgesic prescription was filled.

Current asthma was defined as the presence of a primary or secondary asthma diagnosis as well as receipt of an anti-asthmatic medication in the 1-year period before index analgesic prescription. The ICD-9-CM and ICD-10 medical diagnoses codes were utilized to identify asthma diagnosis [ICD-9-CM: 493; ICD-10: J45, J46].[3, 16-19,22] Oral corticosteroids, inhaled corticosteroids, beta-adrenergic agonists and their combinations, leukotriene modifiers, methylxanthines, and bronchodilators were the *anti-asthmatic medications* included in the study.

An *incident analgesic use* was defined as the receipt of opioid or non-opioid analgesic with no prior use of these medications for 1 year. Generic Product Identifier (GPI) codes were used to identify the prescription opioid analgesics, such as codeine, hydrocodone, and tramadol, and non-opioid analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and other analgesics, such as acetaminophen.

Exclusion Criteria

Individuals who did not have a continuous enrollment in the 1-year period before (baseline) and 7-day period (maximum follow-up for sensitivity analysis) after the index analgesic prescription were excluded from the study sample. Children and adolescents with a malignancy or sickle-cell disease (SCD) were also excluded from the cohort. Additionally, all analgesic users with only a respiratory infection diagnosis presented within 30 days prior to the index analgesic dispensing were excluded as respiratory infections are a common trigger of asthma exacerbations.

Study Design:

It is stated in the package inserts of opioid analgesics that the risk of respiratory side effects is significantly higher in the initial 24-72 hours of the drug administration.[11-14] Therefore, the main analyses focused on asthma exacerbation within 3 calendar days following the index analgesic prescription. Sensitivity analyses were conducted to determine the risk of asthma exacerbation within 4 days and 7 days since the index analgesic prescription.

Outcome Measure:

Asthma Exacerbation

A joint European Respiratory/American Thoracic Society statement proposed a definition of asthma exacerbation for research as *"any of the following service utilizations with an asthma diagnosis in the primary or secondary position: hospitalization, ER visit, or physician office or outpatient visit with a pharmacy claim for oral corticosteroids (OCS)."*[25] This definition has been used in previous studies by Chastek and colleagues.[18]

For the main analysis of this study, we utilized a strict definition and defined asthma exacerbation associated with an analgesic prescription as hospitalization or ER visit with an asthma diagnosis in the primary or secondary position within 3 days of the incident analgesic prescription. For the sensitivity analysis, we tested the robustness of the main findings using a more lenient definition that included not only asthma-associated ER visit and hospitalization but also the dispensing of an oral corticosteroid within 3 days following the incident analgesic prescription.

Covariates:

Patient and provider characteristics

Patient and provider characteristics that could confound the association between receipt of index analgesic and risk of asthma exacerbation were identified during the 1-year period prior to index prescriptions according to the Andersen Behavioral Model.[20,21] Predisposing factors, such as age, gender, self-reported race/ethnicity, and health plan eligibility category (Medicaid vs CHIP), are factors that 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 prior history of procedures, diagnoses, and asthma severity, provide insight into the individual's health status, the likelihood of receiving opioid versus non-opioid analgesics, and the pre-existing risk of having asthma exacerbation.

Asthma severity was defined as asthma-related hospitalization, ER visit, and SABA overuse during the 12 months prior index period. Asthma-related hospitalization and ER visit were defined as correspondent service utilizations with asthma as the primary or the secondary diagnosis.[25] Presence of six or more SABA prescriptions in the 1 year of baseline qualified as an overuse.[22-24]

Statistical Analysis:

Propensity Score Calculation:

Propensity scores (PS) were obtained using a multivariable logistic regression model with receipt of opioid versus non-opioid as the outcome and the patient and provider factors as the potential covariates. Among different PS methods, Inverse Probability Treatment Weighting (IPTW) was applied. IPTW is the inverse of the probability of receiving the respective treatment.[27,28] There are several ways to use the resulting propensity scores (e.g., matching, stratification, modeling), but weighting by a function of the propensity score has several advantages. Weighting allows all patients to contribute to the analysis, whereas matching usually inherently excludes some patients. The PS-based IPTWs are estimated, using Proc psmatch in SAS, to create a pseudopopulation of opioid and alternative analgesic users balanced on all the measured covariates.[26] The balance of covariates between opioid and non-opioid analgesic groups was confirmed using the standardized differences, with a satisfactory threshold value between -0.25 and 0.25.

Regression Analysis:

A weighted logistic regression model was fitted to estimate the adjusted odds ratio (aOR) and the corresponding 95% confidence intervals (CIs) for the risk of asthma exacerbation associated with receipt of opioid versus non-opioid analgesics.

All analyses were performed using SAS Enterprise Guide 8.1 (SAS Institute, Cary, NC) statistical software.[26]

6. RESULTS

Results (Aim 1)

Between 2013 and 2018, 9,529 (4.2%) TCHP patients with current asthma received an incident analgesic. Of these, 2,681 (28.1%) received opioid analgesics and 6,848 (71.9%) received non-opioid analgesics (**Figure 1.1**). The mean and median durations of opioid analgesic prescriptions were 5.5 ± 4.3 days and 5.0 (IQR: 3.0) days, respectively, whereas the mean and median durations of non-opioid analgesic prescriptions were 7.1 ± 5.5 days and 6.0 (IQR: 4.0) days, respectively.

For the opioid analgesic recipients, the average daily Morphine Milligram Equivalent (MME) dose was 18.2 ± 12.8 units, and the median (IQR) was 15.0 (15.0) units. The most filled opioid analgesics by the study cohort were codeine (51.9%), hydrocodone (40.4%), and tramadol (6.6%), whereas the most commonly filled non-opioid analgesics were ibuprofen (73.2%), acetaminophen (22.9%), and naproxen (3.5%).

Descriptive statistics of opioid and non-opioid recipients with current asthma

The distribution and unadjusted rates of socioeconomic, clinical, and prescriber characteristics were compared between the opioid and non-opioid analgesic recipients (**Table 1.1**).

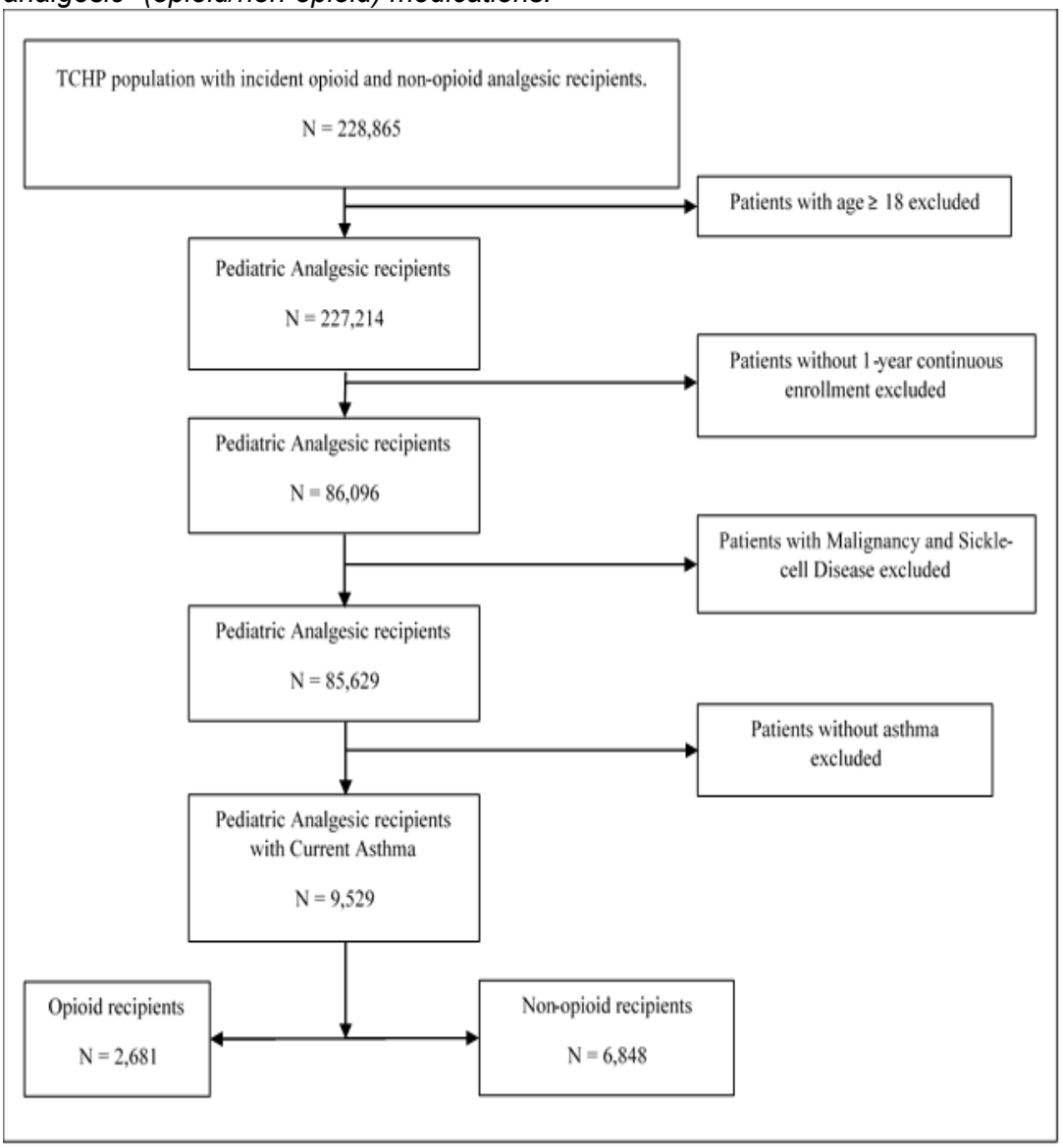
Demographics: The opioid group (N=2,681), compared with the non-opioid group (N=6,848), was older (opioid group: 10.3 ± 4.8 years, non-opioid group: 7.2 ± 4.2 years; p<.0001), had a higher proportion of non-Hispanic White patients (opioid group: 16.8%, non-opioid group: 7.1%; p<.0001), and had a lower proportion of Hispanic children (opioid group: 50.3%, non-opioid group: 60.0%; p<.0001).

Diagnosis and procedures: The most common opioid associated diagnoses and procedures in the opioid recipients (N=2,681) were surgery/procedure (N=790; 29.4%), trauma (N=519; 19.4%), dental surgery/ procedures (N=493; 18.4%), and respiratory infection (N=284; 10.6%). Conversely, the non-opioid analgesic group (N=6,848) was predominantly composed of patients with respiratory infection (N=3,820; 55.8%) and general infection (N=620; 9.1%). Additional analysis on the type of oral opioid analgesics filled by children with respiratory infection showed that 70% (N=200) filled a prescription for codeine, and 24% (N=69) filled for hydrocodone.

Health utilization history indicating uncontrolled asthma: Relatively higher proportions of children in the opioid group had history of asthma-related ER visits (opioid group: 9.6%, non-opioid group: 8.0%; p=0.009) and SABA overuse (opioid group: 9.2%, non-opioid group: 5.5%; p<.0001) compared with those in the non-

opioid group. A similar difference between opioid and non-opioid recipients was not observed in the history of asthma-related hospital admissions. The mean duration between these historical events indicating uncontrolled asthma and the index analgesic dispensing was 163.1 (SD: 96.5) days, and the median was 166.8 (IQR: 140.0) days.

Figure 1.1 *Consort diagram indicating cohort development for current asthma patients with analgesic (opioid/non-opioid) medications.*



Prescriber characteristics: Opioid analgesics (N=2,681) were primarily prescribed by surgeons (N=552, 20.6%), dentists (N=544, 20.3%), primary care providers (PCPs) (N=488, 18.2%), and ER providers (N=401, 15.0%), whereas non-opioid analgesics (N=6,848) were predominantly prescribed by PCPs (N=5,521, 80.6%). Of the 99 patients who received concurrent anti-asthmatic and opioid analgesic prescriptions from the same prescribers, 56 received the prescription from PCPs, and 11 did so from ER providers. The use of opioid analgesic prescriptions in these 99 patients was mainly associated with respiratory infections (N=30), general infections (N=17), and trauma (N=17).

Calendar Time: The number of opioid prescriptions dispensed to children with current asthma increased slightly from 17.5% in 2013 to 20.5% in 2014 and then gradually dropped to 12.1% in 2018. The number of non-opioid analgesic prescription dispensed to the group had a consistent decline from 35.6% in 2013 to 7.8% in 2018.

Table 1.1 *Sociodemographic, clinical, and provider characteristics for opioid and non-opioid analgesic users with current asthma (unadjusted rates).*

Characteristics	Opioids N=2,681 (100%)		Non-opioids N=6,848 (100%)		
	N	%	N	%	p value
Age (Mean ± SD)	10.3 ± 4.8		7.2 ± 4.2		<.0001*
Gender					
Female vs Male	1,187	44.3	3,079	45.0	0.54
Race/ethnicity					
Alaskan American	12	0.4	20	0.3	<.0001*
Non-Hispanic Black	552	20.6	1,215	17.7	
Asian	44	1.6	163	2.4	
Non-Hispanic White	450	16.8	485	7.1	
Hispanic	1,348	50.3	4,107	60.0	
Unknown	275	10.3	858	12.5	
Medicaid eligibility					
STAR vs CHIP[a]	2,393	89.3	6,019	87.9	0.06
Patient Geographical location					
Urban vs Rural	2,648	98.8	6,820	99.6	<.0001*
Provider characteristics					
Dentists	544	20.3	263	3.8	<.0001*
Emergency Room physicians	401	15.0	293	4.3	<.0001*
Obstetrics and Gynecology specialists	35	1.3	34	0.5	<.0001*
Other Specialists	586	21.9	300	4.4	<.0001*
Physician Assistants	72	2.7	421	6.1	<.0001*
Primary Care Providers	488	18.2	5,521	80.6	<.0001*
Surgical specialists (surgeons)	552	20.6	16	0.2	<.0001
Procedures and Diagnoses[b]					
Abdominal Pain	126	4.7	187	2.7	<.0001*
Back pain and/or degenerative back disorders	32	1.2	73	1.1	0.59
Dental Surgery/Procedure	493	18.4	250	3.7	<.0001*
General infections	101	3.8	620	9.1	<.0001*
Generalized pain	52	1.9	103	1.5	0.13
Headache and Migraines	50	1.9	233	3.4	<.0001*
Other musculoskeletal or soft tissue pain and/or disorders	83	3.1	202	2.9	0.71
Outpatient Surgery/Procedure	790	29.4	221	3.2	<.0001*
Respiratory infections	284	10.6	3,820	55.8	<.0001*
Trauma: Fracture, Sprain, Contusion, Wound, other and/or unspecified trauma	519	19.4	332	4.8	<.0001*
Asthma Risk Factors					
History of asthma-related hospitalization	21	0.8	61	0.9	0.56
History of asthma-related ER visit	258	9.6	545	8.0	0.009*
Short-acting Beta Agonist (SABA) overuse	246	9.2	377	5.5	<.0001*
Providers prescribing analgesic and anti-asthmatic medications to the same patient	99	3.7	2977	43.5	<.0001*

[a]CHIP – Children's Health Insurance Program; STAR – State of Texas Access Reform

[b]The procedures and diagnoses were identified based on a 30-day lookback period from the index prescription. Procedures and Diagnoses as indicators for opioid/non-opioid use have been developed based on a priority rating.
*indicates statistical significance.

Opioid utilization across racial/ethnic groups

To further understand the variations of opioid utilization across subgroups of children with asthma, we categorized the analgesic recipients by race/ethnicity (non-Hispanic White: 935, non-Hispanic Black: 1,767, Hispanic: 5,455).

Non-Hispanic White children used significantly more opioid analgesics than their non-Hispanic Black and Hispanic counterparts (non-Hispanic White: 450, 48.1%; non-Hispanic Black: 1,767, 31.2%; Hispanic: 1,348, 24.7%; p<.0001).

Non-Hispanic White children not only received more opioids than children from other racial/ethnic groups for indications such as surgical procedure, trauma, and dental procedures but also received opioids more frequently for low-priority indications, such as respiratory infections, abdominal pain, generalized pain, and general infections (**Figure 1.2**).

Figure 1.2 *Indications for receipt of opioid analgesics across racial/ethnic groups.*

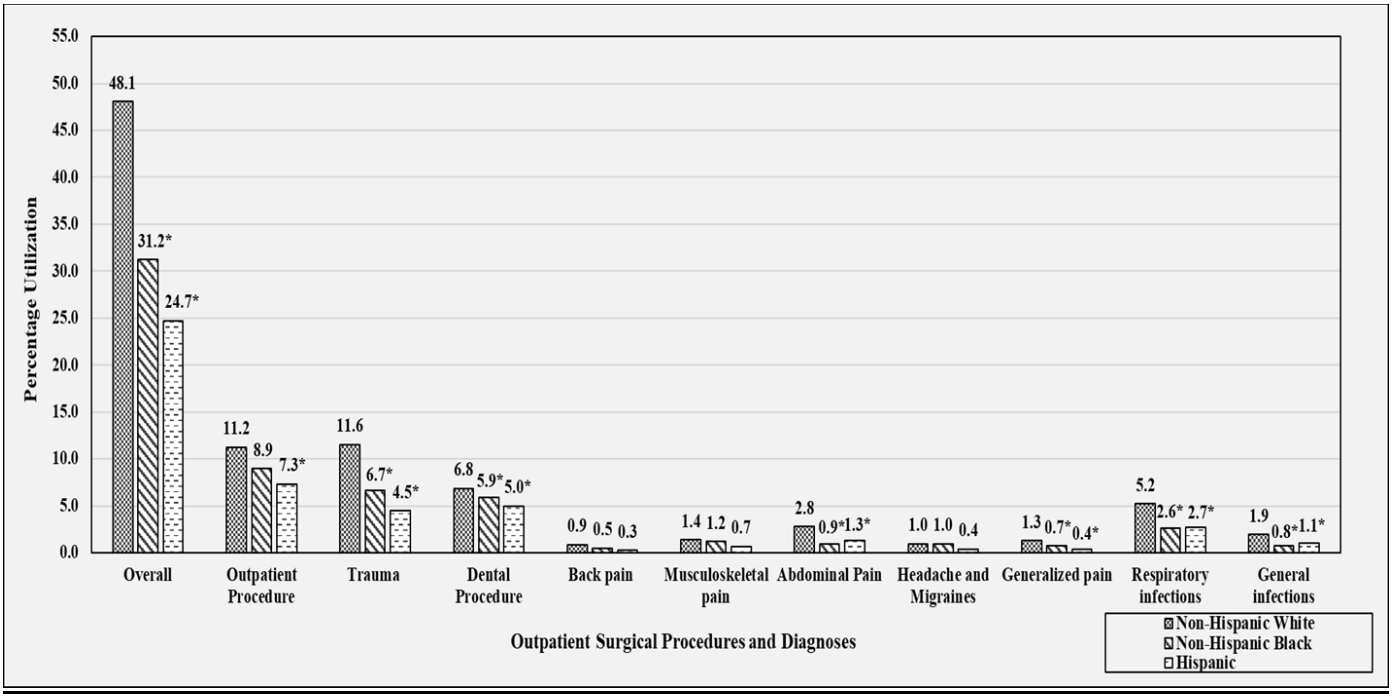


Figure 1.2 legend.

The denominator for each of the bars represents the total children in different racial/ethnic groups: non-Hispanic Whites (N=935), non-Hispanic Black (N=1,767), and Hispanics (N=5,455).

*indicates statistical significance.

Diagnoses and procedures associated with analgesic utilization in children with and without a utilization history indicating uncontrolled asthma

We also categorized analgesic recipients by their histories of asthma-related healthcare utilization indicating poorly controlled asthma (children with asthma related hospitalization, ER visits, and SABA overuse: 1,332; children without the health utilization history: 8,197).

The comparison between children with different histories of asthma-related healthcare utilization (**Figure 1.3**) revealed that those with a history of asthma-related hospitalization, ER visit, and/or SABA overuse received opioids more frequently associated with trauma, respiratory infections (4.7% vs 2.7%, p<.0001), and general infections (1.4% vs 1.0, p=0.0132) than did their counterparts without the healthcare utilization history of uncontrolled asthma.

Figure 1.3 *Opioid indications among patients with and without prior history of uncontrolled asthma*

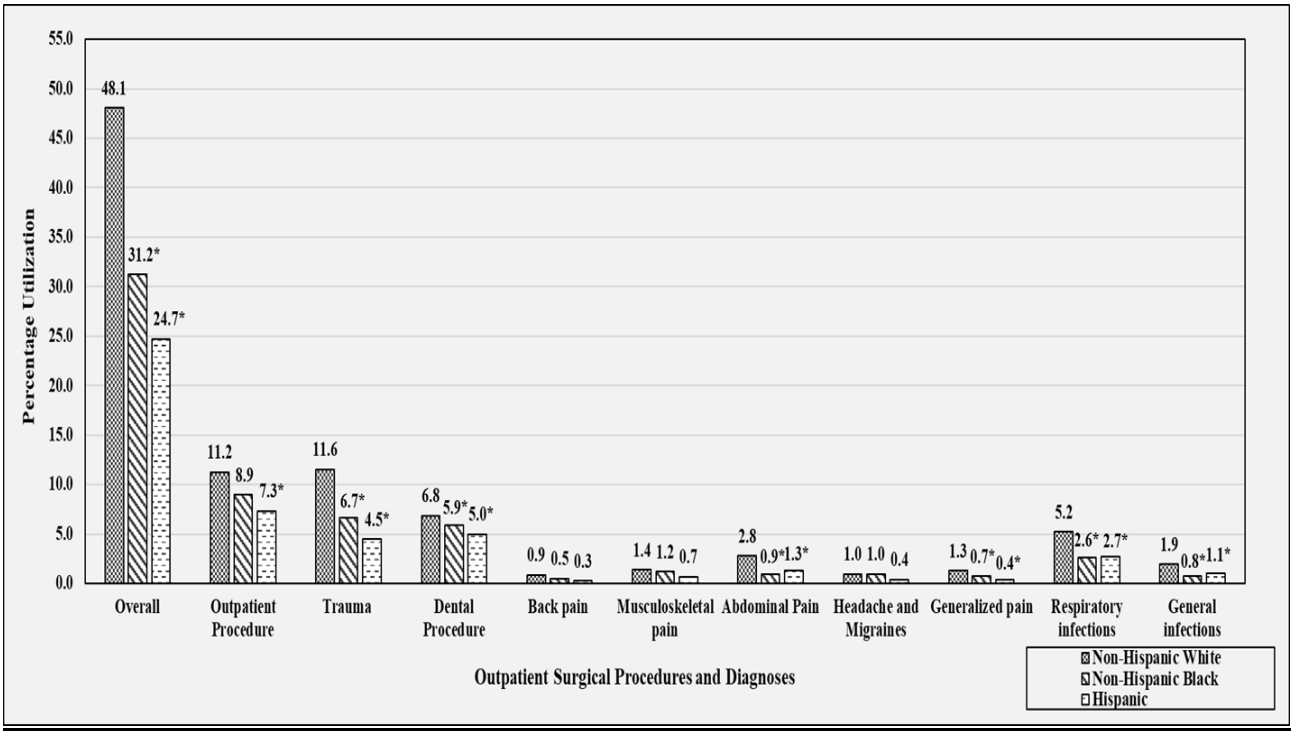


Figure 1.3 legend.
The denominator for each of the bars represents the total children and adolescents with a prior history of asthma-related hospitalizations, ER visits, or SABA overuse (N=1,332) or without (N=8,197).

*indicates statistical significance

Multivariable analysis

Findings of multivariable logistic regression model (**Table 1.2**) confirmed that children and adolescents with current asthma were more likely to receive an opioid analgesic than a non-opioid analgesic when they underwent an outpatient surgery or procedure [aOR: 18.87 (15.2-23.4)] or a dental procedure [aOR: 14.09 (11.5-17.3)] or had trauma [aOR: 5.28 (4.3-6.5)].

The racial/ethnic variation indicated that, compared with their non-Hispanic White counterparts, non-Hispanic Black children were 71% [aOR: 0.39 (0.3-0.5)] and Hispanic children were 49% [aOR: 0.51 (0.4-0.6) less likely to receive an opioid analgesic prescription.

Last, children and adolescents with a history of an asthma-related ER visit or history of SABA overuse were 24% [aOR: 1.24 (1.0-1.5)] and 33% [aOR: 1.33 (1.1-1.7)] more likely to receive an opioid analgesic than were those without these utilizations indicating uncontrolled asthma.

The model was checked for presence of multicollinearity, and all the predictors in the model had a correlation coefficient less than 0.7. Moreover, the multivariable logistic regression model had a C-statistic of 0.88.

Table 1.2 *Predictors of incident opioid analgesic use in children and adolescents with current asthma (adjusted rates).*

Characteristics	Odds Ratio	95% Confidence Interval
Age	1.16*	(1.1 – 1.2)
Gender *[Ref. Male]*		
Female	0.99	(0.9 – 1.1)
Race/ethnicity *[Ref. Non-Hispanic White]*		
Non-Hispanic Black	0.39*	(0.3 – 0.5)
Alaskan American	0.38*	(0.2 – 0.9)
Asian	0.28*	(0.2 – 0.5)
Hispanic	0.51*	(0.4 – 0.6)
Unknown	0.56*	(0.4 – 0.7)
Medicaid Eligibility *[Ref. CHIP]*		
STAR	1.10	(0.9 – 1.3)
Procedures and Diagnoses		
Abdominal Pain	2.50*	(1.9 – 3.3)
Back pain and/or degenerative back disorders	0.97	(0.6 – 1.5)
Dental Surgery/Procedure	14.09*	(11.5 – 17.3)
General infections	0.95	(0.7 – 1.2)
Generalized pain	1.53*	(1.1 – 2.2)
Headache and Migraines	0.59*	(0.4 – 0.8)
Other musculoskeletal or soft tissue pain and/or disorders	1.15	(0.9 – 1.6)
Outpatient Surgery/Procedure	18.87*	(15.2 – 23.4)
Respiratory infections	0.27*	(0.2 – 0.3)
Trauma: Fracture, Sprain, Contusion, Wound, other and/or unspecified trauma	5.28*	(4.3 – 6.5)
Asthma Risk Factors		
History of asthma-related hospitalization	0.69	(0.4 – 1.4)
History of asthma-related ER visit	1.24*	(1.0 – 1.5)
History of short-acting Beta Agonist (SABA) overuse	1.33*	(1.1 – 1.7)

*indicates statistical significance.

Results (Aim 2)

Of the 228,865 pediatric analgesic recipients enrolled in TCHP between January 1, 2013, and December 31, 2018, 56,768 (24.8%) received a diagnosis of asthma and filled an anti-asthmatic prescription during the 1-year period prior to the index analgesic prescription.

After excluding patients with age >18 years (N=343), those with malignancy and sickle-cell disease (N=343), those without continuous eligibility (N=32,982), and those with their primary analgesic use associated with respiratory infections (N=9,741), the final cohort was composed of 13,359 children and adolescents.

Of these, 5,363 (40.1%) received opioid analgesics, and 7,996 (59.9%) received non-opioid analgesics (**Figure 2.1**). The average duration of analgesic therapy was 5.4 (4.1) days in the opioid group and 7.4 (5.9) days in the non-opioid group.

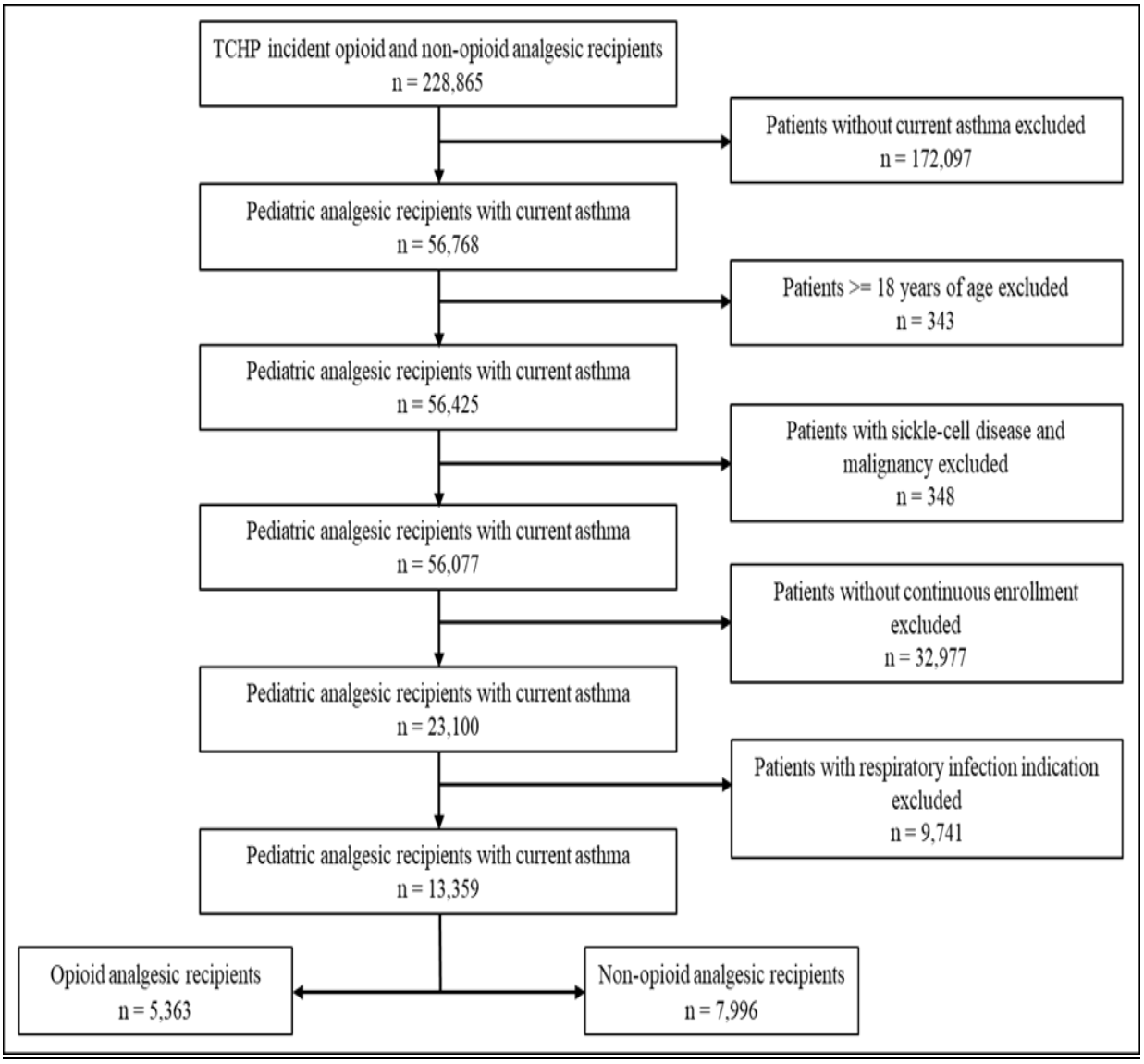
Descriptive characteristics of opioid and non-opioid recipients with current asthma.

Patient Demographics: The opioid analgesic recipients were older [10.2 (4.9) years] than the non-opioid analgesic recipients [7.4 (4.4) years]. The proportion of non-Hispanic White children in the opioid group (17.0%) was two times more than that in the non-opioid group (7.9%).

In contrast, there was a significantly lower proportion of Hispanic children (53.7%) in the opioid group than in the non-opioid group (62.2%) (**Table 2.1**).

Provider Characteristics: The opioid analgesic prescriptions were prescribed commonly by surgical specialists (N=2,195, 40.9%), dentists (N=1,305, 24.3%), and emergency room (ER) prescribers (N=912, 17.0%), whereas the non-opioid analgesics were predominantly prescribed by primary care providers (PCPs) (N=5,660, 70.8%).

Figure 2.1 *Consort diagram indicating cohort development for current asthma patients receiving analgesic (opioid/non-opioid) medications and experiencing an asthma exacerbation.*



Diagnoses and Procedures: The most commonly associated procedures and diagnoses in the opioid recipients were outpatient surgery (N=2,104, 39.2%), trauma (N=1,336, 24.9%), and dental procedures (N=1,305, 24.3%). The majority of the non-opioid recipients received their analgesics for trauma (N=1,716, 21.5%), general infections (N=1,621, 20.3%), and abdominal pain (N=1,389, 17.4%).

Healthcare utilization history associated with uncontrolled asthma: Relatively higher proportion of children in the opioid analgesic group had prior histories of asthma-related ER visits (opioid group: 11.2%; non-opioid group: 6.2%; $p<0.001$) and SABA overuse (opioid group: 4.6%; non-opioid group: 2.7%; $p<0.001$) compared with their non-opioid group counterparts.

Table 2.1 *Covariate Balance Assessment before and after IPTW propensity score adjustment for opioid and non-opioid recipients.*

Characteristics	Before IPTW					After IPTW				
	Opioid N=5,363		Non-opioid N=7,996		Standardized Mean Difference[a]	Opioid N=5,363		Non-opioid N=7,996		Standardized Mean Difference[a]
	n	(n/N)%	n	(n/N)%		n	(n/N)%	n	(n/N)%	
Age (Mean ± SD)	10.2 ± 4.9		7.4 ± 4.4		0.61†	8.6 ± 5.1		8.5 ± 4.7		0.06*†
Gender										
Female vs Male	2,451	45.7	3,686	46.1	-0.01	2,624	47.1	3,633	45.4	0.02*
Race										
Alaskan American	20	0.4	19	0.2	-0.02	11	0.2	25	0.3	0.02*
Asian	90	1.7	145	1.8	0.01	114	2.1	136	1.7	-0.03*
Hispanic	2,877	53.7	4,973	62.2	0.17	2,664	47.8	4,553	56.9	0.08*
Non-Hispanic Black	977	18.2	1,264	15.8	-0.06	1,178	21.1	1,415	17.7	-0.06*
Non-Hispanic White	910	17.0	634	7.9	-0.28†	760	13.6	1,011	12.6	-0.02*†
Unknown	489	9.1	961	12.0	0.09	847	15.2	857	10.7	0.00*
Medicaid eligibility										
Medicaid vs CHIP	4,765	88.9	7,122	89.1	0.01	4,965	89.1	7,104	88.8	0.01*
Provider characteristics*										
Dentists	1,305	24.3	623	7.8	-0.46†	769	13.8	1,149	14.4	-0.02*†
Emergency Room Prescribers	912	17.0	640	8.0	-0.27†	608	10.9	1,002	12.5	0.04*†
Obstetrics and Gynecology specialists	65	1.2	30	0.4	-0.09	35	0.6	57	0.7	-0.02*
Other Specialists	132	2.5	118	1.5	-0.07	117	2.1	169	2.1	-0.06*
Physician Assistant	96	1.8	314	3.9	0.13	155	2.8	248	3.1	-0.01*
Primary Care Providers	658	12.3	5,660	70.8	1.48†	2,778	49.8	3,778	47.2	0.00*†
Surgical Specialists (Surgeons)	2,195	40.9	611	7.6	-0.84†	1,113	20.0	1,594	20.0	-0.01*†
Procedures and Diagnoses										
Abdominal Pain	146	2.7	1,389	17.4	0.50†	452	8.1	907	11.3	0.02*†
Back pain	62	1.2	164	2.1	0.07	96	1.7	133	1.7	-0.02*
Dental Surgery/Procedure	1,305	24.3	623	7.8	-0.46†	769	13.8	1,149	14.4	-0.02*†
General infections	125	2.3	1,621	20.3	0.59†	662	11.9	1,036	13.0	0.03*†
Generalized pain	63	1.2	385	4.8	0.21	335	6.0	271	3.4	0.02*
Headache and Migraines	73	1.4	548	6.9	0.28†	502	9.0	372	4.7	0.01*†
Musculoskeletal pain	125	2.3	556	7.0	0.22	241	4.3	401	5.0	-0.03*
Outpatient Surgery/Procedure	2,104	39.2	908	11.4	-0.67†	1,179	21.2	1,771	22.2	0.00*†
Trauma	1,336	24.9	1,716	21.5	-0.08	1,308	23.5	1,892	23.7	-0.02*

Table 2.1 *Covariate Balance Assessment before and after IPTW propensity score adjustment for opioid and non-opioid recipients (continued)*

Asthma Risk Factors										
History of asthma-related ER visit	598	11.2	499	6.2	-0.17	472	8.5	726	9.1	-0.03*
History of asthma-related hospitalization	103	1.9	65	0.8	-0.1	73	1.3	104	1.3	-0.01*
Short-acting Beta Agonist (SABA) overuse	247	4.6	219	2.7	-0.09	202	3.6	295	3.7	-0.03*
Providers prescribing analgesic and anti-asthmatic medications to the same patient	156	2.9	2,777	34.7	0.89†	1,597	28.7	1,756	22.0	-0.08*†

* Standardized mean differences after propensity score IPT weighing lie between the confidence limits [-0.25 to 0.25] and signify balance of covariates across the two groups (opioid and non-opioid analgesic recipients).

† Standardized mean differences for these covariates before IPT weighting were not balanced; however, after IPT weighting, they are balanced.

IPTW – Inverse Probability of Treatment Weighting

CHIP – Children's Health Insurance Program

Incident asthma exacerbation following the exposure to opioid and non-opioid analgesics

Twenty-four (0.5%) children with an incident opioid analgesic prescription and 22 (0.3%) children with an incident non-opioid analgesic prescription had asthma associated hospital admission or ER visit within 3 days following the analgesic dispense (p=0.09) (**Table 2.2**).

Table 2.2 *Distribution of asthma exacerbation across opioid and non-opioid recipients.*

Patients experiencing asthma exacerbation during follow-up period	**Opioid analgesic recipients N=5,363 (100%)**	**Non-opioid analgesic recipients N=7,996 (100%)**	**p value**
Main Findings[a]			
Asthma exacerbation (3-day follow-up)	24 (0.5)	22 (0.3)	0.09
Sensitivity Findings (on duration of follow-up)[a]			
Asthma exacerbation (4-day follow-up)	28 (0.5)	30 (0.4)	0.21
Asthma exacerbation (7-day follow-up)	37 (0.7)	41 (0.5)	0.19
Sensitivity Findings (on operational definition and duration of follow-up)[b]			
Asthma exacerbation (3-day follow-up)	32 (0.6)	34 (0.4)	0.17
Asthma exacerbation (4 day follow-up)	39 (0.7)	48 (0.6)	0.37
Asthma exacerbation (7-day follow-up)	54 (1.0)	81 (1.1)	0.97

[a]This definition of asthma exacerbation includes service utilizations corresponding to hospitalization or ER visit with an asthma diagnosis.

[b]This definition of asthma exacerbation includes service utilizations corresponding to hospitalization, ER visit, or oral corticosteroid prescription associated with an outpatient visit with an asthma diagnosis claim in the primary or secondary position.

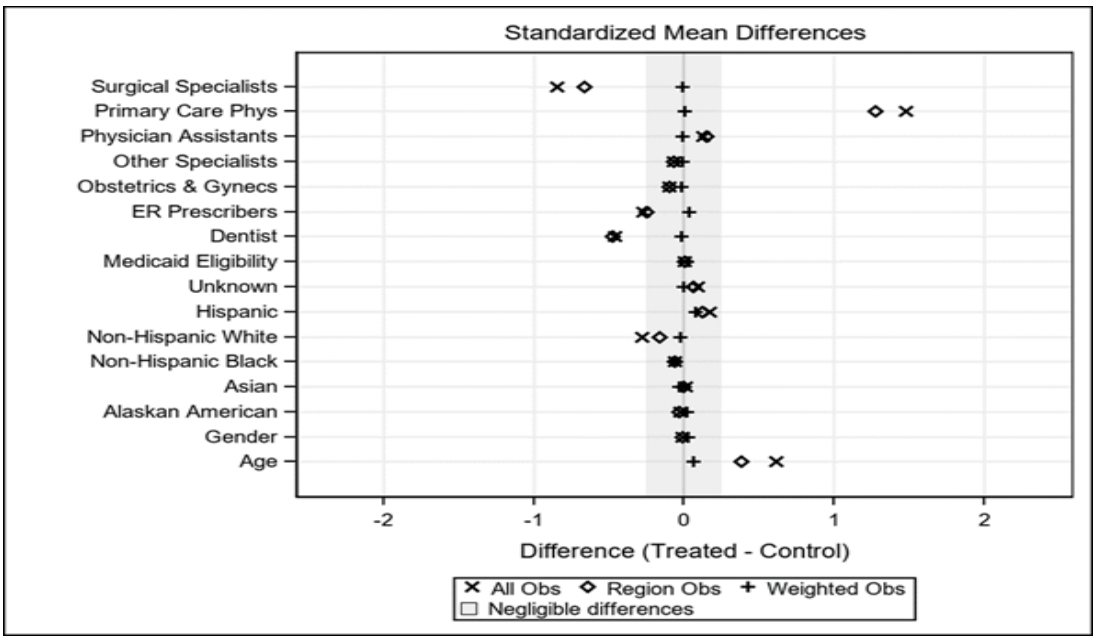
Weighted logistic regression analysis on the risk asthma exacerbation associated with the exposure to opioid versus non-opioid analgesics.

After the adjustment using Inverse IPTW, all the baseline covariates were comparable between opioid and non-opioid analgesic recipients.

The standardized mean differences on covariates that were different prior to the adjustment, such as patient demographics, provider characteristics, patient diagnosis and procedures, and their healthcare utilization history associated with uncontrolled asthma, were not statistically significant (**Table 2.1** and **Figure 2.2**).

The results of IPTW weighted logistic regression (**Table 2.3**) showed that the risk of asthma exacerbation within 3 days of analgesic dispensing was comparable [aOR=1.6 (95% CI: 0.9-2.9)] between opioid and non-opioid recipients.

Figure 2.2 *Covariate balance assessment opioid and non-opioid analgesic recipients after IPTW adjustment.*



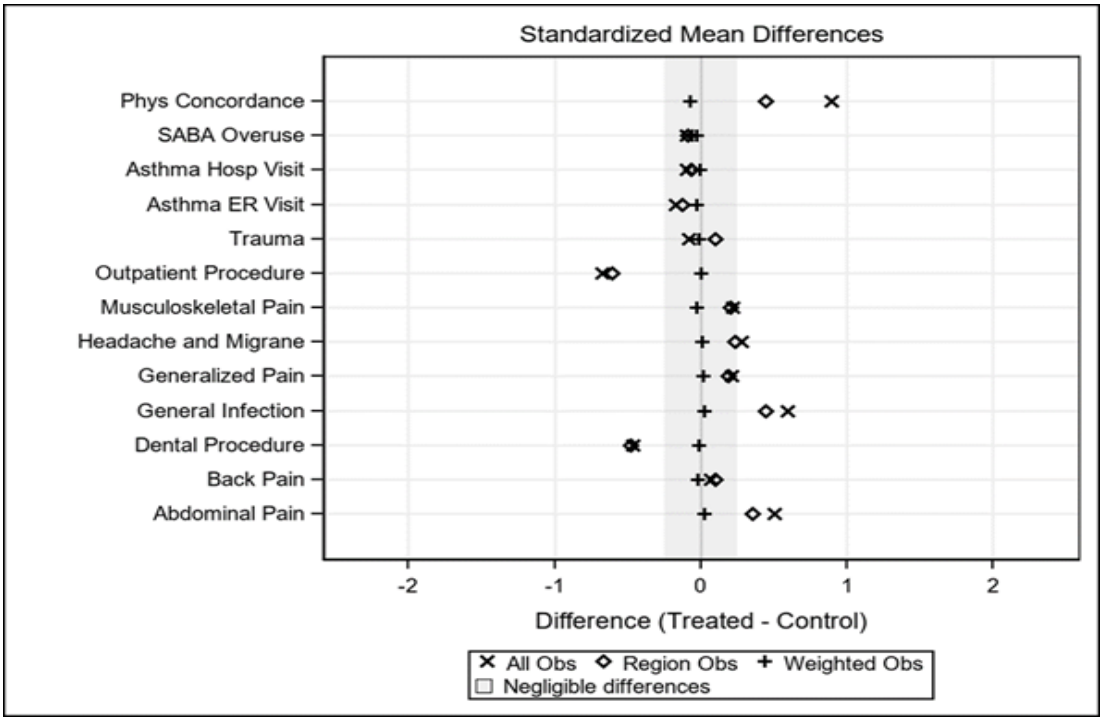


Figure 2.2 legend: The above figure represents the overall covariate balance between the treated (opioid recipients) and control (non-opioid recipients) expressed as standardized mean difference after IPTW adjustment. The weighted observations (+) lie within the -0.25 to 0.25 limit, indicating that, after IPTW propensity score adjustment, the treated and control groups are similar on the basis of all baseline covariates included in the propensity score model.

Sensitivity Analysis on the duration of follow up

The risk of asthma-related ER visits and hospital admissions remained comparable between opioid and non-opioid analgesic recipients despite changing the duration of follow-up to 4 days [aOR=1.0 (95% CI: 0.6-1.7)] and 7 days [aOR= 1.4 (95% CI: 0.9-2.1)] (**Table 2.3**).

Sensitivity Analysis on the Operational Definition of Asthma Exacerbation

Using a more lenient asthma exacerbation definition including asthma-related ER visits, hospital admissions, and OCS use, the adjusted analysis showed that the asthma exacerbation rates were still low and the association between opioid exposure and asthma exacerbation remained statistically insignificant [aOR: 1.4 (0.9-2.2)].

Similarly, for extended follow-up duration of 4 days and 7 days, the risk of asthma exacerbation was comparable and not statistically significant **(Table 2.3).**

Table 2.3 *Association between receipt of opioid versus non-opioid analgesic and risk of asthma exacerbation in children and adolescents (unadjusted and adjusted findings).*

Characteristics	Unadjusted Odds Ratio (95% Confidence Limits)	Adjusted Odds Ratio (95% Confidence Limits)
Main Findings[a]		
opioid vs non-opioid recipients (3-day follow-up)	1.6 (0.9 – 2.9)	1.6 (0.9 – 2.9)
Sensitivity Findings (on duration of follow-up)[a]		
opioid vs non-opioid recipients (4-day follow-up)	1.4 (0.8 – 2.3)	1.0 (0.6 – 1.7)
opioid vs non-opioid recipients (7-day follow-up)	1.3 (0.9 – 2.1)	1.4 (0.9 – 2.1)
Sensitivity Findings (on operational definition and duration of follow-up)[b]		
opioid vs non-opioid recipients (3-day follow-up)	1.4 (0.9 – 2.3)	1.4 (0.9 – 2.2)
opioid vs non-opioid recipients (4-day follow-up)	1.2 (0.8 – 1.9)	1.0 (0.7 – 1.5)
opioid vs non-opioid recipients (7-day follow-up)	1.0 (0.8 – 1.5)	1.1 (0.8 – 1.5)

[a]This definition of asthma exacerbation includes service utilizations corresponding to hospitalization or ER visit with an asthma diagnosis.

[b]This definition of asthma exacerbation includes service utilizations corresponding to hospitalization, ER visit, or oral corticosteroid prescription associated with an outpatient visit with an asthma diagnosis claim in the primary or secondary position.

Unweighted logistic regression and IPT weighted logistic regression models were used for the unadjusted and adjusted analyses, respectively.

7. DISCUSSIONS

Discussion (Aim 1)

The primary finding of our study was that more than a quarter of children with current asthma received an opioid prescription during the study period. Two thirds of the opioid analgesic recipients received the prescriptions following a general surgery/procedure, a dental surgery/procedure, or trauma.

A considerable number of children with current asthma received opioid analgesics following the diagnoses of relatively minor conditions, such as respiratory infections (10.6%), abdominal pain (4.7%), and general infections (3.8%).

A history of uncontrolled asthma was defined in our study as asthma-related hospitalization, ER visit, and SABA prescriptions during the 1-year period prior to the index analgesic dispensing. We observed that children with asthma-related ER visits and SABA overuse, but not asthma-related hospital admission, during the 1-year prior index period had a higher likelihood of receiving opioid dispensing than did those without the utilization history.

Given most of these asthma-related events happened on average 5 to 6 months before the index analgesic dispensing, the higher likelihood of opioid dispensing associated with the healthcare utilization history was unlikely a direct consequence of the service utilization, such as ER visit. Instead, we found these children more frequently received opioid analgesics associated with respiratory infection and general infection than did their counterparts without the service utilization history indicating uncontrolled asthma.

Literature has reported that opioids have been frequently used as cough/pain medications for various respiratory tract infections caused by influenza and respiratory syncytial virus.[29-31] However, such use could lead to serious side effects, such as slowed or difficult breathing, and has been associated with death in children.[32] Our findings on frequent oral opioid analgesic use in asthmatic children with respiratory infection imply that it is a potential area for quality improvement.

Our result has also indicated that the odds of receiving opioid dispensing peaked in 2015 and then gradually dropped back to the 2013 level by the year 2018. The change of opioid utilization in children with current asthma may have reflected the overall decrease in opioid analgesic utilization in the pediatric population as a result of a series of FDA warnings issued during the time period. The FDA started evaluating the risk of tramadol as a pain medication in children and codeine as a cough medication in 2015, and there was a Joint Meeting of multiple FDA Advisory Committees discussing the opioid use in children in 2016.

Following this meeting, the FDA issued a change of the drug label of codeine cough medications in April 2017 with a contraindication and a boxed warning. The contraindication states that *"Codeine should not be used to treat pain or cough in children younger than 12 years."* The age-specific boxed warning is as follows: *"A new Warning to the drug label of codeine to recommend against its use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems."*[33]

Later in January 2018, the FDA further revised the labels of codeine and hydrocodone cough medications. The safety label reads as follows: *"The U.S. Food and Drug Administration (FDA) is requiring safety labeling changes for prescription cough and cold medicines containing codeine or hydrocodone to limit the use of these products to adults 18 years and older because the risks of these medicines outweigh their benefits in children younger than 18."*[34] The decrease in incident opioid analgesic recipients from 2013 to 2018 in our study cohort with asthma is consistent with studies examining the general opioid use in children and adolescents during the similar timeframe,[35,36] potentially due to multiple FDA contraindications and warnings taking effect during this period.[33,34,37-39]

Another important finding of our study is that, irrespective of patient diagnoses and procedures, non-Hispanic Black and Hispanic children were at least 50% less likely to receive an opioid than their non-Hispanic White counterparts were.

Prior studies with similar findings indicated that physicians could potentially react differently to pain in children belonging to different race/ethnicities and may preferentially choose to prescribe White individuals an opioid while prescribing NSAIDs to Blacks and Hispanics with similar pain profiles.[40,41]

The differential prescribing of opioid analgesic according to patients' race/ethicity could be due to implicit biases that *"involve association outside conscious awareness that leads to a negative evaluation of a person on the basis of unimportant characteristics such as race or gender."*[42] A recent survey of academic

pediatricians found that the presence of pro-White implicit bias was associated with decreases in prescribing narcotic medications for post-surgical pain to African Americans, without affecting the White patients.[43]

Prior studies have also shown that caregivers from various racial/ethnic groups have distinctively different preferences about their children's analgesic medication.[44,45] Because caregivers play a vital role in handling medications for children, their influence on deciding which analgesic modality is better could influence the prescriber in prescribing non-opioid analgesics to non-White individuals.[46,47] Additional studies are needed to understand the impact of interplays of physicians' and caregivers' perceptions and preferences on the drastically different pediatric analgesic utilization pattern across racial/ethnic groups.

Last, the drug inserts of many opioid analgesics including codeine, hydrocodone, and tramadol, contraindicate the use of these medications in patients *"with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment."*[11-14] The FDA's decision of including asthma as a contraindication of opioids is supported by potential drug mechanisms of opioids; however, the risk has yet to be proved by either empirical or epidemiological evidence.

The lack of documentation has led to various interpretations on the warning among pediatric clinicians and researchers, with some believing the warning only refers to patients who are undergoing asthma exacerbation and others feeling that it includes all patients with current asthma. Moreover, some studies have also reported that nonsteroidal anti-inflammatory drugs (NSAIDs) also have a modest risk of precipitating an asthma exacerbation.[48,49]

More studies are needed to quantify the relative risk (e.g., asthma exacerbation) associated with the use of opioids versus alternative pain analgesics in children with current asthma, especially among those with non-priority conditions such as respiratory infections and the subgroups with prior healthcare utilization indicating uncontrolled asthma.

Limitation.

Although we applied a previously utilized algorithm[50] for attributing the receipt of analgesic to the specified indication, the study utilizes a pharmacy and medical claims data, and there is no direct link that could establish the fact that the analgesic medication was prescribed for a specific pain diagnosis and/or outpatient procedure. As the study sample was children in Medicaid Managed Care, generalization of the findings to commercially insured populations should be with caution.

Discussion (Aim 2)

Our findings suggested that, among children with asthma, the asthma exacerbation event following an analgesic administration is uncommon (0.3%-0.5%). The risk of asthma-related ER visits and hospitalizations was not significantly different between those who received opioid and non-opioid analgesics in both bivariate and adjusted analysis. The findings remained consistent in sensitivity analyses that altered the operational definitions of observation period and asthma exacerbation.

Opioid use in children has long been a public health concern. Since 2012, FDA has issued a series of labeling change for the use of codeine, tramadol, and hydrocodone in children and adolescents.[27-28] These warnings highlight the potential risk of opioids in precipitating respiratory depression in children with a compromised airway function,[33,34] based on isolated case reports that indicated opioid use could lead to side effects such as difficulty breathing, in rare instances culminating in death.[32]

Similar to other FDA warnings associated with opioid use in children, the FDA contraindication for the use of codeine, hydrocodone, and tramadol in patients *"with acute or severe bronchial asthma"*[11-14] was issued without the support of any published pediatric data. FDA issued this contraindication warning based on what is known about the pharmacological mechanisms of action associated with opioids, rather than the real-world patient data, that may precipitate a risk of asthma exacerbation through various pathways.[4, 6-10]

In the several decades since the FDA contraindication warning was issued, the available evidence supporting the warning has been limited to illicit drug users and adults with opioid use disorder. There have

been case reports of asthma exacerbation among adults following the use of either injectable or inhaled heroin,[51-53] and the use of a transdermal fentanyl patch.[40] The risk of asthma associated with opioid use was also reported in a recent case-control study among adults with opioid use disorder.[41]

Our findings bridge the gap and clarify the safety concern associated using prescription analgesics among children with asthma for pediatric practitioners who often need to prescribe opioid analgesics, such as surgeons, emergency room physicians, and dentists.

The findings suggest that an asthma exacerbation event following a prescription analgesic administration among children with current asthma was uncommon (0.3%-0.5%). Using opioids does not cause a significantly higher risk of asthma exacerbation compared with non-opioid analgesics in the patient population.

Medication safety in vulnerable patient populations, such as children, has always been concerns in the medical society. However, in contrast to its importance, limited data are available to understand the comparative safety between perceived high-risk medications, such as opioids, and their alternatives, such as NSAIDs, which have posed significant barriers to appropriate medication use in children. Additional pediatric data are needed to help policymakers, prescribers, and patients interpret the implication of the FDA warnings for minors.

Despite the significant implication of our study findings, the study has limitations. Our study sample included only Medicaid- and CHIP-enrolled children and adolescents living in southeast Texas. The sample predominantly consisted of Hispanics (53%). The results might not be generalizable to more affluent populations and/or to populations with substantially different ethnicities.

Moreover, a considerable number of pediatric analgesic recipients in our cohort were excluded either due to the lack of continuous Medicaid or CHIP coverage (enrollment) during the study period or due to the lack of a long enough analgesic-free period to establish an incident user status. These patients were excluded to ensure a strong internal validity in terms of identifying the outcome (asthma exacerbation) and its temporally associating with the exposure (receipt of an incident opioid vs non-opioid analgesics). However, the approach has led to a more restrictive cohort that inadvertently limited the generalizability of our findings.

8. CONCLUSIONS

Conclusion for Aim 1

Opioid analgesics are commonly prescribed to children with asthma. The utilization rate is higher among non-Hispanic White children and children with prior asthma-related emergency department visit and short-acting beta agonist overuse. Other than procedures and diagnoses associated with frequent opioid utilization, such as surgical and dental procedures, a considerable number of children with asthma also receive opioids for relatively minor conditions including respiratory infections, abdominal pain, and general infections.

Conclusion for Aim 2

Our findings indicated that asthma exacerbation is uncommon following the dispensing of either opioid or non-opioid analgesic medication in children with current asthma. There was no significant difference in the odds of asthma exacerbation following the dispensing of opioid versus non-opioid analgesics.

9. LIST of PUBILICATIONS

Nair AA, Farber HJ, Chen H. Utilization of opioid versus non-opioid analgesics in Medicaid and CHIP enrolled children with current asthma. *Pharmacoepidemiol Drug Saf*. 2021 Jul 29; doi: 10.1002/pds.5336. [Epub ahead of print. PubMed PMID: 34322934]

Nair AA, Farber HJ, Chen H. Opioid analgesic use and risk of asthma exacerbation in children and adolescents with current asthma. Accepted for publication in *Journal of Managed Care Pharmacy*.

9. REFERENCES:

1. Most Recent Asthma Data, Data Statistics and Surveillance, Asthma, CDC. https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm
2. National Center for Health Statistics. FastStats - Asthma. https://www.cdc.gov/nchs/fastats/asthma.htm
3. Sala KA, Carroll CL, Tang YS, Aglio T, Dressler AM, Schramm CM. Factors associated with the development of severe asthma exacerbations in children. *J Asthma*. Aug 2011;48(6):558-64. doi:10.3109/02770903.2011.585411
4. Werner HA. Status asthmaticus in children: a review. *Chest*. Jun 2001;119(6):1913-29. doi:10.1378/chest.119.6.1913
5. Hlavaty L, Hansma P, Sung L. Contribution of opiates in sudden asthma deaths. *Am J Forensic Med Pathol*. Mar 2015;36(1):49-52. doi:10.1097/PAF.0000000000000138
6. Boom M, Niesters M, Sarton E, Aarts L, Smith TW, Dahan A. Non-analgesic effects of opioids: opioid-induced respiratory depression. *Curr Pharm Des*. 2012;18(37):5994-6004. doi:10.2174/138161212803582469
7. Jungquist CR, Karan S, Perlis ML. Risk factors for opioid-induced excessive respiratory depression. *Pain Manag Nurs*. Sep 2011;12(3):180-7. doi:10.1016/j.pmn.2010.02.001
8. Radke JB, Owen KP, Sutter ME, Ford JB, Albertson TE. The effects of opioids on the lung. *Clin Rev Allergy Immunol*. Feb 2014;46(1):54-64. doi:10.1007/s12016-013-8373-z
9. Dahan A, Aarts L, Smith TW. Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression. *Anesthesiology*. Jan 2010;112(1):226-38. doi:10.1097/ALN.0b013e3181c38c25
10. Martin WR. Opioid antagonists. *Pharmacol Rev*. Dec 1967;19(4):463-521.
11. Hysingla Package Insert. 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206627s004lbl.pdf
12. Vicodin Package Insert. 2017. https://www.rxabbvie.com/pdf/vicodin_apap_300mg_hydrocodone_5mg-7_5mg-10mg_PI.pdf
13. Ultram Package Insert. 2019. Accessed 06-18-2020. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/ULTRAM-pi.pdf
14. Tylenol with Codeine CIII package insert. 2019. Accessed 06-18-2020. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/TYLENOL+WITH+CODEINE-pi.pdf
15. Texas Children's Health Plan. Updated 2020. http://www.texaschildrenshealthplan.org/.
16. Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality: United States, 2005-2009. *Natl Health Stat Report*. Jan 12 2011;(32):1-14.
17. Arellano FM, Arana A, Wentworth CE, Vidaurre CF, Chipps BE. Prescription patterns for asthma medications in children and adolescents with health care insurance in the United States. *Pediatr Allergy Immunol*. Aug 2011;22(5):469-76. doi:10.1111/j.1399-3038.2010.01121.x
18. Chastek B, Korrer S, Nagar SP, et al. Economic Burden of Illness Among Patients with Severe Asthma in a Managed Care Setting. *J Manag Care Spec Pharm*. Jul 2016;22(7):848-61. doi:10.18553/jmcp.2016.22.7.848
19. Dombkowski KJ, Wasilevich EA, Lyon-Callo SK. Pediatric asthma surveillance using Medicaid claims. *Public Health Rep*. Sep-Oct 2005;120(5):515-24. doi:10.1177/003335490512000506
20. Andersen RM. Revisiting the behavioral model and access to medical care: does it matter? *J Health Soc Behav*. Mar 1995;36(1):1-10.
21. Andersen RM. National health surveys and the behavioral model of health services use. *Med Care*. Jul 2008;46(7):647-53. doi:10.1097/MLR.0b013e31817a835d
22. Farber HJ, Silveira EA, Vicere DR, Kothari VD, Giardino AP. Oral Corticosteroid Prescribing for Children With Asthma in a Medicaid Managed Care Program. *Pediatrics*. May 2017;139(5)doi:10.1542/peds.2016-4146
23. Nwaru BI, Ekstrom M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting beta2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. *Eur Respir J*. Apr 2020;55(4)doi:10.1183/13993003.01872-2019

24. Silver HS, Blanchette CM, Kamble S, et al. Relationship between short-acting beta2-adrenergic agonist use and healthcare costs. *Am J Manag Care*. Jan 2011;17(1):19-27.
25. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med*. Jul 1 2009;180(1):59-99. doi:10.1164/rccm.200801-060ST
26. *SAS Enterprise Guide 8.1*. Version 8.1. SAS Institute Inc.; 2019. Accessed October 10, 2019. https://support.sas.com/en/software/enterprise-guide-support.html
27. Brookhart MA, Wyss R, Layton JB, Sturmer T. Propensity score methods for confounding control in nonexperimental research. *Circ Cardiovasc Qual Outcomes*. Sep 1 2013;6(5):604-11. doi:10.1161/CIRCOUTCOMES.113.000359
28. Schulte PJ, Mascha EJ. Propensity Score Methods: Theory and Practice for Anesthesia Research. *Anesth Analg*. Oct 2018;127(4):1074-1084. doi:10.1213/ANE.0000000000002920
29. Coussons-Read ME, Daniels M, Gilmour MI. Morphine alters the immune response to influenza virus infection in Lewis rats. *Adv Exp Med Biol*. 1998;437:73-82. doi:10.1007/978-1-4615-5347-2_9
30. Salimi V, Hennus MP, Mokhtari-Azad T, et al. Opioid receptors control viral replication in the airways. *Crit Care Med*. Jan 2013;41(1):205-14. doi:10.1097/CCM.0b013e31826767a8
31. Tahamtan A, Tavakoli-Yaraki M, Mokhtari-Azad T, et al. Opioids and Viral Infections: A Double-Edged Sword. *Front Microbiol*. 2016;7:970. doi:10.3389/fmicb.2016.00970
32. Niesters M, Overdyk F, Smith T, Aarts L, Dahan A. Opioid-induced respiratory depression in paediatrics: a review of case reports. *Br J Anaesth*. Feb 2013;110(2):175-82. doi:10.1093/bja/aes447
33. Drug Safety and Availability - FDA Drug Safety Communication: FDA Restricts Use of Prescription Codeine Pain and Cough Medicines and Tramadol Pain Medicines in Children; Recommends against Use in Breastfeeding Women (2017).
34. Drug Safety and Availability - FDA Drug Safety Communication: FDA Requires Labeling Changes for Prescription Opioid Cough and Cold Medicines to Limit Their Use to Adults 18 Years and Older (2018).
35. Basco WT, McCauley JL, Zhang J, et al. Trends in Dispensed Opioid Analgesic Prescriptions to Children in South Carolina: 2010–2017. Pediatrics. 2021;147(3):e20200649. doi:10.1542/peds.2020-0649
36. Rizeq YK, Many BT, Vacek JC, et al. Trends in perioperative opioid and non-opioid utilization during ambulatory surgery in children. Surgery. 2019;166(2):172-176. doi:10.1016/j.surg.2019.04.005
37. Drug Safety and Availability - FDA Drug Safety Communication: Safety Review Update of Codeine Use in Children; New Boxed Warning and Contraindication on Use after Tonsillectomy and/or Adenoidectomy (2013).
38. Drug Safety and Availability - FDA Drug Safety Communication: FDA Evaluating the Potential Risks of Using Codeine Cough-and-Cold Medicines in Children (2015).
39. Drug Safety and Availability - FDA Drug Safety Communication: FDA Evaluating the Risks of Using the Pain Medicine Tramadol in Children Aged 17 and Younger (2015).
40. Parmar MS. Exacerbation of asthma secondary to fentanyl transdermal patch. *BMJ Case Rep*. 2009;2009doi:10.1136/bcr.10.2008.1062
41. Oliver P, Hulin J, Mitchell C. A primary care database study of asthma among patients with and without opioid use disorders. *npj Primary Care Respiratory Medicine*. 2020;30(1)doi:10.1038/s41533-020-0174-2
42. Fitzgerald C, Hurst S. Implicit bias in healthcare professionals: a systematic review. *BMC Medical Ethics*. 2017;18(1)doi:10.1186/s12910-017-0179-8
43. Sabin JA, Greenwald AG. The Influence of Implicit Bias on Treatment Recommendations for 4 Common Pediatric Conditions: Pain, Urinary Tract Infection, Attention Deficit Hyperactivity Disorder, and Asthma. *American Journal of Public Health*. 2012;102(5):988-995. doi:10.2105/ajph.2011.300621
44. Groenewald CB, Rabbitts JA, Gebert JT, Palermo TM. Trends in opioid prescriptions among children and adolescents in the United States: a nationally representative study from 1996 to 2012. *Pain*. May 2016;157(5):1021-7. doi:10.1097/j.pain.0000000000000475
45. Ringwalt C, Gugelmann H, Garrettson M, et al. Differential prescribing of opioid analgesics according to physician specialty for Medicaid patients with chronic noncancer pain diagnoses. *Pain Res Manag*. Jul-Aug 2014;19(4):179-85. doi:10.1155/2014/857952

46. Kajioka EH, Itoman EM, Li ML, Taira DA, Li GG, Yamamoto LG. Pediatric prescription pick-up rates after ED visits. Am J Emerg Med. Jul 2005;23(4):454-8. doi:10.1016/j.ajem.2004.10.015
47. Zweigoron RT, Binns HJ, Tanz RR. Unfilled prescriptions in pediatric primary care. Pediatrics. Oct 2012;130(4):620-6. doi:10.1542/peds.2011-3480
48. Lo PC, Tsai YT, Lin SK, Lai JN. Risk of asthma exacerbation associated with nonsteroidal anti-inflammatory drugs in childhood asthma: A nationwide population-based cohort study in Taiwan. *Medicine (Baltimore)*. Oct 2016;95(41):e5109. doi:10.1097/MD.0000000000005109
49. Sturtevant J. NSAID-induced bronchospasm--a common and serious problem. A report from MEDSAFE, the New Zealand Medicines and Medical Devices Safety Authority. *N Z Dent J*. Sep 1999;95(421):84.
50. Chung CP, Callahan ST, Cooper WO, et al. Outpatient Opioid Prescriptions for Children and Opioid-Related Adverse Events. *Pediatrics*. Aug 2018;142(2)doi:10.1542/peds.2017-2156
51. Doshi V, Shenoy S, Ganesh A, Rishi MA, Molnar J, Henkle J. Profile of Acute Asthma Exacerbation in Drug Users. *Am J Ther*. Jan/Feb 2017;24(1):e39-e43. doi:10.1097/MJT.0000000000000118
52. Caponnetto P, Auditore R, Russo C, et al. “Dangerous Relationships”: Asthma and Substance Abuse. *Journal of Addictive Diseases*. 2013;32(2):158-167. doi:10.1080/10550887.2013.795469
53. Underner M, Perriot J, Peiffer G, Jaafari N. Asthma and Heroin Use. *La Presse Médicale*. 2017;46(7-8):660-675. doi:10.1016/j.lpm.2017.06.002