2020

The impact of the FDA warning on post-tonsillectomy opioid prescribing in publicly and privately insured children

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

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Acknowledgements

There are many who offered guidance and assistance throughout this dissertation process. To begin, this work would not have been possible without the support of my advisor, Dr. Chuck Biddle. Dr. Biddle - you exemplify what it means to be a great mentor. Your commitment to this project, your sound comments and insightful feedback helped to develop and refine this research. You are simultaneously busy in your professional work, yet always available to offer edits or advice – a balance that leads me to be both mystified and appreciative. I extend my deepest gratitude to you for chairing my committee and helping bring this project to fruition.

Further acknowledgement and thanks to my entire dissertation committee – Dr. T. Corey Davis, Dr. Pramit Nadpara and Dr. Jackie Shannon. Each of you challenged and enriched my ideas. Dr. Davis, your early involvement in this dissertation assisted me to refine the project and develop realistic timelines. Dr. Nadpara, your methodological and analytical suggestions strengthened the rigor of this dissertation. Dr. Shannon, your challenge of "if true, then what" sharpened my ability to see that research is not the end point itself – rather it is just the beginning. A heartfelt thank you to each of you for serving on my committee.

I am deeply grateful for the collaboration with individuals from my home institution, Oregon Health & Science University, including Dr. Miguel Marino, Dr. Derek Lam and Mr. Joe Fazio. Dr. Marino, I am indebted to you for offering your statistical guidance. This project would not have been realized without your support and I deeply appreciate your time. Dr. Lam, thank you for adding your clinical expertise and departmental knowledge to this dissertation. Joe, I am humbled that you graciously gave of your time to extract the data and help me become acquainted with the dataset. Also, to my many instructors at Virginia Commonwealth University who contributed their expertise to my learning – thank you.

I did not complete this dissertation alone – I owe tremendous thanks to family and friends. Thank you to my fellow PhD cohort for your encouragement, support and friendship. To my parents, Dino and Mary Ann Medori – a very special thank you for always encouraging me to achieve my goals. Saving the best for last, I am eternally thankful for my husband, Cobin Soelberg. He made countless sacrifices – big and small – to support me through this journey. Thank you for your love, partnership and your determination to make me 'take a break' every now and then.

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Abstract

THE IMPACT OF THE FDA WARNING ON POST-TONSILLECTOMY OPIOID PRESCRIBING IN PUBLICLY AND PRIVATELY INSURED CHILDREN

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

Virginia Commonwealth University, 2020.

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Due to reports of significant adverse events, the U.S. FDA placed a *Boxed Warning* on the opioid codeine in February 2013 – contraindicating its use in pediatric patients undergoing tonsillectomy and/or adenoidectomy. Studies conducted in privately insured children showed a reduction in codeine prescribing and a slight increase in alterative opioid prescribing following the FDA warning, yet the extent to which the FDA warning impacted prescribing in publicly insured children is unknown. Using a quasi-experimental interrupted time series design, this study evaluated codeine and alternative opioid prescribing before and after the FDA warning in both publicly and privately insured children and compared prescribing between groups. Data on 5603 children undergoing tonsillectomy and/or adenoidectomy at Oregon Health and Science University from 2010 – 2018 was analyzed via segmented regression analysis. Findings suggest codeine and alternative opioid prescribing decreased in both groups after the FDA warning and prescribing was comparable between groups. There was no difference in the mean level (p = 0.664) or pre-post intervention slopes (p = 0.383) of codeine prescribing and no difference in the mean level (p = 0.103) or pre-post intervention slopes (p = 0.088) of alternative opioid prescribing between groups. Additional findings of interest included the effect of age, procedure

indication and body habitus on opioid prescribing. Of these, young age appeared to influence opioid prescribing to the greatest degree. Results of this study indicate codeine and alternative opioid prescribing decreased after the FDA warning and prescribing did not appear to differ based on health insurance status, though clinical factors appeared to influenced prescribing.

Keywords: pediatric, tonsillectomy, FDA warning, codeine, opioids, health insurance, interrupted time series

Chapter 1: Introduction

Study and Chapter Overview

The purpose of this study is to evaluate opioid prescribing in pediatric post-tonsillectomy and/or adenoidectomy patients before and after the U.S. Food and Drug Administration (FDA) *Boxed Warning* on the opioid codeine, formally published in 2013. This study will seek to assess the impact of the FDA warning on opioid prescribing behaviors in children who underwent tonsillectomy and/or adenoidectomy and examine if prescribing behaviors were influenced by health insurance status. Study results will assess the effect of the FDA warning on codeine prescribing, add additional knowledge on prescribing patterns of alternative/non-codeine containing opioids and help fill a gap in the literature concerning opioid prescribing behaviors in publicly and privately insured pediatric post-tonsillectomy and/or adenoidectomy patients.

This chapter provides a brief background on opioid use in pediatric tonsillectomy and/or adenoidectomy patients and includes a statement of the problem. The study's purpose and significance are summarized, followed by brief introductions to the study's theoretical framework and methodology. Chapter one concludes with an overview of the remaining chapters.

Background

Tonsillectomy, with or without adenoidectomy, is one of the most commonly performed pediatric surgical procedures in the United States (U.S.), with more than 530,000 performed annually in children less than 15 years of age (Baugh et al., 2011). It represents the second most common and ninth most cumulatively expensive reason for care in U.S. children's hospitals (Keren et al., 2012). Though the procedure and care of a patient undergoing tonsillectomy

and/or adenoidectomy is fairly routine, risks do exist – as summarized in Table 1. In particular, children who suffer from sleep-related breathing disorders have a higher preponderance of complications (De Luca Canto et al., 2015; Goldman et al., 2013; Mitchell et al., 2019). Obstructive sleep apnea (OSA) belongs to the continuum of sleep-related breathing disorders and is a common indication for tonsillectomy and/or adenoidectomy. In fact, of the 530,000 pediatric tonsillectomies performed annually, 75% are related to OSA (Patino, Sadhasivam, & Mahmoud, 2013; Roland et al., 2011).

Table 1

Risks and Complications of Tonsillectomy and/or Adenoidectomy

Operative Risks	**Postoperative Complications**
-Trauma to surrounding tissues (teeth, tongue, pharynx, soft palate, pharyngeal wall, carotid artery) -Infection -Airway fire/endotracheal tube ignition -Difficult intubation* -Laryngospasm -Laryngeal edema -Respiratory compromise** -Cardiac arrest -Death or anoxic brain injury**	-Respiratory compromise/apnea*/** -Post-tonsillectomy bleeding/hemorrhage*** -Nausea/vomiting -Pain -Dehydration -Post-obstructive pulmonary edema -Aspiration pneumonitis -Death or anoxic brain injury**

Note: *Higher in children with obesity. **Higher in children with OSA. ***Higher in children without OSA
Information from: (Cote, Lerman, & Anderson. B., 2018; De Luca Canto et al., 2015; Goldman et al., 2013; Mitchell et al., 2019; Statham & Myer, 2010)

OSA has become a major public health concern. Its incidence and severity in the pediatric population have increased, in large-part due to the rising rates of childhood obesity (Marcus et al., 2012; Patino et al., 2013). In the past, a 'watchful waiting' approach was taken for pediatric OSA management. However, when early tonsillectomy was compared with 'watchful waiting' care in randomized controlled trials (RCT), children receiving the surgical intervention

showed reduction of OSA symptoms, normalization of polysomnography (PSG) sleep-study indices and improved quality of life (Garetz et al., 2015; Goldstein et al., 2004; Marcus et al., 2013). A recent Cochrane Database Systematic Review demonstrated high-quality evidence that early tonsillectomy improved PSG indices and moderate-quality evidence that OSA symptoms, quality of life and behavior are improved with early tonsillectomy (Venekamp et al., 2015). Currently, if a child meets criteria for OSA and does not have a contraindication for surgery, tonsillectomy is recommended as the first-line treatment (Marcus et al., 2012). If left untreated, the disorder can be associated with significant morbidity, including long-term cardiopulmonary sequela (Patino et al., 2013).

The tandem rise in early surgical intervention and the growing number of children suffering from obesity and OSA has created the "perfect storm" where perioperative complications, particularly respiratory adverse events, are more likely to occur (Coté, Posner, & Domino, 2014; Marcus et al.,, 2012; Patino et al., 2013). Many of these complications are related to medications that depress the respiratory drive, such as opioids. Opioids exert their action on the μ-receptors, which are located throughout the central nervous system and, to a lesser extent, in the periphery (Pathan & Williams, 2012). Agents that bind to these receptors cause analgesia – but also other unwanted effects, namely sedation and respiratory depression. In children with OSA, these effects are markedly increased due to greater opioid-related sensitivity (Marcus et al., 2012; Patino et al., 2013). Opioids exacerbate pharyngeal collapse, worsen OSA symptoms and can lead to significant complications, including respiratory adverse events or death (Coté et al., 2014). Such complications represent major limitations to the use of opioids in children with OSA.

Additionally, genetic variations in opioid metabolism further amplifies the risk of opioids in children undergoing tonsillectomy and/or adenoidectomy. The role of genetic phenotypes and polymorphisms are known to create noticeable differences in inter-individual drug metabolism. It is well established that pharmacogenetics was a contributing factor in several codeine-related adverse events, yet the extent to which pharmacogenetics play a role in the clinical response to other opioids is not fully elucidated (Parikh, Amolenda, Rutledge, Szabova, & Chidambaran, 2019). Still, it appears as though there is interplay between genetic risk signatures and clinical risk factors in opioid-related adverse events in children undergoing tonsillectomy and/or adenoidectomy (Biesiada et al., 2014) – furthering the conditions that generate the "perfect storm" of complications.

The safety of opioids in children undergoing tonsillectomy and/or adenoidectomy came under intense scrutiny after several unfortunate events and poor outcomes. For decades, providers prescribed the opioid codeine for post-tonsillectomy and/or adenoidectomy pain – however, death and/or serious adverse events were reported after administration of codeine in some children (Cote et al., 2014). A review of cases reported to the U.S. Food and Drug Administration's (FDA) Adverse Event Reporting System between 1969 and 2012 identified 10 deaths and 3 overdoses in children who had undergone tonsillectomy and/or adenoidectomy and were treated with codeine – 8 of which were attributed to OSA related opioid sensitivity and/or genetic variants leading to rapid metabolism of codeine (Coté et al., 2014; Kuehn, 2013; Tobias, Green, & Coté, 2016). Subsequently, the FDA contraindicated the use of codeine in all children undergoing tonsillectomy by placing a *Boxed Warning* – the FDA's strongest warning – on the drug (Kuehn, 2013). Specifically, the 2013 FDA warning advised health care professionals "to prescribe an alternative analgesic [to codeine] for postoperative pain control in children

undergoing tonsillectomy and/or adenoidectomy" (U.S. FDA Drug Safety Communications, 2013).

Encouragingly, two recent analyses found a significant reduction in post-tonsillectomy and/or adenoidectomy codeine prescribing following the FDA warning, with a slight increase in prescribing of alternative opioids (Chua, Shrime, & Conti, 2017; Van Cleve, 2017). These authors, and others, have made meaningful contributions to the literature regarding post-tonsillectomy codeine and opioid prescribing patterns – however, important gaps in knowledge remain.

Gaps in Knowledge

One considerable limitation to recent work in the field is the population of interest. Rates of tonsillectomy and/or adenoidectomy are similar for children insured by Medicaid compared with those insured by private sources (Boss, Marsteller, & Simon, 2012) – though, to date, all relevant studies have examined post-tonsillectomy and/or adenoidectomy codeine and opioid prescribing in *privately* insured children. Knowledge of post-tonsillectomy prescribing practices in *publicly* insured children is unaccounted for. Though it is difficult to tell whether patients with different types of insurance are treated equally, differences in the medical treatment of publicly insured children and/or those of low socioeconomic status (SES) versus privately insured children are suggested (Alexander & Currie, 2017; Boss et al., 2015; Canino et al., 2010; Sabharwal, Zhao, McClemens, & Kaufmann, 2007). Specifically, differences in opioid prescribing in publicly versus privately insured children are documented. A recent study showed pediatric patients with public insurance were more likely to receive an opioid after surgery than those with private insurance (Donohoe, Zhang, Mensinger, & Litman, 2019). However, other studies demonstrate that children with private insurance were prescribed more opioids than their

publicly insured counterparts in non-surgical settings (Groenewald, Rabbitts, Gebert, & Palermo, 2016; Tomaszewski, Arbuckle, Yang, & Linstead, 2018). Though the evidence is mixed, these findings suggest it is plausible that codeine and/or opioid prescribing differs between publicly and privately insured children undergoing tonsillectomy and/or adenoidectomy.

The reasons underlying potential prescribing differences in post-tonsillectomy children are likely subtle and complex. Prescribing decisions may be related to potential implicit or explicit bias based on certain patient characteristics (Donohoe et al., 2019; Sabin & Greenwald, 2012). These attitudes and beliefs may subtly and unintentionally contribute to disparities in prescribing practices. Prescribing decisions may also be explained from a clinical perspective. Providers may prescribe less opioids in publicly insured children due to the higher prevalence of certain comorbid conditions in this patient population. Children of lower SES (viewed as a proxy for public insurance) have an increased prevalence of obesity and sleep-related breathing disorders, such as OSA (Boss et al., 2012; Dudley & Patel, 2016). Given the dangers of the combination of opioids, obesity and OSA, it is reasonable to hypothesize that providers are more cautious in prescribing opioids (e.g. prescribe less opioids) to a population of children with a higher prevalence of these disorders. On the other hand, there is a negative association between SES and pain prevalence in pediatric post-tonsillectomy children, where those with lower SES appear to have a higher pain prevalence. This is evidenced by higher rates of emergency room revisits for pain after tonsillectomy in children with decreasing median incomes (Bhattacharyya & Shapiro, 2014). To avoid increased health care utilization (emergency room revisits), providers may prescribe more opioids to those with public insurance.

The combination of recent studies documenting differences in opioid prescribing in publicly and privately insured children, potential provider biases and clinical explanations for

prescribing differences give reason to believe codeine and/or opioid prescribing may differ in public and private pediatric post-tonsillectomy patients.

Problem Statement

Due to its well-documented safety issues, the opioid codeine is contraindicated in all children undergoing tonsillectomy. It appears that as a result of the FDA warning, codeine prescribing rates have fallen in privately insured U.S. children, with a slight (non-significant) increase in alternative opioid prescriptions. Yet, it is unknown to what extent the FDA warning impacted codeine and alternative opioid prescribing rates in publicly insured children – and if prescribing rates differ between publicly and privately insured children.

Study Purpose and Research Questions

The purpose of this study is to investigate the relationship between the FDA warning and codeine/alternative opioid prescribing in publicly and privately insured children who underwent tonsillectomy and/or adenoidectomy at Oregon Health and Science University (OHSU) between 2010 – 2018. Successful completion of this study will help clarify the impact of the FDA warning and compare prescribing rates of codeine and alternative opioids between publicly and privately insured children. This study will seek to answer two questions:

(1) What is the relationship between the FDA warning and codeine/alternative opioid prescribing in children who underwent tonsillectomy at Oregon Health and Science University (OHSU) between January 2010-December 2018?

(2) Does the relationship between codeine and/or alternative opioid prescribing in pediatric post-tonsillectomy children who underwent tonsillectomy at OHSU between January 2010 and December 2018 vary by health insurance status?

Study Significance

This study examines the significant clinical dilemma of opioid prescribing in children undergoing tonsillectomy and/or adenoidectomy. The study will illuminate the impact of the FDA warning on codeine and alternative opioid prescribing rates in pediatric tonsillectomy and/or adenoidectomy patients and generate new knowledge by evaluating the problem in the context of an understudied population. Publicly insured children, who share similar rates of tonsillectomy and/or adenoidectomy as their privately insured counterparts, have largely been left out of the body of relevant research. Inclusion of health insurance status as an indicator of opioid prescribing rates is substantiated by recent work in the field where certain subgroups of patients, including publicly insured children, were more likely to be prescribed opioids after surgery (Donohoe et al., 2019). Importantly, this study will contribute a meaningful comparison of prescribing rates in publicly versus privately insured post-tonsillectomy children – an analysis that has not been undertaken to date.

Finally, this study advances the body of research in that the implications of codeine substitution remain unclear. In the 'no-codeine' era, prior studies demonstrated a slight, non-significant increase in alternative opioid prescribing (Chua, Shrime, & Conti, 2017; Van Cleve, 2017). Because clinical and genetic risk factors may play a role in both codeine and non-codeine opioid related adverse events (Biesiada et al., 2014), it is important to further the understanding of codeine-substitution and alternative opioid prescribing rates.

Introduction to Theoretical Framework

The Donabedian model will serve as the theoretical framework for the study. Donabedian's landmark article proposed three domains in which the quality of medical care can be assessed – structure, process and outcome (Donabedian, 1966/2005). The assumption of the model is that "good structure increases the likelihood of good processes, and good processes

increase the likelihood of good outcomes" (Donabedian, 1988, p.1145). In this study, the *structure* arm of the triad will be the FDA warning; the *process* arm will be codeine/alternative opioid prescribing practices before and after the FDA warning and the *outcome* will be the number of codeine/alternative opioid prescriptions prescribed.

Emphasizing the need to account for a patient's environmental and/or personal characteristics, Donabedian's model was later modified by Coyle & Battles (1999) to include antecedent conditions. Antecedent conditions are individuals' personal and environmental factors that may influence outcomes of care. Socioeconomic factors, including health insurance status, have been described as pertinent antecedents to quality health care (Coyle & Battles, 1999) – providing justification to include health insurance status as *antecedent* in this study.

The linkage in this study is: The FDA warning (*structure)* will lead to a change in prescribing practices *(process)* and influence the number of codeine and alternative opioid prescriptions *(outcome)*. Health insurance status *(antecedent)* may affect the number of codeine and alternative opioid prescriptions. The theoretical model and linkage will be further explored in Chapter Two.

Assumptions

The primary assumption in this study is that prescribing providers are aware of the FDA *Boxed Warning* on codeine. This assumption can be justified by reviewing the study site's drug formulary, which clearly restricts the use of codeine in children < 18 years of age (Lexicomp Drug Formulary, n.d.). There is also an underlying assumption that the FDA warning for codeine in tonsillectomy and/or adenoidectomy will remain in effect. Given the well-described dangers of codeine in children and the various worldwide agencies recommending against the use of codeine in children (FDA, American Academy of Pediatrics, World Health Organization

(WHO), United Kingdom Medicines and Healthcare Products Regulatory Agency (UK MHRA) European Medicines Agency (EMA) and Health Canada (Tobias et al., 2016)), this assumption can be justified. It is also assumed that no opioid-drug shortages occurred during the study period.

Delimitations

The time-frame of this study is limited to 2010-2018. The starting year (2010) is consistent with prior studies (Chua et al., 2017; Van Cleve, 2017) and will provide data for three consecutive years prior to the 2013 FDA *Boxed Warning* on codeine. In addition, the data source (discussed below) is expected to yield complete, electronic data for the entire study interval. Next, the study sample includes those children who receive care at OHSU and have public or private insurance. Given federal, state and/or organizational medical assistance programs, very few children undergo surgery uninsured at OHSU. In 2016, the proportion of uninsured children in the U.S. was < 5% and in the state of Oregon this percentage is even lower at 3% (Child Trends, 2017; Oregon Health Authority, 2017). Because inclusion of uninsured children would lead to substantially unequal study groups, uninsured children will not be included in the statistical analysis of the health insurance subgroup. Also, children who require post-tonsillectomy and/or adenoidectomy inpatient admissions (planned or unplanned) will be excluded from the study. An inpatient admission allows for greater patient monitoring capabilities (e.g. pulse oximetry and regular, prescribed bedside monitoring by staff), which may increase the propensity for a provider to prescribe post-tonsillectomy and/or adenoidectomy opioids.

A Brief Overview of Methodology

Research design

This study will employ a quasi-experimental, interrupted time-series design with data analyzed via segmented regression analysis. Interrupted time-series analyses are the standard for evaluation of policy actions and segmented regression analyses allow for pre-and post-intervention comparisons (Polit & Beck, 2017). Because this study aims to assess the impact of the FDA warning on pre-and post-FDA warning prescribing practices, this analysis is ideal to address the research questions.

Summary of data source

Data from this study will be extracted from OHSU's electronic health record (EHR) EPIC Hyperspace® platform. The outpatient EPIC Hyperspace® platform was fully integrated into OHSU in 2008. Thus, the data source is expected to yield full and accurate data.

Definition of Terms

- Child/children: An individual under the age of 18 years of age (Oregon Laws Legal Dictionary, 2017).
- Food and Drug Administration Boxed Warning: Denotes labelling on prescription drugs that have serious or life-threatening risks; also known as a "*Black Box*" warning (U.S. Food and Drug Administration, 2012).
- Health insurance: An aggregated category that includes: Private health insurance, Medicare, Medicaid, Children's Health Insurance Program, Department of Defense, and Department of Veterans Affairs. These plans provide insurance against medical losses to eligible individuals and/or families and may directly provide medical care (Center for Medicare and Medicaid Services, n.d.).

- Obstructive Sleep Apnea: "A disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction that disrupts normal ventilation during sleep and normal sleep patterns" (American Thoracic Society, 1995, p. 898).
- Opioid: A group of drugs that bind to opiate receptors in the central and peripheral nervous systems to elicit analgesia (Pathan & Williams, 2012).
- Otolaryngologist/otolaryngology: A physician that provides medical and/or surgical therapy for disease, disorders and/or injuries of the "ears, nose, sinuses, throat, respiratory, and upper alimentary systems, face, jaws, and the other head and neck systems"; may also be known known as ear-nose-throat (ENT) physician (American Medical Association, n.d.).
- Tonsillectomy and/or adenoidectomy: A surgical procedure that completely removes the tonsil, including its capsule, by dissecting the peritonsillar space between the tonsil capsule and the muscular wall; may be performed with or without removal of the adenoids; also known as adenotonsillectomy (Mitchell et al., 2019).
- Private health insurance: Includes health insurance plans marketed by the private-health industry; often employer-connected, but may be purchased on the free market. In private health insurance, premiums are paid to traditional managed care, self-insured health plans and indemnity plans (Center for Medicare and Medicaid Services: Glossary, n.d.).
- Public health insurance: A program run by U.S. federal, state, or local governments where healthcare costs for individuals and/or families are paid for by the government. In the state of Oregon, the Oregon Health Plan comprises Medicaid and the state children's health insurance program (SCHIP), both of which provide low or no-cost health coverage to eligible

children (Center for Medicaid and Medicare Services, n.d.). Medicare (coverage for individuals >65 years) is not pertinent to this study.

Chapter Summary

Chapter One provided a background on codeine and opioid use in pediatric tonsillectomy and/or adenoidectomy patients. It also highlighted opioid prescribing disparities in publicly versus privately insured children and pointed to a knowledge gap in opioid prescribing patterns in pediatric tonsillectomy and/or adenoidectomy patients. The Donabedian model with relevant antecedents was introduced and the study's methodology was overviewed.

The remaining manuscript includes Chapter Two – Chapter Five. Chapter Two provides a comprehensive review of the literature and fully explores the theoretical underpinnings for the study. Chapter Three describes the study's methodology, including research design, study variables, study sample and data analysis plan. Chapters Four and Five include results of the study and discussion of study findings.

Chapter 2: Literature Review

Chapter Overview

This chapter reviews literature pertaining to opioid use in pediatric post-tonsillectomy and/or adenoidectomy patients. The chapter begins by defining pain and postoperative pain, offers a historical perspective on pediatric surgical pain management, discusses the current state of post-tonsillectomy and/or adenoidectomy opioid use and identifies factors that contribute to poor outcomes in pediatric tonsillectomy patients. The research gap is identified, followed by study aims & hypotheses. A detailed discussion of the Donabedian framework as it relates to the study is also included.

Background

Definition of pain

Pain has been defined in many ways, though the definition set forth by The Taxonomy Committee of International Association for the Study of Pain (IASP) offers the most widely accepted designation: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (International Association for the Study of Pain (ISAP), 1994/2017). Pain is a multi-dimensional phenomenon that can be further classified by the pathophysiological mechanism, duration, etiology and anatomic location of pain (World Health Organization (WHO), 2012; IASP, 1994/2017), as discussed in Table 2.

Table 2

Classification and Characteristics of Pain

Classification of Pain	Characteristics of Pain
Pathophysiologic Mechanism	• Nociceptive: arises from tissue injury, tends to be time-limited and responsive to opioids. Nociceptive pain can be further differentiated by the location of activated nociceptors:

	- *Somatic*: activation of nociceptors in either surface tissues (skin, mucosa of mouth, etc.) or in deeper structures (bone, joint, muscle and connective tissue) - *Visceral*: activation of nociceptors located in the internal viscera (thoracic, abdominal organs, etc.) • Neuropathic: arises from nerve cell damage or dysfunction in the peripheral or central nervous systems; tends to be longer lasting and has a less robust response to opioids. • Mixed: nociceptive and neuropathic pain that coexists • Idiopathic: inability to find an underlying cause; may be termed psychogenic pain
Duration	• Acute: onset of pain is sudden and immediately felt following injury; the intensity is generally severe but short in duration • Chronic: continuous or recurrent pain that persists beyond the expected normal time of healing • Episodic/Recurrent: pain that occurs intermittently over a long period of time
Etiology	• Based on the underlying disease and generally classified as malignant or non-malignant
Anatomic Location	• Can be classified by body location (e.g. head, back or neck) or the anatomic function of the affected tissue (e.g. myofascial, rheumatic, skeletal, neurological and vascular)

Note: Information from: WHO 2012; IASP, 1994/2017

Postoperative pain

Postoperative pain is considered a form of acute pain due to surgical trauma, resulting in an inflammatory reaction and a cascade of nociceptive activation (Gupta et al., 2010; WHO, 2012). Different surgical procedures involve specific organs and surrounding tissues, creating various patterns of somatic and/or visceral nociception activation during surgery (IASP, 2017). The quality, anatomic location and severity of postoperative pain is largely a result of this nociceptive activation, though it is also influenced by autonomic, endocrine, metabolic and psychological responses to pain (Brennan, 2011; Gupta et al., 2010). Treatment of acute postoperative pain relies on therapies that modulate pain transmission; the mainstay of postoperative pain therapy in many settings is opioids (Garimella & Cellini, 2013). Effective postoperative pain control is an essential need of any individual undergoing surgery.

Historical perspective on pediatric postoperative pain

The understanding of postoperative pain in children has advanced considerably over the last several decades. Long held assumptions that children are more tolerant of pain, are incapable of pain perception or that provision of pain relief is more harmful than the pain itself, are no longer scientifically or ethically justifiable (Unruh & McGrath, 2014). In the late 19th and early 20th centuries, clinicians believed pediatric patients tolerated postoperative pain well and seldom required medication for the relief of pain after surgery (Unruh, 1992). A classic document by Eland & Anderson (1977) assessed disparities in postoperative pain management between children and adults and noted that postoperative pain in children was vastly undertreated. Though the study was not rigorous, it represented a landmark study highlighting the extreme differences and inadequacy in surgical pain management between children and adults (McGrath, 2011; Unruh, 1992). Several publications followed, including an early systematic study showing a dramatic increase in pediatric pain publications in the 1980's – implying a heightened interest in the field around this time (Guardiola & Banos, 1980; McGrath, 2011). Since then, the conceptualization and treatment of pediatric surgical pain has advanced to appreciate the developmental neurobiology of pain and the importance of adequate analgesia in children (McGrath, 2011; Schechter, 2014).

Disparities in treatment of pediatric pain led organization such as the *Agency for Health Research and Quality* (AHRQ) and the *American Pain Society* (APS) to provide guidelines for pediatric pain management (Cote, Lerman, & Anderson, 2018). The *AHRQ's* 1993 Clinical Practice Guideline for Acute Pain Management in Infants, Children and Adolescents: Operative Procedures (archived and no longer intended to guide medical practice), recommended opioids such as codeine to be used after minor pediatric surgical procedures. The *APS* Task Force on

Pain in Infants, Children and Adolescents (2001) endorsed early treatment of postoperative pain with non-opioids and opioids, providing a specific recommendation only to avoid the opioid meperidine. These guidelines and recommendations, crafted with the best available evidence at the time, served as a platform for safe opioid prescribing practices in children.

Additionally, the World Health Organization (WHO) created initial (1986) and revised (1996) guidelines on pain relief, based on the well-known "analgesic ladder." As shown in Figure 1, the traditional ladder advocates a three-step treatment process, where the first step centers on non-opioids, the intermediate step relies on weak opioids, such as codeine and tramadol, and the final step supports use of stronger opioids, such as morphine (Gray, Collins, & Milani, 2013). Some authors have since devised more recent iterations of the ladder, including a fourth step of interventional approaches (e.g. nerve blocks) for treatment of persistent pain (Cuomo, Bimonte, Forte, Botti, & Cascella, 2019; Vargas-Schaffer, 2010). Creation of the WHO analgesic ladder was significant in that it established the concept of a grading approach to opioid prescribing. Though the WHO analgesic ladder was not specifically intended for the pediatric population nor for postoperative pain, these guidelines have been broadly applied to many patients requiring analgesic therapy – including both pediatric and postoperative patients (Ballantyne, Kalso, & Stannard, 2016; Cartabuke, Tobias, Taghon, & Rice, 2014; Gray et al., 2013; Vargas-Schaffer, 2010).

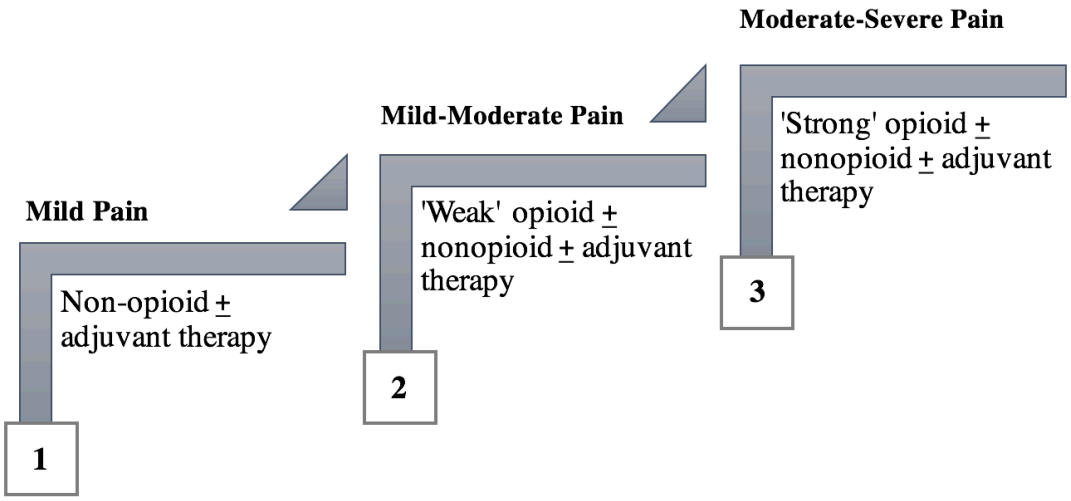


Figure 1. WHO Analgesic Ladder for Pain. Adapted from: (Vargas-Schaffer, 2010; World Health Organization, 2012)

Impact of pediatric postoperative pain

As the understanding of pediatric pain improved, so did the ability to appropriately measure and treat pediatric pain. One of the most notable advances in pediatric pain medicine was the recognition that untreated or undertreated surgical pain leads to short and long-term consequences, including detrimental psychological and physiological effects (McGrath & Craig, 1986; Verghese & Hannallah, 2010). Acute postoperative pain causes fear, distress, behavioral disturbances, disrupted eating and sleeping cycles and harmful neuroendocrine and inflammatory responses (Cote et al., 2018; Lauder & Emmott, 2014). Additionally, the psychological and physiological responses to pain may predispose children to develop chronic pain as adults (Finley, Chorney, & Campbell, 2014). Children experience and process acute postoperative pain, making provision of adequate postoperative pain control a priority.

Perspective on pediatric post-tonsillectomy pain

Pain following tonsillectomy and/or adenoidectomy is very common, representing a major cause of post-surgical morbidity (Baugh et al., 2011; Mitchell et al., 2019). Post-

tonsillectomy and/or adenoidectomy pain is thought to be due to inflammation and irritation of pharyngeal nerve endings and pharyngeal muscle spasms; it often exhibits a bimodal pattern, with pain and functional limitations lasting for up to 7-10 days (Lauder & Emmott, 2014; Rodríguez, Villamor, & Castillo, 2016). Untreated post-tonsillectomy and/or adenoidectomy pain leads to dehydration, nausea/vomiting, dysphagia, weight loss and unplanned hospital readmissions (Lauder & Emmott, 2014; Mitchell et al., 2019). Because the majority of tonsillectomies and/or adenoidectomies are performed on an outpatient basis, pain control is required following hospital discharge. Though non-opioid analgesic regimens may be optimal, opioids are still commonly used, with 6 in 10 post-tonsillectomy children filling a prescription opioid in the perioperative period (Chua et al., 2019).

Codeine in Pediatric Tonsillectomy

Codeine is a weak opioid widely used in the management of mild-moderate pain (He, Lardieri, & Morgan, 2018). It was historically the primary analgesic agent for post-tonsillectomy pain, though it has fallen out of favor due to the risk of serious opioid-related adverse events (Coté et al., 2014). A review of basic opioid pharmacology is offered below, followed by specific information pertaining to codeine analgesia.

Basic opioid pharmacology

Opioids produce their analgesic action by activating opioid receptors, which are located in the central nervous system (brain and spinal cord) and, to a lesser extent, in peripheral tissues (Pathan & Williams, 2012; Trivedi, Shaikh, & Gwinnut, 2008). Three classic types of opioid receptors have been identified: mu, kappa and delta opioid receptors (Hemmings & Egan, 2019). Opioids have a higher affinity for mu-receptors than the kappa or delta receptor subtypes, though all receptor subtypes have important physiological effects (Andrzejowski & Carroll, 2016).

When opioid receptors are activated, a spectrum of physiological effects occur, as shown in Table 3. Notably, respiratory depression and sedation are characteristic of mu-opioid receptor activation.

Table 3

Physiological Effects of Opioid Receptors

	Mu	**Kappa**	**Delta**
Spinal & supraspinal analgesia	Yes	Yes	Yes
Respiratory depression	Yes, marked	No	Possibly, minimal
Sedation	Yes, marked	No	Possibly, minimal
Gastrointestinal effects	Yes	No	Yes
Genitourinary effects	Yes	No	Yes
Euphoria	Yes	No	Possibly, minimal
Dysphoria (restlessness/agitation)	No	Yes	No
Abuse potential	Yes	No	Yes

Note: Adapted from: (Flood, Rathmell, & Shafer, 2015; Hemmings & Egan, 2019; Trescot, Datta, Lee, & Hansen, 2008)

Both endogenous and exogenous substances interact with opioid receptors to elicit a physiological response. Opioid receptors are normally stimulated by endogenous peptides (endorphins, enkephalins, and dynorphins) that are produced in response to noxious stimulation (Trescot, Datta, Lee, & Hansen, 2008). Exogenous substances are naturally occurring, semi-synthetic or synthetic opioid compounds that bind to any subpopulation of the opioid receptor, mimicking the action of endogenous substances (Flood et al., 2015). Activation of the mu-opioid receptor by an exogenous agonist is thought to be the major mechanism in opioid-induced analgesia (Pathan & Williams, 2012).

Morphine, a mu-receptor opioid agonist, is considered the prototypical opioid analgesic to which all others are compared (Hemmings & Egan, 2019; Pathan & Williams, 2012). Many commonly used semisynthetic or synthetic opioids are created by chemical modification or synthesis from the morphine molecule (Flood et al., 2015; Pathan & Williams, 2012). Each modification of the morphine molecule yields a derivative with differing, but "morphine-like", properties (Flood et al., 2015). One particular property that differs among opioid derivatives is analgesic potency. As shown in Table 4, opioids were traditionally classified based upon this property (Trivedi et al., 2008). The designation of opioids based on potency is the basis for the WHO's analgesic ladder and grading approach to opioid prescribing.

Table 4

Opioid Classification Based on Potency

Strong	**Intermediate**	**Weak**
Morphine Meperidine Fentanyl Alfentanil Remifentanil Sufentanil	Buprenorphine Butorphanol Nalbuphine	Codeine Tramadol

Note: Adapted from: Trivedi et al., 2008

Codeine overview

Codeine received U.S. FDA approval in 1950 and has been a commonly used analgesic for postoperative pain in adults and children for more than 50 years (Andrzejowski & Carroll, 2016). In 2011, codeine-containing prescriptions were prescribed to more than 18 million children under 11 years of age – making it the most prescribed opioid at that time (Cartabuke et al., 2014; Chidambaran, Sadhasivam, & Mahmoud, 2017). Codeine is a naturally occurring

alkaloid compound, acting as an agonist at the mu-opioid receptor (Pathan & Williams, 2012). When compared to morphine, it possesses a 200-fold weaker affinity for the mu-opioid receptor – hence its status as a "weak" opioid (Chidambaran et al., 2017; Hansen, Shah, & Benzon, 2016).

Oral codeine is rapidly absorbed, reaching plasma concentration levels within 1 hour of administration in adults and slightly longer in children (Andrzejowski & Carroll, 2016). The half-life of codeine is approximately 3-3.5 hours and therapeutic effects of codeine are similar in adults and children, generally lasting for 4-6 hours (Andrzejowski & Carroll, 2016; Cote et al., 2018). Common side effects of codeine are listed in Table 5. Codeine is eliminated by either direct renal excretion or following metabolism via the cytochrome (CYP) 450 system in the liver (Chidambaran et al., 2017).

Table 5

Common Side Effects of Codeine

Airway and Breathing Effects	**Cardiovascular Effects**	**Central Nervous System Effects**	**Gastrointestinal Effects**	**Other Effects**
-Shortness of breath -Respiratory depression -Decreased cough	-Flushing	-Drowsiness -Sedation -Dizziness -Light-headedness	-Nausea -Vomiting -Constipation	-Sweating

Note: Adapted from: (FDA, 2010; Andrzejowski & Carroll, 2016)

Codeine is a pro-drug, requiring conversion of the drug into its active form to produce analgesia (Chidambaran et al., 2017; Fortenberry, Crowder, & So, 2018; He, Lardieri, & Morgan, 2018). As shown in Figure 2, the drug has three major metabolic pathways: 70-80% of codeine is metabolized by the enzyme UDP-glucuronosyltransferase-2B7 (UGT2B7) into codeine-6-glucuronide (active drug); 5-10% is metabolized by the cytochrome P450 (CYP) 3A4

enzyme into norcodeine (inactive); 10% of the drug undergoes O-demethylation via CYP 2D6 enzyme to morphine (active) (Biesiada et al., 2014; Chidambaran et al., 2017; Fortenberry et al., 2018). The greatest degree of analgesia is produced from the active metabolite morphine (Chidambaran et al., 2017).

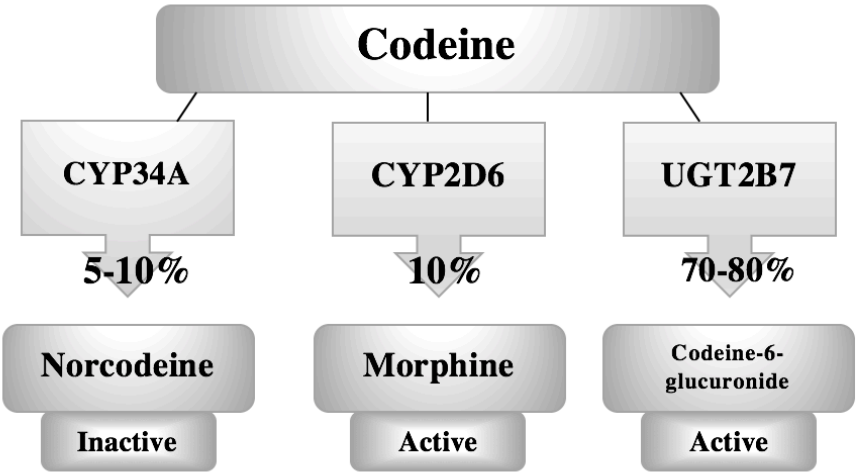


Figure 2. Codeine Metabolism
Note: Adapted from Fortenberry et al., 2008

Background on codeine use in pediatric tonsillectomy

For decades, codeine analgesia was the primary agent for outpatient analgesia after tonsillectomy and/or adenoidectomy in children (Constant et al., 2014; Lauder & Emmott, 2014; Tobias et al., 2016). Otolaryngologists prescribe codeine at greater rates than dentists, pediatricians and general/family practice physicians (Chidambaran et al., 2017). Codeine analgesia was favored by otolaryngologists for post-tonsillectomy and/or adenoidectomy pain for numerous reasons, as outlined in Table 6.

Table 6

Reasons for Codeine Use in Post-tonsillectomy Pediatric Patients

Favorable characteristics of codeine	**Rationale for use in post-tonsillectomy**

Can be administered orally via a liquid or tablet	Oral opioids can be initiated and continued after discharge from the hospital
Is a step-2 analgesic in the WHO analgesic ladder	Was thought to be effective for mild-moderate post-tonsillectomy pain
Is considered a 'weak' opioid	Is weaker than morphine and was thought to have a good safety profile
Causes less postoperative nausea and vomiting than morphine	Nausea/vomiting is a common problem after tonsillectomy and/or adenoidectomy, with an incidence ranging from 15-80%
Greater ease of prescribing	Codeine co-formulated with acetaminophen is the only opioid analgesic classified as a Schedule III controlled substance, allowing for verbal and facsimile prescribing to pharmacies as well as refills with the original prescription; also, the drug did not require triplicate prescription forms in many states
Is relatively inexpensive	Represented a cost-effective therapy option for post-tonsillectomy and/or adenoidectomy pain

Note: Information from: (Chidambaran et al., 2017; Constant et al., 2014; Cote et al., 2018; Garimella & Cellini, 2013; Hansen et al., 2016; Lauder & Emmott, 2014; Semple et al., 1999; WHO, 2012)

Current state of codeine use in pediatric tonsillectomy

The favorable characteristics of codeine have since been outweighed by its association with significant adverse events, including deaths and near deaths. In 2009, a fatality occurred in a healthy 2-year-old boy who was given codeine after adenotonsillectomy (Ciszkowski & Madadi, 2009). This was followed in 2012 by three additional deaths and two cases of respiratory insufficiency in children who underwent adenotonsillectomy (Kelly et al., 2012). In 2013, three additional codeine-related deaths occurred in children aged 4-10 years who were prescribed the recommended weight-based dose of codeine (Friedrichsdorf, Nugent, & Strobl, 2013).

These reports of deaths and near deaths in children receiving standard doses of oral codeine prompted the FDA and international regulatory agencies to review the safety of the drug in children undergoing tonsillectomy and/or adenoidectomy. Subsequently, the FDA, WHO, European Medicines Agency (EMA), the UK Medicines and Healthcare Products Regulatory

Agency (MHRA) and Health Canada made formal recommendations against the use of codeine containing products in all children undergoing tonsillectomy and/or adenoidectomy. Figure 3 depicts the progression of the 'codeine-ban' in children: It was first recommended that codeine be avoided in any child undergoing tonsillectomy and/or adenoidectomy; this has been followed by more recent guidelines to avoid codeine-containing cough elixirs in all children <18 years of age.

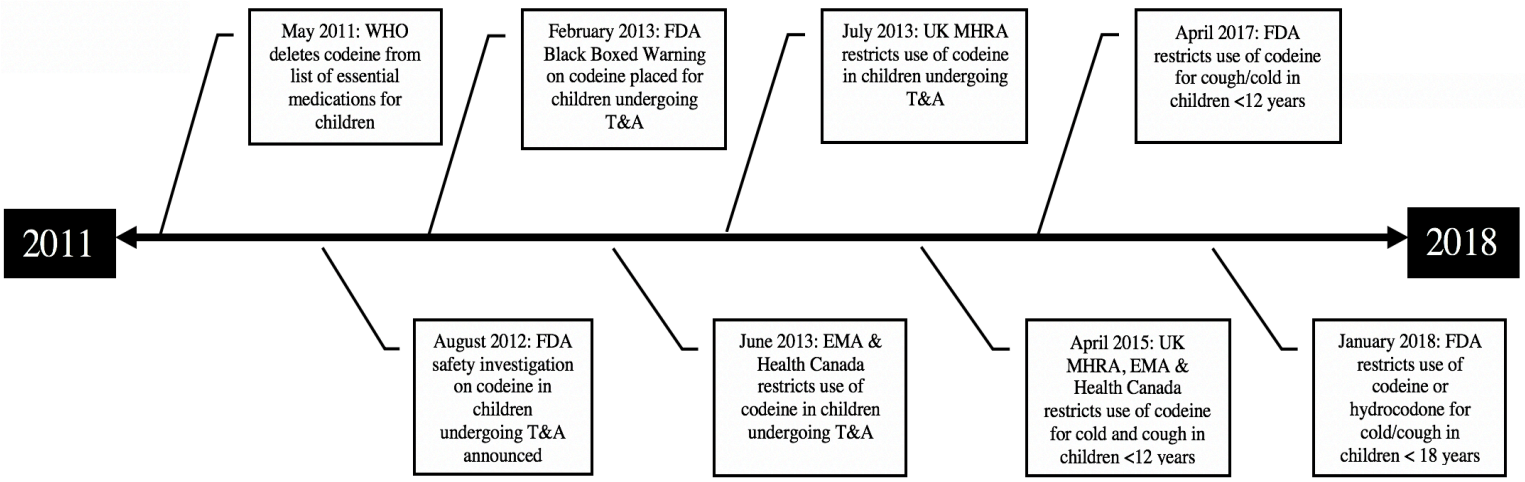


Figure 3. Depiction of the Codeine Ban. Information from (European Medicines Agency, 2013, 2015; Health Canada, 2016; U.S. Food and Drug Administration, 2013, 2018; UK Medicines and Healthcare Products Regulatory Agency, 2013, 2015; World Health Organization Expert Committee, 2011)

Contributing Factors in Post-tonsillectomy Deaths and/or Adverse events

Though codeine plays a major role in post-tonsillectomy deaths and/or adverse events, it is not solely to blame. Rather, several factors have been implicated in the "perfect storm" of post-tonsillectomy complications including comorbid conditions, opioid sensitivity, genetic polymorphisms in opioid metabolism, and other factors (Coté et al., 2014; Cote et al., 2018).

Comorbid conditions

Obesity

Defined by the Center for Disease Control (CDC) as a body mass index >95th percentile for age and gender, obese children are more likely to suffer from a number of comorbid conditions including cardiovascular disease (hypertension, dyslipidemia), respiratory disorders (OSA, asthma), endocrinopathies (diabetes, metabolic syndrome), renal and liver dysfunction (Cote et al., 2018). Obesity presents challenges during the perioperative period and increases the risk of poor outcomes. In a large study of post-tonsillectomy morbidity and mortality, obesity was the second most common predisposing factor for perioperative adverse events (Goldman et al., 2013). Obese children have a higher incidence of adverse respiratory events during and after surgery when compared with normal-weight children (Mortensen, Lenz, Abildstrøm, & Lauritsen, 2011). Increased tissue mass, alterations in respiratory mechanics, reduction in lung capacities and airway narrowing are thought to contribute to the heightened risk profile of obese children (Mortensen et al., 2011; Patino et al., 2013). In 2009, researchers found that obese children represented 21% of all children undergoing tonsillectomy (Nafiu et al., 2009). A decade later, it is likely this percentage has increased.

Obstructive sleep apnea

Over 75% of children presenting for tonsillectomy suffer from OSA (Patino et al., 2013). OSA is a sleep-related breathing disorder that is characterized by intermittent cessation of air exchange that disrupts normal ventilation and sleep patterns (American Thoracic Society, 1996). It is further defined as central (lack of respiratory effort due to a central defect), obstructive (upper airway obstruction) or mixed (central and obstructive problems) and is diagnosed via clinical assessment or polysomnography (PSG) sleep study (Cote et al., 2018; Marcus et al., 2012). Symptoms of OSA include obstructed breathing, snoring, paradoxical chest wall motion,

increased respiratory effort, apneas/hypopneas, hypercarbia and oxygen desaturation. The spectrum of OSA ranges from mild to severe, based on the total number of obstructive episodes and oxygen desaturations during sleep (Cote et al., 2018; Patino et al., 2013). OSA occurs in about 2-5% of all children and can afflict a child of any age, but is more common in children aged 3-7 years (Marcus et al., 2012). It affects boys and girls equally, though the disorder has a greater prevalence in African American and Hispanic children when compared with Caucasian children (Dudley & Patel, 2016).

The incidence of pediatric OSA and sleep-disordered breathing has risen dramatically – in large part due to the rise in childhood obesity (Marcus et al., 2012; Patino et al., 2013). Though pediatric OSA is a multifactorial disease, obesity is a predisposing factor – leading to a higher prevalence of the disorder and exacerbating the symptoms of OSA (Cote et al., 2018; Patino et al., 2013). OSA is reported in 14-59% of obese children, compared to 1-2% in non-obese children, and the degree of OSA parallels the degree of obesity (Cote et al., 2018; Verhulst et al., 2008). In general, children with obesity suffer from the obstructive-type of OSA, where increased resistance to air flow and airway obstruction are characteristic of the disorder (Patino et al., 2013).

Tonsillectomy and adenoidectomy is recommended as the initial treatment in children with OSA, yet the presence of OSA significantly increases the odds for post-tonsillectomy complications (Cote et al., 2018). A recent meta-analysis demonstrated differences in the distribution of post-tonsillectomy complications between children with OSA and those without. Canto et al. (2015) showed children with OSA have a 5-fold increase in the odds for perioperative respiratory events when compared to children without OSA. Also, several recent studies reported unexpected deaths and/or near deaths following tonsillectomy and/or

adenoidectomy related to suspected or confirmed sleep apnea (Coté et al., 2014; Goldman et al., 2013). The risk of complications related to OSA appears to be due to a confluence of factors including impaired hypoxic and hypercarbic ventilatory responses, pharyngeal collapse leading to airway obstruction, opioid sensitivity with exaggerated respiratory depression, and improper post-operative monitoring (Collins, 2015; Coté et al., 2014; Cote et al., 2018; Goldman et al., 2013; Mortensen et al., 2011). Notably, though tonsillectomy and/or adenoidectomy is considered to be an effective treatment for OSA, the symptoms of OSA may become worse during the immediate post-operative period (Marcus, et al., 2012) – making it a particularly vulnerable time.

Opioid sensitivity

Due to the intermittent airway obstruction during sleep that is characteristic of OSA, children with OSA experience recurrent episodes of nocturnal desaturation and hypoxemia (Cote et al., 2018). Although the molecular basis for the effect of nocturnal hypoxemia on opioid receptors is not fully understood, research shows that exposure to nocturnal hypoxemia increases the density of mu-opioid receptors in respiratory-areas of the central nervous system (Johnson & Netzer, 2015; Lam, Kunder, Wong, Doufas, & Chung, 2016). This effect is observed in both animals and humans. In experimental rat pup models, exposure to recurrent hypoxia was linked to upregulated opioid receptors in the brainstem and greater respiratory sensitivity to opioids (Moss, Brown, & Laferrière, 2006; Wu, Li, Wu, & Chen, 2015). Clinical studies are consistent with this finding where children with OSA had a higher incidence of apnea at uniform doses of opioids and required less opioid analgesia following tonsillectomy (Brown, 2009; Waters, McBrien, Stewart, Hinder, & Wharton, 2002). The altered mu-opioid receptor response to opioids results in patients with OSA being analgesic at lower blood levels of opioids (Coté,

2015). Thus, children with OSA require less opioids than their non-OSA counterparts and a normal dose of opioid is a relative overdose in a child with OSA (Coté et al., 2014).

Genetic polymorphisms affecting opioid metabolism

Genetic polymorphisms that contribute to individual variability in opioid-metabolism have been implicated in post-tonsillectomy deaths and near deaths (Andrzejowski & Carroll, 2016; Chidambaran, et al., 2017) . Codeine is particularly affected by genetic polymorphisms and will be discussed following a general overview of drug metabolism.

General overview of drug metabolism

In general, drug metabolism occurs in the liver and is classified as either a Phase I or Phase II reaction, where the former is an oxidative, reduction or hydrolysis reaction and the latter are conjugation reactions (Hemmings & Egan, 2019). Often drugs undergo both phases of metabolism, first undergoing a Phase I reaction to increase the drug's polarity followed by a Phase II reaction to conjugate the drug to a water-soluble compound for subsequent excretion (Flood et al., 2015). Both Phase I and II metabolic pathways involve enzyme systems. Phase I reactions rely primarily on the CYP 450 system, which is a large family of membrane-bound hemeproteins that catalyze the metabolism of endogenous or exogenous compounds (Flood et al., 2015; Hemmings & Egan, 2019). Numerous CYP proteins have been identified and different CYP 450 pathways are classified by similar gene sequences; they are first assigned a family number (e.g. CYP2), then a sub-family letter (e.g. CYP2D) and are differentiated by a number for the specific enzyme (e.g. CYP2D6) (McDonnell & Dang, 2013). The CYP 450 system plays a key role in the metabolism many drugs, including opioids.

Codeine

As discussed above and illustrated in Figure 2, codeine follows three major metabolic pathways to produce active and inactive forms of the drug. The primary analgesic effect of codeine is its conversion to morphine via the CYP450 system, specifically the CYP2D6 enzyme (Chidambaran et al., 2017; Fortenberry et al., 2018; Kirchheiner et al., 2007). The potential dangers of codeine lie primarily in genetic polymorphisms of this enzyme.

Variability in the clinical response to codeine prompted inquiries into the role of genetic polymorphisms of the CYP2D6 enzyme on codeine-related adverse events. The CYP2D6 enzyme is encoded by a gene located on chromosome 22 at 22q.13.1; more than 100 polymorphisms of CYP2D6 have been identified, leading to a broad range of phenotypic activity of the enzyme (Andrzejowski & Carroll, 2016; Chidambaran et al., 2017). Depending on which maternal and paternal alleles an individual inherits, the metabolism profile of codeine varies from poor to ultra-rapid metabolism, drastically affecting the clinical response to codeine (Andrzejowski & Carroll, 2016; Chidambaran et al., 2017; Kirchheiner et al., 2007). The major polymorphisms of CYP2D6, as shown in Table 7, alter the clinical response to codeine by significantly reducing or augmenting the conversion of codeine to morphine (Crews et al., 2012; Fortenberry et al., 2018). This corresponds with either reduction in its intended therapeutic effect or heightened therapeutic effect with the potential for significant morphine toxicity (Crews et al., 2012; Lam et al., 2014).

Table 7

Major Polymorphisms of CYP2D6 Enzyme

Phenotype	**Enzyme Activity Score**	**Genotype**	**Incidence**	**Codeine Analgesic Effect**
Poor metabolizer	0	Two non-functioning alleles	5-10%	Very little analgesic effect

Intermediate metabolizer	0.5	One non-functioning allele & one decreased-functioning allele	2-11%	Reduced analgesic effect
Normal metabolizer	1-2	Two normally functioning alleles	77-92%	Expected analgesic effect
Ultra-rapid metabolizer	2	Gene duplication of normally functioning alleles	1-2%	'Overdose' analgesic effect

Information from: (Andrzejowski & Carroll, 2016; Chidambaran et al., 2017; Coté, 2015; Crews et al., 2012; Dean, 2012)

Genetic testing is available for common CYP2D6 variants (~30 alleles) (Dean, 2012). Both maternal and paternal variant alleles, known as diplotypes, are reported; then an activity score is assigned to each allele in the diplotype, as shown in Table 7 (Andrzejowski & Carroll, 2016; Chidambaran et al., 2017). Though available, the practicality, payer coverage and affordability limit routine preoperative genetic phenotyping (Chidambaran et al., 2017).

Genetic testing has been undertaken in post-mortem analysis of codeine-related fatalities. In 2009, a 2-year-old toddler with OSA suffered fatal respiratory arrest after tonsillectomy and adenoidectomy; post-mortem analysis revealed a serum morphine concentration of 32 nanograms per milliliter (ng/mL) (therapeutic range = 4.5 $\pm$ 2.1 ng/mL) and duplicate CYP2D6 alleles, indicating ultra-rapid metabolizer status (Ciszkowski & Madadi, 2009). Similar cases have since been reported: a 4-year-old boy and a 3-year-old girl with OSA and a 5-year old boy without OSA – post-mortem morphine concentrations in these children were 17.6, 17 and 30ng/mL, respectively; all were found or predicted to have duplicate or mutant CYP2D6 alleles (Kelly et al., 2012). In all cases, the prescribed dose of codeine was appropriate, based on the child's weight, and the reported dose administered by the caregivers were within the boundaries of the prescribed dose.

Limited prospective work has evaluated the role of genetic variations on opioid metabolism. In 2007, Kirchheiner and colleagues administered codeine to 16 individuals with known CYP2D6 gene alterations and found that those with CYP2D6 genotypes predicting ultra-metabolism (gene duplication) had a 50% higher plasma morphine concentration than those without gene duplication (Kirchheiner et al., 2007). Biesiada and colleagues (2014) conducted a prospective study (n=273) to evaluate genetic variants associated with respiratory depression in children undergoing tonsillectomy and adenoidectomy with morphine analgesia. The researchers found inter-individual differences in morphine-related post-operative respiratory depression, where certain genetic alleles helped discriminate between low and high risk for post-operative respiratory depression (Biesiada et al., 2014).

Presently, there are no diseases or conditions known to be linked to CYP2D6 variants – however there is increasing evidence of ethnic variations in cytochromes responsible for drug metabolism (Andrzejowski & Carroll, 2016; Cote et al., 2018). Populations that exhibit ultra-rapid metabolism include Ethiopians (30%), North Africans/Arabs (16-30%), Italians/Greeks/Spaniards/Portuguese (10%) and Caucasians (1-10%) and poor metabolizer populations include Chinese (30%) and Caucasians (5-10%) (Andrzejowski & Carroll, 2016; Chidambaran et al., 2017). However, CYP2D6 cannot be predicted based on ethnicity alone; the only definitive means of knowing genetic signatures is via enzyme mapping (Chidambaran et al., 2017).

Other opioids

The role of genetic polymorphisms affecting codeine metabolism is well documented, however the extent to which pharmacogenetics influences the metabolism of other opioids is evolving. Other mild-moderate opioids, such as tramadol, oxycodone and hydrocodone were

thought to be a safer alternative to codeine – though these drugs may exhibit similar inter-individual genetic variations in metabolism because they are, in part, metabolized by CYP2D6 (Andrzejowski & Carroll, 2016; Chidambaran et al., 2017; Crews et al., 2012). Tramadol and, to a lesser extent, hydrocodone and oxycodone may not be good alternatives to codeine because their metabolism is affected by CYP2D6 activity (Crews et al., 2012; Dean, 2012).

Tramadol is metabolized by two pathways in the liver: moderate metabolism via CYP3A4 and extensive metabolism via CYP2D6. CYP3A4 metabolizes tramadol into an inactive compound, N-desmethytramadol, whereas CYP2D6 metabolizes tramadol into an active compound, O-desmethyltramadol (Fortenberry et al., 2018). The active metabolite has a 200-fold greater affinity for the mu-opioid receptor than the parent drug and is predominantly responsible for the drug's analgesic effect (Crews et al., 2012). A prospective, double blind RCT found tramadol was safer than codeine/acetaminophen in pediatric tonsillectomy and/or adenoidectomy patients, with tramadol causing less respiratory depression and sedation (Friedrichsdorf et al., 2015). However, there is evidence for decreased efficacy of tramadol in poor metabolizers and case reports of respiratory distress and near fatalities in ultra-rapid metabolizers – indicating genetic polymorphisms play a role in the clinical response to tramadol (Crews et al., 2012; Elkalioubie et al., 2011; Poulsen, Arendt-Nielsen, Brøsen, & Sindrup, 1996; Stamer et al., 2007). One recent report highlights a case of severe tramadol-related respiratory depression in a child with OSA undergoing tonsillectomy and adenoidectomy (Orliaguet et al., 2015). As a result, the FDA also took a stance on tramadol administration in pediatric tonsillectomy and/or adenoidectomy patients. In 2017, a *Boxed Warning* and labeling change to avoid tramadol in pediatric tonsillectomy and/or adenoidectomy patients < 18 years of age was announced (U.S. Food and Drug Administration, 2017).

Oxycodone is also metabolized by CYP34A and CYP2D6, though the metabolic profile differs from tramadol in that CYP34A is the predominant metabolic pathway and CYP2D6 plays a relatively minor role (Chidambaran et al., 2017). The byproducts of CYP34A and CYP2D6 metabolism are noroxycodone, a metabolite with weak analgesic properties, and oxymorphone, which possesses 14 times more potency than the parent drug (Chidambaran et al., 2017; Lauder & Emmott, 2014). Current understanding of oxycodone's pharmacogenetics is limited, particularly in pediatrics. In a randomized crossover double-blind study of 10 healthy adult volunteers, oxycodone pharmacodynamics differed depending on CYP2D6 polymorphisms, where ultra-rapid metabolizers experienced increased effects (Samer et al., 2010). Stamer and colleagues (2013) later demonstrated the number of functionally active CYP2D6 alleles had an impact on oxycodone metabolism in adult postoperative patients, causing variation in clinical response to oxycodone. At least one case has been reported where a non-fatal toxicity occurred in an adult patient with impaired CYP2D6 metabolism (Foster, Mobley, & Wang, 2007). There is no FDA contraindication on oxycodone, though more data is required to understand the impact of pharmacogenetics on oxycodone metabolism in children.

Hydrocodone is partially metabolized via CYP3A4 and CYP2D6 into hydromorphone and norhydrocodone, respectively (Chidambaran et al., 2017). Hydromorphone is the active compound and has a 10-to 33-fold greater affinity for mu-opioid receptors as compared with the parent drug (Crews et al., 2012). Again, the pharmacogenetic data for hydrocodone is limited and no pediatric data exists. There is some evidence that hydromorphone is generated at substantially different rates in adults depending on CYP2D6 genotype and that poor metabolizers may have a limited analgesic effect to hydrocodone (Otton et al., 1993; Stauble et al., 2014) – yet there is insufficient data to understand whether ultra-rapid metabolizers

have an increased risk of hydrocodone related toxicity (Crews et al., 2012). No hydrocodone fatalities related to CYP2D have been reported and no FDA warnings have been placed on the drug in the context of pediatric tonsillectomy and/or adenoidectomy.

The differing associations of CYP2D6-related variation in metabolism of codeine and tramadol as compared with oxycodone and hydrocodone may be related to the relative roles of the parent drug and circulating metabolites (Crews et al., 2012; Dean, 2012). Based on pharmacogenetics data, oxycodone and hydrocodone may be less prone to unintended sedation when compared with codeine and tramadol. However, it critical to consider clinical risk factors, such as obesity and OSA, along with genetic risk signatures – as both play a role in opioid-induced adverse events.

Other factors

In addition to comorbid conditions and genetic risk factors, other factors implicated in post-tonsillectomy deaths and/or adverse events include inadequate preoperative assessment for OSA, performing outpatient surgery in high-risk populations and lack of appropriate post-operative monitoring in the hospital or home setting (Coté, 2015; Coté et al., 2014; Patino et al., 2013). These, in addition to opioid therapy, are expressed as preventable factors in post-tonsillectomy deaths and/or adverse events (Coté et al., 2014).

Opioid Prescribing in the Post-codeine Era

There is strong evidence against the use of codeine and evolving evidence that substitution of other opioids may be unsafe in pediatric tonsillectomy and/or adenoidectomy patients. Since the FDA *Boxed Warning* on codeine, two large-scale and one single-center observational study analyzed the impact of the FDA warning on codeine and opioid prescribing

in pediatric tonsillectomy and/or adenoidectomy patients. These studies are described below and summarized in Table 8.

Table 8

Summary of Relevant Literature

Study	Population & Sampling Frame	Outcome Measures	Results	Limitations
Chua et al. (2017)	Post-tonsillectomy and/or adenoidectomy children < 18 years (n=362,992); Truven MarketScan Commercial Claims and Encounters database, years 2010 – 2015.	≥ 1 prescription fill for codeine or other opioids within 7 days of surgery.	Significant reduction in codeine dispensed from 2010 to 2015 in children with and without OSA. Non-significant increase in other opioids dispensed.	Privately insured children only. Claims data captures opioids dispensed, not opioids prescribed. Unable to discern type of providers who prescribed opioids.
Van Cleve (2017)	Post-tonsillectomy and/or adenoidectomy children < 18 years of age (n=230,744); Truven MarketScan Commercial Claims and Encounters database, years 2010 – 2015.	Opioids dispensed from 2 weeks prior until 2 days following tonsillectomy & 14-day postoperative rates of emergency department (ED) visits.	Significant reduction codeine dispensed from 2010 to 2015; Non-significant increase in other opioids dispensed; No change in 14-day ED visit rates.	Demographics not presented. Privately insured children only. Claims data captures opioids dispensed, not opioids prescribed. Unable to discern type of providers who prescribed opioids.
Goldman et al. (2018)	Post-tonsillectomy and adenoidectomy children aged 2-12 years; Medical record data, years 2010 – 2015.	Post-operative opioids prescribed by academic and non-academic otolaryngologists.	Significant reduction in codeine prescribed by academic and non-academic otolaryngologists; No change in post-operative ED visit rates.	Single center study. Health insurance status not reported. Post-operative prescribing time parameters unclear. Did not define "other narcotics".

Using the Truven MarketScan Commercial Claims and Encounters database, Chua and colleagues (2017) identified 362,992 privately insured children who underwent tonsillectomy

and/or adenoidectomy between 2010 – 2015. The researchers measured the occurrence of ≥1 codeine or alternative opioid (hydrocodone, oxycodone and other opioids) prescription fill within 7 days of surgery and made pre-and post-FDA warning comparisons. The monthly rate of change in codeine prescribing following the FDA warning was significant and negative (-13.3; 95% CI = [-14.5 to -12.1]), where codeine prescribing fell from 30.1% in 2010 to 5.1% in 2015 (Chua et al., 2017). Changes in alternative opioid prescribing were found to be slight and non-significant, with 31.7% fills in 2010 and 46.1% in 2015.

Van Cleve (2017) also studied the impact of the FDA warning on opioid prescribing in pediatric post-tonsillectomy patients. Using the same commercial insurance database as Chua et al. (2017), data on 230,477 pediatric tonsillectomies between 2010 – 2015 were analyzed. Acetaminophen-codeine, acetaminophen-hydrocodone, oxycodone or 'other' prescription fills from two weeks prior until two days post-surgery were identified and classified as pre-or post-FDA warning. Van Cleve (2017) found a significant reduction in post-FDA warning codeine prescribing, where the relative risk (RR) of receiving a codeine-containing prescription in the post-FDA warning period was RR=0.31 (95% CI, = [0.31-0.32]). The RR of receiving a hydrocodone or oxycodone-containing prescription in the post-FDA warning period was slightly increased, though not significant.

The Goldman et al. (2018) study added additional knowledge by comparing prescribing practices in academic and non-academic otolaryngologists. Though a significance level was not reported, the researchers noted that academic otolaryngologists' prescribing reached zero faster than the non-academic otolaryngologist group (Goldman, Ziegler, & Burckardt, 2018). The researchers also found an overall 5% reduction in postoperative opioid use by both academic and non-academic otolaryngologists ($p < .001$). However, aside from noting hydrocodone was the

most frequently prescribed post-FDA warning opioid (accounting for 91% of such prescriptions), the study did not report which other opioids were substituted for codeine.

Goldman et al. (2018) did not report granular information on "other narcotics", but both Chua et al. (2017) and Van Cleve (2017) found an increase in alternative opioid prescribing after the FDA warning on codeine. Though these results were non-significant, this data still provides useful trends on which non-codeine containing opioids are substituted for codeine. As shown in Table 9, Chua and colleagues (2017) present detailed information on which alternative opioids have seen the greatest substitution since the FDA warning on codeine. Van Cleve (2017) and Goldman et al. (2018) also found hydrocodone to be the opioid most frequently prescribed in the post-FDA warning era.

Table 9

Substitution Trends of Alternative Opioids

	2010	**2015**
CODEINE	46.8 %	9.1 %
HYDROCODONE	48.4 %	72.7 %
OXYCODONE	3.8 %	17.4 %
OTHER OPIOID	0.1 %	0.8 %

Research Gaps in Post-tonsillectomy Opioid Prescribing

The literature to date contributed beneficial knowledge on the impact of the FDA warning on codeine and opioid prescribing in pediatric tonsillectomy and/or adenoidectomy patients, though important gaps remain. As introduced above, both Chua et al. (2017) and Van Cleve (2017) analyzed the same commercial insurance database – Truven MarketScan

Commercial Claims and Encounters database. This database reports de-identified, patient-level data for over 50 million employee-sponsored insured Americans annually (Truven Healthcare Analytics, 2017). Utilizing this dataset is good for generalizability to other similarly insured U.S. children, though it leaves a segment of the childhood population underrepresented: publicly insured children. Van Cleve (2017) lists this as a "major limitation" to his work (p. 1052) and Chua et al. (2017) note the generalizability of the results to other commercially insured children and to publicly insured children is unclear. Goldman et al. (2018) did not specify insurer status in their work, rather focused on academic versus non-academic prescribing providers. Collectively, no study has evaluated the impact of the FDA warning on publicly insured post-tonsillectomy children, nor has any study compared opioid prescribing between publicly and privately insured post-tonsillectomy children. Children enrolled in Medicaid constitute an important population to study, given an estimated 40% of US children have health insurance coverage by Medicaid (Kaiser Family Foundation, 2018). Additionally, tonsillectomy rates in publicly and privately insured children are similar with rates of 81.5 and 80.6 per 10,000 U.S. children, respectively (Boss et al., 2012) – making post-tonsillectomy opioid prescribing relevant and important in both subsets of children. The extent to which publicly and privately insured children may be treated differently is a source of controversy (Alexander & Currie, 2017) and will be examined below.

Further, both the Chua et al. (2017) and Van Cleve (2017) studies analyzed prescription opioids filled (e.g. dispensed by the pharmacy), rather than opioids prescribed (e.g. written by the provider). Earlier work suggests there is a difference between prescribed and dispensed medications, with high rates of non-dispensing in medications prescribed by general practice providers (Gardner, Dovey, Tilyard, & Gurr E, 1996; Lars, Nilsson, & Johansson, 1995). More recent studies share similar findings where many prescribed medications are not actually

dispensed. Fischer et al. (2010) conducted an analysis of 195,930 electronic prescriptions and found 28% of new medications prescribed by primary care providers were not dispensed. Similarly, another study demonstrated that 31.3% of primary care patients never filled an initial prescription (Tamblyn, Eguale, Huang, Winslade, & Doran, 2014). Though no literature exists on perioperative opioid prescribing versus dispensing, these studies in primary care illuminate the value of assessing opioids prescribed rather than dispensed. Measuring opioids dispensed may underestimate actual prescribing.

Finally, there is a dearth of research evaluating the impact of the FDA warning on codeine or opioid prescribing beyond the year 2015. Both the Chua et al. (2017) and Van Cleve (2017) analyses are encouraging in that codeine prescribing fell as a result of the FDA warning - however, in 2015 residual post-FDA codeine prescribing was shown in both studies, despite the drug's well documented dangers. In 2017, codeine prescribing in pediatric post-tonsillectomy patients was 3.3% - however this reflects only one year of prescribing data (2016-2017) and does not assess longer-term trends (Chua et al., 2019). The longer-term trend of codeine prescribing is an important gap to fill in that the impact of FDA warnings may demonstrate erosion over time. In a study evaluating the 2004 FDA warning on antidepressants in children, the effects of the FDA warning differed in the early-and late-post FDA warning periods. In the years immediately following the FDA warning, a statistically significant decline in antidepressant use was found, but the prevalence of antidepressant use returned to pre-FDA warning levels 5 years later (Kafali, Progovac, Shu-Yeu Hou, & Lê Cook, 2018). This suggests the impact of FDA warnings may fade in the long-run and more frequent reinforcement of drug safety warnings may be necessary. It is currently unknown if the effects of the FDA warning on codeine resulted in a sustained or further reduction in codeine use and/or if alternative opioid prescribing practices

have changed since 2015. The present study will add additional information on codeine and opioid prescribing up to the year 2018. Overall, the current study addresses multiple gaps in the literature by assessing post-tonsillectomy opioid prescribing in public and privately insured children, evaluating opioids prescribed rather than dispensed and extending the study period to understand the longer-term impact of the FDA warning.

Influence of Health Insurance on Medical Treatment

The influence of health insurance on medical treatment is complex. A review of opioid prescribing based on insurance status and the medical treatment of publicly versus privately insured children is presented below.

Introduction

In 2017, the CDC's National Center for Health Statistics reported 54.7% children were privately insured and 41.8% of children were publicly insured (Center for Disease Control, 2017). Public insurance for children via government funded programs includes Medicaid or Children's Health Insurance Plans (CHIP), which are based on income standards expressed as the federal poverty level (Kaiser Family Foundation, 2018). Because only low-income families and children are eligible for public insurance programs, children in economically disadvantaged groups are the most likely to have government health insurance (Child Trend, 2017). Race and ethnicity in children covered by Medicaid/CHIP tends to differ based on U.S. geography, though in 2010 36.5% were White, 24.5% were Black, 35.7% were Hispanic and 4.3% were other/non-Hispanic children (Coyer & Kenney, 2013). Private health insurance refers to plans marketed by the private-health industry as opposed to government run insurance programs; it is primarily provided via employee sponsored programs (Center for Medicaid & Medicare Services, n.d.). In

2017, non-Hispanic White and Asian children were most likely to have private health insurance whereas Hispanic children were least likely (Berchick, Hood, & Barnett, 2018).

Differences in the treatment of publicly insured versus privately insured children are documented across many venues, including prescribing practices, access to specialty care, hospital admissions/readmissions and healthcare utilization. Literature pertaining to opioid prescribing practices in publicly versus privately insured children, emphasized below, is scant and mixed; additional information on the differences in medical treatment of publicly versus privately insured children is summarized in Table 10.

Opioid prescribing based on insurance status

A recent study from a large academic pediatric hospital assessed trends in postoperative opioid prescribing in pediatric post-surgical patients. Donohoe and colleagues (2019) conducted a retrospective evaluation of 65,190 pediatric outpatient surgical encounters from 2013 to 2017 and measured the rate of post-surgical opioid prescribing and duration of therapy. The researchers found the rate of prescribing remained stable throughout the study period, though the duration of therapy declined ($p < 0.001$). Certain subgroups of patients had a greater likelihood of receiving an opioid prescription, including females ($p < 0.0001$) and those with public insurance ($p < 0.05$). Opioids were also more likely to be prescribed in patients who did not disclose their ethnicity and those of non-white descent ($p < 0.0001$). Additionally, the odds of receiving an opioid prescription were greater for otolaryngology procedures compared with all other procedure types ($p < 0.0001$). This study gives reason to believe that opioid prescribing patterns in children undergoing tonsillectomy may differ between publicly and privately insured children.

However, other studies reveal that opioid prescribing is actually decreased in publicly insured children. A cross-sectional analysis of 69,152 pediatric emergency department (ED) patients was undertaken to evaluate factors associated with opioid prescribing. Those using Medicaid as their primary payment method had a significantly lower likelihood of being prescribed an opioid (OR = 0.74, 95% CI = [0.67-0.81]) compared with those using private insurance (Tomaszewski et al., 2018). This study also revealed that white patients were more likely to be prescribed an opioid (OR 1.34, 95% CI = [1.19-1.50]) compared with nonwhite patients. However, this study was not conducted in the perioperative setting, limiting its generalizability to post-tonsillectomy children.

Additionally, Fortuna and colleagues (2010) assessed prescribing rates of controlled substances (opioids) for injury and non-injury related visits in adolescents and young adults across multiple settings, including outpatient clinics and emergency departments. Using National Hospital Ambulatory Medical Care Survey data from 2005 to 2007, this study showed uninsured patients were consistently prescribed controlled substances at higher rates than those with private insurance ($p < 0.001$) (Fortuna, Robbins, Caiola, Joynt, & Halterman, 2010). Though this study does not address post-operative opioid prescribing, it further highlights prescribing differences based on health insurance status.

Though inconsistent, the general body of knowledge indicates there are variations in opioid prescribing patterns and one factor associated with these variations appears to be insurance status. Plausible explanations for differences in opioid prescribing in pediatric post-tonsillectomy patients may be related to implicit or explicit biases based on certain patient characteristics or clinical reasoning, as discussed in Chapter 1.

Medical treatment based on insurance status

Additional evidence illustrates that publicly insured children may be treated differently than their privately insured counterparts. These studies, summarized in Table 10, collectively represent treatment differences that may be, in part, based on insurance status.

Table 10

Treatment Differences in Publicly versus Privately Insured Children

Study	*Design & Subjects*	*Measures*	*Conclusions*
(Alexander & Currie, 2017)	Retrospective review of children between 3 months and 13 years of age who presented at a New Jersey hospital ED between 2006 and 2012	Likelihood of hospital admission during high flu-weeks	Likelihood of hospital admission favored privately insured children for admission, especially when hospitals are capacity constrained
(Boss et al., 2015)	Retrospective review of outpatient otolaryngology clinic children with a new diagnosis of sleep-disordered breathing and without a PSG sleep study (n=136)	Days from initial evaluation to sleep study & days from initial evaluation to adenotonsillectomy	Children with OSA who had public insurance had longer intervals from initial evaluation to sleep study ($p = 0.001$) or surgery ($p = 0.001$)
(Bisgaier & Rhodes, 2011)	Prospective study of two paired phone calls separated by 1 month to 273 randomly selected specialty pediatric medical clinics in one Midwest county	Ability to make an appointment at a specialty clinic (eight specialty clinics investigated)	Significant differences in provider acceptance of Medicaid/CHIP versus private insurance. Average wait time for publicly insured children was 22 days longer ($p < 0.005$); 66% of publicly insured children were denied an appointment compared with 11% of privately insured children ($p < 0.0001$)
(Chang et al., 2014)	Retrospective cohort study evaluating Medicaid (n=6,435) & commercially (n=4592) insured children who newly started asthma treatment	Total number of asthma prescriptions	Total number of asthma prescriptions possessed by Medicaid children were higher compared with privately insured children (29.5% vs 12.8%; $p < 0.01$)

(Sabharwal et al., 2007)	Retrospective evaluation of children < 18 years with an extremity injury requiring orthopedic consultation after visiting the ED (n= 125)	Time from initial presentation to time until orthopedic consultation	52% of children with private insurance received orthopedic care within 24 hours compared with 22% with public insurance (p = 0.013)

The complexity of health and health care invites many alternative explanations for these findings, including delay/avoidance of health care due to low-literacy, limited health-related knowledge, perceptions of health care and transportation, cost or other access barriers (Arpey et al., 2017; Smith et al., 2018; Polit & Beck, 2017). Still, health insurance status seems to influence some aspects of health and health care, including prescribing patterns.

Theoretical Framework

The following section details the theoretical underpinnings of the study and applies the theoretical constructs within the context of the study.

Introduction

Defining the quality of healthcare is challenging. Many problems stem from the notion that quality is inherently difficult to define. The Institute of Medicine (IOM) initially defined quality as "the degree to which health services for individuals and populations increases the likelihood of desired health outcomes and are consistent with current professional knowledge" (Institute of Medicine, 1990, p.21). Later, the IOM presented a new conceptualization of quality to include six domains of quality healthcare – care that is safe, timely, patient-centered, effective, equitable and efficient (Institute of Medicine, 2001).

Quality of care is a central matter in this study. Evaluating codeine and opioid prescribing in publicly and privately insured pediatric post-tonsillectomy patients aligns with the IOM's quality conceptualizations of safety (halting codeine prescribing) and equity of care (in all

children, regardless of health insurance status). The Donabedian model will serve as a framework to define how quality will be measured in this study.

The Donabedian model

In pursuit of evaluating quality in healthcare, Avedis Donabedian worked to define and develop techniques to measure the quality of healthcare; his research contributed an influential body of work on the theory and practice of quality in healthcare (Ayanian & Markel, 2016). As shown in Figure 4, Donabedian's landmark article proposed three domains in which the quality of healthcare can be assessed – structure, process and outcome (S-P-O) (Donabedian, 1966/2005). The assumption of the model is "good structure increases the likelihood of good processes, and good processes increases the likelihood of good outcomes" (Donabedian, 1988, p.1145). It is integral to note that structure, process and outcome do not themselves constitute elements of quality – rather they are vehicles by which quality can be assessed. The following narrative will describe each arm of Donabedian's triad.

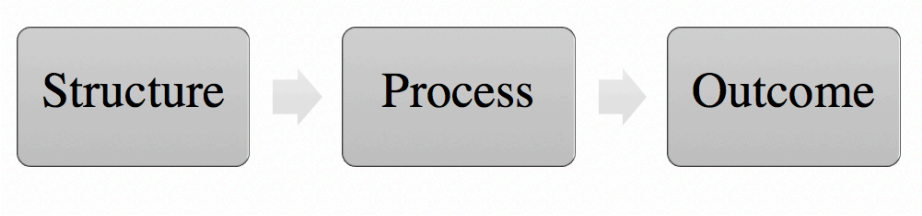


Figure 4. The Donabedian Model

Shi & Singh (2015) describe structure as the foundation of quality healthcare. The structure of care relates to the organization of health care delivery and can be viewed at the system, organizational or individual level (Kleinman & Dougherty, 2013). The structure arm of the triad refers to characteristics or attributes of the setting in which care occurs and instrumentalities that produce care within those settings (Donabedian, 1966/2005). Facility

resources, qualifications of providers/organizations, administrative structure, governance systems and fiscal components are aspects of Donabedian's structure arm. Structure may also include administrative and related processes that support and direct the provision of care (Shi & Singh, 2015; Donabedian, 1966/2005). The assumption, as delineated by Donabedian (1966/2005), is "given the proper settings and instrumentalities, good medical care will follow" (p. 695).

Another approach to quality assessment is to evaluate the process of care itself. The process arm of the triad represents what is actually done in giving and receiving care and includes all components of delivered care (Donabedian, 1988). Performance of the healthcare provider can be assessed by both technical and interpersonal aspects. Best practice, or the process that is "known or believed to produce the greatest improvement in health", is used to judge the goodness of technical performance or effectiveness of delivered care (Donabedian, 1988, p. 1743). Interpersonal aspects of care comprise effective provider-patient communication based on dignity, respect, compassion and concern (Shi & Singh, 2015). Again, the assumption by Donabedian (1966/2005) is when "good" medical care has been applied, "good" outcomes will follow. Processes can be evaluated by means of appropriateness of medical care, technical competence, coordination of care, acceptability of care and interpersonal performance (Donabedian, 1966/2005). Process measures are actionable (e.g. can modify a process to reflect best practice) and can be directly targeted to improve quality (Glance, Neuman, Martinez, Pauker, & Dutton, 2011).

Finally, the outcome of medical care is a frequently used indicator to evaluate quality of care. It denotes the effect of care on the health status of the patient and population; its evaluation may broadly encompass recovery, restoration of function and survival (Donabedian, 1988; Donabedian, 1966/2005). Shi & Singh (2015) describe outcomes as final results comprising

health status, recovery/improvement, mortality, iatrogenic illnesses, re-hospitalization, disease incidence and prevalence and patient satisfaction. Because outcomes are relatively concrete, valid, widely accepted and amenable to precise measurement, using outcomes as indicators of quality is common and advantageous – so long as the outcomes are clearly defined and relevant (Donabedian, 1966/2005). Outcomes "by and large, remain the ultimate validators of the effectiveness and quality of medical care" (Donabedian, 1966/2005, p. 694).

The components of Donabedian's triad were discussed distinctly to provide information on each domain in which quality can be assessed. Yet, this approach to quality assessment is only possible "because good structure increases the likelihood of good processes, and good processes increase the likelihood of good outcomes" (Donabedian, 1988, p. 1145). Thus, a unidirectional relationship exists among these elements. This relationship between S-P-O makes Donabedian's model a useful framework to evaluate the influence of structural and process-related factors on outcomes. As shown in Table 11, this triad has been widely adopted and used extensively to evaluate the quality of healthcare.

Table 11

Donabedian's Model Applied to Evaluate the Quality of Healthcare

Study	Design/Population	Structure	Process	Outcome
(Hannan et al., 2001)	Retrospective review of patients undergoing carotid endarterectomy (CE) (n = 3644)	n/a	Surgical approach and/or medication administration in patients undergoing CE	Death or stroke
(Gardner, Gardner, & O'Connell, 2014)	Mixed methods study evaluating nurse practitioner (NP) services using stakeholder surveys (n=36) and in-	Settings for NP services (6 service settings)	Clinical services provided by NP's (technical competence and scope of practice)	Quality of care (safety and patient satisfaction)

	depth interviews (n=24)			
(Liu, Singer, Sun, & Camargo, 2011)	Retrospective review of patients boarded in an emergency department	Overflow of boarded patients to the hallway	Delays or errors in diagnosis or treatment	Quality of care (length of stay, patient satisfaction, adverse outcomes)
(Moore, Lavoie, Bourgeois, & Lapointe, 2015)	Retrospective review of patients treated in 57 trauma systems (n= 63, 971)	Trauma accreditation reports	Conformity to established clinical processes	Mortality, length of stay, unplanned readmissions, complications
(Profit et al., 2010)	Synthesis of various frameworks of quality of care to form composite indicators for quality of care	Nurse-to-patient ratio, intensivist in-house 24 hours per day	Medication safety practices, central line and ventilator assisted pneumonia processes	Infection rates, pneumonia rates, mortality
(Tsai, Joynt, Orav, Gawande, & Jha, 2013)	Retrospective review of Medicare patients discharged after hospitalization for six indexed procedures (n= 479, 471)	Hospital size, teaching status, region	Adherence to surgical process measures	Hospital readmission rates

Application of Donabedian's model

This study explores the linkage of Donabedian's S-P-O constructs, as illustrated in Figure 5, where the FDA warning *(structure)* will lead to a change in prescribing practices *(process)* and influence the number of codeine and alternative opioid prescriptions *(outcome)*. An adaptation to the model includes health insurance status, where health insurance status *(antecedent)* may affect the number of codeine and alternative opioid prescriptions.

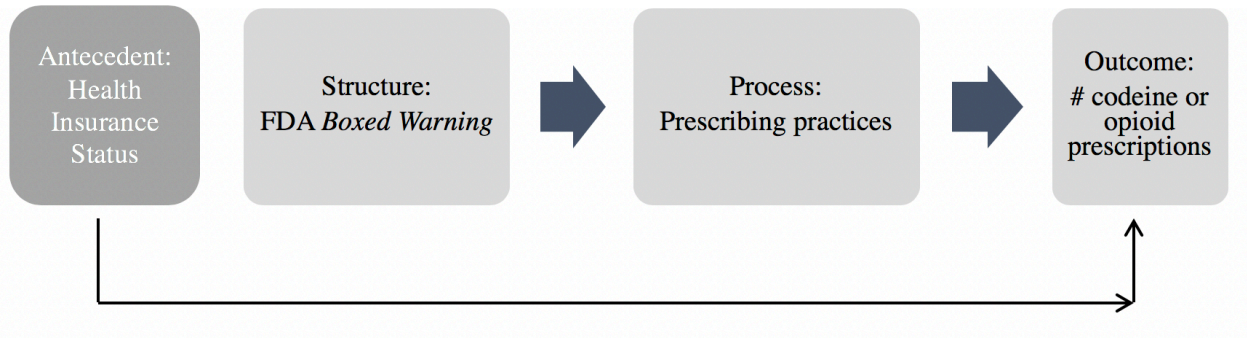


Figure 5. Application of Donabedian's Structure-Process-Outcome model

In this study, the structure arm of the triad is viewed at the system level, where the FDA warning is an administrative/regulatory process that supports and directs the provision of care. Prescribing practices are consistent with actual care rendered, fitting within Donabedian's process arm. Outcomes, or final results, are the actual number of codeine/opioid prescriptions received by pediatric post-tonsillectomy and/or adenoidectomy patients.

The Donabedian model was modified by Coyle & Battles (1999) to include antecedent conditions, or factors that may significantly influence the outcomes of care. Antecedent conditions account for the patient's environmental and/or personal characteristics – the former includes cultural, social, political and physical aspects and the latter includes genetics, socio-demographics, health attitudes, beliefs and preferences (Coyle & Battles, 1999). Health insurance status is described as a pertinent socio-demographic antecedent to quality health care in Coyle & Battles' (1999) adaptation of the model, providing justification to include health insurance status as *antecedent* in this study.

Research Aims and Hypotheses

Aim 1: Evaluate post-tonsillectomy codeine prescribing in publicly and privately insured children who underwent tonsillectomy and/or adenoidectomy at OHSU before and after the 2013 FDA warning on codeine.

Hypothesis one (H_1): In publicly and privately insured post-tonsillectomy and/or adenoidectomy children at OHSU, rates of codeine prescribing (level and/or trend) decreased following the 2013 FDA warning on codeine.

Aim 2: Compare post-tonsillectomy codeine prescribing in publicly and privately insured children who underwent tonsillectomy and/or adenoidectomy at OHSU before and after the 2013 FDA warning on codeine.

Hypothesis two (H_2): There is a difference in codeine prescribing (level and/or trend) between publicly and privately insured post-tonsillectomy and/or adenoidectomy children at OHSU.

Aim 3: Examine all other post-tonsillectomy opioid prescribing (oxycodone, hydrocodone) in publicly and privately insured children who underwent tonsillectomy at OHSU before and after the 2013 FDA warning on codeine.

Hypothesis three (H_3): In publicly and privately insured post-tonsillectomy and/or adenoidectomy children at OHSU, rates of alternative opioid prescribing (level and/or trend) increased following the 2013 FDA warning on codeine.

Aim 4: Compare post-tonsillectomy other opioid prescribing in publicly and privately insured children who underwent tonsillectomy and/or adenoidectomy at OHSU before and after the FDA warning on codeine.

Hypothesis four (H_4): There is a difference in other opioid prescribing (level and/or trend) between publicly and privately insured post-tonsillectomy and/or adenoidectomy children at OHSU.

Chapter Summary

Post-tonsillectomy adverse events result from a variety of factors including opioids, comorbid conditions and genetic risk signatures. Codeine, and potentially other opioids, should

be avoided in all post-tonsillectomy and/or adenoidectomy children due to the risk significant adverse events. Studies have evaluated the impact of the FDA warning on codeine and opioids in privately insured children, but no study has done so in publicly insured children. Though the evidence is mixed, studies suggest insurance status may influence prescribing patterns. The purpose of this study is to fill the research gap of codeine/opioid prescribing in publicly insured post-tonsillectomy and/or adenoidectomy children and compare prescribing rates between publicly versus privately insured children.

Chapter 3: Methodology

Chapter Overview

The purpose of this study is to examine the impact of the FDA warning on codeine/opioid prescribing in children undergoing tonsillectomy and/or adenoidectomy at Oregon Health and Science University (OHSU) and to evaluate if prescribing practices vary based on health insurance status. The previously described Donabedian model provides the theoretical framework to inform the study. Donabedian's constructs of structure, process and outcome will guide operationalization of study variables and evaluation of study data.

Chapter Three describes the study's research methodology, including research design, population, and sampling information. A detailed description of the study's variables, discussion of the data source, overview of data collection procedures and a summary of the data analysis plan is presented. This section concludes with an account of the validity of research design.

Research Design

This study will evaluate the impact of the FDA warning on opioid prescribing in pediatric post-tonsillectomy patients by employing a quasi-experimental, interrupted time series (ITS) study design. An ITS design provides understanding of patterns of change over time and evaluates the effects of a planned or unplanned intervention (Velicer, Hoeppner, & Goodwin, 2012). The 'time series' represents repeated observations of a particular event collected over time in a defined population and the 'interruption' signifies the intervention (Polit & Beck, 2017). The most common ITS design includes two segments where the first comprises rates of the event prior to the intervention or policy change and the second represents the rates after the intervention or policy change (Penfold & Zhang, 2013). Series of observations on the same outcome can test immediate and gradual effects of the intervention or policy change (Taljaard, McKenzie, Ramsay, & Grimshaw, 2014). This study design is particularly useful when the

investigator does not have control over the implementation of an intervention, when randomization is not feasible and when a control group is lacking (Penfold & Zhang, 2013; Polit & Beck, 2017). Time series designs can be prospective or retrospective, or a combination of both (Polit & Beck, 2017). This study will employ a retrospective design and obtain data from the health system's electronic health record (EHR).

An ITS design is an appropriate methodology for this study for several reasons. First, ITS designs are the standard for evaluating the impact of policy changes, public health interventions or quality improvement programs (Bernal, Cummins, & Gasparrini, 2017; Penfold & Zhang, 2013; Ray, 1997). The design is particularly suited to assess interventions/policies that are instituted at a population level over a defined period of time (Bernal et al., 2017). The ITS methodology aligns with the current study's aim of evaluating the effects of a policy/regulatory change (FDA warning) on repeated outcomes (prescribing practices) in a defined population (pediatric post-tonsillectomy patients). Next, this study contains a naturally occurring intervention (FDA warning) that represents the 'interruption' in the ITS design. This feature allows for clear differentiation of pre-and post-intervention periods and repeated pre-and post-intervention measures. Additionally, similar studies utilized the ITS study methodology to evaluate opioid prescribing practices, as summarized in Table 12. Finally, it would not be feasible nor ethical to randomize participants to intervention and control arms within the context of the FDA warning on codeine; this warning applied nationally to all post-tonsillectomy children immediately after the warning was announced.

Table 12

Interrupted Time Series Methodology in Opioid-prescribing Studies

Study	**Objective**	**Data Source**	**Time series comparisons**

(Bohnert, Guy, & Losby, 2018)	If release of the 2016 CDC *Guidelines for Prescribing Opioids for Chronic Pain** corresponded to declines in opioid prescribing practices in U.S. adults	Retail pharmacy data from 2012-2017	Compared pre-and post-CDC guideline monthly prescribing measures (dosage, supply, opioid/benzodiazepine overlap)
(Boyle et al., 2019)	If sharing individual provider prescribing data with other providers* impacted the rates of opioid prescriptions written for adult patients discharged from the ED	Single center community hospital EHR data from 2015-2016	Compared pre-and post-intervention number of discharge prescriptions written by each clinician
(Chua et al., 2017)	If the FDA *Boxed* Warning* on codeine resulted in a reduction in codeine and/or opioid prescribing in children who underwent tonsillectomy	Prescription data from the Truven MarketScan Commercial Claims Encounters database from 2012-2015	Compared pre-and post-FDA warning codeine and opioid prescribing rates
(Fernandes et al., 2016)	If the national clinical practice guidelines* and/or drug policy interventions* impacted opioid prescribing rates or opioid-toxicity hospitalizations in Canadian citizens	Prescription data from the Ontario Drug Benefit database from 2003-2014	Compared pre-and post-intervention rates of prescribing, dose of opioid prescribing and opioid-related ED visits and hospitalizations
(Meisenberg, Grover, Campbell, & Korpon, 2018)	If a multilevel opioid intervention* reduced opioid prescribing in inpatient and outpatient adult patients	Single center community hospital EHR data from 2016-2018	Compared pre-and post-intervention morphine milligram equivalents (MME) per month, MME per prescription and rates of opioid prescriptions
(Ranapurwala, Carnahan, Brown, Hinman, & Casteel, 2019)	If Iowa's prescription monitoring program* (PMP) reduced opioid prescribing patterns in adults	Iowa's private health insurance claims database from 2003-2014	Compared pre-and post PMP daily MME dosage, MME per prescription, supply of opioids and overall prescribing rates
(Van Cleve, 2017)	If the FDA *Boxed* Warning* on codeine resulted in a reduction in codeine and/or opioid prescribing in pediatric post-tonsillectomy patients	Prescription data from the Truven MarketScan Commercial Claims Encounters database from 2012-2015	Compared pre-and post-FDA warning codeine/opioid prescribing rates and ED visits.

*I = "Interruption" in the design

Data Source

The data source for this study is OHSU's EHR platform, EPIC Hyperspace®. The outpatient EPIC Hyperspace® platform was fully integrated into OHSU in 2008. Thus, the data source is expected to yield complete, electronic data from 2010-2018. Data will be extracted by the OHSU Pharmacy Informatics team; information regarding data collection is detailed below.

Population and Sample

Target population & accessible population

The target population for this study is U.S. pediatric patients up to 18 years of age undergoing tonsillectomy and/or adenoidectomy on an outpatient basis. The accessible population is children up to 18 years of age who presented to OHSU between January 2010 through December 2018 for outpatient tonsillectomy and/or adenoidectomy.

Sampling strategy

In retrospective evaluation of EHR data, sampling refers to the method by which cases or records are selected from the accessible population or database. A convenience sampling method is the most common method for selecting cases or records from an EHR over a specific time frame (Worster & Haines, 2004). In this study, the EHR represents the sampling frame and the sampled population will be all eligible patients who underwent tonsillectomy and/or adenoidectomy at OHSU between January 2010 through December 2018. The number of cases in the sample will be limited to the number of cases performed at OHSU. This convenience sampling strategy is expected to produce adequate data, as OHSU otolaryngology surgeons perform nearly 300-400 such cases annually.

Eligibility criteria

Inclusion and exclusion criteria are presented and justified in Table 13, below.

Table 13

Inclusion and Exclusion Criteria

	Criteria	Justification
Inclusion	Male or female patient presenting for outpatient tonsillectomy and/or adenoidectomy at OHSU	The FDA warning applies to all children undergoing tonsillectomy and/or adenoidectomy, regardless of demographic characteristics or indication for tonsillectomy.
	Age 0-18 years	The FDA warning applies to all children < 18 years of age.
	Public or private insurance	No study has compared post-tonsillectomy opioid prescribing in publicly versus privately insured children. Research suggests insurance status may impact opioid prescribing practices (Donohoe et al., 2019).
Exclusion	Date of surgery between February 2013 – March 2013	The month the FDA warning was announced (February 2013) plus the month after (March 2013) will be excluded. Exclusion of the month/month after accounts for a "wash out" effect (Polit & Beck, 2017).
	A combined procedure of any type	A combined procedure of any type may influence post-operative pain severity may increase the likelihood of a post-operative opioid prescription (Donohoe et al., 2019.; Fortuna et al., 2010).
	Inpatient admission following tonsillectomy	Inpatient admission allows for greater patient monitoring capabilities, which may increase the likelihood a provider would prescribe post-tonsillectomy and/or adenoidectomy opioids.
	Uninsured children	Due to federal and state initiatives, the percentage of uninsured children in Oregon is < 3%. This low rate of uninsured children would lead to inadequate observations per time period and unbalanced study groups. Uninsured children will not be included in the statistical model for the health insurance stratified analysis.

Power analysis

In ITS, power is a function of a variety of factors including the number of time points, the distribution of time points before and after the intervention, the degree to which data are correlated across time (autocorrelation), expected effect size and the presence of confounders (Bernal et al., 2017). As a result, there are no fixed limits regarding the number of time points –

though it has been suggested that studies with few time points and small effect sizes may be underpowered (Bernal et al., 2017; Zhang, Wagner, & Ross-Degnan, 2011). Time points are defined as a continuous sequence of observations on a population, taken repeatedly at equal intervals over time; there is no standard measurement interval – weekly, monthly and yearly time points are described in health policy literature (Bernal, Cummins, & Gasparrini, 2018; Hudson, Fielding, & Ramsay, 2019). In ITS, power increases with the number of time points and/or if the number of time points before and after the intervention are equally distributed. The latter is rarely practical whereas former is imperative, as a sufficient number of time points are required to properly analyze time-series data (Bernal et al., 2017; Wagner, Soumerai, Zhang, & Ross-Degnan, 2002). Power also increases when autocorrelation is small, when effect size is large and when changes in both the regression slope and level is expected; all of these values are often difficult to establish *a priori* (Zhang et al., 2011).

Using simulated-based power calculations, Zhang et al. (2011) described acceptable methods for calculating power in health policy time-series research designs. With a significance level of alpha (α) = 0.05, models with greater than 80% power to detect moderate effect sizes require 24 or more time points. Samples as small as 12 time points should be used with caution as unreliable power estimates and Type II error may be introduced (Wagner et al., 2002; Zhang et al., 2011). In addition to a sufficient number of time points, ITS requires an adequate number of observations at each time point (Hawley, Ali, Berencsi, Judge, & Prieto-Alhambra, 2019). There appears to be no distinct minimum number of observations at each time point, though >100 is desirable to achieve an acceptable level of variability at each time point (Wagner et al., 2002). Table 14 details the components of power analysis considered for this study.

Table 14

Components of Power Analysis

Anticipated effect size	Small. Based on conservative estimates from the literature (Chua et al., 2017; Van Cleve, 2017)
Anticipated autocorrelation	Unknown. If autocorrelation is unknown, using a range of 0.1 and 0.5 is recommended. This is consistent with previous policy evaluation time-series studies (Zhang et al., 2011)
Anticipated change in level and slope	Based on previous studies, both a level and slope change are anticipated, with a greater change in the level when compared with the slope (Chua et al., 2017)
N= Total number of time points (time points = months)	Pre-intervention: 31 time points (January 2010 – July 2012) Post-intervention: 69 time points (April 2013 – December 2018) Total N = 100
n = Total number of observations at each time point (observations = number of tonsillectomies per time point)	25-30, assuming 300-400 tonsillectomies per year
Balance of design	Unbalanced. The post-intervention period includes a greater distribution of time points. Pre- and post-intervention periods in health policy research are often unbalanced (Bernal et al., 2017)
Confounders	Seasonal variation in rate of tonsillectomies may influence power

The relatively low number of observations at each time point, unbalanced design, small effect size and potential seasonal variation may be offset by the sufficiently long sampling period and adequate number of time points (Polit & Beck, 2017; Wagner et al., 2002). Power is also enhanced in this study due to population-level repeated measures of the outcome over an extended period of time, a well-defined pre-and-post health policy change period and equally spaced observation intervals (Hawley et al., 2019). Based on Zhang's et al. (2011) simulated power analysis, the estimated power for a model with both a slope and level change, a small effect size, unbalanced pre-and post-intervention periods, autocorrelation range between 0.1-0.5 and $\alpha = 0.05$, power is expected to be 0.76 – 0.99. Thus, this study is appropriately powered.

Data Collection

The tool used to collect data in this study will be the OHSU health system's EHR. An EHR is unbiased (non-reactive) and inexpensive way to collect data (Polit & Beck, 2017). EHR's collect longitudinal, electronic data during routine delivery of health care and generally include demographic, administrative, claims (medical and pharmacy), clinical, and patient-centered data (Cowie et al., 2017). Collecting data via the EHR is an appropriate method given this study aims to evaluate clinical, demographic, medical and pharmacy data that has been collected over time during routine tonsillectomies and/or adenoidectomies.

Variables and Measures

Table 15 shows study variables that will be collected and their associated measurement. In this study the predictor variables are the intervention (FDA Warning) and time (months pre- and post-FDA warning). The outcome variables include rates of codeine and other post-tonsillectomy opioid prescribing. Additional demographic (age, gender, race) and clinical (OSA status, body mass index [BMI] percentile) variables will be collected to assess group comparability and to evaluate if prescribing is influenced by demographic or clinical factors; health insurance payer information will be collected to assess if prescribing varies by insurance status. Procedural data and date of surgery will be collected for each child. Note: *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD*-9-CM) and *Procedure Codes* (*ICD-10-PSC)*, *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD*-10-*CM*) and *Procedure Codes* (*ICD-10-PCS*) and *Current Procedural Codes (CPT)* are further detailed in Appendix A.

Table 15

Study Variables and Measurement

Variable Collected	Measurement	Type of Variable
Sleep related breathing disorder and/or OSA diagnosis	*ICD-9-CM** codes: 327.23 and/or 780.57 within 90 days of DOS *ICD*-10-*CM** codes: G47.33 and/or G47.30 within 90 days of DOS	Categorical [OSA/no OSA]
Tonsillectomy and/or adenoidectomy surgical procedure	*CPT* codes*:* 42820, 42821, 42825, 42826, 42830, 42831 and/or 42835, 42836 on DOS *ICD-9-PCS* codes*:*28.2, 28.3 and/or 28.6 on DOS *ICD-10-PCS* codes: 0CTP0ZZ, 0CTPXZZ, 0CTQ0ZZ, 0CTQXZZ, 0C5P0ZZ, 0C5PXZZ, 0C5Q0ZZ, 0C5QXZZ, 0CBP0ZZ, 0CBPXZZ, 0CBQ0ZZ and/or 0CBQXZZ on DOS	n/a – all children included in the study underwent tonsillectomy and/or adenoidectomy
Time	Date of service (month/year) associated with CPT and/or *ICD-9/10-PCS* code(s) for tonsillectomy and/or adenoidectomy	Continuous
FDA *Boxed Warning*	Measured using the date of the FDA warning (February 2013) to denote pre-FDA warning or post-FDA warning periods	Categorical [pre or post-FDA warning period]
Age	Age at DOS; obtained via demographic information	Continuous variable, collapsed into categorical variables
Gender	Male or female gender; obtained via demographic information	Categorical [male/female]
Height	Height in meters	Continuous
Weight	Weight in kilograms	Continuous
Body Mass Index [BMI]	Weight in kilograms divided by the square of height in meters	Categorical [underweight, normal weight, overweight, obese]
Race	Race (as defined by the CDC's revised race standards); obtained via demographic information	Categorical [0 = American Indian, Alaskan Native, Native Hawaiian or Other Pacific Islander, 1= Asian, 2= Black, 3= White]
Health insurance status	Payer information; obtained via administrative claims	Categorical [private/public]
Post-tonsillectomy codeine prescribed (0-2 days) **If prescribed:**	Prescription data; obtained from pharmacy claims Dose (milligram/kilogram [mg/kg]) of codeine prescribed	Continuous [rates of codeine** prescribing, expressed in %] Continuous

Post-tonsillectomy alternative opioid prescribed (0-2 days)	Prescription data; obtained from pharmacy claims	Continuous [rates of other*** opioid prescribing, expressed in %]
If prescribed:	Dose (milligram/kilogram [mg/kg]) of alternative opioid prescribed	Continuous

*ICD-9-CM and PCS effective until 10/1/2015; ICD-10-CM and PCS effective 10/2/2015 - present
**Codeine = Includes codeine alone or any codeine-containing drug – the most common being codeine with acetaminophen
***Other opioids = Hydrocodone, oxycodone, tramadol

Data management

All data will be extracted from OHSU's EHR, exported to Microsoft® Excel and entered into the IBM® Statistical Package for the Social Sciences (SPSS) statistical software. Confidentiality of the data will be maintained through use of a password protected, encrypted OHSU issued laptop. Any hard copies of subject information will be stored in a locked cabinet and made accessible only to those directly involved in the study. Study records (electronic and/or hard copy) will be made available for review only to those directly involved in the study and the Institutional Review Boards (IRB) of OHSU and Virginia Commonwealth University (VCU).

Protection of Human Subjects

This study collects secondary data from the medical record, does not require consent and represents no more than minimal risk to subjects. Subject information will be recorded in a manner that the identity of the human subjects cannot readily be ascertained directly or indirectly. Subject identifiers will be treated as confidential per the Health Insurance Portability and Accountability ACT (HIPAA) of 1996; identifiers will not be used in published information or disseminated otherwise.

Children are a vulnerable population addressed in the federal regulations of research conduct (45 CFR 46 Subpart D; 21 CFR 50 Subpart D). From a regulatory perspective, this study

falls into the "minimal risk" category and no additional protection is required beyond that of appropriate IRB approval from OHSU and VCU, and abiding by the ethical standards of research conduct (Welch et al., 2015).

Data Analysis

Data cleaning

After data extraction, the variables will be named and data will be cleaned using procedures described by Tabachnick and Fidell (2013). First, descriptive statistics will be evaluated for accuracy of data input, including assessment of normality, out-of-range values and outliers. Next, missing data will be assessed; if data is missing, a missing value analysis will be performed to identify the extent and pattern of missing data. Linearity between the independent (time) and dependent (prescribing rates) variables within each regression segment will be assess via residual plots (Wagner et al., 2002). Autocorrelation will be assessed and, if present, will be dealt with via adjustment of standard errors as suggested by Tabachnick and Fidell (2013).

Descriptive statistics

Descriptive statistics will be generated to describe the characteristics of children undergoing tonsillectomy at OHSU between January 2010 – December 2018. For each study year the following will be reported: Sample size, gender (% male and female), age (% 0-4.9 years, 5-9.9 years, 10-18 years) weight status (% underweight, normal weight, overweight or obese), race (% American Indian, Alaskan Native, or Other Pacific Islander, Asian, Black or African American and White), health insurance status (% public and private) and OSA status (% with and without OSA).

Time-series analysis

Segmented regression analysis is a statistical method for modelling ITS data and will be used in this study to assess the impact of the FDA warning on codeine and opioid prescribing in post-tonsillectomy children. This is a well-established method to test the hypothesis that an intervention caused a significant change in the outcome over time (Valsamis, Ricketts, Husband, & Rogers, 2019; Wagner et al., 2002). Segmented regression is an adaptation of linear regression where separate regressions are performed for periods before and after an intervention (Tabachnick & Fidell, 2013; Valsamis et al., 2019). The regression coefficients of the model estimate the pre-intervention slope, the level change at the intervention point and the slope change from pre-intervention to post-intervention (Kontopantelis, Doran, Springate, Buchan, & Reeves, 2015). Figure 6 further describes the slope and level changes within the context of an ITS design.

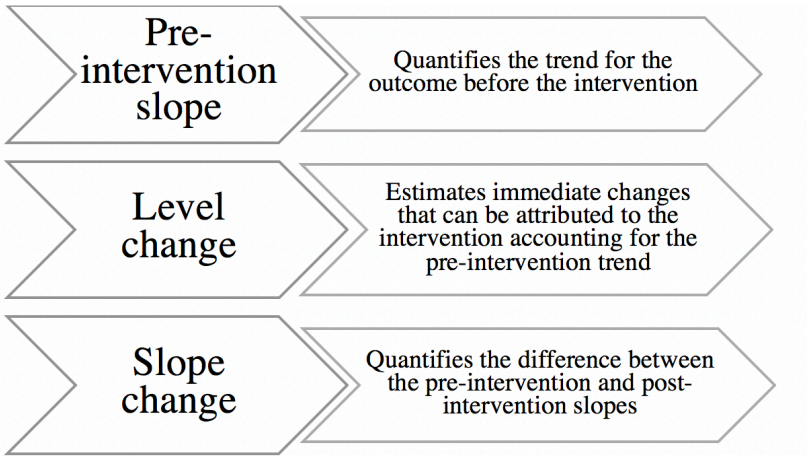


Figure 6. Slope and Level Changes in Interrupted Time Series Designs. Information from: (Kontopantelis et al., 2015)

The two segments in this study will be defined as the pre-FDA or post-FDA warning periods and the intervention, or 'interruption', will be the FDA warning. Segmented linear regression will quantify changes in the level and slope in the pre-and post-FDA warning periods, then estimate if the differences are statistically significant. The level and trend estimates will

provide information on the immediate (level change) and/or gradual (trend or slope change) effects of the FDA warning. The segmented regression equation that will be used for this study, adapted from Wagner et al. (2002), is: $Y_t = \beta_0 + \beta_1 * time_t + \beta_2 * intervention_t + \beta_3 * time\ after + \varepsilon_t$

Where **Y** = mean number of prescriptions in month *t*
time = time in months at time *t* from the start of the observation period
intervention = time *t* occurring before or after the FDA warning
time after = number of months after the FDA warning at time *t*
β_0 = baseline level of number of prescriptions per month at time zero
β_1 = change in the mean number of prescriptions that occurs with each month pre-FDA warning
β_2 = level change in the mean number of monthly prescriptions immediately after the FDA warning
β_3 = trend change in the mean number of monthly prescriptions after the FDA warning, compared with the monthly trend before the FDA warning
ε_t = error term at time *t* represents variation not explained by the model

The first regression model will evaluate codeine prescribing in publicly and privately insured post-tonsillectomy children at OHSU, addressing hypothesis one (H_1). The second regression model will evaluate alternative opioid prescribing in publicly and privately post-tonsillectomy children at OHSU, addressing H_3. The impact of health insurance on codeine (H_2) and alternative opioid (H_4) prescribing will be assessed using an additional regression model. This model will test whether associations vary among children with public versus private insurance. To accomplish this, interaction terms between the covariate of interest (health insurance status) and the three ITS components relating to the pre-intervention slope, level change, and change in slope will be evaluated (Kontopantelis et al., 2015). For all statistical tests, *p*-values and confidence intervals will be reported; two-sided *p*-values of ≤ 0.05 will be considered clinically significant. Data will also be presented graphically via time series plots.

Assumptions and Threats

The key study design assumption is that without the intervention (FDA warning), pre-intervention prescribing trends would continue unchanged into the post-intervention period and

no external factors systematically affect the trends (Kontopantelis et al., 2015; Tabachnick & Fidell, 2013). To evaluate external factors that could bias the results, the FDA's Drug Shortages Database (https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm) will be searched to assess for shortages of codeine, oxycodone, hydrocodone or tramadol. Also, the literature will be examined for other interventions (known as co-interventions) that may confound the results. The aforementioned will address the threat of history bias. Next, time series designs may exhibit seasonal fluctuation due to cyclic variation in illnesses, preferences or clinical practice (Bernal et al., 2018; Wagner et al., 2002). Seasonality in this study may occur related to varying rates of tonsillectomies per month, however a sufficiently long sampling period reduces this threat.

Statistically, segmented regression assumes data are collected regularly over time at equally spaced intervals. This assumption will be met, as the observation points in this study will be collected at regular, monthly intervals. Also, analysis of time-series data requires that correlation of the data points across time is accounted for (Tabachnick & Fidell, 2013; Zhang et al., 2011). Statistical procedures will be performed to account for data points that are close together in time and tests for autoregulation will be reported. If autocorrelation is present, it will be controlled for statistically by adjusting the standard errors, as described by Tabachnik and Fidell (2013). These procedures, along with an appropriate power analysis, distinct pre-and post-intervention periods and accurate measurement tools, enhance the statistical conclusion validity of this study.

Convenience sampling increases the external validity of this study, though threatens internal validity (Polit & Beck, 2017). However, because this study observes a single population (pediatric post-tonsillectomy patients) over an extended period of time, threats due to between-group differences, such as selection bias or unmeasured confounders, are minimized (Bernal et

al., 2018). Additionally, because ITS designs model the baseline trend, within-group characteristics that randomly fluctuate or slowly change over time are controlled for (Bernal et al., 2018; Kontopantelis et al., 2015). Still, demographic information (age, gender, race) will be collected and accounted for statistically if group differences are significant.

Measurement error is a potential threat in this study. This concern is reduced as no changes in the measurement of the variables and/or data collection methods will occur. Additionally, due to institutional and regulatory oversight, opioid prescribing is tightly-controlled and generally free of errors. It is possible that early in the study period paper/written-prescriptions, versus current electronic prescriptions (e-prescriptions), were prescribed. However, all paper prescriptions were required to be entered into the EHR, minimizing this concern. Finally, an outlier assessment will be conducted to evaluate for inconsistent data points that may constitute measurement error.

Internal validity is also threatened due to lack of a control group. However, it is infeasible to select a group that was not exposed to the FDA warning on codeine, as this warning applied nationally to all children undergoing tonsillectomy. Though a control group leads to stronger inferences, an ITS design without a control group represents a valid quasi-experimental design (Polit & Beck, 2017).

Temporal sequencing does not pose a threat in this study as the timing of the FDA *Boxed Warning* is distinct (February 2013). Pre-FDA warning outcomes (prescribing practices) will be measured to serve as a reference point and change in the level and/or slope of the outcome in the post-FDA warning is evidence to support temporality (Polit & Beck, 2017). The month of the FDA warning (February 2013) and the month following (March 2013) will be excluded as a "wash out" period.

Chapter Summary

This chapter presented the methodological details for the study, including a description of the planned ITS research design and data analysis methods that will be used to evaluate the impact of the FDA warning on codeine/opioid prescribing in pediatric-post-tonsillectomy patients at OHSU. Information regarding the sampling method, eligibility criteria, variables, data collection and management was presented. The chapter concluded with a discussion of study assumptions and threats to study validity. Chapter Four will present results of the study.

Chapter 4: Results

Chapter Introduction

The dangers of codeine in children undergoing tonsillectomy and/or adenoidectomy are well documented. Codeine prescribing should be avoided in all pediatric post-tonsillectomy and/or adenoidectomy patients, regardless of demographic or clinical characteristics. The purpose of this study was to examine the impact of the FDA warning on codeine/other opioid prescribing in children undergoing tonsillectomy and/or adenoidectomy at OHSU and to evaluate if prescribing practices vary based on health insurance status.

This study evaluated the impact of the FDA warning on opioid prescribing in pediatric post-tonsillectomy patients by employing a quasi-experimental, interrupted time series (ITS) design. This design provided understanding of opioid prescribing patterns over time and evaluated the effects of the FDA warning on codeine and other opioid prescribing. This chapter describes data preparation and statistical analyses that were employed to accomplish the study's aims. The chapter begins with a review of data extraction procedures, including a description of study exclusion criteria, followed by an overview of data cleaning/preparation and statistical assumption testing. Descriptive analysis and statistical modeling are presented. The chapter concludes with a summary of the study findings.

Review of Data Extraction

After IRB approval from OHSU and VCU, the data was extracted from OHSU's EHR platform (EPIC Hyperspace®), deidentified and coded with unique patient identifiers by the OHSU Pharmacy Informatics team. The data was transferred via email in a xls.doc (Microsoft Excel®) following OHSU data-security protocols. Greater than 99% of opioid prescribing

occurred within 0-2 days after tonsillectomy and therefore this prescribing interval was used. Insurer information was confirmed for all children on the day of procedure plus two days.

The initial dataset contained 108 months (January 2010-December 2018). When the unit of time for analysis equaled month, the total number of cases at each observation interval was small ($n < 20$), potentially introducing error into the analysis and threatening validity of inferences. Rather than monthly observations, data was grouped into 4-month observation intervals to assure adequate observations per unit of time. Appendix B displays the months included in each observation interval. To accommodate for the ITS analysis and to have clear differentiation between the pre-and post-FDA warning periods, the first and last months of data (months 1 and 108, respectively) were removed. Two months of data in time period 25 were excluded due to outlier values, as discussed below. The month the FDA warning was issued (February 2013) and the following month (March 2013) were excluded. Figure 7 depicts the study exclusions. A total of 26 observation intervals were included in the analysis; observation intervals 1-9 comprised the preintervention period and 10-26 were the postintervention period.

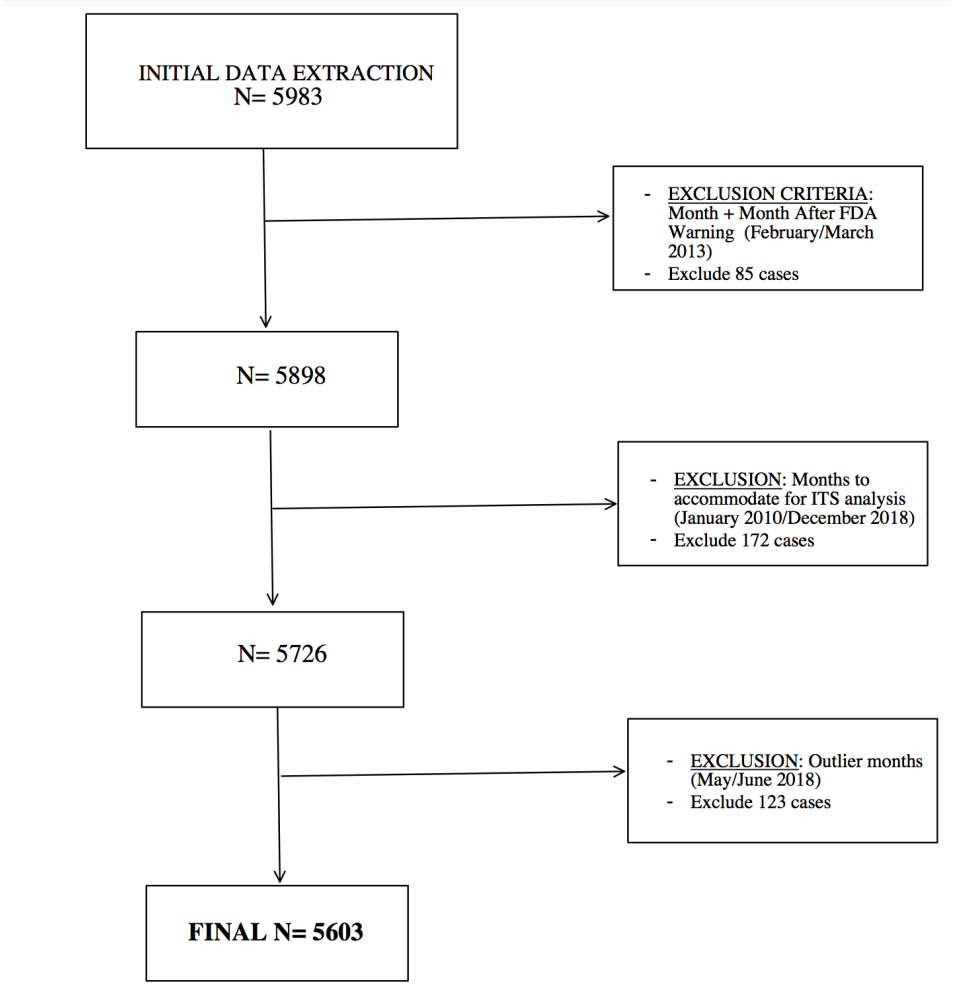


Figure 7. Study Exclusion Flow Chart

Data Preparation

The data was cleaned and coded using SPSS. Study variables were coded as shown in Table 16. Study months were ordered chronologically and coded as pre-or post-FDA warning period. Gender was categorized as males and females. Age was collapsed into three categories (0-4.9, 5-9.9 and 10-18 years) for clinical relevance and to approximate even groups. Though race was recorded as White (81.3%), Multiracial (8.4%), Black (3.3%), Asian (2.4%), American Indian (1.3%), Other Pacific Islander (0.2%) or unknown (0.1%), for analyses it was categorized as White, Non-white or missing. Insurer was classified as public, private or self. The OHSU

Otolaryngology billing department was consulted to assist in classifying insurers into respective categories. Health care programs for military personnel (Tricare, ChampVA, VA Community Outsource) represented < 2% of the sample and were included in the private insurer group. See Appendix C for a list of insurers included in each category. Body Habitus was derived from BMI percentile (based on age, gender, height and weight) and collapsed into normal, non-normal (underweight, overweight or obese) or missing BMI percentile. Procedure indication denoted the primary diagnosis associated with the procedure CPT code and was categorized as OSA versus non-OSA. Non-OSA indications included tonsillar or/or adenoidal hypertrophy, tonsillitis, adenoiditis and other. Opioids prescribed indicated whether a child did (yes) or did not (no) receive an opioid prescription within 0-2 days post-tonsillectomy and/or adenoidectomy. Opioid type included codeine-containing products or other opioids. Other opioids were non-codeine containing products (oxycodone or hydrocodone-containing products); no children in the study were prescribed the opioids tramadol, morphine or hydromorphone and therefore they were not included in the variable.

Table 16

Study Variables and Coding

Variable	**Coding**
Study months (time)	Ordered chronologically and coded as 0: Pre_FDA 1: Post_FDA
Gender	0: Males 1: Females
Age	0: 0-4.9 years 1: 5-9.9 years 2: 10-18 years
Race	0: White 1: Non-White
Insurer	0: Public 1: Private 2: Self

Body Habitus	0: BMI percentile Normal 1: BMI percentile Non-Normal 2: BMI percentile Missing
Procedure Indication	0: OSA 1: Non-OSA
Opioids Prescribed	0: Yes 1: No
Opioid Type	0: Codeine Containing Opioid 1: Other Opioids (Oxycodone or hydrocodone containing opioid)

Assumption Testing

Histograms with normal curve overlays for each variable were examined and are illustrated in Appendix D. The normalized plot of residuals for each dependent variable were inspected via Kernel Density plots and the data satisfactorily met the assumption of normality (See Appendix E). Linearity of the preintervention trends was checked via visualization of scatter plots. Data on the variable 'other opioids' met the assumption of linearity. The 'codeine' variable exhibited a somewhat irregular pattern in the pre-intervention period; transformations on the variable did not markedly improve linearity. Therefore, the data was left in its original form to retain the metrics for purposes of interpretation. Time series data inherently violate the assumption of independence of residuals because of autocorrelation over time (Tabachnik & Fidell, 2013). Autocorrelation of errors at various lags were examined via the Cumby-Huizinga test for autocorrelation. Autocorrelation was present at lag 1 but not any higher order lags and, therefore, lag(1) was included in the models. Newey-West standard errors were used in each model to handle autocorrelation and possible heteroskedasticity. Visual inspection of time series plots did not reveal a seasonal pattern in opioid prescribing.

The time-series plots were examined for outliers. Discrepant cases were found in time period 25 (T25), which contained months April-July 2018. The discrepant cases were attributed to May and June 2018, where zero opioids were prescribed during those months. Data for T25

was re-extracted by the Pharmacy Informatics team to confirm accuracy of data extraction. The otolaryngology surgical group verified there were no co-interventions during that time and the pharmacy team did not find evidence of opioid shortages. The Information Technology department confirmed an EPIC Hyperspace upgrade during that time. Given the magnitude of discrepancy and a plausible technological fault, the outliers were dealt with via exclusion. The remaining observations in T25 (April and July 2018) were used to populate opioid prescribing for the observation interval. A sensitivity analysis was conducted where data from T24 was carried forward to replace the T25 observation interval. No changes to the model occurred, confirming the robustness of findings.

A missing values analysis was conducted. Data was complete for all variables with the exception of race and body habitus (BMI). Because the variable race had only 3.1% missing data and was not a critical variable for hypothesis testing, the variable was not altered. The BMI variable contained 15% missing values. Missing values for BMI were attributed to missing height information from the EHR. The majority of missing values occurred in the first two study years with 65.7% and 36.3% missing in 2010 and 2011, respectively. Missingness continued to a lesser extent throughout the remaining study years (range 4.7-12.8%). The frequency of missing BMI percentile data is presented in Table 17. Younger children, those who were self-insured, and children with a primary diagnosis of non-OSA tended to have higher percentages of missing BMI percentile data. Little MCAR test was conducted on the BMI variable and showed the data were not missing at random ($Chi^2 = 24.4$, df =1, $p = 0.00$). The missing data was dealt with via multiple imputation. Multiple imputation makes no assumptions about the type of missing data (random or non-random) and can be applied to time-series data (Tabachnik & Fidell, 2013). Therefore, multiple imputation was used (5 imputations) to estimate BMI from variables that

were complete and known to predict BMI (age, gender and weight). The missing data was replaced with the pooled results of the imputations.

Table 17

Frequency of Missing BMI Percentile Data

	Missing N (%)
Gender	M= 467 (15.6) F= 374 (14.4)
Age	0-4.9 = 458 (22.2) 5-9.9 = 284 (11.5) 10-18 = 99 (9.3)
Race	White = 705 (15.6) Non-White= 121 (13.2) Missing = 15 (8.8)
Insurance Status	Public= 422 (14) Private= 396 (15.8) Self = 23 (24)
Primary Diagnosis	OSA = 481(11.3) Non-OSA = 360 (26.7)

Descriptive Analysis

Descriptive statistics were generated for demographics, clinical characteristics and opioid prescribing for each study year as summarized in Tables 18-20. A total of 5603 children underwent tonsillectomy and/or adenoidectomy during the study period. On the whole, the number of procedures increased over time. Male and female patients underwent the procedure at similar rates. Tonsillectomy and/or adenoidectomy was most often performed in children age 5-9.9 years. A greater proportion of the sample were White children. Children with public or private insurance appeared to undergo the procedure at comparable rates. Most children had a normal body habitus. The percentage of opioid prescribing decreased over time and the trend in the type of opioid prescribed changed with time (see Figure 8). Hydrocodone was the most

commonly prescribed opioid in the early study period (years 1 and 2) whereas oxycodone was more commonly prescribed in subsequent years. Codeine prescribing was low throughout the study period, ranging from 0-3.6%. Demographic and clinical composition of the study groups (pre-and post-FDA warning groups) will be discussed below.

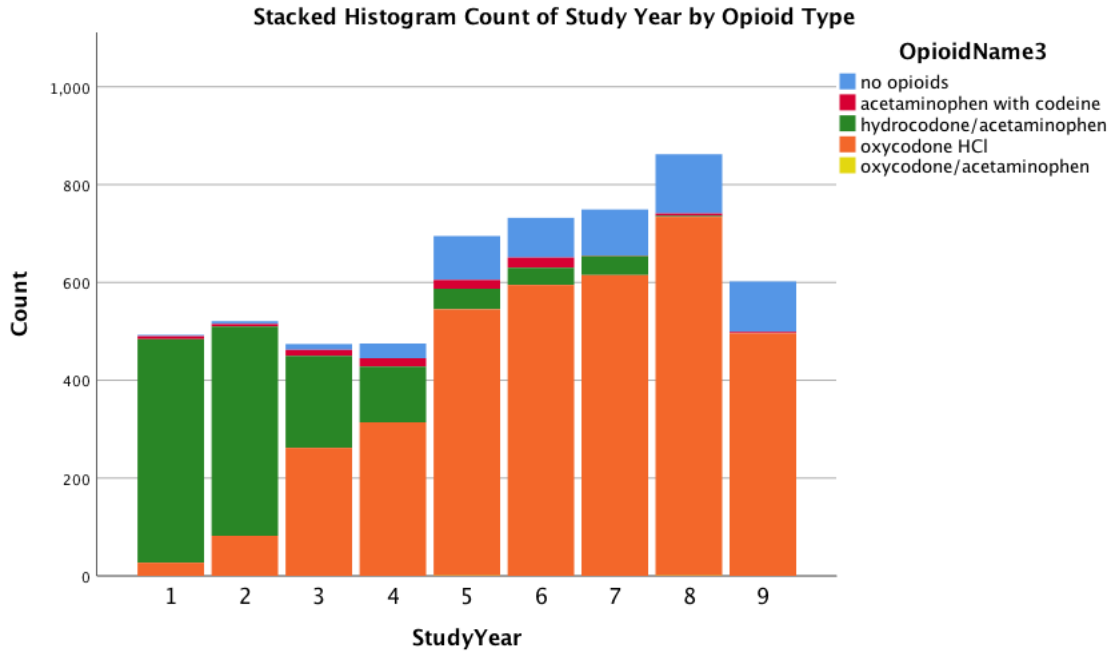


Figure 8. Histogram of Study Year by Opioid Type

Table 18

Yearly Demographic Characteristics of the Sample

	2010*	**2011**	**2012**	**2013****	**2014**	**2015**	**2016**	**2017**	**2018*****
Sample size	493	521	474	475	695	732	749	862	602
Gender									
Males N (%)	262 (53.1)	274 (52.6)	262 (55.3)	254 (53.5)	377 (54.2)	378 (51.6)	403 (53.8)	473 (54.9)	319 (53)
Females N (%)	231 (46.9%)	247 (47.4)	212 (44.7)	221 (46.5)	318 (45.8)	354 (48.4)	346 (46.2)	389 (45.1)	283 (47)
Age (years)									
0-4.9 N (%)	175 (35.5)	219 (42)	177 (37.3)	189 (39.8)	280 (40.3)	250 (34.2)	271 (36.2)	301 (34.9)	202 (33.6)

5-9.9 N (%)	220 (44.6)	227 (43.6)	206 (43.5)	194 (40.8)	274 (39.4)	335 (45.8)	328 (43.8)	400 (46.4)	286 (47.5)
10-18 N (%)	98 (19.9)	75 (14.4)	91 (19.2)	92 (19.4)	141 (20.3)	147 (20.1)	150 (20)	161 (18.7)	114 (18.9)
Race									
White N (%)	406 (82.4)	434 (83.3)	391 (82.5)	394 (82.9)	567 (81.6)	601 (82.1)	605 (80.8)	667 (77.4)	450 (74.8)
Non-white N (%)	84 (17)	81 (15.5)	78 (16.5)	73 (15.4)	110 (15.8)	107 (14.6)	112 (15)	152 (17.6)	118 (19.6)
Missing N (%)	3 (0.6)	6 (1.2)	5 (1.1)	8 (1.7)	18 (2.6)	24 (3.3)	32 (4.3)	43 (5)	34 (5.6)
Insurer									
Public N (%)	242 (49.1)	300 (57.6)	251 (53)	255 (53.7)	346 (49.8)	381 (52)	411 (54.9)	475 (55.1)	349 (58)
Private N (%)	249 (50.5)	219 (42)	222 (46.8)	220 (46.3)	302 (43.5)	312 (42.6)	336 (44.9)	385 (44.7)	253 (42)
Self-Pay N (%)	2 (0.4)	2 (0.4)	1 (0.2)	0	47 (6.8)	39 (5.3)	2 (0.3)	2 (0.2)	0

*Excludes January 2010
**Excludes February & March 2013
***Excludes May, June & December 2018

Table 19

Yearly Clinical Characteristics of the Sample

	2010*	**2011**	**2012**	**2013****	**2014**	**2015**	**2016**	**2017**	**2018*****
Body Habitus									
Original									
Normal N (%)	83 (16.8)	162 (31.1)	212 (44.7)	227 (47.8)	325 (46.8)	391 (53.4)	389 (51.9)	422 (49)	300 (49.8)
Non-Normal N (%)	86 (17.4)	170 (32.6)	223 (47)	200 (42.1)	281 (40.4)	303 (41.4)	325 (43.4)	397 (46.1)	266 (44.2)
Missing N (%)	324 (65.7)	189 (36.3)	39 (8.2)	48 (10.1)	89 (12.8)	38 (5.2)	35 (4.7)	43 (5)	36 (6)
Imputed									
Normal N (%)	352 (71.4)	319 (61.2)	245 (51.7)	268 (54.6)	400 (57.6)	423 (57.8)	420 (56.1)	460 (53.4)	331 (54.9)
Non-Normal N (%)	141 (28.6)	202 (38.8)	229 (48.3)	207 (43.6)	295 (42.4)	309 (42.2)	329 (43.9)	402 (46.6)	271 (45.1)
Procedure Indication									
OSA N (%)	180 (36.5)	391 (75)	371 (78.3)	388 (81.7)	543 (78.1)	590 (80.6)	594 (79.3)	710 (82.4)	490 (81.4)

Non-OSA N (%)	313 (63.5)	130 (25)	103 (21.7)	87 (18.3)	152 (21.9)	142 (19.4)	155 (20.7)	152 (17.6)	112 (18.6)

*Excludes January 2010
**Excludes February & March 2013
***Excludes May, June & December 2018

Table 20

Yearly Opioid Prescribing in the Sample

	2010*	**2011**	**2012**	**2013****	**2014**	**2015**	**2016**	**2017**	**2018*****
Opioid Prescribed									
Yes N (%)	490 (99.4)	515 (98.8)	462 (97)	445 (93.7)	605 (87.1)	651 (88.9)	655 (87.4)	741 (86)	499 (82.9)
No N (%)	3 (0.6)	6 (1.2)	12 (3)	30 (6.3)	90 (12.9)	81 (11.1)	94 (12.6)	121 (14)	103 (17.1)
Type of Opioid									
Acetaminophen w/ codeine N (%)	6 (1.2)	5 (1)	12 (2.5)	17 (3.6)	18 (2.6)	21 (2.9)	1 (0.1)	5 (0.6)	3 (0.4)
Hydrocodone/ acetaminophen N (%)	457 (92.7)	428 (82.1)	188 (39.7)	114 (24)	42 (6)	35 (4.8)	39 (5.2)	2 (0.2)	0
Oxycodone N (%)	27 (5)	82 (15.7)	262 (55.3)	314 (66.1)	544 (78.3)	595 (81.3)	615 (82.1)	733 (85)	496 (68.4)
Oxycodone/ acetaminophen N (%)	0	0	0	0	1 (0.1)	0	0	1 (0.1)	0

*Excludes January 2010
**Excludes February & March 2013
***Excludes May, June & December 2018

Table 21 shows the demographic summaries of children in the pre-and post-FDA warning periods. A total of 1527 tonsillectomy and/or adenoidectomy cases were performed in the pre-FDA warning period and 4076 were performed in the post-FDA warning period. Pearson chi-square tests for independence were used to assess for group differences in the categorical variables of gender, age, race, insurance status, body habitus and procedure indication. There were no differences in gender ($p = 0.945$), age ($p = 0.110$), race ($p = 0.421$) or insurance status ($p = 0.209$) in the pre-and post-FDA periods. The distribution of body habitus and procedure indication differed between the pre-and post-FDA warning periods. Compared with the pre-FDA

warning period, more children had a procedure indication of OSA in the post-FDA period ($p < 0.001$). Also, children in the post-FDA warning period had a greater frequency of having a non-normal BMI percentile ($p < 0.001$). Therefore, stratified analyses were conducted on the subgroups of body habitus and procedure indication.

Table 21

Characteristics of the Sample in the Pre-and Post-FDA Warning Periods

	Pre-FDA (*N=1527)* N (%)	Post-FDA (*N=4076)* N (%)	P-value
Gender	M=817 (53.5) F= 710 (46.5)	M=2185 (53.6) F=1891 (46.4)	0.945
Age	0-4.9 = 591 (38.7) 5-9.9 = 668 (43.7) 10-18 = 268 (17.6)	0-4.9 = 1473 (36.1) 5-9.9 = 1802 (44.2) 10-18 = 801(19.7)	0.100
Race	White = 1268 (83) Non-White = 245 (16.1) Missing = 14 (0.9)	White = 3247 (79.7) Non-White= 670 (16.4) Missing = 159 (3.9)	0.421
Insurance Status	Public = 811 (53.1) Private = 711 (46.6) Self = 5 (0.3)	Public= 2199 (53.9) Private= 1787 (43.8) Self = 90 (2.2)	0.209
Body Habitus	Normal = 939 (61.6) Non-Normal= 586 (38.4)	Normal= 2277 (55.8) Non-Normal= 1798 (44.2)	< 0.001*
Procedure Indication	OSA = 970 (63.4) Non-OSA = 557 (36.6)	OSA = 3287 (80.6) Non-OSA = 789 (19.4)	< 0.001*

*Chi^2 analysis, two tailed p-value set to a significance of 0.05

Additional comparisons were made during descriptive analysis to assess baseline opioid prescribing in the pre-FDA warning periods. As shown in Table 22, opioid prescribing did not appear to differ by demographic or clinical characteristics in the pre-FDA warning period. Based on visual inspection of simple time series line plots (see Figures 9a-c), age, procedure indication and body habitus appeared to influence opioid prescribing. Additional analytical models were conducted to explore the impact of the FDA warning in these subgroups.

Table 22

Opioid Prescribing in the Pre-FDA Warning Period

Pre-FDA Warning	Opioid Y (N= 1504)	Opioid N (N=23)	P-value
Gender			
Male	802 (98.2)	15 (1.8)	0.256
Female	702 (98.9)	8 (1.1)	
Age			
0-4.9 years	580 (98.1)	11 (1.9)	0.462
5-9.9 years	658 (98.5)	10 (1.5)	
10-18 years	266 (99.3)	2 (0.7)	
Race			
White	1249 (98.5)	19 (1.5)	0.779
Non-White	241 (98.4)	4 (1.6)	
Insurance			
Public	803 (99)	8 (1)	0.073
Private	696 (97.9)	15 (2.1)	
Procedure Indication			
OSA	957 (98.7)	13 (1.3)	0.428
No OSA	547 (98.2)	10 (1.8)	
Body Habitus			
BMI Normal	927 (98.6)	13 (1.4)	0.669
BMI Non-Normal	577 (98.3)	10 (1.7)	

*Chi^2 analysis, two tailed p-value set to a significance of 0.05

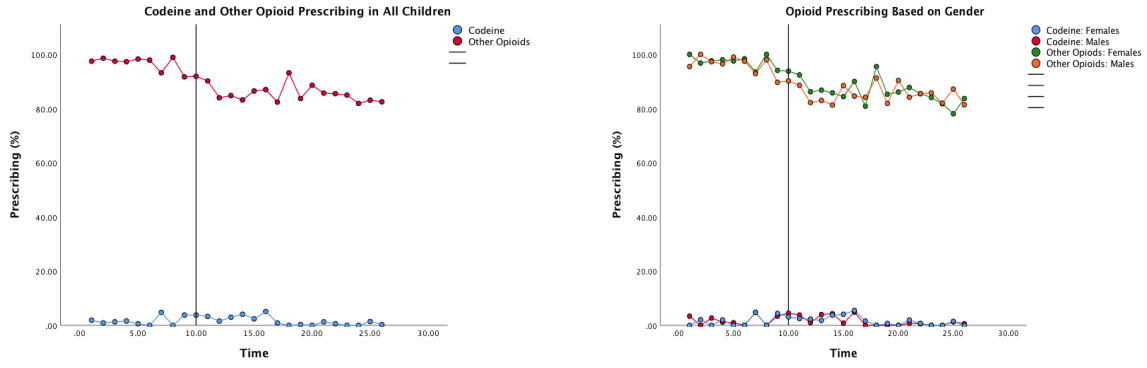


Figure 9a. Simple Time Series Plots of Opioid Prescribing in All Children & Subgroup Gender

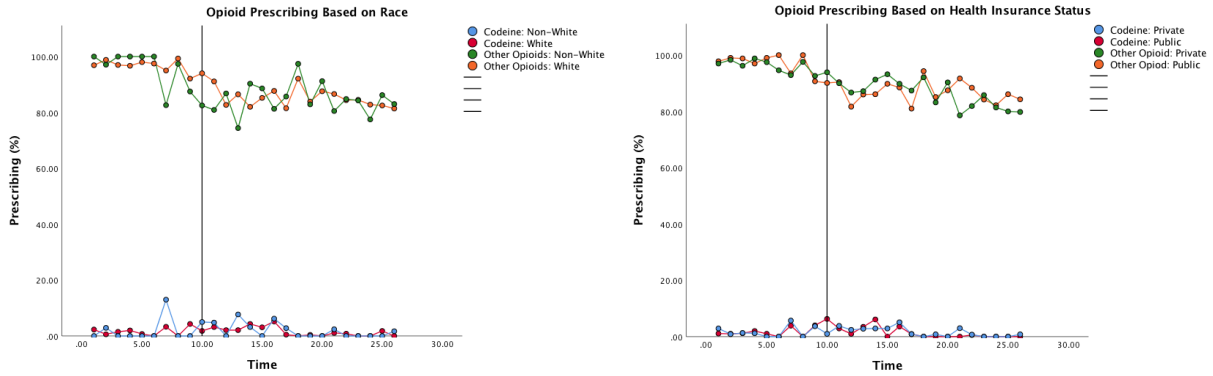


Figure 9b. Simple Time Series Plots of Opioid Prescribing in Subgroups Gender & Insurance Status

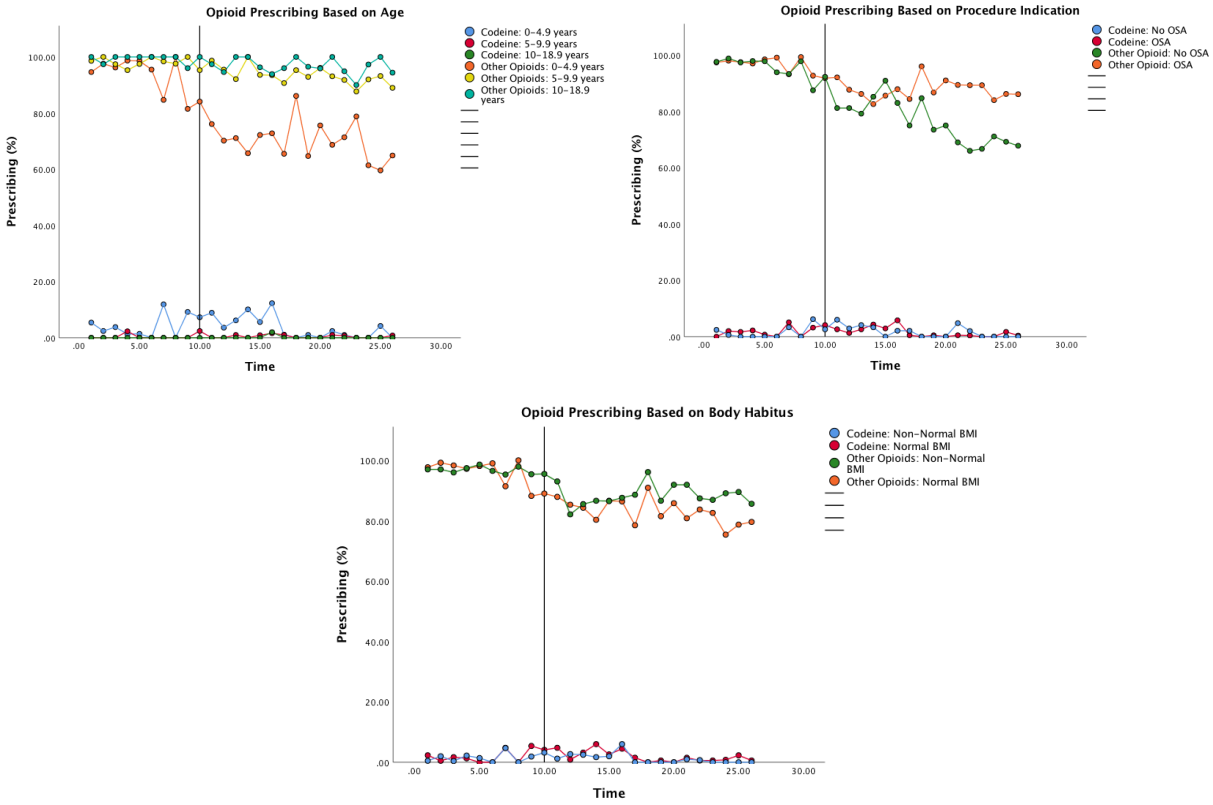


Figure 9c. Simple Time Series Plots of Opioid Prescribing in Subgroups Age, Procedure Indication & Body Habitus

Statistical Analysis

Data was imported from SPSS into Stata and analyzed in Stata using the *itsa* command. An ITS analysis using segmented linear regression was used to compare opioid prescribing before and after the FDA warning. Time periods 1-9 comprised the preintervention segment and time periods 10-26 were the postintervention segments. The rate (percentage) of opioid prescribing (codeine or other opioids) was used as the outcome measure. The rate of prescribing was calculated as the number of prescriptions per time period divided by the total number of cases per time period. Statistical models were analyzed to assess level or slope changes in opioid prescribing over time. Additional estimates were generated from the *posttrend* command in Stata. *Posttrend* provides estimates of the postintervention trend ($\beta_1 + \beta_3$), considering both the preintervention trend (β_1) and the difference in pre-and post-intervention trends (β_3). The *posttrend* estimate shows the average percentage of opioid prescribing at each interval after the FDA warning. The coefficients of the models were estimated by ordinary least-squared regression. The regression equation used was:

$$Y_t = \beta_0 + \beta_1 * \text{time}_t + \beta_2 * \text{intervention}_t + \beta_3 * \text{time after} + \varepsilon_t$$

Where **Y** = mean number of prescriptions in month *t*
time = time in months at time *t* from the start of the observation period
intervention = time *t* occurring before or after the FDA warning
time after = number of months after the FDA warning at time *t*
β_0 = baseline level of number of prescriptions per month at time zero
β_1 = change in the mean number of prescriptions that occurs with each time period pre-FDA warning (preintervention trend)
β_2 = level change in the mean number of monthly prescriptions immediately after the FDA warning
β_3 = trend change in the mean number of monthly prescriptions after the FDA warning, compared with the monthly trend before the FDA warning
ε_t = error term at time *t* represents variation not explained by the model

Separate ITS models were conducted for hypothesis testing. First, codeine and other opioid prescribing in the pre-and post-FDA warning periods was assessed for the entire sample (all children undergoing tonsillectomy and/or adenoidectomy), then subgroups were analyzed. Subgroup analyses included insurance status, age, procedure indication and body habitus. These subgroups were included based on the aims of the study and findings during descriptive analysis.

Opioid Prescribing in All Children

Prior to subgroup analyses, data were analyzed for opioid prescribing in all children undergoing tonsillectomy and/or adenoidectomy during the study period. Two models were performed: (1) Codeine prescribing (2) Other opioid prescribing in all children. Prescribing was expressed in percentages where the number of opioid prescriptions (codeine or other opioids) per time period was divided by the total number of cases per time period. Results are presented and discussed below.

Codeine Prescribing in All Children

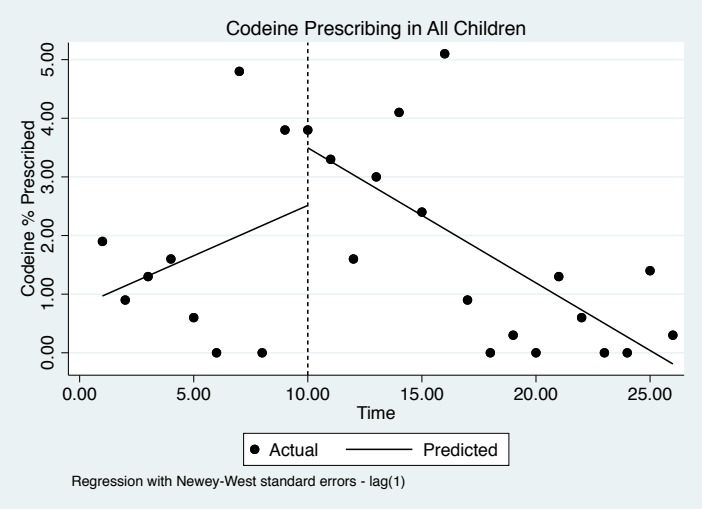


Figure 10. Time Series Graph of Codeine Prescribing in All Children

As shown in the Table 23, the starting level of codeine prescribing in all children undergoing tonsillectomy and/or adenoidectomy was estimated at 0.97%. Codeine prescribing

did not significantly change in the time periods prior to the FDA warning ($p = 0.139$). In the first time period of the FDA warning, there was not a significant decrease in codeine prescribing ($p = 0.275$). The difference between the pre-and post-intervention slopes was significant ($p = 0.004$, CI = [-.66, -.15]). The postintervention trend in codeine prescribing was significant and negative ($p = 0.001$, CI = [-0.33, -0.14]. Figure 10 illustrates the time series graph for codeine prescribing in all children. The predicted codeine prescribing line in the pre-intervention period did not appear to fit the observed data well. Additional models were generated including a Newey-West model with a linear smoother (*itsa smoother)* and a generalized linear model (*itsa Prais)*. Results were comparable and therefore the original model was retained.

These results indicate the FDA warning did not have an abrupt (level) effect on codeine prescribing. However, a significant slope change suggests a treatment effect over time, or a gradual downward trend in codeine prescribing after the FDA warning. After introduction of the FDA warning, codeine prescribing decreased every time period in the post-intervention period at a rate of 0.23%.

Other Opioid Prescribing in All Children

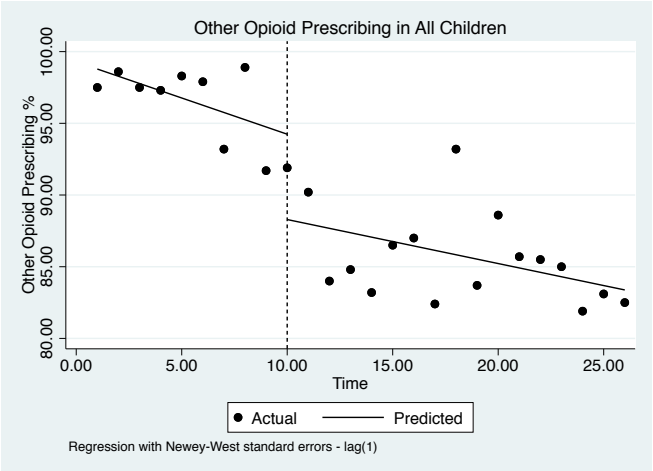


Figure 11. Time Series Graph of Other Opioid Prescribing in All Children

As shown in the Table 23, the starting level of other opioid prescribing in all children undergoing tonsillectomy and/or adenoidectomy was estimated at 98.8%. Other opioid prescribing appeared to decrease every time period prior to the FDA warning by 0.5% (p = 0.019, CI = [–0.92, -0.09]). In the first time period of the FDA warning, there was a significant decrease in other opioid prescribing by 5.9% (p = 0.019, CI = [-10, -.1.0]). The difference between the pre-and post-intervention slopes was not significant (p = 0.35). The postintervention trend in other opioid prescribing was significant and negative (p = 0.05, CI= [-0.6, -0.01]). Figure 11 illustrates the time series graph for other opioid prescribing in all children.

These results indicate an abrupt intervention effect (level change) rather than a gradual treatment effect. Immediately after the FDA warning, other opioid prescribing in all children undergoing tonsillectomy and/or adenoidectomy decreased by 5.9%. Opioid prescribing continued to decrease by 0.31% each time interval following the FDA warning.

Table 23

Regression Table for Codeine and Other Opioid Prescribing in All Children

Variable	Coefficient	Estimates	t-statistic	P-value	95% Confidence Interval
Codeine Prescribing [All children]	β_0 (Intercept)*	0.97	2.14	0.043	0.03, 1.9
	β_1 (Pre-Slope)	0.17	1.53	0.139	-0.06, 0.4
	β_2 (Level change)	0.98	1.12	0.275	-0.83, 2.8
	β_3 (Slope change)	-0.40	-3.25	0.004**	-.66, -.15
	$\beta_1 + \beta_3$ (Post-Slope)	-0.23	-5.02	0.001**	-0.33, -0.14
Other Opioid Prescribing [All children]	β_0 (Intercept)	98.8	142.2	0.000	97.3, 100.2
	β_1 (Pre-Slope)	-0.51	-2.53	0.019	-0.92, -0.91
	β_2 (Level change)	-5.95	-2.50	0.02*	-10.8, -1.02
	β_3 (Slope change)	0.19	0.95	0.354	-0.23, 0.63
	$\beta_1 + \beta_3$ (Post-Slope)	-0.31	-2.12	0.045**	-0.61, -0.01

* The intercept represents the start of the data series; the p-values and/or confidence intervals are not useful in interpretation.
**significance $p \leq 0.05$

Opioid Prescribing Based on Insurance Status

To accomplish the study's aims, ITS models were performed to evaluate opioid prescribing in publicly and privately insured children. Self-insured children were not included in the statistical models. Prescribing was expressed in percentages where the number of opioid prescriptions (codeine or other) in each group per time period was divided by the total number of cases in each group per time period. For example, codeine prescribing in publicly insured children was expressed as: Total # of codeine prescriptions in publicly insured children per time period (numerator) / Total # of cases in publicly insured children per time period (denominator). Models were performed to evaluate codeine and other opioid prescribing in each group, addressing H_1 and H_3. Additional models compared codeine (H_2) and other opioid (H_4) prescribing between groups.

H_1: Codeine Prescribing in Publicly and Privately Insured Children

The first aim of this study evaluated codeine prescribing in publicly and privately insured children who underwent tonsillectomy and/or adenoidectomy at OHSU before and after the 2013 FDA warning on codeine and tested the following hypothesis (H_1): In publicly and privately insured post-tonsillectomy and/or adenoidectomy children at OHSU, rates of codeine prescribing (level and/or trend) decreased following the 2013 FDA warning on codeine. Separate single group ITS analyses were performed for codeine prescribing in publicly and privately insured children, as presented below.

Codeine Prescribing in Publicly Insured Children

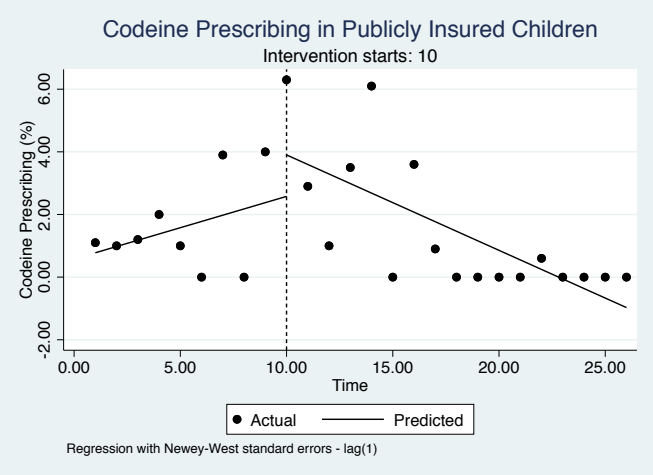


Figure 12. Time Series Graph of Codeine Prescribing in Publicly Insured Children

As shown in Table 24, the starting level of codeine prescribing in publicly insured children undergoing tonsillectomy and/or adenoidectomy was estimated at 0.8%. Codeine prescribing did not appear to change significantly in time periods prior to the FDA warning (p = 0.058). In the first time period of the FDA warning, there was no significant change in codeine prescribing (p = 0.146). The difference between the pre-and post-intervention slopes was significant (p = 0.003, CI = [-0.81, -0.2]). The postintervention trend in codeine prescribing was significant and negative (p = < 0.001, CI= [-0.46, -0.15]). Figure 12 illustrates the time series graph for codeine prescribing in publicly insured children.

These results indicate the FDA warning did not have an abrupt (level) effect on codeine prescribing in publicly insured children. However, the slope of the regression line changed significantly after the FDA warning, suggesting a change in the trend of codeine prescribing in the post-FDA period. After the introduction of the FDA warning, opioid prescribing decreased every time period in the post-intervention period at a rate of 0.3%. These results indicate a gradual downward trend in codeine prescribing in publicly insured children.

Codeine Prescribing in Privately Insured Children

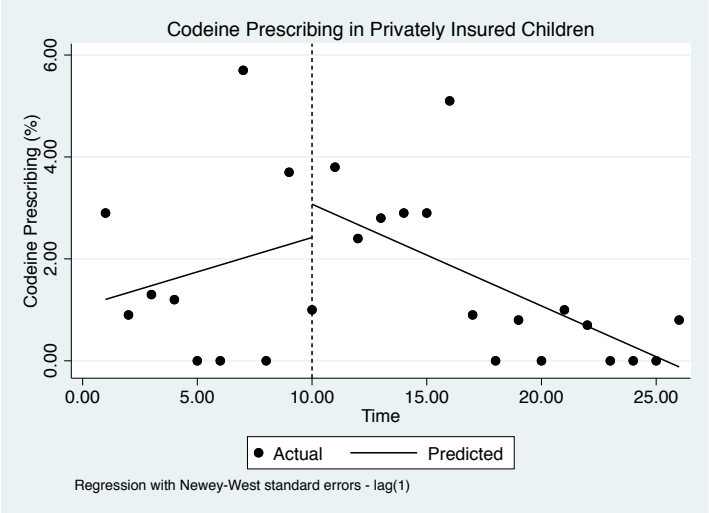


Figure 13. Time Series Graph of Codeine Prescribing in Privately Insured Children

As shown in Table 24, the starting level of codeine prescribing in privately insured children undergoing tonsillectomy and/or adenoidectomy was estimated at 1.2%. Codeine prescribing did not appear to change significantly in time periods prior to the FDA warning (p = 0.394). In the first time period of the FDA warning, there was not a significant change in codeine prescribing (p= 0.611). The difference between the pre-and post-intervention slopes was significant (p = 0.034, CI = [-0.64, -0.03]). The postintervention trend in codeine prescribing was significant and negative (p = 0.006, CI= [-0.30, -0.09]). Figure 13 illustrates the time series graph for codeine prescribing in privately insured children. The predicted codeine prescribing line in the pre-intervention period did not appear to fit the observed data well. Additional models were generated including a Newey-West model with a linear smoother (*itsa smoother)* and a generalized linear model (*itsa Prais)*. Results were comparable and therefore the original model was retained.

The findings in privately insured children were similar to that of publicly insured children. There was not an immediate (level) change in codeine prescribing in publicly insured

children, but a significant slope change indicated a gradual reduction in codeine prescribing after the FDA warning. The trend of the time series after the FDA warning demonstrated that codeine prescribing decreased in privately insured children every time period in the post-intervention period at a rate of 0.14% and the decrease was significant.

Table 24

Regression Table for Codeine Prescribing in Publicly and Privately Insured Children

Variable	Parameter	Coefficient	t-statistic	P-value	95% Confidence Interval
Codeine Prescribing [Publicly insured]	β_0 (Intercept)	0.78	2.44	0.023	0.12, -1.4
	β_1 (Pre-Slope)	0.2	2.00	0.058	-0.01, 0.41
	β_2 (Level change)	1.32	1.5	0.147	-0.5, 3.1
	β_3 (Slope change)	-0.50	-3.41	0.003*	-0.81, -0.2
	$\beta_1 + \beta_3$ (Post-Slope)	-0.304	-3.96	< 0.001*	-0.46, -0.15
Codeine Prescribing [Privately insured]	β_0 (Intercept)	1.2	1.61	0.121	-0.35, 2.7
	β_1 (Pre-Slope)	0.135	0.87	0.394	-0.19, 0.46
	β_2 (Level change)	0.653	0.52	0.611	-1.96, 3.27
	β_3 (Slope change)	-0.33	-2.26	0.034*	-0.64, -0.03
	$\beta_1 + \beta_3$ (Post-Slope)	-0.19	-4.02	0.006*	-0.30, -0.09

*significance $p \leq 0.05$

The hypothesis was supported. Rates of codeine prescribing decreased in the post-FDA warning period in publicly and privately insured children. The change in codeine prescribing was not abrupt in either group, rather both groups demonstrated a more gradual downward trend in codeine prescribing. There was a significant slope change in codeine prescribing and significant downward (negative) slope of the postintervention trend in both groups, indicating codeine prescribing decreased after the FDA warning.

H_2: Codeine Prescribing in Publicly versus Privately Insured Children

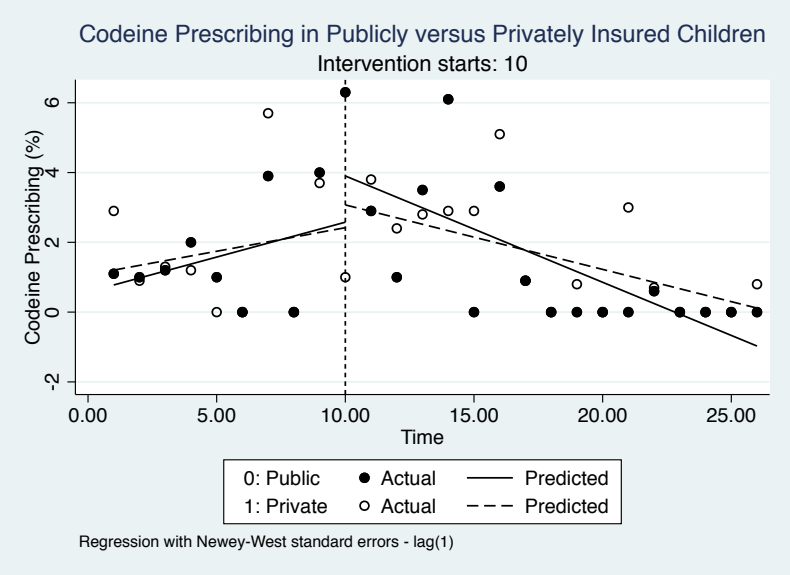


Figure 14. Time Series Graph of Codeine Prescribing in Publicly versus Privately Insured Children

The second aim of this study compared codeine prescribing in publicly and privately insured children who underwent tonsillectomy and/or adenoidectomy at OHSU before and after the 2013 FDA warning on codeine and tested the following hypothesis (H_2): There is a difference in codeine prescribing (level and/or trend) between publicly and privately insured post-tonsillectomy and/or adenoidectomy children at OHSU. A multiple group ITS was performed to compare codeine prescribing publicly and privately insured children. Additional parameters were added to the model (β_4 - β_7) for group comparison:

β_4: Difference in level of the outcome between treatment and control group prior to intervention
β_5: Difference in slope of the outcome between treatment and controls prior to intervention
β_6: Difference between treatment and control groups in the level of the outcome immediately following the intervention
β_7: Difference between treatment and control groups in the slope of the outcome after the intervention, compared with the preintervention.
Posttrend: Difference in postintervention treatment versus control ($\beta_5 + \beta_7$)

A key assumption to a multiple group ITS is that the change in the level or trend in the outcome variable is presumed to be the same for both groups. Parameters β_4 and β_5 play an

important role in establishing balance between treatment and control groups; groups that have *p*-values > 0.05 on both β4 and β5 can be used as controls in the model (Linden & Adams, 2015). As shown in Table 25, the initial mean level and slope difference between privately and publicly insured children were not significant ($p = 0.602$ and $p = 0.762$, respectively), indicating the groups were comparable on baseline level and trend. There was no significant difference in treatment effect (level change) during the first time period of the intervention ($p = 0.664$) and no significant difference in pre–post trends among groups ($p = 0.383$). The postintervention trends between groups did not differ ($p = 0.198$). Figure 14 depicts the time series graph for publicly versus privately insured children. These results do not support the hypothesis. There does not appear to be a difference in codeine prescribing between publicly and privately insured children as a result of the FDA warning.

Table 25

Regression Table for Codeine Prescribing in Publicly versus Privately Insured Children

Variable	Parameter	Coefficient	t-statistic	P-value	95% Confidence Interval
Codeine Prescribing [Public versus Private]	β_4 (Baseline level)	-0.43	-0.52	0.602	-0.18, 0.45
	β_5 (Baseline trend)	0.065	0.35	0.762	-0.31, 0.44
	β_6 (Level difference)	0.67	0.44	0.664	-2.42, 3.76
	β_7 (Slope difference)	-0.18	-0.88	0.383	-0.61, 0.24
	$\beta_5 + \beta_7$ (Post-Slope difference)	-0.12	-1.3	0.198	-0.3, 0.06

*significance $p \leq 0.05$

H_3: Other Opioid Prescribing in Publicly and Privately Insured Children

The third aim of this study examined other opioid prescribing (oxycodone, hydrocodone) in publicly and privately insured children who underwent tonsillectomy at OHSU before and after the 2013 FDA warning on codeine and tested the following hypothesis (H_3): In publicly and privately insured post-tonsillectomy and/or adenoidectomy children at OHSU, rates of other

opioid prescribing (level and/or trend) increased following the 2013 FDA warning on codeine. Separate single group ITS analyses were performed for codeine prescribing in publicly and privately insured children, as presented below.

Other Opioid Prescribing in Publicly Insured Children

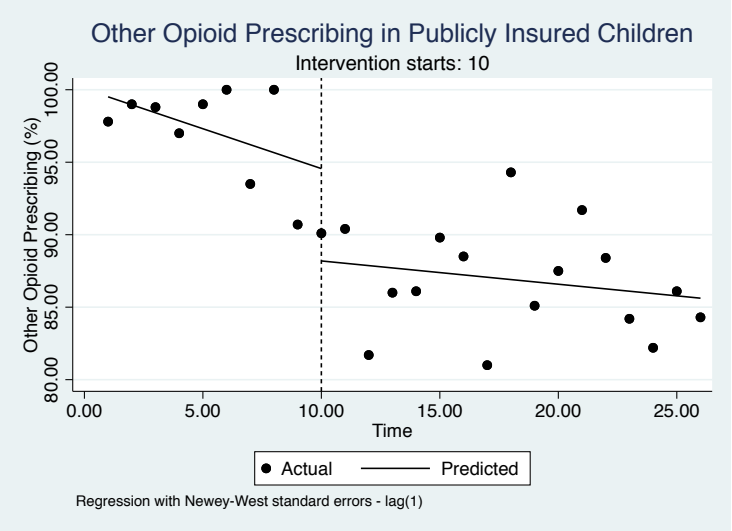


Figure 15. Time Series Graph of Other Opioid Prescribing in Publicly Children

As shown in Table 26, the starting level of other opioid prescribing in publicly insured children undergoing tonsillectomy and/or adenoidectomy was estimated at 99.5%. Other opioid prescribing did not change significantly in time periods prior to the FDA warning ($p = 0.068$). In the first time period of the FDA warning, there was a significant decrease in other opioid prescribing by 6.4% ($p = 0.022$, CI = [-11.7, -.1.0]). The difference between the pre-and post-intervention slopes was not significant ($p = 0.214$). The postintervention trend was not significant ($p = 0.306$). Figure 15 represents the time series graph for other opioid prescribing in publicly insured children.

These results suggest an abrupt (level) treatment effect on opioid prescribing in publicly insured children, where the FDA warning resulted in a significant and immediate reduction in

opioid prescribing. The postintervention trend did not continue downward after the initial reduction in other opioid prescribing, rather prescribing remained relatively flat.

Other Opioid Prescribing in Privately Insured Children

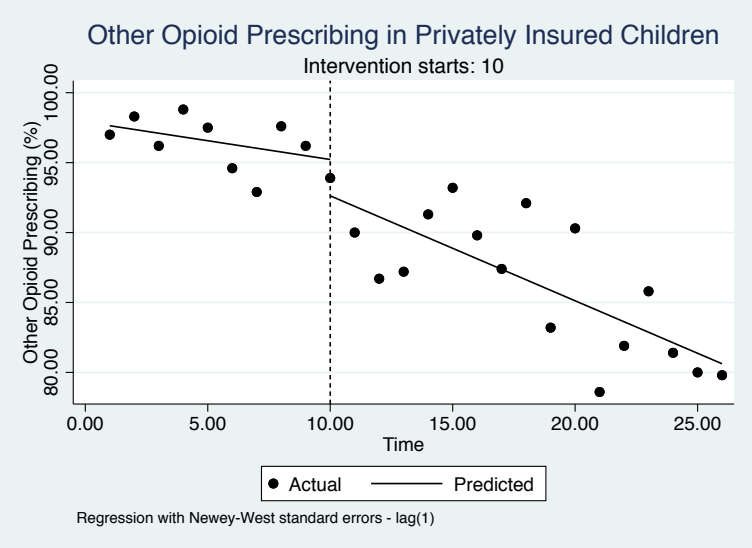


Figure 16. Time Series Graph of Other Opioid Prescribing in Privately Children

The starting level of other opioid prescribing in privately insured children undergoing tonsillectomy and/or adenoidectomy was estimated at 97.6% (see Table 26). Other opioid prescribing did not significantly decrease in time periods prior to the FDA warning ($p = 0.108$). In the first time period of the FDA warning, there was not a significant decrease in other opioid prescribing ($p = 0.210$). The difference between the pre-and post-intervention slopes was significant ($p = 0.036$, CI = [-.93, -.03]. The postintervention trend was significant and negative ($p = <0.001$, CI = [-1.04, -0.5]). Figure 16 shows the time series graph of other opioid prescribing in privately insured children.

These results indicate the FDA warning did not have an abrupt (level) change on other opioid prescribing in privately insured children. However, a treatment effect over time (slope change) in other opioid prescribing in privately insured children was demonstrated. After the FDA warning, other opioid prescribing fell each time period by 0.75%.

Table 26

Regression Table for Other Opioid Prescribing in Publicly and Privately Insured Children

Variable	Parameter	Coefficient	t-statistic	P-value	95% Confidence Interval
Other Opioid Prescribing [Publicly Insured]	β_0 (Intercept)	99.5	100.63	0.000	97.5, -101.6
	β_1 (Pre-Slope)	-0.55	1.92	0.068	-1.14, 0.44
	β_2 (Level change)	-6.37	-2.47	0.022*	-11.7, -1.02
	β_3 (Slope change)	0.389	1.28	0.214	-0.24,1.01
	$\beta_1 + \beta_3$ (Post-Slope)	-0.16	-1.05	0.306	-0.48, 0.16
Other Opioid Prescribing [Privately Insured]	β_0 (Intercept)	97.64	0.476	0.000	96.65, 98.62
	β_1 (Pre-Slope)	-0.27	-1.68	0.108	-0.6, 0.06
	β_2 (Level change)	-2.59	-1.29	0.210	-6.8, 1.6
	β_3 (Slope change)	-0.48	-2.23	0.036*	-0.93, -0.03
	$\beta_1 + \beta_3$ (Post-Slope)	-0.75	-5.32	<0.001*	-1.04, -0.45

*significance $p \leq 0.05$

The hypothesis was not supported; rates of other opioid prescribing did not increase following the FDA warning. Rather, rates of other opioid prescribing decreased in both publicly and privately insured children after the FDA warning. Interestingly, publicly insured children saw an immediate (level) change whereas privately insured children saw a gradual (slope) change in other opioid prescribing. Still, both groups had a significant reduction in other opioid prescribing in the post-FDA warning period.

H_4: Other Opioid Prescribing in Publicly versus Privately Insured Children

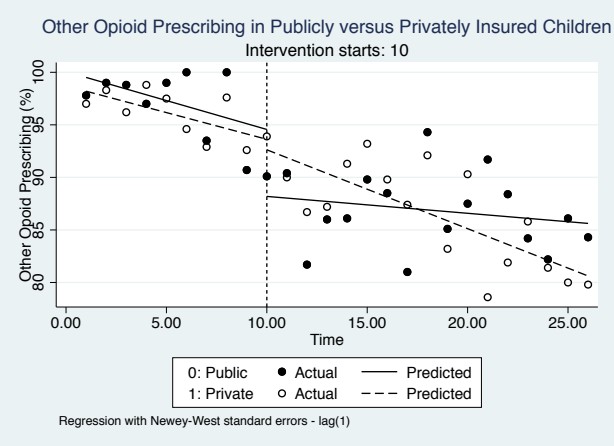


Figure 17. Time Series Graph of Other Opioid Prescribing in Publicly versus Privately Insured Children

The final aim of this study compared other opioid prescribing in publicly and privately insured children who underwent tonsillectomy and/or adenoidectomy at OHSU before and after the FDA warning on codeine and tested the following hypothesis (H_4): There is a difference in alternative opioid prescribing (level and/or trend) between publicly and privately insured post-tonsillectomy and/or adenoidectomy children at OHSU.

A multiple group ITS was performed to compare other opioid prescribing in publicly and privately insured children. As discussed above, additional parameters (β_4 - β_7) were added to the model and coefficients β_4 and β_5 were assessed to assure comparable baseline estimates between groups. As shown in Table 27, the initial level and slope difference between publicly and privately insured children were not significant ($p = 0.271$ and $p = 0.898$, respectively), indicating the groups were comparable on baseline level and trend. There was no significant difference in treatment effect (level change) during the first time period of the intervention ($p = 0.103$) and no significant difference in pre–post trends among groups ($p = 0.088$). The difference in the trend of the time series after the FDA warning was significant ($p = 0.007$, CI = [0.71, 1.1]). However, this can be explained by the manner in which other opioid prescribing decreased in each group. Publicly insured children demonstrated and immediate (level) change followed by a relatively flat trend, whereas privately insured children demonstrated a slower downward trend in other opioid prescribing. Figure 17 illustrates the time series graph for other opioid prescribing in publicly and privately insured children.

The hypothesis was not supported. Though there was a difference in the manner in which opioid prescribing changed (level versus trend), other opioid prescribing decreased in both publicly and privately insured children after the FDA warning.

Table 27

Regression Table for Other Opioid Prescribing in Publicly versus Privately Insured Children

Variable	Parameter	Coefficient	t-statistic	P-value	95% Confidence Interval
Other Opioid Prescribing [Public and Private]	β_4 (Baseline level)	1.31	1.11	0.271	-1.1, 3.6
	β_5 (Baseline trend)	-0.04	-0.13	0.898	-0.69, 0.61
	β_6 (Level difference)	-5.37	-1.66	0.103	-11.9, 1.14
	β_7 (Slope difference)	0.63	1.74	0.088	-0.1, 1.4
	$\beta_5 + \beta_7$ (Post-Slope difference)	0.59	-2.8	0.007*	0.17, 1.1

*significance $p \leq 0.05$

Additional Analyses: Age, Procedure Indication & Body Habitus

Descriptive analysis suggested that age, procedure indication and body habitus may influence opioid prescribing in children undergoing tonsillectomy. Additional models were performed for each variable. Results are presented and discussed below.

Opioid Prescribing Based on Age

As shown in Table 28, pre-intervention rates of codeine prescribing in children age 0-4.9 years was estimated at 2.4%. Codeine prescribing in children age 0-4.9 years decreased after the FDA warning, evidenced by a significant slope change in the post-intervention period when compared with the preintervention period ($p = 0.012$, CI = [-1.5, -0.23]). In the postintervention period, codeine prescribing in children age 0-4.9 years decreased by 0.53% with each time period following the FDA warning ($p = 0.001$, CI = [-0.8, -0.3]). However, codeine prescribing in children age 5-9.9 and 10-18 years did not significantly decrease after the FDA warning (no level or slope change). This is likely due to very low pre-intervention codeine prescribing rates in these age subgroups. Pre-intervention codeine prescribing rates were 0.41% in children 5-9.9 years and nearly 0% in children 10-18 years.

Table 28

Regression Table for Codeine Prescribing Based on Age

Variable	Parameter	Coefficient	t-statistic	P-value	95% Confidence Interval
Codeine [0-4.9 years]	β_0 (Intercept)	2.4	1.65	0.114	-0.63, 5.4
	β_1 (Pre-Slope)	0.38	1.2	0.241	-0.28, 1.04
	β_2 (Level change)	2.11	0.9	0.380	-2.8, 7.0
	β_3 (Slope change)	-0.91	-2.75	0.012*	-1.5, -0.23
	$\beta_1 + \beta_3$ (Post-Slope)	-0.53	-4.7	0.001*	-0.8, -0.3
Codeine [5-9.9 years]	β_0 (Intercept)	0.41	0.94	0.358	-0.49, 1.3
	β_1 (Pre-Slope)	-0.38	-0.54	0.521	-0.16, 0.08
	β_2 (Level change)	0.86	1.79	0.088	-0.14, 1.85
	β_3 (Slope change)	-0.008	-0.12	0.908	-0.15, 0.13
Codeine [10-18 years]	β_0 (Intercept)	0.002	0.68	0.507	-0.005, 0.009
	β_1 (Pre-Slope)	-0.001	-0.69	0.495	-0.005, 0.01
	β_2 (Level change)	0.205	0.98	0.340	-0.23, 0.64
	β_3 (Slope change)	-0.009	-0.79	0.437	-0.033, 0.015

*significance $p \leq 0.05$

Other opioid prescribing in children age 0-4.9 was estimated at 98.9% (see Table 29). Other opioid prescribing abruptly decreased (level change) by 11.9% after the FDA warning (p = 0.03, CI = [-2.7, 1.04]). Other opioid prescribing in the preintervention period in children age 5-9.9 was estimated at 97.9%. Other opioid prescribing in this age group (5-9.9 years) did not abruptly decrease after the FDA warning, but a significant slope change suggests a gradual decrease in other opioid prescribing in the post-FDA warning period (p = 0.017, CI = [-0.86, -0.09]. Other opioid prescribing was estimated at 99.8% for children age 10-18 years. Children in this age group did not experience a significant level or slope change in other opioid prescribing in the post-FDA warning period.

Overall, it appears that the FDA warning had the most profound effect on codeine and other opioid prescribing in the youngest children (0-4.9 years). Figure 18 shows the time series graphs (codeine and other opioids) for children age 0-4.9 years. Children age 5-9.9 demonstrated

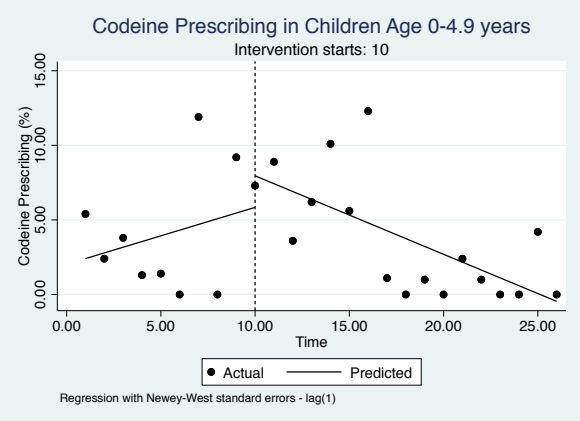
gradual changes in other opioid prescribing, but no change in codeine prescribing. The oldest children (age 10-18) did not demonstrate changes in codeine or other opioid prescribing.

Table 29

Regression Table for Other Opioid Prescribing Based on Age

Variable	Parameter	Coefficient	t-statistic	P-value	95% Confidence Interval
Other Opioids [0-4.9 years]	β_0 (Intercept)	98.9	41.8	0.00	94.01, 103.8
	β_1 (Pre-Slope)	-1.19	-2.09	0.05*	-2.34, -0.01
	β_2 (Level change)	-11.87	-2.27	0.03*	-2.7, -1.04
	β_3 (Slope change)	0.54	0.93	0.364	-0.66, 1.73
Other Opioids [5-9.9 years]	β_0 (Intercept)	97.9	92.89	0.000	95.8, 100.2
	β_1 (Pre-Slope)	0.085	0.51	0.618	-0.26, 0.43
	β_2 (Level change)	2.06	-1.67	0.109	-4.6, -0.5
	β_3 (Slope change)	-0.47	-2.57	0.017*	-0.85, -0.09
Other Opioids [10-18 years]	β_0 (Intercept)	99.8	120.5	0.00	98,1, 101.5
	β_1 (Pre-Slope)	-0.14	-0.63	0.536	-0.58, 0.31
	β_2 (Level change)	-0.41	-0.22	0.829	-4.3, 3.5
	β_3 (Slope change)	-0.02	-0.10	0.925	-0.53, 0.48

*significance $p \leq 0.05$



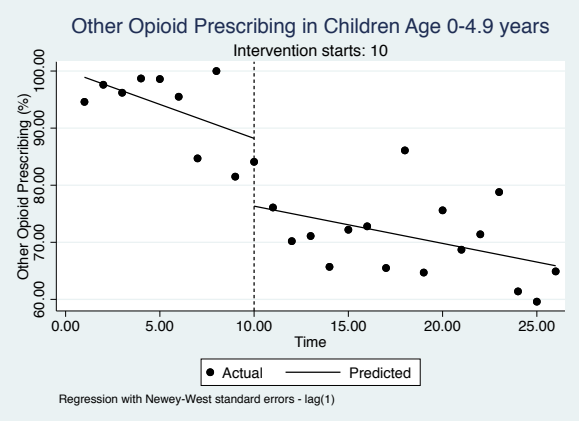


Figure 18. Time Series Graphs of Codeine and Other Opioid Prescribing in Children Age 0-4.9 years

Opioid Prescribing Based on Procedure Indication

Codeine prescribing in children with OSA was estimated at 0.9% in the preintervention period (see Table 30). Codeine prescribing did not significantly decrease in the time periods

prior to the FDA warning ($p = 0.086$). After the FDA warning, there was not a significant level change ($p = 0.099$). However, a significant postintervention slope change (compared to the preintervention slope) indicated a gradual reduction in codeine prescribing after the FDA warning ($p = 0.004$, CI = [-0.68, -0.15]). Findings were similar for codeine prescribing in children without OSA, where the FDA warning did not appear to abruptly decrease codeine prescribing ($p = 0.729$), but a slope change indicated a gradual reduction in codeine prescribing in the post-FDA warning period ($p = <0.05$, CI = [-1.13, -0.12]. When children with and without OSA were compared, there were no differences in the level ($p = 0.928$), slope ($p = 0.963$) or postintervention trends ($p = 0.847$) of codeine prescribing.

Table 30

Regression Table for Codeine Prescribing Based Procedure Indication

Variable	Parameter	Coefficient	t-statistic	P-value	95% Confidence Interval
Codeine Prescribing [OSA]	β_0 (Intercept)	0.9	1.8	0.086	-0.13, 0.42
	β_1 (Pre-Slope)	0.19	1.73	0.099	-0.38, 0.42
	β_2 (Level change)	0.80	0.83	0.413	-1.2, 2.8
	β_3 (Slope change)	-0.41	1.8	0.004*	-0.68, -0.15
	$\beta_1 + \beta_3$ (Post-Slope)	-0.22	-3.69	0.0013*	-0.35, -0.1
Codeine Prescribing [No OSA]	β_0 (Intercept)	0.06	0.05	0.964	-2.4, 2.55
	β_1 (Pre-Slope)	0.33	1.21	0.283	-0.23, 0.9
	β_2 (Level change)	0.62	0.35	0.729	-3.04, 4.2
	β_3 (Slope change)	-0.57	-2.12	0.046*	-1.13, -0.12
	$\beta_1 + \beta_3$ (Post-Slope)	-0.24	-4.07	0.005*	-0.36, -0.12
Codeine Prescribing [OSA versus no OSA]	β_4 (Baseline level)	0.84	1.21	0.23	-0.22, 0.89
	β_5 (Baseline trend)	-0.14	-0.48	0.631	-0.74, 0.45
	β_6 (Level difference)	-0.18	0.09	0.928	-3.87, 4.2
	β_7 (Slope difference)	0.16	0.05	0.963	-2.36, 2.48
	$\beta_5 + \beta_7$ (Post-Slope difference)	0.016	0.195	0.847	-0.15, 0.18

*significance $p \leq 0.05$

Other opioid prescribing in the preintervention period in children with OSA was estimated at 98.4% (see Table 31). Other opioid prescribing did not decrease significantly in the pre-intervention period ($p = 0.062$). After the FDA warning, there was an abrupt decrease in other opioid prescribing by 6.2% in children with OSA ($p = 0.016$, CI = [-11.2, -1.3]. The postintervention trend (relative to the preintervention trend) was not significant ($p = 0.273$) These findings indicated an immediate treatment effect in other opioid prescribing in children with OSA. The postintervention trend estimate was not significant suggesting that after the immediate reduction in other opioid prescribing, prescribing remained relatively flat.

In children without OSA, other opioid prescribing in the preintervention period was estimated at 99.5%. Other opioid prescribing decreased significantly each time period in the pre-intervention period by 0.9% ($p = 0.009$, CI = [-1.6, -0.3]. After the FDA warning, there was not a significant level or slope change. However, the postintervention trend was significant and negative ($p = 0.038$, CI = [-1.9, -.42]. Other opioid prescribing in children without OSA decreased by 1.2% each time period after the FDA warning.

When other opioid prescribing in children with and without OSA was compared (see Figure 19), there was no difference in the immediate treatment effect (level) or differences in the pre-and postintervention slopes. However, there was a significant difference in the post-intervention estimates. Other opioid prescribing decreased in children with OSA by 0.12% in each time period after the FDA warning whereas other opioid prescribing in children without OSA decreased by 1.2% ($p = 0.01$, CI = [0.7, 1.8]). After the immediate reduction in other opioid prescribing in children with OSA, prescribing remained relatively flat whereas the time series trend after the intervention continued to decrease for children without OSA.

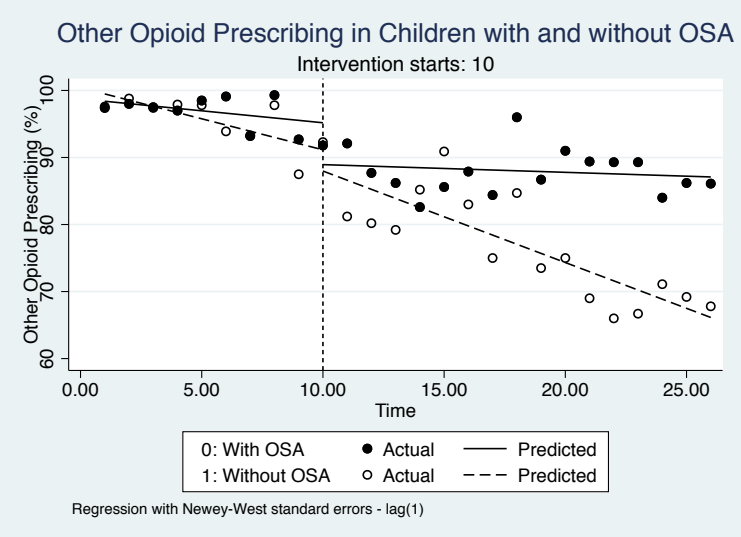


Figure 19. Time Series Graph of Other Opioid Prescribing in Children with and without OSA

Table 31

Regression Table for Other Opioid Prescribing Based on Procedure Indication

Variable	Parameter	Coefficient	t-statistic	P-value	95% Confidence Interval
Other Opioid Prescribing [OSA]	β_0 (Intercept)	98.4	153.3	0.00	97.1, 99.7
	β_1 (Pre-Slope)	-0.35	-1.97	0.062	-0.73, 0.02
	β_2 (Level change)	-6.2	-2.60	0.016*	-11.2, -1.3
	β_3 (Slope change)	0.24	1.12	0.273	-0.2, 0.68
	$\beta_1 + \beta_3$ (Post-Slope)	-0.11	-0.71	0.483	-0.45, 0.22
Other Opioid Prescribing [no OSA]	β_0 (Intercept)	99.5	93.43	0.00	97.3, 101.7
	β_1 (Pre-Slope)	-0.93	-2.87	0.009*	-1.6, -0.3
	β_2 (Level change)	-3.16	-0.85	0.403	-10.9, 4.5
	β_3 (Slope change)	-0.44	-1.21	0.238	-1.2, 0.31
	$\beta_1 + \beta_3$ (Post-Slope)	-1.18	-3.23	0.004*	-1.9, -0.42
Other Opioid Prescribing [OSA versus no OSA]	β_4 (Baseline level)	-1.09	-0.88	0.385	-3.6, 1.4
	β_5 (Baseline trend)	0.57	1.54	0.130	-0.18, 1.3
	β_6 (Level difference)	-3.83	-0.7	0.489	-11.9, 5.8
	β_7 (Slope difference)	0.68	1.62	0.113	-0.16, 1.5
	$\beta_5 + \beta_7$ (Post-Slope difference)	1.06	2.67	0.01*	0.26, 1.8

*significance $p \leq 0.05$

Opioid Prescribing Based on Body Habitus

Codeine prescribing in children with normal body habitus was estimated at 0.72% in the preintervention period (see Table 32). Codeine prescribing did not appear to decrease significantly in the preintervention period ($p = 0.341$), nor did it abruptly decrease after the FDA warning ($p = 0.157$). However, a significant slope change in codeine prescribing indicated a gradual reduction in codeine prescribing in the post-FDA warning period ($p = 0.018$, CI = [-0.89, -.0.1]). Findings were similar in children with non-normal body habitus. Codeine prescribing in children with non-normal body habitus was estimated at 1.1% in the preintervention period. Codeine prescribing did not decrease significantly in the preintervention period, nor did it abruptly decrease after the FDA warning. However, a significant slope change in codeine prescribing indicated a gradual reduction in codeine prescribing in the post-FDA warning period ($p = 0.001$, CI = [-0.48, -.1.62]).

When codeine prescribing was compared in children with normal versus non-normal body habitus, there was no difference in the level ($p = 0.949$), slopes ($p = 0.382$) or postintervention trend estimates ($p = 0.678$). Codeine prescribing did not appear to differ in children with normal versus non-normal body habitus.

Table 32

Regression Table for Codeine Prescribing Based on Body Habitus

Variable	Parameter	Coefficient	t-statistic	P-value	95% Confidence Interval
Codeine Prescribing [Normal BMI]	β_0 (Intercept)	0.72	0.97	0.341	-0.82, 2.26
	β_1 (Pre-Slope)	0.26	1.47	0.157	-0.11, 0.64
	β_2 (Level change)	0.78	0.61	0.551	-1.89, 3.45
	β_3 (Slope change)	-0.49	-2.55	0.018*	-0.89, -0.1
	$\beta_1 + \beta_3$ (Post-Slope)	-0.23	-3.52	0.002*	-0.36, -0.1
Codeine Prescribing	β_0 (Intercept)	1.1	3.83	0.001	0.48, 1.62
	β_1 (Pre-Slope)	0.1	1.04	0.311	-0.10, 0.30

[Non-Normal BMI]	β_2 (Level change)	0.89	1.01	0.325	-0.94, 2.7
	β_3 (Slope change)	-0.3	-2.93	0.001*	0.48, 1.62
	$\beta_1 + \beta_3$ (Post-Slope)	-0.2	-5.9	<0.001*	-0.27, -0.13
Codeine Prescribing [Normal versus Non-Normal BMI]	β_4 (Baseline level)	-0.33	-0.42	0.306	-0.09, 0.29
	β_5 (Baseline trend)	0.16	0.80	0.427	-0.25, 0.57
	β_6 (Level difference)	-0.3	1.56	0.949	-3.2, 3.0
	β_7 (Slope difference)	-0.19	-0.88	0.382	-0.63, 0.25
	$\beta_5 + \beta_7$ (Post-Slope difference)	-0.03	-0.41	0.687	-0.17, 0.12

*significance $p \leq 0.05$

Other opioid prescribing in children with normal body habitus was estimated at 99.7% (see Table 33). Other opioid prescribing decreased by 0.8% in each time period in prior to the FDA warning ($p = 0.028$, CI = [-1.49, -0.1]. There was not a significant level or slope change, however the trend of the time series after the intervention shows a significant reduction in other opioid prescribing by 0.5% in each time period after the FDA warning ($p = 0.003$, CI = [-0.76, -0.26]). In children with non-normal body habitus, other opioid prescribing was estimated at 97.2% in the preintervention period and did not appear to change significantly in the time periods prior to the FDA warning (p =0.202). After the FDA warning, other opioid prescribing abruptly decreased (level change) by 6.88% ($p = 0.022$, CI = [-12.6, -1.1]). The postintervention slope, when compared with the preintervention slope, was not significant ($p = 0.894$). These results indicate an immediate rather than a delayed treatment effect in other opioid prescribing in children with non-normal body habitus.

Other opioid prescribing did not appear to differ in children with normal versus non-normal body habitus, however because of differences in baseline level (β_4) and slope ($\beta 5$) group comparisons may be biased and are not adequate for comparison.

Table 33

Regression Table for Other Opioid Prescribing Based on Body Habitus

Variable	Parameter	Coefficient	t-statistic	P-value	95% Confidence Interval
Other Opioid Prescribing [Normal BMI]	β_0 (Intercept)	99.74	87.83	0.000	97.38, 102.1
	β_1 (Pre-Slope)	-0.8	-2.35	0.028*	-1.49, -0.1
	β_2 (Level change)	-5.12	-1.95	0.063	-10.55, 0.31
	β_3 (Slope change)	0.28	0.82	0.422	-0.43, 0.99
	$\beta_1 + \beta_3$ (Post-Slope)	-0.51	-4.23	0.003*	-0.76, -0.26
Other Opioid Prescribing [Non-Normal BMI]	β_0 (Intercept)	97.2	244.7	0.000	96.4, 98
	β_1 (Pre-Slope)	-0.1	-1.32	0.202	-0.26, 0.06
	β_2 (Level change)	-6.88	-2.47	0.022*	-12.64, -1.11
	β_3 (Slope change)	0.03	0.14	0.894	-0.42, 0.48
	$\beta_1 + \beta_3$ (Post-Slope)	-0.07	-0.31	0.76	-0.54, 0.4
Other Opioid Prescribing [Normal versus Non-Normal BMI]	β_4 (Baseline level)	2.55	2.12	0.04*	0.12, 4.9
	β_5 (Baseline trend)	-0.69	-2.0	0.05*	-1.39, 0.005
	β_6 (Level difference)	1.75	0.46	0.648	-5.9, 9.45
	β_7 (Slope difference)	0.25	0.62	0.541	-0.57, 1.1
	$\beta_5 + \beta_7$ (Post-Slope difference)	-0.44	-1.72	0.09	-0.92

*significance $p \leq 0.05$

Summary of Findings

After the FDA warning, codeine and other opioid prescribing decreased in the entire sample. Interestingly, codeine prescribing gradually decreased over time whereas an immediate treatment effect was demonstrated in other opioid prescribing. Varying times of the treatment effect (immediate versus delayed) was commonly seen when analyzing subgroups. All subgroups demonstrating a reduction in codeine prescribing in the post-FDA warning period showed a gradual treatment effect. Other opioid prescribing decreased immediately in some subgroups, whereas it fell more gradually in others.

Codeine and other opioid prescribing did not appear to be influenced by health insurance status. Both publicly and privately insured children demonstrated a reduction in codeine and

other opioids after the FDA warning period. Decreases in codeine prescribing in both publicly and privately insured children were gradual and there were no differences in codeine prescribing when groups were compared. The timing of the treatment effect differed between groups when considering other opioid prescribing. An immediate change in other opioid prescribing was demonstrated in publicly insured children and a more gradual decrease in other opioid prescribing occurred in privately insured children.

Age appeared to influence codeine and other opioid prescribing with the most notable impact on the youngest children in the sample. A gradual reduction in codeine prescribing and an immediate fall in other opioid prescribing were found in children age 0-4.9 years. Other opioid prescribing fell gradually in the post-FDA warning period in children age 5-9.9 years, but codeine prescribing did not change significantly in this age group. Neither codeine or other prescribing changed significantly in the oldest children in the sample (age 10-18 years).

Children with a procedure indication of OSA or non-OSA demonstrated similar and gradual reductions in codeine prescribing after the FDA warning. Both groups saw a reduction in other opioid prescribing, but differed in terms of timing of the treatment effect. Children with OSA showed an immediate decrease in other opioid prescribing after the FDA warning; after this immediate reduction, other opioid prescribing remained relatively flat in the postintervention period. Children without OSA demonstrated a more gradual reduction in other opioid prescribing after the FDA warning; the post intervention trend in this group continued to decrease each time period after the FDA warning.

Finally, children with normal or non-normal body habitus demonstrated similar and gradual reductions in codeine prescribing after the FDA warning. Again, both groups had a reduction in other opioid prescribing, but differed in terms of timing of the treatment effect.

Other opioid prescribing fell gradually in children with normal body habitus, whereas children with non-normal body habitus demonstrated an immediate decrease in other opioid prescribing.

Chapter Summary

This chapter presented the descriptive and statistical analysis of the study. Using an ITS study design, patterns of opioid prescribing in children undergoing tonsillectomy and/or adenoidectomy were evaluated. The primary questions of this study sought to assess if health insurance status influenced opioid prescribing. Findings of this study revealed that both publicly and privately insured children saw significant reductions in codeine and/or other opioid prescribing after the FDA warning. Additional findings of interest included the effect of age, procedure indication and body habitus on opioid prescribing. Of these, young age appeared to influence prescribing to the greatest degree. Chapter Five will discuss the theoretical and practical implications of the results, limitations of the study and recommendations for future research.

Chapter 5: Discussion

Chapter Introduction

This chapter reviews the study findings and explores the practical and theoretical implications of the findings. A brief synopsis of the study purpose, methodology and analyses are presented. Limitations are discussed and the chapter concludes with recommendations for future research.

Summary and Overview of the Problem

Tonsillectomy, with or without adenoidectomy, is one of the most commonly performed pediatric surgeries in the U.S. (Baugh et al., 2011). The procedure and care of a child undergoing tonsillectomy and/or adenoidectomy is fairly routine – however, reports of deaths and near deaths highlight the significant complications that can occur in children undergoing the procedure. Many complications are related to medications that depress the respiratory drive, such as opioids. Opioids provide post-tonsillectomy analgesia, but they also lead to unwanted effects such as sedation and respiratory depression. Clinical and/or genetic risk factors further heighten the danger of post-tonsillectomy opioids. Obstructive sleep apnea (OSA) belongs to the continuum of sleep related breathing disorders and is a common indication for tonsillectomy and/or adenoidectomy. Children with OSA are sensitive to the respiratory depressant effects of opioids and experience a higher preponderance of perioperative adverse events (De Luca Canto et al., 2015; Goldman et al., 2013; Mitchell et al., 2019). Obesity, which increases the likelihood of developing OSA, also heightens a child's risk of perioperative complications (Cote et al., 2018; Patino et al., 2013). Additionally, it is well established that polymorphisms in the genes responsible for codeine metabolism contributed to several post-tonsillectomy and/or adenoidectomy deaths (Cote et al., 2014). As a result, the FDA contraindicated the use of codeine in all children undergoing the procedure by placing a *Boxed Warning* on the drug. The

2013 FDA warning advised health care professionals "to prescribe an alternative analgesic [to codeine] for postoperative pain control in children undergoing tonsillectomy and/or adenoidectomy" (U.S. FDA Drug Safety Communications, 2013).

Recent analyses found a significant reduction in post-tonsillectomy and/or adenoidectomy codeine prescribing following the FDA warning, however these studies were conducted on a sample of children with private insurance (Chua et al., 2017; Van Cleve, 2017). It is unknown to what extent the FDA warning impacted codeine and alternative opioid prescribing rates in publicly insured children. Examining this problem in the context of an understudied population (publicly insured children) was important for two reasons. First, when compared to children with private insurance, rates of tonsillectomy and/or adenoidectomy are similar for children insured by Medicaid (Boss et al., 2012). Second, differences in opioid prescribing between publicly and privately insured children are documented (Donohue et al., 2019; Tomaszewski et al., 2018). Therefore, understanding prescribing behaviors in both publicly and privately insured children fills an important gap in the literature.

Purpose of the Study and Research Questions

The purpose of this study was to investigate the relationship between the FDA warning and codeine/alternative opioid prescribing in publicly and privately insured children who underwent tonsillectomy and/or adenoidectomy at OHSU between 2010 – 2018. This study sought to answer two research questions: (1) What is the relationship between the FDA warning and codeine/alternative opioid prescribing in children who underwent tonsillectomy at Oregon Health and Science University (OHSU) between January 2010-December 2018? (2) Does the relationship between codeine and/or alternative opioid prescribing in pediatric post-tonsillectomy children who underwent tonsillectomy at OHSU between January 2010 and December 2018 vary

by health insurance status? Results of this study clarified the impact of the FDA warning on codeine/other opioid prescribing and compared prescribing between publicly and privately insured children.

Review of Theory

The Donabedian model served as the framework for the study. Donabedian's landmark article proposed three domains in which the quality of medical care can be assessed – structure, process and outcome (Donabedian, 1966/2005). The assumption of the model is that "good structure increases the likelihood of good processes, and good processes increase the likelihood of good outcomes" (Donabedian, 1988, p.1145). In this study, the *structure* arm of the triad was the FDA warning, the *process* arm was opioid prescribing practices and the *outcome* was the number of codeine/other opioid prescriptions prescribed before and after the FDA warning. Building on Donabedian's theory, Coyle & Battles (1999) advocated that antecedent conditions, or personal and/or environmental factors that may influence the outcomes of care, be incorporated into the model. In this study, health insurance status was included as an antecedent condition that may influence opioid prescribing.

Review of Methodology

A quasi-experimental, interrupted time series (ITS) study design was used to assess opioid prescribing before and after the FDA warning. This study included two time-series segments and one interruption. The pre-FDA warning period was the first time-series segment, the interruption was the FDA warning and the second time-series segment was the post-FDA warning period. The ITS methodology facilitated an understanding of prescribing patterns over time and evaluated the immediate and gradual effects of the FDA warning on codeine/other opioid prescribing.

Following IRB approval from VCU and OHSU, data was extracted from OHSU's EHR (Epic Hyperspace®). The sample included children who underwent tonsillectomy and/or adenoidectomy at OHSU from 2010-2018. The data was cleaned, coded into categories (age, gender, race, insurance status, OSA status and body habitus) and prepared for analysis. Descriptive analysis was undertaken to provide basic information of the sample and to highlight potential relationships between variables. Statistical analysis addressed prescribing practices in all children and subgroups of interest, addressing all study hypotheses.

Review of Study Findings and Application to the Literature

Descriptive Findings

Several noteworthy findings during descriptive analysis were discovered. First, the trend of opioid prescribing changed throughout the study years where a progressive decline in the percentage of children who received any opioid following tonsillectomy and/or adenoidectomy was demonstrated. A decrease in the percentage of children who were prescribed opioids occurred between 2013 and 2014, coinciding with the FDA warning; this will be further explored below. Additionally, the type of opioid prescribed changed over the study period. Hydrocodone was the most commonly prescribed opioid early in the study period (years 2010 and 2011) and prescribing continued modestly through 2013. Hydrocodone prescribing fell substantially in 2014, corresponding with two events: (1) the U.S. Drug Enforcement Agency and Department of Justice's rescheduling of hydrocodone products from Schedule III to Schedule II and (2) the FDA warning on codeine. Drug scheduling of opioids denotes their abuse potential (lowest abuse potential with Schedule IV and highest with Schedule I) – though scheduling also enables or prohibits providers to refill controlled substances (U.S. Department of Justice, 2014). The reduction in hydrocodone prescribing may be reflective of its scheduling change – however,

another plausible explanation exists. Like codeine, hydrocodone is a prodrug and requires substantial metabolism by the CYP2D6 enzyme to produce its active form (hydromorphone). Though there is insufficient information to understand whether different CYP2D6 phenotypes influence hydrocodone's metabolism (and a dearth of case reports about pediatric overdose/toxicity with hydrocodone), it's plausible that providers elected to avoid prescribing drugs that may demonstrate CYP2D6 phenotypic variability in drug metabolism. After 2014, oxycodone-containing products (which do not rely as substantially on CYP2D6 metabolism) became the most frequently prescribed opioid for pediatric post-tonsillectomy patients at OHSU. Interestingly, other studies found hydrocodone to be the opioid most frequently prescribed in the post-FDA warning era (Goldman et al., 2018; Chua et al., 2017; Van Cleve, 2017). These differences may be related to provider or institutional preferences.

Several demographic characteristics of the sample merit elaboration. First, the majority of the sample included children in the youngest or middle-age categories (age 0-4.9 and 5-9.9 years, respectively). This is consistent with prior studies (Boss et al., 2012) and logical when considering the incidence of OSA peaks between 2-8 years of age (Patino et al., 2013). Next, similar to other age-related studies, there was an incidental finding of an increase in OSA and non-normal body habitus over time. The percentage of children with OSA increased steadily from 2010-2018 and the percentage of children with a non-normal body habitus was greater in the post-FDA warning period. Finally, consistent with prior studies, this study demonstrated that tonsillectomy and/or adenoidectomy was performed at the same rate regardless of gender or insurer status (Boss et al., 2012).

Statistical Analysis

Opioid Prescribing in All Children

Before hypothesis testing, codeine/other opioid prescribing was analyzed in the entire sample. Other opioid prescribing fell abruptly after the FDA warning, yet codeine prescribing fell more gradually. This is in contrast to other similar studies, where codeine prescribing fell abruptly and other opioid prescribing slightly increased following the FDA warning (Chua et al., 2017; Van Cleve, 2017). In this present study, codeine prescribing appeared to increase in the time periods preceding the FDA warning and remained unchanged or slightly higher in the time periods immediately following the FDA warning – thereafter, codeine prescribing began to fall. The reasons behind this are unclear and difficult to explain clinically or empirically. Observing changes in outcomes prior to a treatment is consistent with an "anticipation effect" (Malani & Reif, 2015) – however it would be assumed that providers would decrease (not increase) codeine prescribing in anticipation of the FDA warning. It is plausible that prescribing providers were unaware of the FDA warning – or were aware, yet initially disregarded the warning. Also, if providers did not observe codeine-related adverse events based on their prior experience with the drug, it is conceivable they were skeptical of the FDA warning. Gathering further evidence to substantiate the aforementioned was difficult. Given the study site was an academic health center in a large metropolitan area, it is likely information on the FDA warning was disseminated to prescribing providers. Thus, it is plausible that one or more providers did not initially change prescribing practices, explaining the slower decline in codeine prescribing following the FDA warning.

Also, Chua et al. (2017) and Van Cleve (2017) found other opioid prescribing slightly increased following the FDA warning on codeine. In contrast, this present study found a significant decrease in other opioid prescribing in the post-FDA warning period. It's conceivable that providers in this study reduced prescribing of other opioids (oxycodone and hydrocodone)

because they are stronger, higher-potency opioids with a greater perceived risk of adverse events. Also, rather than relying on opioids for post-tonsillectomy pain, providers may have responded to the FDA warning by incorporating non-opioid agents for post-tonsillectomy pain – resulting in a decrease in overall opioid prescribing.

Opioid Prescribing Based on Insurance Status

Following analyses of the health insurance subgroup, it was found that one of the four hypotheses was supported. Each hypothesis and its application to the literature will be discussed, below.

H_1: In publicly and privately insured post-tonsillectomy and/or adenoidectomy children at OHSU, rates of codeine prescribing (level and/or trend) decreased following the 2013 FDA warning on codeine.

Rates of codeine prescribing decreased in both publicly and privately insured children after the FDA warning and therefore this hypothesis was supported. This present study observed a significant slope change in codeine prescribing in both groups, indicating a gradual decline in codeine prescribing in the post-FDA warning period. Prior studies showed a reduction in codeine prescribing after the FDA warning, yet evaluated prescribing in privately insured children only (Chua et al., 2017; Van Cleve, 2017). This study adds to the body of knowledge by demonstrating a reduction in codeine in both publicly and privately insured children.

H_2: There is a difference in codeine prescribing (level and/or trend) between publicly and privately insured post-tonsillectomy and/or adenoidectomy children at OHSU.

Codeine prescribing did not differ between publicly and privately insured children and therefore this hypothesis was not supported. Literature pertaining to opioid prescribing practices in publicly versus privately insured children is scant and mixed. Some studies found children with

public insurance were more likely to receive an opioid (Donohue et al., 2019) while other studies found publicly insured children were less likely to receive an opioid (Tomaszewski et al., 2018). In this study, it was hypothesized that prescribing disparities may exist due to provider biases and/or clinical explanations. However, this study found equitable prescribing between public and privately insured children. These findings are encouraging, but add little clarity to the mixed evidence base.

H_3: In publicly and privately insured post-tonsillectomy and/or adenoidectomy children at OHSU, rates of other opioid prescribing (level and/or trend) increased following the 2013 FDA warning on codeine.

Rates of other opioid prescribing decreased in both publicly and privately insured children and thus this hypothesis was not supported. Based on prior studies, it was hypothesized the FDA warning would result in an increase in other opioid prescribing as a result of substituting an alternative opioid for codeine (Chua et al., 2017; Van Cleve, 2017). However, a reduction in other opioid prescribing in privately and publicly insured children was found. In this current study, the FDA warning appeared to decrease prescribing of not only codeine, but also non-codeine opioids. As discussed above, providers may have reduced other opioid prescribing in favor of non-opioid post-tonsillectomy analgesics.

H_4: There is a difference in alternative opioid prescribing (level and/or trend) between publicly and privately insured post-tonsillectomy and/or adenoidectomy children at OHSU.

Other opioid prescribing did not differ significantly between publicly and privately insured children and therefore this hypothesis was not supported. Both groups demonstrated a reduction in other opioid prescribing in the post-FDA warning period, however the timing of the treatment effect differed. Publicly insured children saw an immediate and abrupt reduction in other opioid

prescribing compared to a more gradual reduction in privately insured children. This may be related to a higher baseline level of other opioid prescribing in publicly insured children (99.5%) when compared with privately insured children (97.6%). Also, publicly insured children in this study had a greater frequency of OSA (59.6% versus 40.4%) and a greater occurrence of a non-normal body habitus (63.1% versus 39.6%) than did privately insured children – which may have prompted an abrupt treatment response in publicly insured children.

Incidental Findings: Opioid Prescribing Based on Age, Procedure Indication and Body Habitus

Additional findings in various subgroups were of interest. The youngest children in the sample (0-4.9 years) had the highest starting level of codeine prescribing in the pre-FDA warning period (2.4%). Codeine, considered a relatively weak opioid, was initially thought to be safer than other stronger opioids. Prior to the FDA warning, the perceived safety profile of codeine may have given providers confidence to prescribe the drug to the youngest children. Codeine prescribing in children age 0-4.9 years decreased following the FDA warning, but prescribing did not change in children age 5-9.9 or 10-18 years. This is likely due to very low pre-intervention codeine prescribing rates in the latter age groups (0.41% and nearly 0%, respectively). Additionally, the youngest children saw a significant and immediate reduction in other opioid prescribing after the FDA warning whereas older children demonstrated a gradual or no reduction in other opioid prescribing. Two plausible explanations exist. First, younger children are higher risk for post-tonsillectomy respiratory compromise (Cote et al., 2015). Also, many of the post-tonsillectomy codeine-related deaths occurred in young children (2-10 years). These factors may have prompted providers to be more cautious in prescribing opioids to younger children. Next, it is documented that older children and adults report higher post-tonsillectomy pain than younger children (Alm, Stalfors, Nerfeldt & Ericsson, 2017; Eriksson,

Nilsson, Bramhagen, Idvall & Ericsson, 2017), possibly explaining why other opioid prescribing was not reduced in children age 10-18 years.

Opioid prescribing based on procedure indication (OSA versus no-OSA) showed codeine prescribing fell gradually in both groups. Other opioid prescribing also fell in both groups, but the timing of the treatment effect differed. In children with OSA, an immediate reduction in other opioid prescribing occurred. This may be reflective of the heightened risk of perioperative adverse respiratory events in children with OSA. Canto et al. (2015) reported children with OSA have a 5-fold increase in the odds for perioperative respiratory events when compared to children without OSA. Also, studies reported unexpected post-tonsillectomy and/or adenoidectomy deaths and/or near deaths in children with suspected or confirmed sleep apnea (Coté et al., 2014; Goldman et al., 2013). Children without OSA also demonstrated a reduction in other opioid prescribing, though at a more gradual pace. Interestingly, the post-intervention slope of other opioid prescribing in children without OSA trended downward, but remained relatively flat in children with OSA. It is plausible that children without OSA underwent adenoidectomy only, which tends to be less painful and requires fewer opioid analgesics. Conversely, children with OSA likely underwent combined tonsillectomy and adenoidectomy, which is a more painful procedure – possibly explaining the relatively flat postintervention trend seen in this group.

Next, children with normal and non-normal body habitus experienced a decline in codeine and other opioid prescribing. Again, the timing of the treatment effect of other opioid prescribing differed. Children with non-normal body habitus showed an immediate reduction in other opioid prescribing whereas children with a normal body habitus demonstrated a more gradual decline. These findings may be explained given non-normal body habitus, particularly obesity, increases the risk for perioperative adverse respiratory events in children undergoing

tonsillectomy and/or adenoidectomy (Goldman et al., 2013; Mortensen et al., 2011). However, because of the distribution of the sample in this study, the non-normal body habitus category contained children who were underweight, overweight or obese. Therefore, it cannot be assumed that all children in the non-normal category were obese. Still, these findings illustrate that body habitus impacted the timing in which other opioid prescribing fell.

Contribution to the Literature

This study clarified the local impact of the FDA warning on codeine prescribing and added additional knowledge on codeine/other opioid prescribing in an understudied population. Prior studies evaluated pre-and post-FDA warning opioid prescribing in privately insured children only. This study expanded the knowledge base by including publicly insured children in the sample – and by comparing prescribing in publicly versus privately insured children. This study also illustrated opioid prescribing trends from 2010 – 2018 and provided information on the most commonly prescribed post-tonsillectomy opioids at OHSU. Additionally, this study evaluated opioids prescribed rather than opioids dispensed, which better assesses actual prescribing practices. Findings from this study are relevant both theoretically and practically, as discussed below.

Study Implications

Theoretical Implications

Quality of care was a central matter in this study. Using the Institute of Medicine's conceptualizations of quality, this study defined quality in terms of safety (halting codeine prescribing) and equity of care (in all children, regardless of health insurance status). The Donabedian model served as a framework for how quality was measured in this study. Using the constructs of structure, process and outcome a linkage was made between the FDA warning

(structure), prescribing practices (processes) and number of opioid prescriptions (outcomes). Results of this study support the linkage where prescribing practices and the number of opioid prescriptions changed as a result of the FDA warning. This was evidenced by an immediate or gradual reduction in codeine and other opioid prescribing in the post-FDA warning period (main and subgroup analyses). However, differences in prescribing between publicly and privately insured children were not apparent – therefore health insurance status did not appear to be an antecedent factor that influenced outcomes. Still, Donabedian's model served as a useful framework to evaluate the influence of structural and process-related factors on outcomes.

Practical Implications

Results have practical implications for providers who prescribe opioids and care for children undergoing tonsillectomy and/or adenoidectomy. The FDA warning reduced both codeine and other opioid prescribing at OHSU. Rather than substituting other opioids for codeine, it appears the FDA warning prompted providers to prescribe less opioids, in general. This shift in prescribing is encouraging and aligns with recent recommendations to reduce opioid prescribing in pediatric tonsillectomy and/or adenoidectomy patients (Mitchell et al., 2019). Additionally, this current study revealed that oxycodone is now the most frequently prescribed opioid in pediatric tonsillectomy and/or adenoidectomy patients at the study site. This is an important finding as the knowledge base regarding the impact of pharmacogenetics on oxycodone metabolism in children develops. Though the CYP34A enzyme is the primary metabolic pathway of oxycodone, the enzyme CYP2D6 plays a partial role. Children with atypical CYP2D6 phenotypes (extensive metabolizers) appear to have higher exposure to oxycodone's active metabolite, oxymorphone (Balyan et al., 2017). Oxycodone-related toxicity has not been reported in post-tonsillectomy children – however, providers should consider the

risks (clinical and genetic) of prescribing the drug. Also, results of this study offer an opportunity to reinforce the dangers of codeine prescribing in children undergoing tonsillectomy and/or adenoidectomy. Codeine prescribing in the latter study years was very low – however, there is evidence of some residual codeine prescribing (0.4% in 2018). This study serves as a useful reminder that codeine should be avoided in this population. Finally, this study illustrates that clinical risk factors appear to influence prescribing practices, at least to some extent. It should continue to be emphasized that young children, children with OSA or obese children are at greater risk for opioid-related adverse events.

Limitations

This study has limitations. Although the ITS design is regarded as a strong quasi-experimental research design, this study is observational and does not account for all factors that may influence opioid prescribing. Inherent to the ITS design, threats due to between or within-group differences are minimized (Bernal et al., 2018; Kontopantelis et al., 2015). Still, demographic variables were collected and stratified analyses were conducted on groups that exhibited differences in the pre-and post-FDA warning periods. Next, an ITS design relies on equally spaced observation intervals and clear differentiation of the pre-and post-intervention periods. Because of inadequate sample size for monthly observation intervals, data were grouped into 4-month observation intervals. Fewer observation intervals may have resulted in loss of statistical power, however adequate observations at each observation interval likely offsets this. Finally, the pre-intervention trend of the variable codeine exhibited a somewhat irregular pattern. Violation of the assumption of linearity does not invalidate the analysis, but does weaken it. Attempts were made to transform the variable, but linearity was not markedly improved.

Retaining the variable in its original form allowed metrics of interpretation to be meaningful and consistent across groups.

Next, the EHR was used as the data collection tool in this study. The EHR is generally regarded as an unbiased data collection tool, however its accuracy relies on individual users who input the data. The BMI variable had considerable missing data due to missing height information from the EHR. The missing data was imputed from relevant variables (age, gender, weight) – still, this introduces bias into the variable. Also, the procedure indication variable (OSA versus no OSA) relies on CPT and/or ICD codes that tend to be more useful for billing purposes than clinical purposes. It is conceivable that some children who had evidence of a sleep-related breathing disorder – but did not have a formal sleep study – were not given a formal CPT and/or ICD diagnosis of OSA. Additionally, the non-OSA group in the post-intervention period was small and estimates may be biased on account of small N. Age groups were uneven with the majority (>80%) of children in the 0-4.9- or 5-9.9-year categories, potentially introducing bias into the analyses of opioid prescribing in older children (10-18 years). Next, it was surprising that measurement error afflicted the opioid prescribing variable. As previously discussed, a plausible EHR technological fault led to a biased estimate of opioid prescribing in time period 25, necessitating data exclusion. However, a sensitivity analysis showed the data exclusion did not alter the analysis. Finally, the pharmacy informatics team was unable to extract the dose of opioid prescribed. The binary yes/no variable of opioid prescribing cannot account for possible opioid dose reductions that may have occurred in the post-FDA warning period.

The study site was a large, academic medical center and study findings may not generalize to other institutions or populations. Demographic characteristics of the sample,

surgical techniques and prescribing practices may differ across facilities. Also, this study included only children who underwent outpatient tonsillectomy and/or adenoidectomy. All children were assumed to be candidates for outpatient surgery, without major comorbidities. However, clinical characteristics were limited only to OSA status and body habitus; therefore, it cannot be determined if some children possessed additional comorbidities that may have influenced prescribing practices.

Combined procedures were intended to be excluded, though the data was not filtered for this exclusion. However, it was estimated by the otolaryngology team that only a small number of tonsillectomy and/or adenoidectomies were combined with other non-otolaryngology procedures. Further, data from OHSU's perioperative patient registry (Multicenter Perioperative Outcomes Group e-system) showed < 5% of outpatient tonsillectomy and/or adenoidectomies were combined with other non-otolaryngology procedures. All opioids in the dataset were prescribed by otolaryngologists – which linked the opioid prescription to the tonsillectomy and/or adenoidectomy procedure. Still, combined procedures represent a potential confounder and limitation to the study.

Finally, no evidence of codeine, hydrocodone or oxycodone shortage were found via the U.S. FDA's Drug Shortages Database. However, local shortages or supply chain disruptions cannot be excluded.

Conclusions and Recommendations for Future Research

The 2013 FDA warning on codeine led to significant changes in codeine and other opioid prescribing in all children; insurance status did not appear to influence prescribing practices. Findings from this study are encouraging, but evidence regarding the medical treatment of publicly versus privately insured children remains mixed. Achieving equity in healthcare

delivery requires a comprehensive research agenda that considers all sociodemographic variables that may influence care, including health insurance status. Therefore, the influence of health insurance status on opioid prescribing should be further explored in future, larger-scale studies. These studies should be conducted in varied settings including perioperative, emergency department and primary care settings – in both academic and non-academic/community facilities. Additionally, qualitative or mixed-method studies may be beneficial to better understand possible implicit and/or explicit biases in prescribing practices and/or perceptions of regulatory drug warnings. Future studies should also consider variables not measured in this study, including surgical technique and dose of opioid prescribed. Next, further studies should ascertain the impact of genetic variation on oxycodone metabolism in children. Finally, studies should examine whether non-opioid medications have been substituted for opioids. Tonsillectomy remains a painful procedure. Research should address the adequacy of analgesia as the opioid prescribing trend shifts downward.

Appendix A

- *ICD-9-CM* codes:
  - 327.23 (OSA (pediatric)(adult))
  - 780.57 (unspecified sleep apnea)
- *ICD-9-PCS* codes:
  - 28.2 (tonsillectomy without adenoidectomy)
  - 28.3 (tonsillectomy with adenoidectomy)
  - 28.6 (adenoidectomy without tonsillectomy)
- *ICD-10-CM* codes:
  - G47.33 (OSA (pediatric)(adult))
  - G47.30 (unspecified sleep apnea)
- *ICD-10-PCS* codes:
  - 0CTP0ZZ (resection of tonsils, open approach)
  - 0CTPXZZ (resection of tonsils, external approach)
  - 0CTQ0ZZ (resection of adenoids, open approach)
  - 0CTQXZZ (resection of adenoids, external approach)
  - 0C5P0ZZ (destruction of tonsils, open approach)
  - 0C5PXZZ (destruction of tonsils, external approach)
  - 0C5Q0ZZ (destruction of adenoids, open approach)
  - 0C5QXZZ (destruction of adenoids, external approach)
  - 0CBP0ZZ (excision of tonsils, open approach)
  - 0CBPXZZ (excision of tonsils, external approach)
  - 0CBQ0ZZ (excision of adenoids, open approach)
  - 0CBQXZZ (excision of adenoids, external approach)
- *CPT* codes:
  - 42820, 42821, 42825, 42826, 42830, 42831, 42835, 42836 (Excision and Destruction Procedures on the Pharynx, Adenoids, and Tonsils)

Appendix B

Time Period	Months	Intervention Period
1	2-5 (Feb 2010 – May 2010)	Pre
2	6-9 (June 2010 – Sept 2010)	Pre
3	10-13 (Oct 2010 – Jan 2011)	Pre
4	14-17 (Feb 2011 – May 2011)	Pre
5	18-21 (June 2011 – Sept 2011)	Pre
6	22-25 (Oct 2011 – Jan 2012)	Pre
7	26-29 (Feb 2012 – May 2012)	Pre
8	30-33 (June 2012 – Sept 2012)	Pre
9	34-37 (Oct 2012 – Jan 2013)	Pre
10	40-43 (Apr 2013 – July 2013)	Post
11	44-47 (Aug 2013– Nov 2013)	Post
12	48-51 (Dec 2013 – Mar 2014)	Post
13	52-55 (Apr 2014 – July 2014)	Post
14	56-59 (Aug 2014 – Nov 2014)	Post
15	60-63 (Dec 2014 – Mar 2015)	Post
16	64-67 (Apr 2015 – July 2015)	Post
17	68-71 (Aug 2015 – Nov 2015)	Post
18	72-75 (Dec 2015 – Mar 2016)	Post
19	76-79 (Apr 2016 – July 2016)	Post
20	80-83 (Aug 2016 – Nov 2016)	Post
21	84-87 (Dec 2016 – Mar 2017)	Post
22	88-91 (Apr 2017 – July 2017)	Post
23	92-95 (Aug 2017 – Nov 2017)	Post
24	99-99 (Dec 2017 – Mar 2018)	Post
25	100-103 (Apr 2018 – July 2018)	Post
26	104-107 (Aug 2018 – Nov 2018)	Post

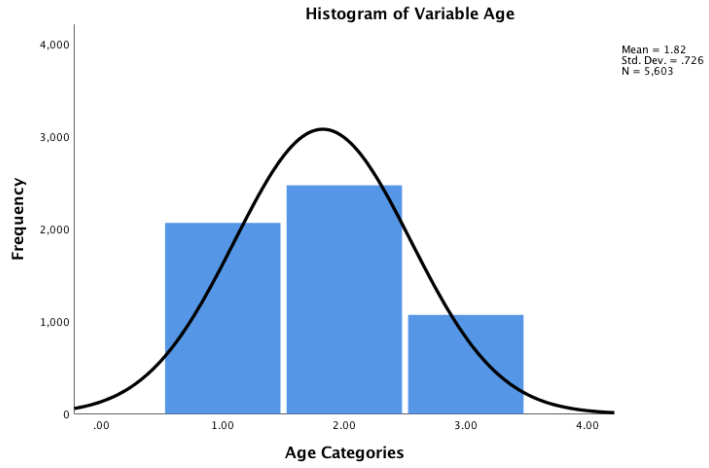
Appendix C

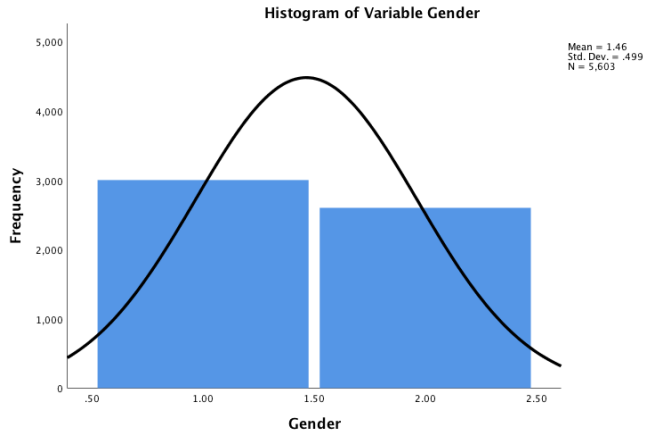
Public	Private
AETNA DIRECT	AGENCIES FEDERAL
AETNA NETWORK AETNA NETWORK	AMERIGROUP APPLE HEALTH
AETNA OHSU 250	CAREOREGON MEDICARE ADV
AETNA OHSU 60/50	CAWEM INPT
AETNA OHSU PPO	CAWEM NON COV
ALLEGIANCE	CCO ADVANCED HEALTH
APWU	CCO ALLCARE HEALTH PLAN
ATRIO EXCHANGE	CCO CAREOR HEALTH SHARE
BAY AREA HOSPITAL	CCO CASCADE HLTH ALLIANCE
BC MEDADVANTAGE	CCO COLUMBIA PACIFIC
BCBS ILLINOIS	CCO EASTERN OR
BCBS MASSACHUSETTS	CCO FAMILYCARE INC
BCBS MINNESOTA	CCO INTERCOMMUNITY HTLH
BCBS OUT OF STATE	CCO JACKSON CARE CONNECT
BEECH ST	CCO KAISER HEALTH SHARE
BLUE CROSS CALIFORNIA	CCO PACIFICSOURCE
BLUE CROSS FEDERAL	CCO PRIMARYHLTH JSPHN CTY
BRIDGESPAN EXCHANGE	CCO PROVIDENCE HLTH SHARE
*CHAMPVA	CCO TRILLIUM COMMUNITY
CIGNA	CCO TUALITY HEALTH SHARE
CIGNA NETWORK	CCO UMPQUA HEALTH ALLIANCE
COMMERCIAL GROUP	CCO WILLAMETTE VALLEY COM HLTH
CORESOURCE AETNA	CCO YAMHILL COMMUNITY
COVENTRY FIRST HEALTH	CHPW APPLE HEALTH
FIRST CHOICE HEALTH	CHPW APPLE HEALTH
GEHA	CHPW CUP APPLE HEALTH
GREAT WEST NETWORK	COORD CARE APPLE HEALTH
GWH CIGNA	MEDICARE A & B
HEALTH FUTURE MANAGED CARE	CUP APPLE HEALTH
HEALTHNET HMO/POS/EPO/CC	IDAHO MEDICAID
HEALTHNET MEDICARE PPO	INDIAN HEALTH SERVICE
HEALTHNET PPO	MOLINA APPLE HEALTH
HMA/RGA	MOLINA KAISER APPLE HEALTH
KAISER ADDED CHOICE	OHP CAREOREGON PLUS
KAISER PEDIATRIC	OHP CAREOREGON STANDARD
LIFE TRAC TRANSPLANT	OHP CASCADE PLUS
LIFEWISE	OHP DOCS PLUS
LIFEWISE IN NETWORK FIRST CHOICE	OHP DOUGLAS PLUS
LOOMIS COMPANY BENEFITS	OHP DOUGLAS STANDARD
MERITAIN HEALTH	OHP FAMILY CARE PCO PLUS
MODA AFFINITY	OHP FAMILY CARE PLUS
MODA BEACON	OHP INTERCOMMUNITY PLUS
MODA CONNEXUS	OHP LANE PLUS
MODA HEALTH ODS OHSU 250	OHP MARION POLK PLUS
MODA HEALTH OHP ODS PLUS	OHP MIDROGUE PLUS
MODA MEDICARE PPO	OHP PACIFICSOURCE PLUS
MODA OEBB CONNEXUS	OHP PACIFICSOURCE STANDARD

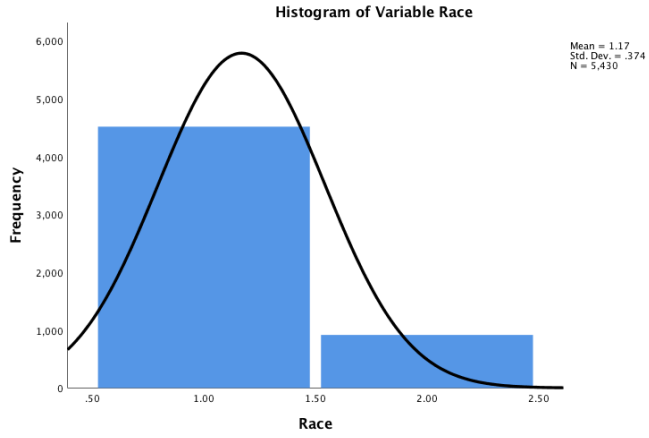
MODA OHSU PPO	OHP PCCM PLUS
MODA PEBB	OHP PLUS OPEN CARD
MODA SUMMIT	OHP PROV HEALTH PLUS
MODA SUMMIT PEBB	OHP TUALITY HEALTHPLUS
MODA SYNERGY SUMMIT	OMAP STANDARD
MULTIPLAN	OREGONS HEALTH CO OP
MULTIPLAN WRAP	PACIFICSOURCE MEDICARE
NALC	PROJECT ACCESS NOW
PACIFICSOURCE	SAMARITAN HEALTHY KIDS
PACIFICSOURCE HEALTHY KIDS	SAMARITAN MEDICARE
ESSENTIALS/EXPLORER	UHC WEST WA APPLE HEALTH
PHP OPEN IPCO	WA COMM HEALTH
PHP PEBB STATEWIDE	WA MEDICAID CUP
PHP PERSONAL IPCO	WA MEDICAID FEDERAL
PREMERA OF WA ALASKA	WARM SPRINGS MANAGED CARE
PRIVATE HEALTH CARE SYSTEMS	
PROV PREF DIRECT	
PROVIDENCE CHOICE PEBB	
PROVIDENCE EXCHANGE	
PROVIDENCE HEALTH	
PROVIDENCE HEALTH PERSONAL OPTION	
PROVIDENCE PREF	
REGENCE ACCESS	
REGENCE BC MEDADVANTAGE PPO	
REGENCE BCBS	
REGENCE BCBS OHSU PLUS	
REGENCE BCBS PAR	
SAMARITAN HEALTH	
SHRINERS	
*TRICARE	
*TRICARE WEST HEALTHNET	
TUALITY HEALTHCARE	
UMR UHC	
UNITED HEALTHCARE	
UNITED HEALTHCARE NETWORK	
UNITED HLTHCARE	
*VA COMMUNITY OUTSOURCE	
*VA TRIWEST	

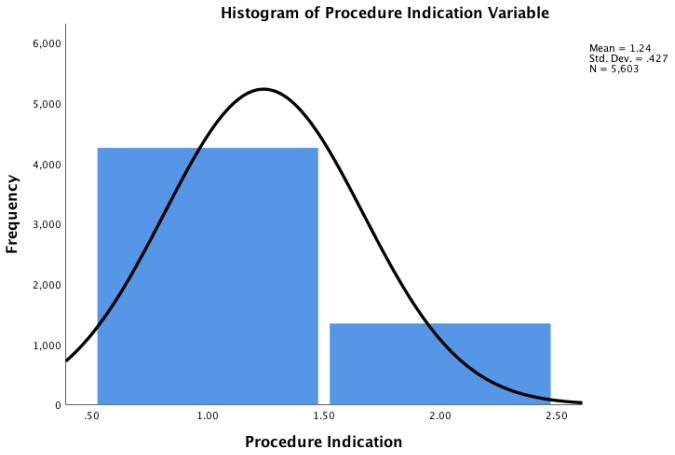
*Health Insurance Coverage provided by the government to military personnel. Employment-connected, not income based and therefore classified as private.

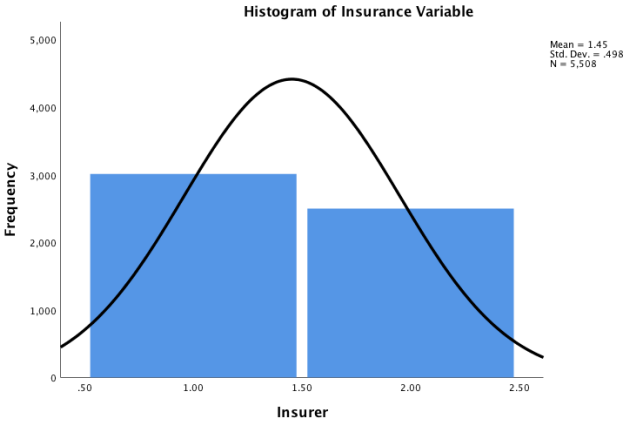
Appendix D

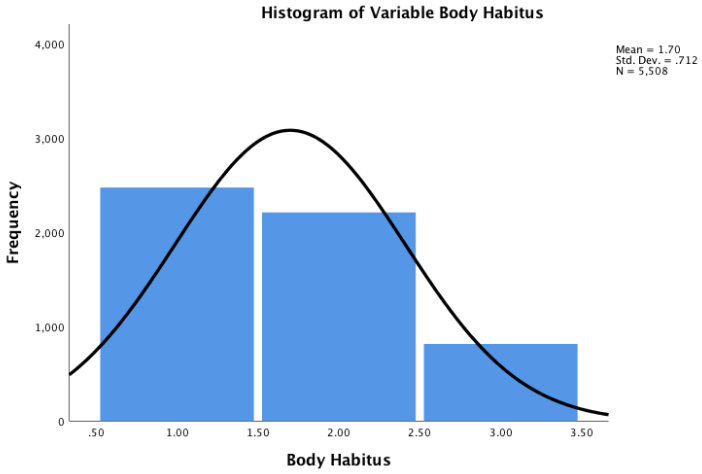




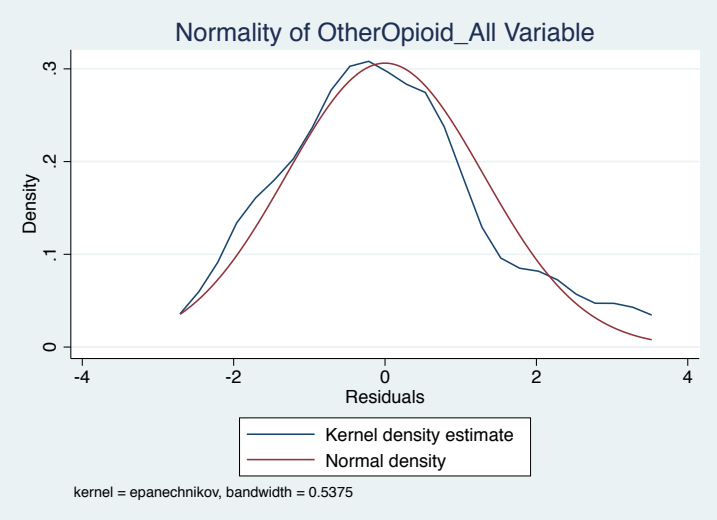


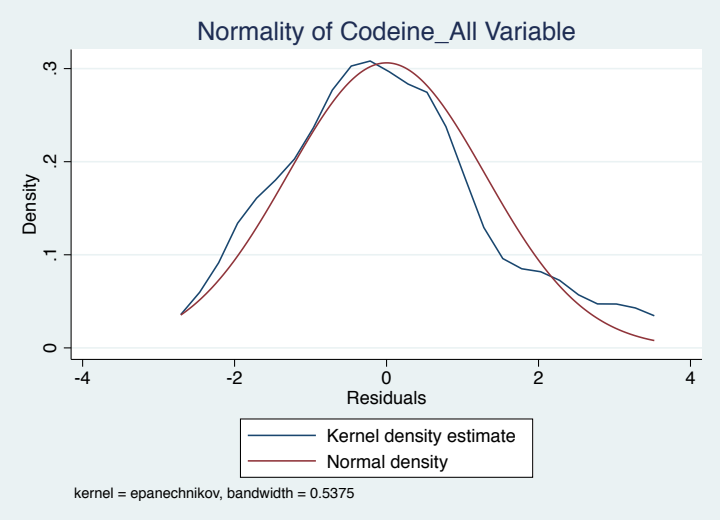






Appendix E





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Vita

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