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Pediatric Drug Utilization Review

BACKGROUND PACKAGE ADDENDUM

Date:	September 1, 2016
Reviewers:	Tracy Pham, Pharm.D. Division of Epidemiology II
	Jennie Wong, Pharm.D. Division of Epidemiology II
	Mohamed Mohamoud, Pharm.D. MPH Division of Epidemiology II
Team Leaders:	Rajdeep Gill, Pharm.D. Division of Epidemiology II
	Cynthia Kornegay, Ph.D. Division of Epidemiology II
Deputy Director for Drug Utilization:	LCDR Grace Chai, Pharm.D. Division of Epidemiology II
Office Director:	Gerald Dal Pan, M.D., M.H.S. Office of Surveillance and Epidemiology
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EXECUTIVE SUMMARY

A joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), the Drug Safety and Risk Management Advisory Committee (DSaRM), and Pediatric Advisory Committee (PAC) will be held on September 15-16, 2016 to discuss the purpose and the conduct of clinical trials of opioid analgesics in pediatric patients. In preparation for this upcoming joint advisory committee meeting, this review examined the national utilization patterns of opioid analgesics in the pediatric population (0-16 years) from 2011 through 2015 in the U.S. outpatient retail setting. The drug utilization analyses in this review will be used as background information to provide context for the meeting's discussion.

In the U.S. outpatient retail setting, pediatric patients 16 years of age and younger accounted for approximately 4% (2.5 million patients) of the total 66.5 million patients of any age who received dispensed prescriptions for opioid analgesics in 2015. The majority of pediatric patients were ages 7-16 years. There was a 34% decrease in the number of pediatric patients from 2011 to 2015. Annually within each respective pediatric age group examined, approximately 98.5% or more of patients in each pediatric age group received IR opioid analgesic prescriptions, and 1.6% or less of patients in each pediatric age group received ER/LA opioid analgesic prescriptions throughout the study period. Combination hydrocodone-acetaminophen IR and combination codeine-acetaminophen IR were the most commonly dispensed IR opioid analgesics while methadone, fentanyl transdermal, single-ingredient oxycodone ER, and morphine ER were the most commonly dispensed ER/LA opioid analgesics to pediatric patients with slight variations by patient age. Overall, trends in dispensed prescription data were similar to unique patient utilization data. In 2015, pediatricians were the top prescriber specialty for both IR and ER/LA opioid analgesics in patients ages 0-1 years and for ER/LA opioid analgesics in patients ages 2-6 years and 7-16 years. Dentists were the top prescriber specialty for IR opioid analgesics in patients ages 2-6 years and 7-16 years.

Analyses of duration of use for opioid analgesics were also conducted for the calendar year 2015 in a study sample of patients with claims for prescriptions dispensed from outpatient retail pharmacies. Consistent with dispensed prescription trends above, higher numbers of pediatric patients were dispensed IR opioid analgesics, of which the majority of patients were treated for shorter durations. These data are consistent with dispensing of IR opioid analgesic for the management of pain associated with an acute injury or dental procedure. A small number of pediatric patients were exposed to ER/LA opioid analgesics; of these, patients were treated for longer durations of use compared to the IR opioids. This finding is consistent with ER/LA opioid analgesic utilization in patients with medical illnesses which cause chronic pain. The majority of pediatric patients on ER/LA opioid analgesics had durations of therapy for less than 31 days; a small subset of patients had longer durations of therapy.

Based on U.S. office-based physician survey data, hernia was the top diagnosis associated with the use of IR opioid analgesics in patients ages 0-1 years from outpatient retail setting. Injuries and burns were the top diagnoses reported in patients ages 2-6 years and 7-16 years in association with the use of IR opioid analgesics. Diagnoses associated with the use of ER/LA opioid analgesics were not captured for the pediatric population in this data source most likely due to the low pediatric utilization of these products. These findings are consistent with patterns of pediatric use observed in dispensed prescriptions and duration of use analyses.

The majority of opioid analgesics are currently not labeled for use in children 16 years of age and younger. However, our analyses show that opioid analgesics, both IR and ER/LA products, are prescribed and dispensed to pediatric patients aged 16 years and younger in the outpatient retail setting.

Therefore, studies of opioid analgesics in pediatric patients are necessary to inform health care providers of the safe use and proper dosing of opioid analgesics in the management of pain in children.

1 INTRODUCTION

The Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), the Drug Safety and Risk Management Advisory Committee (DSaRM), and Pediatric Advisory Committee (PAC) joint meeting will be held on September 15-16, 2016. The purpose of this meeting is to discuss the studies of opioid analgesics in children, and the data on safe use and dosing in children who are appropriate for these products and has already received treatment with opioid analgesics on an off-label basis. In preparation for this upcoming meeting, this review provides context and background information on the U.S. outpatient retail utilization patterns for opioid analgesics, both extended-release/long-acting (ER/LA) and immediate-release (IR) opioid analgesics, in the pediatric population (0-16 years) from 2011 through 2015.

1.1 BACKGROUND

Opioid analgesics are an effective option to treat moderate to severe pain. In August 2015, extended-release oxycodone (OxyContin) was approved for use in opioid-tolerant pediatric patients aged 11 years to 16 years with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.[1] The addition of the labeling language for pediatric patients for OxyContin has resulted in widespread comments from the public, much of which reflected a misunderstanding of the purpose of studying opioid analgesics and the use of these products in children.

The upcoming joint advisory committee (AC) meeting will provide a forum for FDA and stakeholders to discuss the studies of opioid analgesics in children, to both educate the public, and to obtain advice from the committee on certain aspects of the types of pediatric studies. The studies are not intended to expand the use of opioids in children, but rather to provide data to inform on the safe use and dosing in children who are appropriate for these products and has already received treatment with opioid analgesics on an off-label basis.

2 METHODS AND MATERIALS

Proprietary databases available to the Agency were used to conduct the drug utilization analyses in this review (see Appendix B for full database descriptions).

2.1 PRODUCTS INCLUDED

The following extended-release/long-acting and immediate-release opioid analgesics are included in the analyses of the review. This review focused on opioid analgesic products largely dispensed in the outpatient retail setting. Injectable and suppository formulations of opioid analgesics were excluded as well as opioid-containing Medication-Assisted Therapy (MATs) products and opioid-containing cough/cold products due to the different indications and settings of care.

Extended-Release/Long-Acting Formulation (ER/LA)	Immediate-Release Formulation (IR)
• Buprenorphine Transdermal • Fentanyl Transdermal • Hydrocodone • Hydromorphone	• Butorphanol • Codeine • Codeine-Acetaminophen • Hydrocodone-Acetaminophen

• Methadone • Morphine • Morphine-Naltrexone • Oxycodone • Oxycodone-Acetaminophen • Oxymorphone • Tapentadol • Tramadol	• Hydrocodone-Ibuprofen • Hydromorphone • Levorphanol • Meperidine • Meperidine-Promethazine • Morphine • Opium • Oxycodone • Oxycodone-Acetaminophen • Oxycodone-Ibuprofen • Oxymorphone • Pentazocine-Acetaminophen • Pentazocine-Naloxone • Propoxyphene • Propoxyphene-Acetaminophen • Tapentadol • Tramadol • Tramadol-Acetaminophen • Transmucosal Immediate-Release Fentanyl (TIRF)

The following opioid analgesics were not included in the analyses of the review because they were either not approved or marketed in the U.S. during the study time period.

- As of June 11th, 2016, combination oxycodone-naloxone ER (Targiniq) has not been marketed in the U.S.[2]
- As of July 2nd, 2016, single-ingredient morphine ER (Morphabond) has not been marketed in the U.S.[3]
- Single-ingredient oxycodone ER (Xtampza ER) was approved on April 26th, 2016.[4]
- Single-ingredient buprenorphine film (Belbuca) was approved on October 23rd, 2015, but was not marketed in the U.S. until February 22nd, 2016.[5]

2.2 DETERMINING SETTINGS OF CARE

Based on the IMS Health, IMS National Sales Perspectives™ database, approximately 72%, 27%, and 1% of bottles/packages of opioid analgesics were distributed to outpatient retail pharmacies, non-retail settings, and mail-order/specialty settings, respectively, in 2015.[a] As a result, outpatient retail pharmacy utilization patterns of these opioid analgesics were examined. Data from the mail-order/specialty and non-retail pharmacy settings are not included in this review.

2.3 DATA SOURCES USED

[a] Source: IMS Health, IMS National Sales Perspectives™. Year 2015. Data extracted June 2016. File: NSP 2016-241 total opioids channel 6-29-2016.xlsx

2.3.1 Prescription Data

The IMS Health, National Prescriptions Audit™ database was used to provide national estimates of prescriptions dispensed to pediatric patients for opioid analgesics, stratified by patient age (0-1, 2-6, and 7-16 years), from U.S. outpatient retail pharmacies from 2011 through 2015. The top five prescriber specialties data were also obtained from this database for 2015; prescriptions written by veterinary medicine prescribers were excluded from the prescription analyses to exclude possible non-human use of opioid analgesics.

2.3.2 Patient Data

The Symphony Health Solutions' Integrated Dataverse® (IDV) database was used to provide national estimates of pediatric patients who received a prescription dispensed for opioid analgesics, stratified by patient age (0-1, 2-6, and 7-16 years), from U.S. outpatient retail pharmacies from 2011 through 2015. To exclude possible non-human use of opioid analgesics such as prescriptions written by veterinary medicine prescribers, we excluded patients who paid cash for dispensed prescriptions written by the following prescriber specialties: All Other, Not Known, Other Specialty, and Other; veterinary medicine prescribers are captured under these specialty categories in this database. Patients were included in the study if they received dispensed prescriptions written by these unspecified specialties and were covered by commercial insurance plans, Medicare Part D, and Medicaid.

2.3.3 Duration of Use

Symphony Health Solutions' Integrated Dataverse® (IDV) was also used to provide duration of use analyses of the most frequently dispensed IR and ER/LA analgesic opioids in a study sample of pediatric patients ages 0-16 years with dispensed prescription claims from U.S. outpatient pharmacy settings for 2015. Based on the pediatric utilization of the total opioid analgesic market, we selected the most frequently dispensed IR analgesic opioids (products included in the analysis were hydrocodone/acetaminophen, codeine/acetaminophen and oxycodone IR) and ER/LA analgesics opioids (products included in the analysis were oxycodone ER, morphine ER, fentanyl transdermal patches and methadone). For this analysis, patients with cash only or unspecified prescriber specialty prescriptions were excluded.

To determine the duration of use of the most frequently dispensed opioid analgesics, a crude analysis of treatment episodes was conducted. A treatment episode was defined as the period of time that a patient had uninterrupted therapy with a product of interest. The duration of a treatment episode is defined as the number of days between the start and end dates of the episode, which is determined by summing days' of supply of all prescriptions. The total treatment episode duration is the sum of the days for each episode for a product within the selected study period. Duration of therapy was determined based on a frequency distribution of the therapy durations for each patient for the specified product. Based on the minimum and the maximum therapy duration for each respective patient, patients were divided into 10 equal groups or deciles. To account for patient behavior and short gaps between subsequent prescriptions, we allowed a grace period of 50% of the days' supply of the last prescription.

2.3.4 Indications for Use

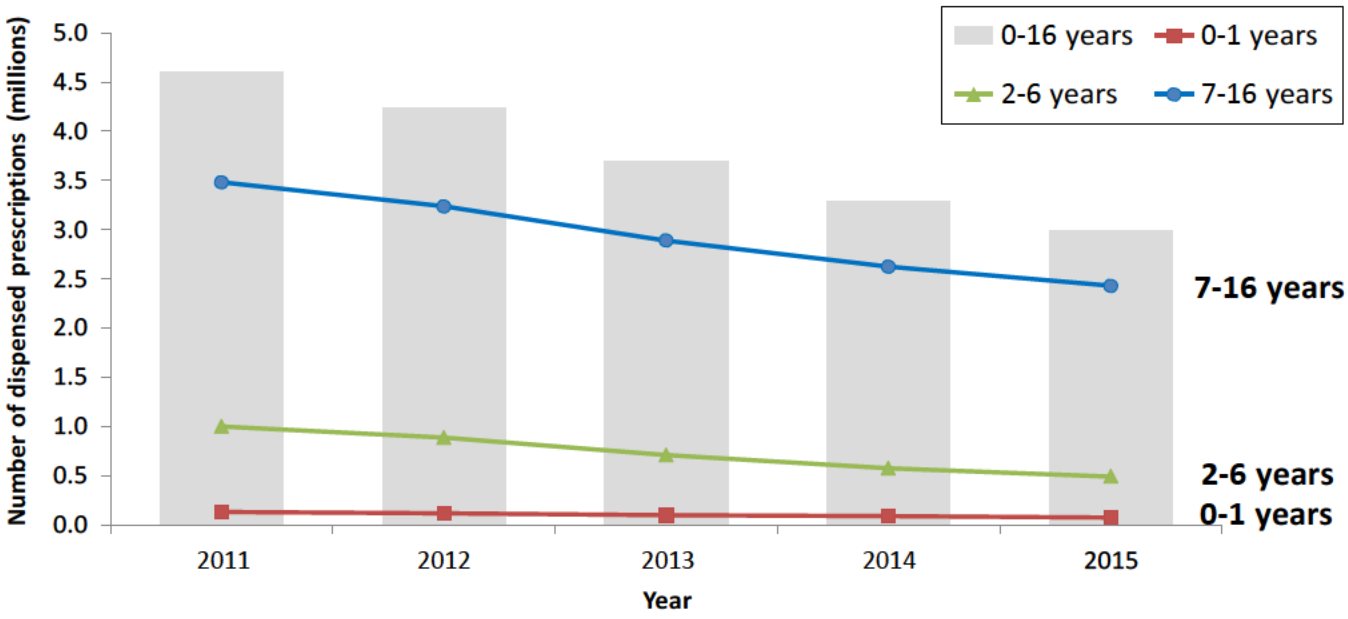
The Encuity Research, LLC., TreatmentAnswers™ with Pain Panel database was used to obtain the common diagnoses associated with the use of opioid analgesics in the pediatric population, stratified by patient age (0-1, 2-6, and 7-16 years), as reported by U.S. office-based physician surveys for 2015. Drug use mentions for diagnoses associated with the use of opioid analgesics were identified using ICD-10-CM codes.

3 RESULTS

3.1 PRESCRIPTION DATA

Figure 1 below and Tables 1 a-c in Appendix A provide national estimates of total prescriptions dispensed to the pediatric population (0-16 years) for opioid analgesics from U.S. outpatient retail pharmacies. In 2015, approximately 226 million total prescriptions were dispensed for opioid analgesics. Pediatric patients 16 years of age and younger accounted for 1% (3 million prescriptions) of total dispensed prescriptions in 2015. Of the prescriptions dispensed to pediatric patients, 81% of prescriptions (2.4 million prescriptions) were dispensed to patients ages 7-16 years, followed by patients ages 2-6 years at 16% of prescriptions (489,000 prescriptions), and patients ages 0-1 years at 2% of prescriptions (72,000 prescriptions). The total number of prescriptions dispensed to pediatric patients (0-16 years) for opioid analgesics decreased by 35% from 4.6 million prescriptions in 2011 to 3 million prescriptions in 2015.

Figure 1. National estimates of total *prescriptions* dispensed to pediatric patients (0-16 years) for opioid analgesics from U.S. outpatient retail pharmacies, years 2011-2015



*Source: IMS Health, National Prescription Audit™. Years 2011-2015. Data extracted June **2016.***

Data included opioid analgesics with oral, transdermal, and nasal **formulations.*

Throughout the examined time period, IR opioid analgesics accounted for 97% or more, and ER/LA opioid analgesics accounted for 3% or less of the total opioid analgesic prescriptions dispensed annually for each pediatric age group.

Among the IR opioid analgesic prescriptions dispensed to patients ages 0-1 years, approximately 47.5%, 32%, and 12% of prescriptions were dispensed for combination hydrocodone-acetaminophen IR, combination codeine-acetaminophen IR, and single-ingredient oxycodone IR, respectively. Among the ER/LA opioid analgesic prescriptions dispensed to patients ages 0-1 years, approximately 83%, 10%, 3%, and 2% of prescriptions were dispensed for methadone, fentanyl transdermal, morphine ER, and single-ingredient oxycodone ER, respectively.

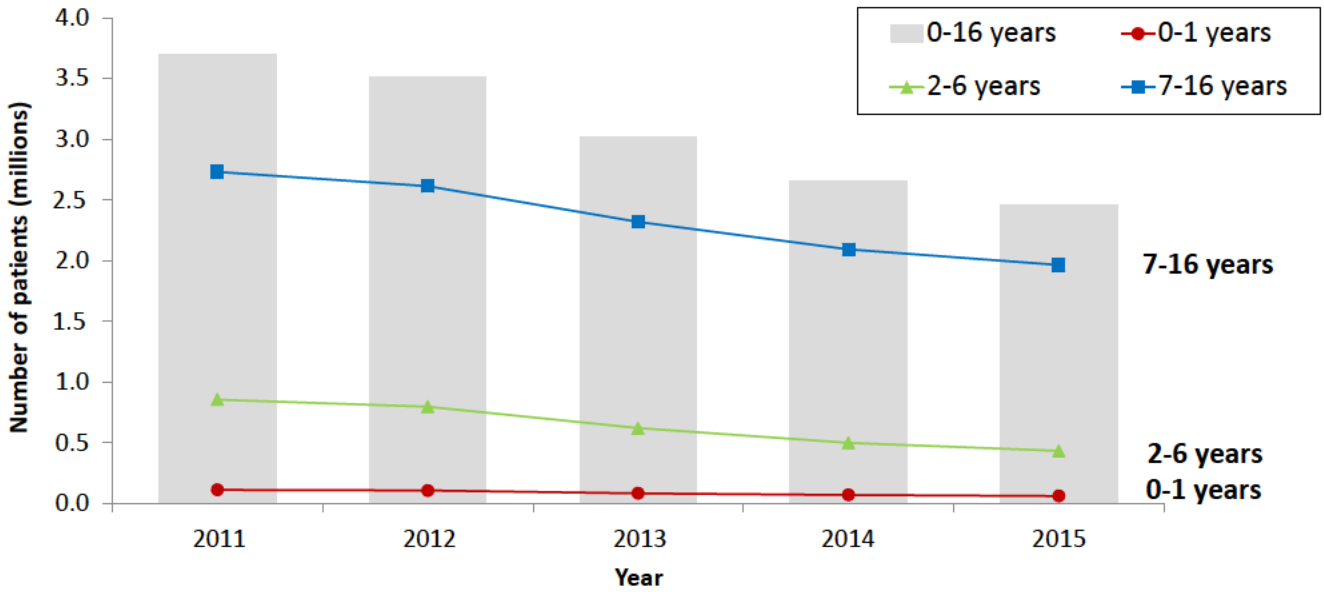
Among the IR opioid analgesic prescriptions dispensed to patients ages 2-6 years, approximately 45%, 41%, and 7% of prescriptions were dispensed for combination codeine-acetaminophen IR, combination hydrocodone-acetaminophen IR, and single-ingredient oxycodone IR, respectively. Among the ER/LA opioid analgesic prescriptions dispensed to patients ages 2-6 years, approximately 49%, 38%, 6%, and 5% of prescriptions were dispensed for methadone, fentanyl transdermal, morphine ER, and single-ingredient oxycodone ER, respectively.

Among the IR opioid analgesic prescriptions dispensed to patients ages 7-16 years, approximately 46%, 34%, and 7% of prescriptions were dispensed for combination hydrocodone-acetaminophen IR, combination codeine-acetaminophen IR, and combination oxycodone-acetaminophen IR, respectively. Among the ER/LA opioid analgesic prescriptions dispensed to patients ages 7-16 years, approximately 26.5%, 26%, 20%, and 19% of prescriptions were dispensed for morphine ER, single-ingredient oxycodone ER, methadone, and fentanyl transdermal, respectively.

3.2 Patient Data

Figure 2 below and Tables 2 a-c in Appendix A provide national estimates of total unique pediatric patients 16 years of age and younger who received prescriptions dispensed for opioid analgesics from U.S. outpatient retail pharmacies. In 2015, approximately 66.5 million total patients received prescriptions dispensed for opioid analgesics. Pediatric patients 16 years of age and younger accounted for 4% (2.5 million patients) of total patients in 2015. Of the total pediatric patients, 80% of patients (2 million patients) were ages 7-16 years, followed by patients ages 2-6 years at 18% (431,000 patients), and patients ages 0-1 years at 2.5% (61,000 patients). The total number of pediatric patients 16 years of age and younger who received prescriptions dispensed for opioid analgesics decreased by 34% from 3.7 million patients in 2011 to 2.5 million patients in 2015. Overall, trends in patient utilization across time were similar to dispensed prescription data.

Figure 2. National estimates of *pediatric patients* ages 0-16 years who received dispensed prescriptions for opioid analgesics* from U.S. outpatient retail pharmacies, years 2011-2015



Source: Symphony Health Solutions' Integrated Dataverse® (IDV). Years 2011-2015. Data extracted August 2016.

**Data included opioid analgesics with oral, transdermal, and nasal formulations.*

Throughout the examined time period, approximately 98.5% or more of patients in each pediatric age groups received IR opioid analgesic prescriptions, and 1.6% or less of patients in each pediatric age group received ER/LA opioid analgesic prescriptions.

Among patients ages 0-1 years who received IR opioid analgesic dispensed prescriptions, approximately 47%, 33%, and 11% of patients received a dispensed prescription for combination hydrocodone-acetaminophen IR, combination codeine-acetaminophen IR, or tramadol IR, respectively. Among patients ages 0-1 years who received ER/LA opioid analgesic dispensed prescriptions, approximately 64%, 29%, 2%, and 2% of patients received a dispensed prescription for methadone, fentanyl transdermal, morphine ER, or single-ingredient oxycodone ER, respectively.

Among patients ages 2-6 years who received IR opioid analgesic dispensed prescriptions, approximately 46%, 42%, and 5.5% of patients received a dispensed prescription for combination codeine-acetaminophen IR, combination hydrocodone-acetaminophen IR, or single-ingredient oxycodone IR, respectively. Among patients ages 2-6 years who received ER/LA opioid analgesic dispensed prescriptions, approximately 68%, 24%, 5%, and 2% of patients received a dispensed prescription for fentanyl transdermal, methadone, morphine ER, or single-ingredient oxycodone ER, respectively.

Among patients ages 7-16 years who received IR opioid analgesic dispensed prescriptions, approximately 48%, 37%, and 9% of patients received a dispensed prescription for combination hydrocodone-acetaminophen IR, combination codeine-acetaminophen IR, or tramadol IR, respectively. Among patients ages 7-16 years who received ER/LA opioid analgesic dispensed prescriptions, approximately 30%, 28%, 26%, and 10.5% of patients received a dispensed prescription for single-ingredient oxycodone ER, fentanyl transdermal, morphine ER, or methadone, respectively.

3.3 DURATION OF USE

Table 3 in Appendix A shows an analysis of the median and mean duration of therapy in days in pediatric patients 0-16 years of age for the most frequently dispensed IR (hydrocodone/acetaminophen, codeine/acetaminophen, oxycodone IR) and ER/LA analgesic opioids (oxycodone ER, morphine ER, fentanyl transdermal patches and methadone). All patients in a study sample with prescription claims for the selected opioids dispensed from of outpatient retail pharmacies for year 2015 were included in the analysis.

Amongst IR opioid anagesics, the median treatment episode duration was 6 days for hydrocodone/acetaminophen, 5 days for codeine/acetaminophen, and 6 days for oxycodone IR. The corresponding mean treatment episode duration was slightly higher at 7.3 days for hydrocodone/acetaminophen, 6.6 days for codeine/acetaminophen and 9.4 days for oxycodone IR.

Amongst ER opioid analgesics, the median treatment episode duration for ranged from 11 (oxycodone ER) to 31 days (fentanyl transdermal and methadone). The mean treatment episode duration ranged from 26 (oxycodone ER) to 77 days (methadone). Of note, in general the mean duration of therapy for the ER/LA products were higher than the medians. These data indicate that the majority of pediatric patients on ER/LA opioid analgesics had shorter durations of therapy (i.e., for less than 31 days), a small subset of patients had longer duration of therapy.

Table 4 in Appendix A show pediatric patient counts by minimum and maximum days of therapy for the IR and ER/LA opioid analgesics. In the study sample, over 90% of pediatric patients (950,290 total pediatric patients) with prescriptions dispensed for hydrocodone/acetaminophen had duration of therapy of less than 2 weeks. Over 90% of pediatric patients with prescriptions claim for codeine/acetaminophen

(679,447 total pediatric patients), and oxycodone IR (79,117 total pediatric patients) prescription claim had duration of therapy of less than 2 weeks.

In the study sample, for ER/LA opioid analgesics, approximately 80% of pediatric patients with prescription claim for oxycodone ER (1,412 total pediatric patients), morphine ER (1,325 total pediatric patients) had duration of therapy of less than 31 days. Approximately 50% of pediatric patients with prescription claim for fentanyl transdermal patches (529 total pediatric patients) and oral methadone (1,130 total pediatric patients) had duration of therapy of less than 31 days.

3.4 PRESCRIBER SPECIALTIES

Table 5 in Appendix A provides the national estimates of prescriptions dispensed for opioid analgesics, stratified by patient age and the top five prescriber specialties, from U.S. outpatient retail pharmacies during year 2015.

Among pediatric patients ages 0-1 years, pediatricians were the top prescriber specialty, accounting for 32% and 52% of prescriptions dispensed for IR and ER/LA opioid analgesics, respectively.

Among pediatric patients ages 2-6 years and 7-16 years, dentists were the top prescriber specialty for IR opioid analgesics at 19% of prescriptions dispensed to patients ages 2-6 years, and 29% of prescriptions dispensed to patients ages 7-16 years. Meanwhile, pediatricians were the top prescriber specialty for ER/LA opioid analgesics at 33% of prescriptions dispensed to patients ages 2-6 years, and 35% of prescriptions dispensed to patients ages 7-16 years.

3.5 INDICATIONS FOR USE

Table 6 in Appendix A provides the diagnoses (ICD-10) in terms of drug use mentions[b] associated with the use of opioid analgesics, stratified by patient age, as reported by U.S. office-based physician surveys in 2015.

Among the IR opioid analgesics, hernia (ICD-10 K40.9 and K43.9) was the top diagnosis (52.5% of drug use mentions) in pediatric patients ages 0-1 years. In the older pediatric population, injuries and burns (ICD-10 S00.x-T30.0) were the top diagnoses associated with the use of IR opioid analgesics at 39% of drug use mentions in pediatric patients ages 2-6 years, and 53% of drug use mentions in pediatric patients ages 7-16 years. Although the drug use mentions were low, IR opioid analgesics appear to be used for conditions associated with chronic pain in patients ages 2-6 years and 7-16 years, such as cancer, osteoarthritis, abdominal pain, and sickle-cell disease.

Of note, there were no diagnoses captured in the pediatric population in association with the use of ER/LA opioid analgesics most likely due to the low pediatric utilization of these products.

4 DISCUSSION

Analyses of utilization trends in the outpatient retail setting show that opioid analgesics are prescribed and dispensed to pediatric patients. In 2015, pediatric patients 16 years of age and younger accounted for 4% (2.5 million patients) of the total 66.5 million patients of any age who received dispensed prescriptions for

[b] Encuity Research, LLC uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

opioid analgesics; the majority of patients were ages 7-16 years. There was a 34% decrease in the number of pediatric patients from 2011 to 2015; although the reason for this decrease is unknown, a similar decline in use was seen among adult patients during the study period. Of note, the utilization of oxycodone ER in pediatric patients was low and decreased over the study time period. However, because pediatric labeling for OxyContin was approved in August 2015, our findings may not reflect the effect of this labeling on the pediatric utilization trends of oxycodone ER.

Among all the pediatric age groups, the vast majority of opioid analgesic utilization was for the IR products. Of these, combination hydrocodone-acetaminophen IR and codeine-acetaminophen IR were the most commonly dispensed IR products to pediatric patients. Although pediatric ER/LA opioid analgesic utilization was low, methadone, fentanyl transdermal, oxycodone ER, and morphine ER were the most commonly dispensed products.

Based on the duration of use analyses of these products, IR opioid analgesics appear to be utilized for shorter duration compared to ER/LA opioid analgesics in pediatric patients. This finding is consistent with dispensing of IR opioid analgesics for the management of acute or breakthrough pain associated with an acute injury or a dental procedure. Conversely, ER/LA opioid analgesics appear to be utilized for longer duration, consistent with utilization in patients with medical illnesses which cause chronic pain. The majority of pediatric patients on ER/LA opioid analgesics had durations of therapy for less than 31 days; a small subset of patients had longer duration of therapy.

According to survey data, office-based physicians reported utilization of IR opioid analgesics primarily in association with acute conditions such as treatment of hernia in infants and injuries and/or burns in children. No indication data was captured for ER/LA opioid analgesics in the physician survey database most likely due to the low pediatric utilization of these products. Diagnosis data are not directly linked to dispensed prescriptions; the diagnoses data were obtained from surveys of a sample of 3,200 office-based physicians with 115 pain specialists reporting on patient activity during one day per month. Because of the small sample sizes captured with correspondingly large confidence intervals, these data should be interpreted with caution and may not represent national trends.

Research has found that poorly treated or untreated childhood pain can cause negative long-term impacts on the psychological development in adulthood.[6] Appropriate pain management is important in improving the quality of life of children. Management of pain usually involves a multimodal approach; because of their analgesic and antipyretic properties, acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are combined with opioid analgesics to reduce opioid dose and side effects.[7] However, pain management in children may be inadequate due to the lack of knowledge on pain assessment and management, especially for chronic pain, in addition to the communication barriers unique to children.[6] Treatment guidelines such as the World Health Organization (WHO) guideline for the management of persisting pain in children states there is no other class of medicines than strong opioids that is effective in the management of moderate and severe pain. Strong opioids are an essential element in pain management.[8]

Immediate-Release opioid analgesics are commonly used for acute and breakthrough pain where immediate pain relief is needed for causes such as an injury, post-surgical procedures, and dental restorative treatment and extractions, consistent with the utilization data by prescriber specialty and the physician survey data. Extended-Release/Long-Acting (ER/LA) opioid analgesics are more appropriate for chronic persistent pain in children previously treated with IR opioids for medical illnesses such as cancer, which might cause long-term pain and require prolonged release of analgesics to relief pain for better compliance and dose scheduling. Pediatric utilization of methadone is often used to treat newborns

and infants born to mothers on opioids.[9] Our findings based on dispensed prescriptions claims data and physician survey data are consistent with utilization for these indications.

The prescriptions claims data should be interpreted with caution due to the following limitations: 1) some pediatric utilization findings may be a result of errors such as wrong date of birth on prescriptions; however, medical charts were not available for validation; 2) the prescription and patient estimates are nationally projected data based on a robust sample of the U.S. retail pharmacies, these data should be interpreted with caution for the low patient or prescription numbers which are based on very small sample sizes; and 3) because the prescription and patient estimates are obtained from two different databases, which capture different samples of prescription claims and have different projection methodologies, the patient and prescription data trends may be slightly different, especially for products with low utilization (See Appendix B for full database descriptions).

The duration-of-use analysis should be interpreted with the following limitations in mind: 1) because we used dispensing data obtained from outpatient pharmacies, our results are not generalizable to the inpatient setting; 2) our analysis may underestimate the duration of therapy of opioid analgesics in pediatric patients because it was restricted to 2015; 3) all analyses were conducted at the active moiety and formulation level (e.g. oxycodone ER), effects due to product-level variations is unknown; 4) our analysis assessed exposure to each selected opioid analgesic independently of other products; therefore, patients may be counted more than once for respective opioids; 5) the analyses did not assess patients who may have switched opioid analgesic or were on multiple opioid analgesics during the study period.

To date, the safety and efficacy of most opioid analgesics in patients aged 16 years and younger have not been established or labeled. Furthermore, there are few clinical guidelines for managing chronic pain in children. Additional research and clinical studies of opioid analgesics in children are necessary to inform health care providers of the safe use and proper dosing of opioid analgesics in the management of pain in children.

As a final note, a brief search of the literature identified one study evaluating opioid analgesics use in a non-random sample of 626 hospitals. This study found two million out of five million (40%) of pediatric hospitalizations from 2007 to 2012 were exposed to opioids. The most commonly used opioids in the inpatient setting were morphine, fentanyl, and hydromorphone. Similar to our results which examined outpatient pharmacy data, pediatric utilization of opioid analgesics increased with age. Of the patients treated with these products, the overall mean length of opioid analgesic therapy was 4.6 days (median 2.9 days). However, there was a wide variation across hospitals in the type of opioid used and the length of therapy used, even after adjusting for several patient and hospital characteristics.[10]

5 CONCLUSIONS

A nationally estimated number of 2.5 million pediatric patients ages 16 years and younger received dispensed prescriptions for opioid analgesics in the outpatient setting in 2015. Our findings show that pediatric utilization accounted for 4% of total patients treated with opioid analgesics. Although the appropriateness of prescribing cannot be determined from our analyses, these data are consistent with utilization following pain management principles. However, patient outcomes related to the pediatric utilization of opioid analgesics were not available and is an area in need of further research. Furthermore, the majority of opioid analgesics are not labeled for use in children 16 years of age and younger. These reasons highlight the need to study opioid analgesics in pediatric patients to inform health care providers of the safe use and the proper dosing of these drug products in the management of pain in pediatric patients.

6 REFERENCES

1. U.S. Food and Drug Administration: Drugs@FDA. *OxyContin Label Information*. Accessed April 2016. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
2. U.S. Food and Drug Administration. *Report of Postmarketing Experience: Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report (PBRER/PSUR) for Oxycodone/Naloxone (OXN) Preparations*. Silver Spring: Document Archiving, Reporting and Regulatory Tracking System (DARRTS) 2016. DARRTS Electronic Document Room (EDR). 25 July 2016.
3. U.S. Food and Drug Administration. *Morphabond Periodic Adverse Drug Experience Report 04-03-16 to 07-02-16 (Q3)*. Silver Spring: Document Archiving, Reporting and Regulatory Tracking System (DARRTS) 2016. DARRTS Electronic Document Room (EDR). 25 July 2016.
4. U.S. Food and Drug Administration: Drugs@FDA. *Xtampza ER Drug Details*. Accessed 25 July 2016. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails
5. Endo International PLC. *Endo Announces Launch of Belbuca™ (buprenorphine) Buccal Film for Chronic Pain Management*. PR Newswire 22 February 2016. Accessed 25 July 2016. http://www.prnewswire.com/news-releases/endo-announces-launch-of-belbuca-buprenorphine-buccal-film-for-chronic-pain-management-300223508.html
6. Mathews L. *Pain in Children: Neglected, unaddressed and mismanaged*. Indian J Palliat Care 2011;17, Suppl S1:70-3. Accessed 22 July 2016. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3140088/
7. Verghese ST, Hannallah RS. *Acute Pain Management in Children*. J Pain Res. 2010; 3: 105–123. Accessed 25 July 2016. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3004641/
8. WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses. Geneva, World Health Organization, 2012. Accessed 25 July 2016. http://apps.who.int/iris/bitstream/10665/44540/1/9789241548120_Guidelines.pdf
9. Johnston A, Metayer J, Robinson E. *Management of Neonatal Opioid Withdrawal*. Perinatal Quality Collaborative of North Carolina. Accessed 25 July 2016. http://www.pqcnc.org/documents/nas/nasresources/VCHIP_5NEONATAL_GUIDELINES.pdf
10. Womer J et al. *Variation of Opioid Use in Pediatric Inpatients Across Hospitals in the U.S.* J Pain symptom Mange 2014;48: 903-914.

7 APPENDIX A: TABLES

Table 1. National estimates of total *prescriptions* dispensed for opioid analgesics, stratified by patient age, from U.S. outpatient retail pharmacies, years 2011-2015

	Year 2011		Year 2012		Year 2013		Year 2014		Year 2015	
	TRxs	%	TRxs	%	TRxs	%	TRxs	%	TRxs	%
Total Prescriptions Dispensed for Opioid Analgesics	**256,320,289**	***100.0%***	**258,891,737**	***100.0%***	**250,198,107**	***100.0%***	**242,907,042**	***100.0%***	**226,176,312**	***100.0%***
0-16 years	4,607,090	*1 8%*	4,234,286	*1 6%*	3,689,373	*1 5%*	3,281,145	*1 4%*	2,988,067	*1 3%*
0-1 years	128,981	*2 8%*	114,251	*2 7%*	94,167	*2 6%*	85,388	*2 6%*	71,617	*2 4%*
2-6 years	998,273	*21 7%*	884,987	*20 9%*	706,780	*19 2%*	572,985	*17 5%*	489,190	*16 4%*
7-16 years	3,479,836	*75 5%*	3,235,048	*76 4%*	2,888,426	*78 3%*	2,622,772	*79 9%*	2,427,261	*81 2%*
17+ years	245,728,461	*95 9%*	249,811,875	*96 5%*	241,806,160	*96 6%*	235,157,857	*96 8%*	221,887,696	*98 1%*
Unknown Age	5,984,738	*2 3%*	4,845,576	*1 9%*	4,702,575	*1 9%*	4,468,039	*1 8%*	1,300,549	*0 6%*

Source: IMS Health, National Prescript on Aud t™. Years 2011-2015. Data extracted June 2016. File: NPA 2016-241 total opioids AC age specialty ad hoc 6-6-2016.xlsx

Table 1a. National estimates of *prescriptions* dispensed for opioid analgesics to the *pediatric patients ages 0-1 years*, stratified by active ingredient, from U.S. outpatient retail pharmacies, years 2011-2015

	Year 2011		Year 2012		Year 2013		Year 2014		Year 2015	
	TRxs	%	TRxs	%	TRxs	%	TRxs	%	TRxs	%
Total Prescriptions Dispensed to Pediatric Patients	**4,607,090**	***100.0%***	**4,234,286**	***100.0%***	**3,689,373**	***100.0%***	**3,281,145**	***100.0%***	**2,988,067**	***100.0%***
0-1 years	**128,981**	***2.8%***	**114,251**	***2.7%***	**94,167**	***2.6%***	**85,388**	***2.6%***	**71,617**	***2.4%***
Immediate-Release (IR) Opioids	**125,692**	***97.4%***	**111,498**	***97.6%***	**91,726**	***97.4%***	**83,036**	***97.2%***	**69,707**	***97.3%***
Hydrocodone/Acetaminophen	35,051	*27 9%*	37,454	*33 6%*	39,433	*43 0%*	38,182	*46 0%*	33,112	*47 5%*
Codeine/Acetaminophen	75,364	*60 0%*	58,523	*52 5%*	38,405	*41 9%*	29,873	*36 0%*	22,499	*32 3%*
Oxycodone	3,155	*2 5%*	3,598	*3 2%*	4,470	*4 9%*	6,663	*8 0%*	8,408	*12 1%*
Tramadol Morphine	6,215	*4 9%*	7,099	*6 4%*	4,969	*5 4%*	4,972	*6 0%*	4,038	*5 8%*
Oxycodone/Acetaminophen	1,203	*1 0%*	1,091	*1 0%*	946	*1 0%*	812	*1 0%*	783	*1 1%*
Meperidine	3,688	*2 9%*	3,154	*2 8%*	3,093	*3 4%*	2,208	*2 7%*	571	*0 8%*
Hydromorphone	233	*0 2%*	164	*0 1%*	125	*0 1%*	72	*0 1%*	98	*0 1%*
Tramadol/Acetaminophen	109	*0 1%*	108	*0 1%*	78	*0 1%*	74	*0 1%*	60	*0 1%*
Codeine	94	*0 1%*	60	*0 1%*	51	*0 1%*	36	*<0 1%*	40	*0 1%*
Hydrocodone/Ibuprofen	35	*<0 1%*	30	*<0 1%*	7	*<0 1%*	21	*<0 1%*	29	*<0 1%*
Opium	98	*0 1%*	49	*<0 1%*	34	*<0 1%*	41	*<0 1%*	23	*<0 1%*
Butorphanol	384	*0 3%*	148	*0 1%*	103	*0 1%*	66	*0 1%*	18	*<0 1%*
Tapentadol	7	*<0 1%*	1	*<0 1%*	5	*<0 1%*	1	*<0 1%*	18	*<0 1%*
Pentazocine/Naloxone	36	*<0 1%*	8	*<0 1%*	4	*<0 1%*	3	*<0 1%*	6	*<0 1%*
Transmucosal Immediate-Release Fentanyl (TIRF)	5	*<0 1%*	1	*<0 1%*	1	*<0 1%*	1	*<0 1%*	5	*<0 1%*
Oxymorphone	--	--	3	*<0 1%*	2	*<0 1%*	5	*<0 1%*	--	--
Oxycodone/Ibuprofen	14	*<0 1%*	6	*<0 1%*	--	--	4	*<0 1%*	--	--
Pentazocine/Acetaminophen	--	--	1	*<0 1%*	--	--	--	--	--	--
	--	--	1	*<0 1%*	--	--	--	--	--	--
Extended-Release/Long-Acting (ER/LA) Opioids	**3,289**	***2.6%***	**2,753**	***2.4%***	**2,441**	***2.6%***	**2,352**	***2.8%***	**1,909**	***2.7%***
Methadone	2,408	*73 2%*	1,979	*71 9%*	1,862	*76 3%*	1,999	*85 0%*	1,583	*82 9%*
Fentanyl Transdermal	561	*17 0%*	506	*18 4%*	365	*15 0%*	195	*8 3%*	199	*10 4%*
Morphine	115	*3 5%*	130	*4 7%*	141	*5 8%*	84	*3 6%*	63	*3 3%*
Oxycodone	129	*3 9%*	79	*2 9%*	45	*1 8%*	36	*1 5%*	33	*1 7%*
Oxymorphone	39	*1 2%*	36	*1 3%*	11	*0 5%*	17	*0 7%*	15	*0 8%*
Hydrocodone	--	--	--	--	--	--	2	*0 1%*	8	*0 4%*
Tramadol	29	*0 9%*	14	*0 5%*	6	*0 2%*	7	*0 3%*	6	*0 3%*
Tapentadol	--	--	2	*0 1%*	1	*<0 1%*	3	*0 1%*	2	*0 1%*
Buprenorphine Transdermal	7	*0 2%*	7	*0 3%*	3	*0 1%*	4	*0 2%*	1	*0 1%*
Hydromorphone	--	--	--	--	6	*0 2%*	3	*0 1%*	--	--
Morphine/Naltrexone	1	*<0 1%*	--	--	--	--	--	--	--	--
Oxycodone/Acetaminophen	--	--	--	--	--	--	2	*0 1%*	--	--

Source: IMS Health, National Prescript on Aud t™. Years 2011-2015. Data extracted June 2016. File: NPA 2016-241 total opioids AC age specialty ad hoc 6-6-2016.xlsx

Table 1b. National estimates of *prescriptions* dispensed for opioid analgesics to the *pediatric patients ages 2-6 years*, stratified by active ingredient, from U.S. outpatient retail pharmacies, years 2011-2015

	Year 2011		Year 2012		Year 2013		Year 2014		Year 2015	
	TRxs	%	TRxs	%	TRxs	%	TRxs	%	TRxs	%
Total Prescriptions Dispensed to Pediatric Patients	**4,607,090**	***100.0%***	**4,234,286**	***100.0%***	**3,689,373**	***100.0%***	**3,281,145**	***100.0%***	**2,988,067**	***100.0%***
2-6 years	**998,273**	***21.7%***	**884,987**	***20.9%***	**706,780**	***19.2%***	**572,985**	***17.5%***	**489,190**	***16.4%***
Immediate-Release (IR) Opioids	**996,391**	***99.8%***	**883,138**	***99.8%***	**705,279**	***99.8%***	**571,335**	***99.7%***	**487,710**	***99.7%***
Codeine/Acetaminophen	620,174	*62 2%*	508,482	*57 6%*	347,478	*49 3%*	262,303	*45 9%*	217,401	*44 6%*
Hydrocodone/Acetaminophen	321,864	*32 3%*	314,457	*35 6%*	293,229	*41 6%*	240,389	*42 1%*	200,890	*41 2%*
Oxycodone	9,052	*0 9%*	12,668	*1 4%*	18,813	*2 7%*	25,492	*4 5%*	35,649	*7 3%*
Meperidine	22,042	*2 2%*	20,670	*2 3%*	20,207	*2 9%*	18,483	*3 2%*	17,399	*3 6%*
Tramadol	9,445	*0 9%*	13,770	*1 6%*	13,080	*1 9%*	14,503	*2 5%*	12,608	*2 6%*
Morphine	1,601	*0 2%*	1,659	*0 2%*	2,100	*0 3%*	2,194	*0 4%*	2,212	*0 5%*
Oxycodone/Acetaminophen	11,342	*1 1%*	10,807	*1 2%*	9,838	*1 4%*	7,478	*1 3%*	1,031	*0 2%*
Hydromorphone	271	*<0 1%*	237	*<0 1%*	223	*<0 1%*	273	*<0 1%*	288	*0 1%*
Codeine Opium	219	*<0 1%*	189	*<0 1%*	107	*<0 1%*	94	*<0 1%*	131	*<0 1%*
Tramadol/Acetaminophen	166	*<0 1%*	36	*<0 1%*	46	*<0 1%*	23	*<0 1%*	45	*<0 1%*
Hydrocodone/Ibuprofen	63	*<0 1%*	50	*<0 1%*	53	*<0 1%*	29	*<0 1%*	24	*<0 1%*
Tapentadol	83	*<0 1%*	66	*<0 1%*	52	*<0 1%*	39	*<0 1%*	16	*<0 1%*
Butorphanol	35	*<0 1%*	26	*<0 1%*	16	*<0 1%*	5	*<0 1%*	7	*<0 1%*
Pentazocine/Naloxone	1	*<0 1%*	7	*<0 1%*	29	*<0 1%*	19	*<0 1%*	6	*<0 1%*
Transmucosal Immediate-Release Fentanyl (TIRF)	11	*<0 1%*	2	*<0 1%*	--	--	2	*<0 1%*	3	*<0 1%*
Oxymorphone	9	*<0 1%*	1	*<0 1%*	1	*<0 1%*	1	*<0 1%*	1	*<0 1%*
Pentazocine/Acetaminophen	10	*<0 1%*	5	*<0 1%*	5	*<0 1%*	6	*<0 1%*	--	--
Oxycodone/Ibuprofen	1	*<0 1%*	2	*<0 1%*	2	*<0 1%*	2	*<0 1%*	--	--
	2	*<0 1%*	5	*<0 1%*	--	--	--	--	--	--
Extended-Release/Long-Acting (ER/LA) Opioids	**1,882**	***0.2%***	**1,849**	***0.2%***	**1,500**	***0.2%***	**1,651**	***0.3%***	**1,480**	***0.3%***
Methadone	887	*47 1%*	900	*48 7%*	746	*49 7%*	859	*52 0%*	722	*48 8%*
Fentanyl Transdermal	698	*37 1%*	687	*37 2%*	492	*32 8%*	530	*32 1%*	559	*37 8%*
Morphine	105	*5 6%*	99	*5 4%*	117	*7 8%*	147	*8 9%*	84	*5 7%*
Oxycodone	102	*5 4%*	78	*4 2%*	66	*4 4%*	57	*3 4%*	72	*4 9%*
Tramadol	47	*2 5%*	30	*1 6%*	18	*1 2%*	16	*0 9%*	22	*1 5%*
Oxymorphone	31	*1 6%*	20	*1 1%*	14	*0 9%*	20	*1 2%*	8	*0 5%*
Tapentadol	1	*0 1%*	7	*0 4%*	5	*0 3%*	5	*0 3%*	5	*0 3%*
Buprenorphine Transdermal	10	*0 5%*	25	*1 4%*	29	*1 9%*	12	*0 7%*	3	*0 2%*
Hydromorphone	--	--	2	*0 1%*	14	*0 9%*	2	*0 1%*	2	*0 1%*
Hydrocodone	--	--	--	--	--	--	--	--	1	*0 1%*
Oxycodone/Acetaminophen	--	--	--	--	--	--	3	*0 2%*	1	*0 1%*

Source: IMS Health, National Prescript on Aud t™. Years 2011-2015. Data extracted June 2016. File: NPA 2016-241 total opioids AC age specialty ad hoc 6-6-2016.xlsx

Table 1c. National estimates of *prescriptions* dispensed for opioid analgesics to the *pediatric patients ages 7-16 years*, stratified by active ingredient, from U.S. outpatient retail pharmacies, years 2011-2015

	Year 2011		Year 2012		Year 2013		Year 2014		Year 2015	
	TRxs	%	TRxs	%	TRxs	%	TRxs	%	TRxs	%
Total Prescriptions Dispensed to Pediatric Patients	**4,607,090**	***100.0%***	**4,234,286**	***100.0%***	**3,689,373**	***100.0%***	**3,281,145**	***100.0%***	**2,988,067**	***100.0%***
7-16 years	**3,479,836**	***75.5%***	**3,235,048**	***76.4%***	**2,888,426**	***78.3%***	**2,622,772**	***79.9%***	**2,427,261**	***81.2%***
Immediate-Release (IR) Opioids	**3,464,055**	***99.5%***	**3,220,021**	***99.5%***	**2,874,402**	***99.5%***	**2,609,660**	***99.5%***	**2,415,455**	***99.5%***
Hydrocodone/Acetaminophen	1,650,215	*47 6%*	1,557,447	*48 4%*	1,453,002	*50 5%*	1,303,855	*50 0%*	1,106,876	*45 8%*
Codeine/Acetaminophen	1,335,877	*38 6%*	1,168,981	*36 3%*	941,612	*32 8%*	808,954	*31 0%*	813,172	*33 7%*
Oxycodone/Acetaminophen	218,615	*6 3%*	202,222	*6 3%*	187,347	*6 5%*	184,586	*7 1%*	179,176	*7 4%*
Tramadol	149,218	*4 3%*	179,182	*5 6%*	173,992	*6 1%*	181,620	*7 0%*	166,871	*6 9%*
Oxycodone Meperidine	46,063	*1 3%*	54,114	*1 7%*	66,605	*2 3%*	84,201	*3 2%*	108,000	*4 5%*
Hydrocodone/Ibuprofen	21,030	*0 6%*	19,315	*0 6%*	17,583	*0 6%*	15,580	*0 6%*	13,744	*0 6%*
Tramadol/Acetaminophen	19,076	*0 6%*	16,994	*0 5%*	14,782	*0 5%*	12,042	*0 5%*	8,206	*0 3%*
Hydromorphone	9,235	*0 3%*	8,074	*0 3%*	7,080	*0 2%*	6,844	*0 3%*	7,927	*0 3%*
Morphine	5,914	*0 2%*	5,854	*0 2%*	5,550	*0 2%*	5,587	*0 2%*	5,476	*0 2%*
Codeine	4,537	*0 1%*	4,391	*0 1%*	4,568	*0 2%*	4,658	*0 2%*	4,361	*0 2%*
Tapentadol	1,473	*<0 1%*	1,370	*<0 1%*	898	*<0 1%*	707	*<0 1%*	807	*<0 1%*
Butorphanol	1,195	*<0 1%*	874	*<0 1%*	503	*<0 1%*	382	*<0 1%*	328	*<0 1%*
Pentazocine/Naloxone	419	*<0 1%*	486	*<0 1%*	342	*<0 1%*	244	*<0 1%*	215	*<0 1%*
Transmucosal Immediate-Release Fentanyl (TIRF)	544	*<0 1%*	319	*<0 1%*	290	*<0 1%*	280	*<0 1%*	182	*<0 1%*
Opium	110	*<0 1%*	43	*<0 1%*	35	*<0 1%*	16	*<0 1%*	46	*<0 1%*
Oxymorphone	92	*<0 1%*	34	*<0 1%*	32	*<0 1%*	34	*<0 1%*	35	*<0 1%*
Oxycodone/Ibuprofen	96	*<0 1%*	81	*<0 1%*	34	*<0 1%*	17	*<0 1%*	19	*<0 1%*
Levorphanol	216	*<0 1%*	157	*<0 1%*	84	*<0 1%*	38	*<0 1%*	11	*<0 1%*
Pentazocine/Acetaminophen	2	*<0 1%*	1	*<0 1%*	--	--	2	*<0 1%*	2	*<0 1%*
Meperidine/Promethazine	113	*<0 1%*	81	*<0 1%*	63	*<0 1%*	12	*<0 1%*	--	--
Propoxyphene/Acetaminophen	9	*<0 1%*	1	*<0 1%*	--	--	1	*<0 1%*	--	--
	6	*<0 1%*	--	--	--	--	--	--	--	--
Extended-Release/Long-Acting (ER/LA) Opioids	**15,781**	***0.5%***	**15,028**	***0.5%***	**14,025**	***0.5%***	**13,112**	***0.5%***	**11,806**	***0.5%***
Morphine	3,499	*22 2%*	3,548	*23 6%*	3,264	*23 3%*	3,198	*24 4%*	3,133	*26 5%*
Oxycodone	4,723	*29 9%*	4,313	*28 7%*	4,042	*28 8%*	3,549	*27 1%*	3,025	*25 6%*
Methadone	2,889	*18 3%*	2,658	*17 7%*	2,749	*19 6%*	2,516	*19 2%*	2,410	*20 4%*
Fentanyl Transdermal	3,293	*20 9%*	3,161	*21 0%*	2,524	*18 0%*	2,476	*18 9%*	2,192	*18 6%*
Tramadol	886	*5 6%*	838	*5 6%*	858	*6 1%*	727	*5 5%*	570	*4 8%*
Buprenorphine Transdermal	142	*0 9%*	137	*0 9%*	212	*1 5%*	193	*1 5%*	218	*1 9%*
Oxymorphone	284	*1 8%*	212	*1 4%*	164	*1 2%*	133	*1 0%*	94	*0 8%*
Oxycodone/Acetaminophen	--	--	--	--	--	--	165	*1 3%*	66	*0 6%*
Tapentadol	8	*0 0%*	87	*0 6%*	125	*0 9%*	107	*0 8%*	41	*0 3%*
Hydromorphone	41	*0 3%*	73	*0 5%*	87	*0 6%*	44	*0 3%*	35	*0 3%*
Hydrocodone	--	--	--	--	--	--	5	*<0 1%*	18	*0 2%*
Morphine/Naltrexone	17	*0 1%*	--	--	--	--	--	--	2	*<0 1%*

Source: IMS Health, National Prescript on Aud t™. Years 2011-2015. Data extracted June 2016. File: NPA 2016-241 total opioids AC age specialty ad hoc 6-6-2016.xlsx

Table 2. National estimates of total *patients* who received prescriptions dispensed for opioid analgesics, stratified by patient age*, from U.S. outpatient retail pharmacies, years 2011-2015

	Year 2011		Year 2012		Year 2013		Year 2014		Year 2015	
	Patients (N)	%	Patients (N)	%	Patients (N)	%	Patients (N)	%	Patients (N)	%
Total Patients on Opioid Analgesics	**74,354,914**	***100.0%***	**74,170,663**	***100.0%***	**71,981,834**	***100.0%***	**69,313,582**	***100.0%***	**66,503,028**	***100.0%***
0-16 years	3,696,469	*5.0%*	3,512,496	*4.7%*	3,020,392	*4.2%*	2,660,016	*3.8%*	2,455,960	*3.7%*
0-1 years	111,168	*3.0%*	105,326	*3.0%*	82,839	*2.7%*	69,104	*2.6%*	61,010	*2.5%*
2-6 years	854,653	*23.1%*	795,726	*22.7%*	618,645	*20.5%*	498,145	*18.7%*	431,481	*17.6%*
7-16 years	2,730,648	*73.9%*	2,611,444	*74.3%*	2,318,908	*76.8%*	2,092,767	*78.7%*	1,963,469	*79.9%*
17+ years	70,656,695	*95.0%*	70,656,395	*95.3%*	68,959,785	*95.8%*	66,652,042	*96.2%*	64,045,743	*96.3%*
Unknown Age	1,750	*<0.1%*	1,772	*<0.1%*	1,657	*<0.1%*	1,524	*<0.1%*	1,325	*<0.1%*

Source: Symphony Health Solut ons' Integrated Dataverse® (IDV). Years 2011-2015. Data extracted August 2016. File: SHSIDV 2016-241 pediatric opio ds AC age ad hoc 8-17-2016.xlsx

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).

**Patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the indiv dual age categories or time per ods. For this reason, summing patients across patient age bands and time per ods is not advisable and will result in overestimates of patient counts.

Table 2a. National estimates of *pediatric patients* ages 0-1 years* who received prescriptions dispensed for opioid analgesics, stratified by active ingredient, from U.S. outpatient retail pharmacies, years 2011-2015

	Year 2011		Year 2012		Year 2013		Year 2014		Year 2015	
	Patients (N)	%	Patients (N)	%	Patients (N)	%	Patients (N)	%	Patients (N)	%
Total Pediatric Patients on Opioid Analgesics	**3,696,469**	***100.0%***	**3,512,496**	***100.0%***	**3,020,392**	***100.0%***	**2,660,016**	***100.0%***	**2,455,960**	***100.0%***
0-1 years	**111,168**	***3.0%***	**105,326**	***3.0%***	**82,839**	***2.7%***	**69,104**	***2.6%***	**61,010**	***2.5%***
Immediate-Release (IR) Opioids	**109,885**	***98.8%***	**104,075**	***98.8%***	**81,720**	***98.6%***	**68,105**	***98.6%***	**60,075**	***98.5%***
Hydrocodone/Acetaminophen	30,998	*28.2%*	35,592	*34.2%*	35,019	*42.9%*	30,817	*45.2%*	27,967	*46.6%*
Codeine/Acetaminophen	70,737	*64.4%*	58,983	*56.7%*	36,930	*45.2%*	26,104	*38.3%*	19,821	*33.0%*
Tramadol	4,175	*3.8%*	4,694	*4.5%*	4,729	*5.8%*	6,024	*8.8%*	6,606	*11.0%*
Oxycodone	1,503	*1.4%*	2,072	*2.0%*	2,431	*3.0%*	3,443	*5.1%*	5,087	*8.5%*
Oxycodone/Acetaminophen	3,188	*2.9%*	3,304	*3.2%*	2,914	*3.6%*	1,971	*2.9%*	542	*0.9%*
Morphine	422	*0.4%*	476	*0.5%*	409	*0.5%*	370	*0.5%*	380	*0.6%*
Meperidine	142	*0.1%*	95	*0.1%*	82	*0.1%*	49	*0.1%*	56	*0.1%*
Codeine	26	*<0.1%*	23	*<0.1%*	26	*<0.1%*	38	*0.1%*	43	*0.1%*
Hydromorphone	59	*0.1%*	68	*0.1%*	53	*0.1%*	40	*0.1%*	35	*0.1%*
Hydrocodone/Ibuprofen	80	*0.1%*	75	*0.1%*	41	*0.1%*	36	*0.1%*	29	*<0.1%*
Tramadol/Acetaminophen	59	*0.1%*	69	*0.1%*	62	*0.1%*	33	*<0.1%*	23	*<0.1%*
Opium	6	*<0.1%*	4	*<0.1%*	4	*<0.1%*	3	*<0.1%*	6	*<0.1%*
Butorphanol	--	--	--	--	3	*<0.1%*	--	--	3	*<0.1%*
Tapentadol	17	*<0.1%*	14	*<0.1%*	--	--	4	*<0.1%*	1	*<0.1%*
Oxymorphone	1	*<0.1%*	3	*<0.1%*	--	--	1	*<0.1%*	1	*<0.1%*
Pentazocine/Naloxone	3	*<0.1%*	3	*<0.1%*	1	*<0.1%*	--	--	--	--
Transmucosal Immediate-Release Fentanyl (TIRF)	1	*<0.1%*	3	*<0.1%*	--	--	--	--	--	--
Oxycodone/Ibuprofen	--	--	1	*<0.1%*	--	--	--	--	--	--
Pentazocine/Acetaminophen	--	--	1	*<0.1%*	--	--	--	--	--	--
Extended-Release/Long-Acting (ER/LA) Opioids	**1,377**	***1.2%***	**1,341**	***1.3%***	**1,185**	***1.4%***	**1,057**	***1.5%***	**1,001**	***1.6%***
Methadone	972	*70.6%*	905	*67.5%*	855	*72.2%*	735	*69.5%*	645	*64.4%*
Fentanyl Transdermal	312	*22.7%*	326	*24.3%*	257	*21.7%*	256	*24.2%*	294	*29.4%*
Morphine	43	*3.1%*	55	*4.1%*	32	*2.7%*	29	*2.7%*	23	*2.3%*
Oxycodone	26	*1.9%*	33	*2.5%*	25	*2.1%*	14	*1.3%*	19	*1.9%*
Tramadol	12	*0.9%*	7	*0.5%*	3	*0.3%*	10	*0.9%*	6	*0.6%*
Oxymorphone	7	*0.5%*	11	*0.8%*	9	*0.8%*	8	*0.8%*	6	*0.6%*
Hydrocodone	--	--	--	--	--	--	1	*0.1%*	4	*0.4%*
Tapentadol	--	--	3	*0.2%*	--	--	1	*0.1%*	3	*0.3%*
Buprenorphine Transdermal	6	*0.4%*	3	*0.2%*	5	*0.4%*	3	*0.3%*	1	*0.1%*
Oxycodone/Acetaminophen	--	--	--	--	--	--	1	*0.1%*	1	*0.1%*
Hydromorphone	--	--	--	--	1	*0.1%*	--	--	--	--

Source: Symphony Health Solutions' Integrated Dataverse® (IDV). Years 2011-2015. Data extracted August 2016. File: SHSIDV 2016-241 pediatric opioids AC age ad hoc 8-17-2016.xlsx

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).

**Patient age subtotals may not sum exactly due to patients aging during the study per od, and may be counted more than once in the indiv dual age categories or time per ods. For this reason, summing patients across patient age bands and time per ods is not advisable and will result in overestimates of patient counts.

Table 2b. National estimates of *pediatric patients* ages 2-6 years* who received prescriptions dispensed for opioid analgesics, stratified by active ingredient, from U.S. outpatient retail pharmacies, years 2011-2015

	Year 2011		Year 2012		Year 2013		Year 2014		Year 2015	
	Patients (N)	%	Patients (N)	%	Patients (N)	%	Patients (N)	%	Patients (N)	%
Total Pediatric Patients on Opioid Analgesics	**3,696,469**	***100.0%***	**3,512,496**	***100.0%***	**3,020,392**	***100.0%***	**2,660,016**	***100.0%***	**2,455,960**	***100.0%***
2-6 years	**854,653**	***23.1%***	**795,726**	***22.7%***	**618,645**	***20.5%***	**498,145**	***18.7%***	**431,481**	***17.6%***
Immediate-Release (IR) Opioids	**853,912**	***99.9%***	**794,953**	***99.9%***	**617,930**	***99.9%***	**497,368**	***99.8%***	**430,765**	***99.8%***
Codeine/Acetaminophen	565,216	*66.2%*	489,071	*61.5%*	330,074	*53.4%*	244,684	*49.2%*	197,495	*45.8%*
Hydrocodone/Acetaminophen	273,444	*32.0%*	282,090	*35.5%*	255,298	*41.3%*	207,152	*41.6%*	181,566	*42.1%*
Oxycodone	4,746	*0.6%*	7,368	*0.9%*	10,094	*1.6%*	14,598	*2.9%*	23,494	*5.5%*
Tramadol	6,755	*0.8%*	10,382	*1.3%*	12,555	*2.0%*	19,586	*3.9%*	20,991	*4.9%*
Meperidine	13,710	*1.6%*	13,735	*1.7%*	13,728	*2.2%*	13,069	*2.6%*	13,321	*3.1%*
Morphine	702	*0.1%*	874	*0.1%*	1,037	*0.2%*	1,104	*0.2%*	1,132	*0.3%*
Oxycodone/Acetaminophen	10,526	*1.2%*	10,942	*1.4%*	9,199	*1.5%*	6,949	*1.4%*	742	*0.2%*
Codeine Hydromorphone	162	*<0.1%*	153	*<0.1%*	120	*<0.1%*	159	*<0.1%*	205	*<0.1%*
Hydrocodone/Ibuprofen	156	*<0.1%*	152	*<0.1%*	150	*<0.1%*	129	*<0.1%*	153	*<0.1%*
Tramadol/Acetaminophen	93	*<0.1%*	74	*<0.1%*	48	*<0.1%*	45	*<0.1%*	19	*<0.1%*
Butorphanol	67	*<0.1%*	62	*<0.1%*	36	*<0.1%*	33	*<0.1%*	18	*<0.1%*
Oxymorphone	1	*<0.1%*	3	*<0.1%*	3	*<0.1%*	3	*<0.1%*	6	*<0.1%*
Opium Tapentadol	3	*<0.1%*	--	--	8	*<0.1%*	4	*<0.1%*	4	*<0.1%*
Propoxyphene	1	*<0.1%*	4	*<0.1%*	4	*<0.1%*	1	*<0.1%*	3	*<0.1%*
Pentazocine/Naloxone	19	*<0.1%*	13	*<0.1%*	11	*<0.1%*	6	*<0.1%*	1	*<0.1%*
Oxycodone/Ibuprofen	--	--	--	--	--	--	--	--	1	*<0.1%*
	3	*<0.1%*	1	*<0.1%*	3	*<0.1%*	--	--	--	--
	--	--	1	*<0.1%*	--	--	--	--	--	--
Extended-Release/Long-Acting (ER/LA) Opioids	**952**	***0.1%***	**1,007**	***0.1%***	**929**	***0.2%***	**934**	***0.2%***	**882**	***0.2%***
Fentanyl Transdermal	538	*56.5%*	574	*57.0%*	577	*62.1%*	620	*66.4%*	599	*67.9%*
Methadone	291	*30.6%*	304	*30.2%*	248	*26.7%*	208	*22.3%*	208	*23.6%*
Morphine	68	*7.1%*	82	*8.1%*	58	*6.2%*	62	*6.6%*	48	*5.4%*
Oxycodone	35	*3.7%*	24	*2.4%*	20	*2.2%*	24	*2.6%*	21	*2.4%*
Tramadol	14	*1.5%*	16	*1.6%*	11	*1.2%*	14	*1.5%*	15	*1.7%*
Oxymorphone	10	*1.1%*	7	*0.7%*	11	*1.2%*	6	*0.6%*	3	*0.3%*
Buprenorphine Transdermal	6	*0.6%*	4	*0.4%*	4	*0.4%*	5	*0.5%*	1	*0.1%*
Tapentadol	--	--	4	*0.4%*	12	*1.3%*	1	*0.1%*	1	*0.1%*
Hydrocodone	--	--	--	--	--	--	1	*0.1%*	--	--
Hydromorphone	--	--	1	*0.1%*	1	*0.1%*	--	--	--	--

Source: Symphony Health Solutions' Integrated Dataverse® (IDV). Years 2011-2015. Data extracted August 2016. File: SHSIDV 2016-241 pediatric opioids AC age ad hoc 8-17-2016.xlsx

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).

**Patient age subtotals may not sum exactly due to patients aging during the study per od, and may be counted more than once in the indiv dual age categories or time per ods. For this reason, summing patients across patient age bands and time per ods is not advisable and will result in overestimates of patient counts.

Table 2c. National estimates of *pediatric patients* ages 7-16 years* who received prescriptions dispensed for opioid analgesics, stratified by active ingredient, from U.S. outpatient retail pharmacies, years 2011-2015

	Year 2011		Year 2012		Year 2013		Year 2014		Year 2015	
	Patients (N)	%	Patients (N)	%	Patients (N)	%	Patients (N)	%	Patients (N)	%
Total Pediatric Patients on Opioid Analgesics	**3,696,469**	***100.0%***	**3,512,496**	***100.0%***	**3,020,392**	***100.0%***	**2,660,016**	***100.0%***	**2,455,960**	***100.0%***
7-16 years	**2,730,648**	***73.9%***	**2,611,444**	***74.3%***	**2,318,908**	***76.8%***	**2,092,767**	***78.7%***	**1,963,469**	***79.9%***
Immediate-Release (IR) Opioids	**2,728,552**	***99.9%***	**2,609,332**	***99.9%***	**2,317,015**	***99.9%***	**2,090,554**	***99.9%***	**1,961,468**	***99.9%***
Hydrocodone/Acetaminophen	1,327,421	*48.6%*	1,291,460	*49.5%*	1,194,727	*51.6%*	1,060,895	*50.7%*	934,918	*47.7%*
Codeine/Acetaminophen	1,212,133	*44.4%*	1,099,363	*42.1%*	883,374	*38.1%*	748,698	*35.8%*	721,016	*36.8%*
Tramadol	112,428	*4.1%*	135,812	*5.2%*	143,319	*6.2%*	169,893	*8.1%*	172,905	*8.8%*
Oxycodone/Acetaminophen	199,341	*7.3%*	189,674	*7.3%*	172,154	*7.4%*	161,550	*7.7%*	152,589	*7.8%*
Oxycodone	30,551	*1.1%*	37,243	*1.4%*	42,931	*1.9%*	53,430	*2.6%*	74,668	*3.8%*
Meperidine	16,691	*0.6%*	15,341	*0.6%*	13,807	*0.6%*	12,928	*0.6%*	12,241	*0.6%*
Hydrocodone/Ibuprofen	16,558	*0.6%*	15,245	*0.6%*	12,703	*0.5%*	10,145	*0.5%*	7,140	*0.4%*
Tramadol/Acetaminophen	8,929	*0.3%*	8,126	*0.3%*	7,090	*0.3%*	6,506	*0.3%*	6,888	*0.4%*
Hydromorphone	3,728	*0.1%*	3,808	*0.1%*	3,259	*0.1%*	3,139	*0.2%*	3,059	*0.2%*
Morphine	2,183	*0.1%*	2,222	*0.1%*	2,302	*0.1%*	2,379	*0.1%*	2,291	*0.1%*
Codeine	1,339	*<0.1%*	1,249	*<0.1%*	950	*<0.1%*	956	*<0.1%*	1,064	*0.1%*
Tapentadol	986	*<0.1%*	694	*<0.1%*	327	*<0.1%*	240	*<0.1%*	185	*<0.1%*
Pentazocine/Naloxone	391	*<0.1%*	290	*<0.1%*	236	*<0.1%*	223	*<0.1%*	159	*<0.1%*
Butorphanol	166	*<0.1%*	163	*<0.1%*	106	*<0.1%*	81	*<0.1%*	74	*<0.1%*
Oxycodone/Ibuprofen	227	*<0.1%*	180	*<0.1%*	86	*<0.1%*	37	*<0.1%*	14	*<0.1%*
Oxymorphone	30	*<0.1%*	25	*<0.1%*	9	*<0.1%*	8	*<0.1%*	8	*<0.1%*
Transmucosal Immediate-Release Fentanyl (TIRF)	41	*<0.1%*	18	*<0.1%*	9	*<0.1%*	6	*<0.1%*	6	*<0.1%*
Opium	3	*<0.1%*	1	*<0.1%*	7	*<0.1%*	6	*<0.1%*	4	*<0.1%*
Levorphanol	1	*<0.1%*	1	*<0.1%*	--	--	--	--	3	*<0.1%*
Pentazocine/Acetaminophen	87	*<0.1%*	61	*<0.1%*	48	*<0.1%*	5	*<0.1%*	--	--
Meperidine/Promethazine	4	*<0.1%*	--	--	--	--	--	--	--	--
Propoxyphene/Acetaminophen	1	*<0.1%*	--	--	--	--	--	--	--	--
Extended-Release/Long-Acting (ER/LA) Opioids	**7,613**	***0.3%***	**7,637**	***0.3%***	**6,763**	***0.3%***	**6,554**	***0.3%***	**5,863**	***0.3%***
Oxycodone	3,100	*40.7%*	2,863	*37.5%*	2,579	*38.1%*	2,096	*32.0%*	1,765	*30.1%*
Fentanyl Transdermal	1,648	*21.6%*	1,746	*22.9%*	1,503	*22.2%*	1,771	*27.0%*	1,628	*27.8%*
Morphine	1,782	*23.4%*	1,875	*24.6%*	1,610	*23.8%*	1,543	*23.5%*	1,537	*26.2%*
Methadone	830	*10.9%*	794	*10.4%*	708	*10.5%*	615	*9.4%*	613	*10.5%*
Tramadol	430	*5.6%*	487	*6.4%*	437	*6.5%*	426	*6.5%*	319	*5.4%*
Buprenorphine Transdermal	59	*0.8%*	55	*0.7%*	86	*1.3%*	92	*1.4%*	75	*1.3%*
Oxycodone/Acetaminophen	--	--	--	--	--	--	122	*1.9%*	56	*1.0%*
Oxymorphone	90	*1.2%*	67	*0.9%*	58	*0.9%*	65	*1.0%*	29	*0.5%*
Tapentadol	4	*0.1%*	51	*0.7%*	45	*0.7%*	27	*0.4%*	14	*0.2%*
Hydrocodone	--	--	--	--	--	--	3	*<0.1%*	13	*0.2%*
Hydormorphone	7	*0.1%*	16	*0.2%*	15	*0.2%*	14	*0.2%*	10	*0.2%*
Morphine/Naltrexone	6	*0.1%*	--	--	--	--	--	--	1	*<0.1%*

Source: Symphony Health Solut ons' Integrated Dataverse® (IDV). Years 2011-2015. Data extracted August 2016. File: SHSIDV 2016-241 pediatric opioids AC age ad hoc 8-17-2016.xlsx

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).

**Patient age subtotals may not sum exactly due to patients aging during the study per od, and may be counted more than once in the indiv dual age categories or time per ods. For this reason, summing patients across patient age bands and time per ods is not advisable and will result in overestimates of patient counts.

Table 3. Duration of therapy for selected immediate release (IR) and extended release (ER) opioids dispensed from US outpatient pharmacy settings to a sample* of pediatric patients ages 0-16 years, in 2015

Products	Number of Patients	Days of Therapy	
		Median	Mean
Hydrocodone/acetaminophen	950,290	6.0	7.3
Codeine/acetaminophen	679,447	5.0	6.6
Oxycodone IR	79,117	6.0	9.4
Oxycodone ER	1,412	11.0	26.1
Morphine ER	1,325	13.0	36.0
Methadone oral	1,130	31.0	77.0
Fentanyl transdermal patches	529	31.0	69.8

* excludes patients with cash or unspecified prescriber specialty prescriptions.

Source: Symphony Health Solutions Integrated Dataverse (IDV), 2015, Extracted July 2016.

Table 4. Estimated duration of therapy by deciles for a sample* of pediatric patients ages 0-16 years dispensed selected immediate release (IR) and extended release (ER) opioids, in the outpatient pharmacy setting, in 2015

		DECILES									
Products	**Number of patients**	1	2	3	4	5	6	7	8	9	10
Hydrocodone/acetaminophen	950,290	1 - 3	3 - 4	4 - 4	4 - 5	5 - 6	6 - 6	6 - 7	7 - 9	9 - 12	12 - 365
Codeine/acetaminophen	679,447	1 - 3	3 - 4	4 - 4	4 - 4	4 - 5	5 - 6	6 - 6	6 - 8	8 - 11	11 - 365
Oxycodone IR	79,117	1 - 3	3 - 4	4 - 4	4 - 6	6 - 6	6 - 7	7 - 9	9 - 11	11 - 16	16 - 365
Oxycodone ER	1,412	1 - 4	4 - 5	5 - 6	6 - 7	8 - 11	11 - 11	12 - 16	16 - 31	31 - 49	49 - 365
Morphine ER	1,325	1 - 5	5 - 6	6 - 8	8 - 11	11 - 13	13 - 16	16 - 31	31 - 32	32 - 84	85 - 365
Methadone oral	1,130	1 - 6	6 - 10	11 - 16	16 - 28	29 - 31	31 - 46	46 - 67	68 - 120	121 - 259	263 - 365
Fentanyl transdermal patches	529	1 - 6	6 - 13	13 -16	16 - 30	30 - 31	31 - 32	32 - 58	58 - 93	93 - 238	238 - 365

* excludes patients with cash or unspecified prescriber specialty prescriptions

Source: Symphony Health Solution Integrated Dataverse (IDV), 2011 - 2015, Extracted July 2016

Table 5. National estimates of total *prescriptions* dispensed for opioid analgesics, stratified by patient age and the top five prescriber specialties, from U.S. outpatient retail pharmacies, year 2015

	Year 2015	
	TRxs	%
Total Prescriptions Dispensed for Opioid Analgesics	**226,176,312**	***100.0%***
0-1 years	**71,617**	***<0.1%***
Immediate-Release (IR) Opioids	**69,707**	***97.3%***
Pediatrician	22,434	*32.2%*
Hospitalist	7,885	*11.3%*
Urology	7,198	*10.3%*
Emergency Medicine	4,155	*6.0%*
Nurse Practitioner	3,855	*5.5%*
All Others	24,181	*34.7%*
Extended-Release/Long-Acting (ER/LA) Opioids	**1,909**	***2.7%***
Pediatrician	989	*51.8%*
Unspecified	200	*10.5%*
Neonatal-Perinatal Medicine	168	*8.8%*
Hospitalist	164	*8.6%*
Primary Care Practitioners	125	*6.5%*
All Others	263	*13.8%*
2-6 years	**489,190**	***0.2%***
Immediate-Release (IR) Opioids	**487,710**	***99.7%***
Dentist	94,666	*19.4%*
Otolaryngology	90,256	*18.5%*
Pediatrician	87,345	*17.9%*
Emergency Medicine	42,422	*8.7%*
Physician Assistant	25,613	*5.3%*
All Others	147,408	*30.2%*
Extended-Release/Long-Acting (ER/LA) Opioids	**1,480**	***0.3%***
Pediatrician	484	*32.7%*
Primary Care Practitioners	264	*17.8%*
Unspecified	211	*14.3%*
Nurse Practitioner	161	*10.9%*
Internal Medicine	102	*6.9%*
All Others	258	*17.4%*
7-16 years	**2,427,261**	***1.1%***
Immediate-Release (IR) Opioids	**2,415,455**	***99.5%***
Dentist	709,806	*29.4%*
Emergency Medicine	253,681	*10.5%*
Pediatrician	244,256	*10.1%*
Orthopedic Surgery	188,833	*7.8%*
Physician Assistant	178,385	*7.4%*
All Others	840,494	*34.8%*
Extended-Release/Long-Acting (ER/LA) Opioids	**11,806**	***0.5%***
Pediatrician	4,102	*34.7%*
Orthopedic Surgery	1,402	*11.9%*
Nurse Practitioner	1,290	*10.9%*
Hospitalist	923	*7.8%*
Physician Assistant	766	*6.5%*
All Others	3,323	*28.1%*
17+ years	**221,887,696**	***98.1%***
Unknown Age	**1,300,549**	***0.6%***

Source: IMS Health, National Prescription Audit™. Year 2015. Data extracted June 2016. File: NPA 2016-241 total opioids AC age specialty 6-6-2016.xlsx

Table 6. Diagnoses associated with the use of opioid analgesics as reported by U.S. office-based physician surveys, stratified by patient age, year 2015

	Year 2015	
	Uses	%
Total Use Mentions of Opioid Analgesics	**78,337,000**	***100.0%***
0-16 years	2,550,000	*3 3%*
0-1 years	99,000	*3 9%*
Immediate-Release (IR) Opioids	99,000	*100 0%*
Hernia (K40.9 and K43.9)	52,000	*52 5%*
Hypospadias, unspecified (Q54.9)	30,000	*30 3%*
Burn of unspecified degree of wrist and hand (T23.0)	9,000	*9 2%*
Neonatal withdrawal symptoms from maternal use of drugs of addiction (P96.1)	8,000	*7 6%*
Extended-release/Long-Acting (ER/LA) Opioids	--	--
2-6 years	495,000	*19 4%*
Immediate-Release (IR) Opioids	495,000	*100 0%*
Injuries and burns (S42.x-T30.0)	191,000	*38 6%*
Hernia (K40.9, K42.0, and K42.9)	93,000	*18 8%*
Encounter for follow-up examination after completed treatment for conditions other than malignant neoplasm (Z09)	92,000	*18 6%*
Osteoarthritis, join disorders, and dorsopathies (M19.9, M25.5, and M54.9)	44,000	*8 9%*
Unspecified abdominal pain (R10.9)	19,000	*3 8%*
Acute embolism and thrombosis of deep veins of lower extremity (I82.4)	17,000	*3 4%*
Ptosis of eyelid (H02.4)	14,000	*2 8%*
Presence of otological and audiological implants (Z96.2)	13,000	*2 6%*
Chronic tonsillitis and adenoiditis (J35.0)	11,000	*2 2%*
Chronic pain, not elsewhere classified (G89.2)	2,000	*0 4%*
Extended-release/Long-Acting (ER/LA) Opioids	--	--
7-16 years	1,956,000	*76 7%*
Immediate-Release (IR) Opioids	1,956,000	*100 0%*
Injuries and burns (S00.x-T25.0)	1,032,000	*52 8%*
Encounter for follow-up examination after completed treatment for conditions other than malignant neoplasm (Z09)	404,000	*20 7%*
Diseases of the musculoskeletal system and connective tissue (M19.9-M79.6)	104,000	*5 3%*
Diseases of the skin and subcutaneous tissue (L03.0, L60.0, and L72.3)	83,000	*4 2%*
Congenital malformations and deformations of the musculoskeletal system (Q65.8, Q67.6,	66,000	*3 4%*
Diseases of the genitourinary system (N47, N62, and N63)	63,000	*3 2%*
Neoplasms (C72.3 and D23.9)	50,000	*2 6%*
Sickle-cell disease without crisis (D57.1)	46,000	*2 4%*
Diseases of the ear and mastoid process (H66.9 and H92.0)	32,000	*1 6%*
Thyrotoxicosis with diffuse goiter (E05.0)	28,000	*1 4%*
Unilateral inguinal hernia, without obstruction or gangrene (K40.9)	24,000	*1 2%*
All other diagnoses	24,000	*1 2%*
Extended-release/Long-Acting (ER/LA) Opioids	--	--
17+ years	74,091,000	*94 6%*
Unknown Age	1,696,000	*2 2%*

Source: Encuity Research, LLC., TreatmentAnswers™. Year 2015. Data extracted June 2016. File: PDDA_2016-241_total_opioids_age_ICD10_dx4_6-29-2016.xls

8 APPENDIX B: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS Health, National Prescription Audit

The National Prescription Audit (NPA™) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

NPA receives over 3.5 billion prescription claims per year, captured from a sample of the universe of approximately 59,400 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 88% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 45 - 75% (varies by class and geography) of mail service pharmacies and approximately 70-85% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

Symphony Health Solutions' Integrated Dataverse® (IDV)

Symphony Health Solutions' Integrated Dataverse® (IDV) contains longitudinal patient data sources that capture adjudicated prescription, medical, and hospital claims across the United States for all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The IDV contains over 10 billion prescriptions claims linked to over 220 million unique prescription patients of with an average of 4.2 years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 140 million prescription drug patients are linked to a diagnosis. The overall sample represents over 54,000 pharmacies, 1,500 hospitals, 800 outpatient facilities, and 80,000 physician practices.

Encuity Research, LLC., TreatmentAnswers™ with Pain Panel

Encuity Research, LLC., TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products

mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.