

FDA Briefing Document
**Joint Meeting of the Drug Safety and Risk Management
(DSaRM) Advisory Committee and Anesthetic and Analgesic
Drug Products Advisory Committee (AADPAC)**

September 10-11, 2020

Oxycontin Abuse Deterrent Formulation (ADF)

Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought our reviews of the results of required postmarketing studies (Postmarketing Requirements 3051-1, 3051-2, 3051-3, and 3051-4) that evaluated the effect of the reformulation of OXYCONTIN (oxycodone hydrochloride extended-release tablets, manufactured by Purdue Pharma L.P., NDA 022272) on abuse, misuse, and fatal and non-fatal overdose associated with OXYCONTIN, and our reviews of other information from the published literature related to whether this product has resulted in a meaningful reduction in these outcomes, and related to the broader public health impact of OXYCONTIN's reformulation to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

1 INTRODUCTION AND BACKGROUND

1.1 PURPOSE OF THIS ADVISORY COMMITTEE MEETING

We are convening a joint meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) Advisory Committees to discuss and solicit committee members' opinions on the results of the OxyContin abuse-deterrent formulation (ADF) postmarketing requirement (PMR) study findings, as well as related findings from the published literature, that evaluate whether the postmarketing data indicate that OxyContin's reformulation did deter its abuse by snorting and injecting, as expected based on experimental data. While FDA recognizes that an ADF of a single product cannot solve the opioid crisis, we are asking the committees to discuss and provide their viewpoints on broader public health impacts, both positive and negative, of OxyContin's reformulation within the complex and evolving landscape of opioid use, abuse, addiction, and overdose.

**A note on terminology and stigma: In this briefing document, FDA frequently uses the term abuse when discussing data related to reformulated OxyContin. With regard to ADFs, FDA considers abuse to refer to the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect.¹ We recognize that some language can perpetuate stigma and negative bias toward individuals with substance use disorders and create barriers to effective treatment. For example, the term abuse has been identified as having a high association with negative judgments and punishment.² The term abuse is used here to describe a specific behavior that confers a risk of adverse health outcomes; it is not intended to imply moral judgment. FDA is committed to reducing stigma, expanding therapeutic options, and ensuring access to evidence-based treatment for individuals with substance use disorders.*

1.2 BRIEF HISTORY OF ABUSE-DETERRENT FORMULATION (ADF) OPIOID ANALGESIC DEVELOPMENT AND MARKETING IN THE U.S.

Some general history of ADF development provides context for considering the reformulation of OxyContin (oxycodone hydrochloride extended-release tablets, Purdue Pharma L.P.) and the impact this formulation had on abuse and related outcomes. For roughly a decade, FDA has encouraged the development of ADF opioid analgesics. While recognizing that ADF technology cannot make an opioid analgesic abuse-proof or non-addictive, FDA has supported ADF

¹ Abuse-deterrent Opioids—Evaluation and Labeling: Guidance for Industry. April 2015.

² National Institute on Drug Abuse: Words Matter - Terms to Use and Avoid When Talking About Addiction. <https://www.drugabuse.gov/nidamed-medical-health-professionals/health-professions-education/words-matter-terms-to-use-avoid-when-talking-about-addiction>

development as one of many strategies intended to mitigate the harms associated with prescription opioid abuse while maintaining access to opioid analgesics for patients who need them. ADF development has primarily focused on deterring abuse by snorting and injection of extended-release (ER) opioid analgesic products. Non-oral routes of abuse, particularly injection, are associated with risks such as soft-tissue infections, endocarditis, and transmission of HIV and hepatitis C; additionally, ER products typically contain larger amounts of opioid than immediate-release (IR) products and therefore pose increased risks to those abusing these drugs if the medications are manipulated (e.g., crushed or dissolved) to cause the active ingredient to “dose dump,” i.e., to be released all at once. To date, however, extended-release/long-acting (ER/LA) opioid analgesics represent less than 10 percent of the outpatient opioid analgesic prescriptions dispensed in the United States;³ the remainder consists of IR opioid analgesics, predominantly IR opioid-acetaminophen combination products. ADFs comprise approximately 25% of ER/LA opioid analgesic prescriptions dispensed. Recognizing that most opioid analgesic misuse and abuse occurs through the oral route, FDA has encouraged development of products with properties that could meaningfully deter all relevant forms of abuse, including the common method of abuse, swallowing intact tablets or capsules.

In April 2015, FDA issued final guidance, *Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry*,⁴ outlining the agency’s current thinking on the studies that should be conducted to demonstrate that a given opioid formulation has abuse-deterrent properties. The guidance outlines several principles for evaluating the abuse-deterrent characteristics of an opioid formulation. First, studies should be scientifically rigorous, incorporating use of appropriate comparators and endpoints, and should take into consideration the known routes of abuse and whether the deterrent effects can be expected to have a meaningful impact on specific routes as well as the overall abuse of the product. The guidance describes four categories of studies to evaluate the abuse-deterrent characteristics of an opioid formulation:

Category 1: Laboratory-based in vitro manipulation and extraction studies

Category 2: Pharmacokinetic studies

Category 3: Clinical abuse potential studies (i.e., “drug liking” studies)

Category 4: Postmarket studies (i.e., epidemiologic studies)

The guidance states that the goal of postmarketing (Category 4) studies is to determine whether the marketing of a product with abuse-deterrent properties results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting. It also notes that because the science of abuse deterrence is relatively new and methods for evaluating those technologies are evolving, FDA intends to take a flexible, adaptive

³ Source: IQVIA, National Prescription Audit (NPA) and static data 2006-2011. January 2006-December 2019. Static data extracted March 2017, 2012-2017 data extracted February 2018, 2018 data extracted March 2019, 2019 data extracted Jan 24, 2020

⁴ <https://www.fda.gov/media/84819/download>

approach to evaluation and labeling of potentially abuse-deterrent products. The agency also stated that because of the evolving nature of this field, no absolute magnitude of effect could be set for establishing abuse-deterrence, and that it intended to consider the totality of evidence when reviewing the results of studies evaluating abuse-deterrence.

As of 2019, ADF opioid analgesics represented approximately two percent of the opioid analgesic market,³ and multiple ADF opioid analgesic products approved by FDA have been voluntarily withdrawn by their application holders or are not currently being marketed. In November 2017, FDA issued final guidance on evaluation of generic ADF opioid analgesics, *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products: Guidance for Industry*.⁵ To date, no generic versions of ADF opioid analgesics have been approved.

1.3 REGULATORY HISTORY OF REFORMULATED OXYCONTIN

FDA approved the original formulation of OxyContin in December 1995. In the first decade following approval, the product became widely abused, often following manipulation to defeat its extended-release properties and to administer it via unintended routes. In April 2010, the FDA approved a reformulated version of OxyContin, which contained a matrix of high molecular weight (HMW) polyethylene oxide (PEO) to make the tablet more difficult to manipulate (i.e., crush, dissolve in solution) for purposes of abuse, particularly via snorting and injection. In August 2010, Purdue stopped shipping original OxyContin to pharmacies and began shipment of the reformulated product. At the time of approval of reformulated OxyContin, FDA required that the application holder conduct postmarketing studies to determine whether the reformulation actually resulted in a decrease in the risks of misuse and abuse, and their consequences, addiction, overdose, and death. Following an October 2010 Advisory Committee meeting discussing Purdue’s proposed postmarketing studies, the agency provided Purdue with additional questions and design considerations relating to these studies, acknowledging that this was a new area of scientific inquiry without established methods or data sources.

At the time of reformulated OxyContin’s approval in April 2010, FDA required a risk evaluation and mitigation strategy (REMS) for this product. ([See Division of Risk Management memo](#)) The REMS consisted of elements to assure safe use (ETASU), which included healthcare provider training and Dear Healthcare Professional letters. In addition, the REMS included a Medication Guide, since it was determined that OxyContin had serious risks that may affect a patient’s decision to use, or continue to use, OxyContin. In July 2012, OxyContin became a member of the shared system Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics (ER/LA) REMS. Under the ER/LA REMS, application holders were required to make continuing education (CE) programs available to prescribers. The CE courses were required to include the content and messages of a “blueprint” developed by FDA for this purpose. The ER/LA REMS was expanded

⁵ <https://www.fda.gov/media/96643/download>

and modified in September 2018 to include all application holders of immediate-release (IR) opioid analgesics that are expected to be used in the outpatient setting and that are not already covered by another REMS program. The Opioid Analgesic REMS requires that training be made available to healthcare providers, including prescribers, nurses, and pharmacists, involved in the treatment and monitoring of patients with pain. The currently approved FDA Blueprint focuses on the fundamentals of acute and chronic pain management and provides a contextual framework for the safe prescribing of opioid analgesics. The Opioid Analgesic REMS also includes a Patient Counseling Guide for healthcare providers to assist in properly counseling patients on their responsibilities for using these medicines safely and to provide patients with additional written safety information.

In April 2013, FDA approved a supplemental application for reformulated OxyContin, approving changes to Section 9.2 of the product labeling that describe certain abuse-deterrent properties of the reformulated product. [See April 2013 Federal Register Notice] The new labeling language described the findings of the *in vitro* manipulation studies, pharmacokinetic studies, and clinical abuse potential studies (i.e., Category 1-3 studies) submitted by the application holder, and included the following summary statement about reformulated OxyContin's abuse-deterrent properties based on these findings [See OxyContin Prescribing Information]:

The in vitro data demonstrate that OXYCONTIN has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the in vitro data, also indicate that OXYCONTIN has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OXYCONTIN by these routes, as well as by the oral route, is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of OXYCONTIN on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

Also in April 2013, the FDA determined that the benefits of original OxyContin no longer outweighed its risks and that original OxyContin had been withdrawn from sale for reasons of safety or effectiveness. This determination was made because original OxyContin provided the same therapeutic benefits as reformulated OxyContin but posed an increased potential for abuse by certain routes of administration, when compared to reformulated OxyContin. In addition, FDA determined that the reformulated product may be safer than the original by deterring certain types of misuse in a therapeutic context, for example misusing the product by crushing it and then sprinkling it onto food or to administer it through a gastric tube. Accordingly, the agency did not accept or approve any abbreviated new drug applications (generics) that relied upon the approval of original OxyContin. The agency reached this decision following careful review and analysis of data from *in vitro* manipulation studies, pharmacokinetic studies, and clinical abuse potential

(“drug liking”) studies, as well as early findings of postmarketing studies that suggested, but did not confirm, a reduction in non-oral abuse of reformulated OxyContin in the community, compared to the original formulation. In reaching its decision, FDA also considered several relevant citizen petitions and comments submitted to the public dockets associated with these petitions. [See April 2013 Federal Register Notice]

In October 2014, Purdue submitted a labeling supplement requesting placement of a claim in the labeling describing a real-world effect of the abuse-deterrent formulation (ADF) of OxyContin. An Advisory Committee meeting was scheduled to be held on July 7 and 8, 2015, to discuss the results of postmarketing studies submitted to support this claim. CDER prepared briefing materials for Committee members that included CDER’s review of the study findings (in accordance with its usual practice). On June 22, 2015, the materials were also provided to Purdue, consistent with the process described in the Agency’s *Guidance for Industry: Advisory Committee Meetings – Preparation and Public Availability of Information Given to Advisory Committee Members*. Purdue submitted a request to withdraw the supplement. The Advisory Committee meeting was subsequently cancelled; consequently, there was no public discussion of the results of the supplement or supporting studies that were submitted. [See Regulatory History Memorandum]

In March 2016, FDA issued a new postmarketing requirement (PMR) letter, formalizing the required studies and milestone dates. CDER’s review of the studies included in Purdue’s October 2014 submission helped refine the agency’s thinking about which studies and analyses would best inform our ability to assess whether the reformulated OxyContin actually deterred abuse and its adverse consequences. In addition to three studies assessing the impact of the ADF on OxyContin abuse rates (PMRs 3051-1, 3051-2, and 3051-3), the agency required a claims-based study linked to mortality data to assess the impact of the reformulation on fatal and non-fatal opioid overdose (3051-4). However, the FDA review team determined that given the limitations of the available data (particularly, poor performance of code-based algorithms to measure abuse and addiction in electronic healthcare data), retrospective data would not be capable of rigorously evaluating whether the OxyContin’s reformulation resulted in a decreased risk of addiction. The PMRs required that the application holder submit protocols and statistical analysis plans for FDA review and approval. [See Regulatory History Memorandum]

In September 2019, the application holder submitted the last of the final study reports for the four PMR studies evaluating the effectiveness of the ADF in reducing OxyContin abuse and related outcomes, including fatal and non-fatal overdose, in the post-approval setting.

1.4 PUBLIC HEALTH GOALS AND CONSIDERATION OF A BENEFIT-RISK FRAMEWORK FOR OPIOID ANALGESICS WITHIN A COMPLEX SYSTEM

Since the approval of reformulated OxyContin in 2010, the environment in which prescription opioid analgesics are prescribed, used, and abused has changed considerably. Prescribing of both ER and IR opioid analgesics has declined³—likely due to growing awareness of the serious risks associated with opioids and the combined effect of efforts to mitigate this crisis, such as opioid analgesic prescribing guidelines, REMS, other prescriber education programs, state legislation, prescription drug monitoring programs, law enforcement activity, changes to opioid analgesic labeling, and payer and health system restrictions on opioid analgesic prescribing. Meanwhile, potent, inexpensive heroin and illicitly manufactured fentanyl and fentanyl analogues have become readily available in many areas, contributing to shifting opioid abuse patterns and resulting in a precipitous rise in overdose deaths involving these substances.^{6,7} The proliferation of online drug trafficking has further removed barriers to accessing the illicit drug market,⁸ making illicit opioids easier to obtain than prescription drugs in some communities.⁹

FDA's regulatory decisions relating to opioids are guided by its goal to protect and advance public health. Achieving this goal involves ensuring that safe and effective therapies are available to meet the medical needs of people living with pain, maximizing the safety of those products, and conveying accurate information that can enable the public (patients, healthcare providers, insurers, and others) to make informed evidence-based decisions about the use of these products. At the same time, FDA has an imperative to make positive contributions to addressing the evolving public health crisis of addiction and overdose involving opioids.

Benefit-risk assessment is a foundation for FDA's regulatory review of all human drugs and biologics. Considerations guiding FDA's decision-making specific to opioid analgesics are outlined in the *Draft Guidance to Industry: Opioids Analgesic Drugs – Considerations for Benefit-Risk Assessment Framework*.¹⁰ In general, FDA considers the benefits and risks to the patient when the drug is used as labeled. Additionally, for regulatory decisions regarding opioids, FDA considers the public health risks of the drug related to misuse, abuse, opioid use disorder, accidental exposure, and overdose in both patients and others, as well as any properties of the drug that may mitigate such risks.

Using this broader public health lens, FDA's benefit-risk assessment considers different populations who may be affected by the regulated product and/or by FDA's decision-making regarding that product. FDA recognizes that people's need for, experiences with, and risks related to opioid analgesics are all individual. Thus, in the case of opioid analgesics, "population" is used

⁶ Richard G. Frank, Ph.D., and Harold A. Pollack, Ph.D. Addressing the Fentanyl Threat to Public Health *N Engl J Med* 2017; 376:605-607.

⁷ Hedegaard H, Minino AM, Warner M; NCHS Data Brief No. 329, November 2018.

<https://www.cdc.gov/nchs/data/databriefs/db329-h.pdf>

⁸ https://www.rand.org/pubs/research_reports/RR1607.html

⁹ <https://www.drugabuse.gov/publications/opioid-facts-teens/opioids-heroin>

¹⁰ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/opioid-analgesic-drugs-considerations-benefit-risk-assessment-framework-guidance-industry>

3 Populations

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to characterize a set of individuals in general terms by their pain therapeutic needs and opioid use behaviors. *It is important to note that individuals may simultaneously fit into multiple populations and may move in and out of populations depending on their current situation.* This characterization of populations, however, can be useful in considering the different benefits and risks of ADF opioid analgesics and the potential for different, including unintended, impacts in different groups. Broadly speaking, three important populations may be particularly relevant to evaluating the impact of OxyContin's reformulation as an ADF:

- *Individuals who require opioid analgesics for the treatment of pain, under the care of a healthcare provider (i.e., the intended population).* Importantly, these individuals may simultaneously fit into another category described below. A central goal for this population is availability of safe and effective therapies to manage their medical needs while minimizing the risks of opioid analgesic misuse and abuse, addiction, and overdose. A potential safety benefit of ADF opioid analgesics related specifically to this population is a reduction in medication errors related to crushing extended-release opioid analgesics, for example in patients with feeding tubes [See 2013 Federal Register Notice]. However, unintended adverse effects from added excipients may include choking, dysphagia, and rare intestinal obstruction, as described in the current OxyContin labeling based on postmarketing reports received by FDA following the product's reformulation [See section 2.4.1 of this memo].
- *Individuals who misuse or abuse opioid analgesics but do not regularly manipulate these products for use by routes (e.g., snorting, injecting) other than the intended route.* These individuals may obtain opioids from their own prescription or from other sources, and are considered to be at risk of harms from oral nonmedical use as well as transitioning to snorting or injection and the harms associated with these behaviors. These individuals may also engage in risky use of alcohol, other pharmaceuticals, or illicit substances. Important goals for this population are to reduce harms associated with nonmedical use of opioid analgesics, including harms associated with the transition to manipulation and non-oral use (e.g., infectious complications of injection), and risk of progression to more severe stages of a substance use disorder, overdose, and death.
- *Individuals who regularly manipulate opioid analgesics for use by routes (e.g., snorting, injecting) other than the intended route.* These behaviors may be associated with a more severe substance use disorder, and these individuals may be more likely to engage regularly in polysubstance use, including risky alcohol use, nonmedical use of other pharmaceuticals, and use of heroin or other illicit substances. A key goal related to this population is to reduce the likelihood and frequency of risky behaviors and adverse outcomes (e.g., injection-related harms, overdose) associated with these behaviors.

It is clear that the opioid crisis remains one of the most complex public health issues facing the United States today, increasingly comprised of addiction and overdose that involve multiple drugs and drug classes. Effectively addressing the crisis is requiring multiple interventions—products, technologies, policies, and regulatory actions— working together. Evaluating the net public health impact of any one intervention is extremely challenging against a backdrop of many concurrent interventions and the ever-changing landscape. Aligned with recommendations made by the National Academies of Science, Engineering and Medicine,¹¹ FDA has begun to adopt a systems-based approach to assessing the benefits and risks of potential regulatory actions that may make meaningful gains in addressing the opioids crisis.¹² A systems approach focuses on an understanding of the underlying mechanisms of the crisis and assessing the potential short- and long-term effects of interventions to address the crisis, including intended and potential unintended consequences. Assessing ADF opioid analgesics through a systems approach means considering the broader ecosystem of interrelated clinical, sociocultural, economic, and policy factors that can affect opioid analgesic use, misuse, and subsequent health outcomes. It also means considering the decisions and behaviors of multiple stakeholders: healthcare providers, patients, communities, insurers and others. And finally, it means considering remaining uncertainties in our understanding of the system and the impact of various interventions.

2 FDA REVIEWS AND ANALYSES: SUMMARY OF FINDINGS

2.1 FDA ANALYSES OF PRESCRIPTION DISPENSING TRENDS FOR OXYCONTIN AND OTHER OPIOID ANALGESICS ([SEE DRUG UTILIZATION REVIEW](#))

To support and contextualize our review of the OxyContin postmarketing data, FDA drug use analysts used the IQVIA, National Prescription Audit (NPA)TM database to provide the estimated number of prescriptions and tablets dispensed for original OxyContin, reformulated OxyContin, oxycodone ER original (brand and generic), reformulated oxycodone ER (“authorized generic”), and other opioid analgesics from U.S. outpatient retail pharmacies from 2006 through 2019.

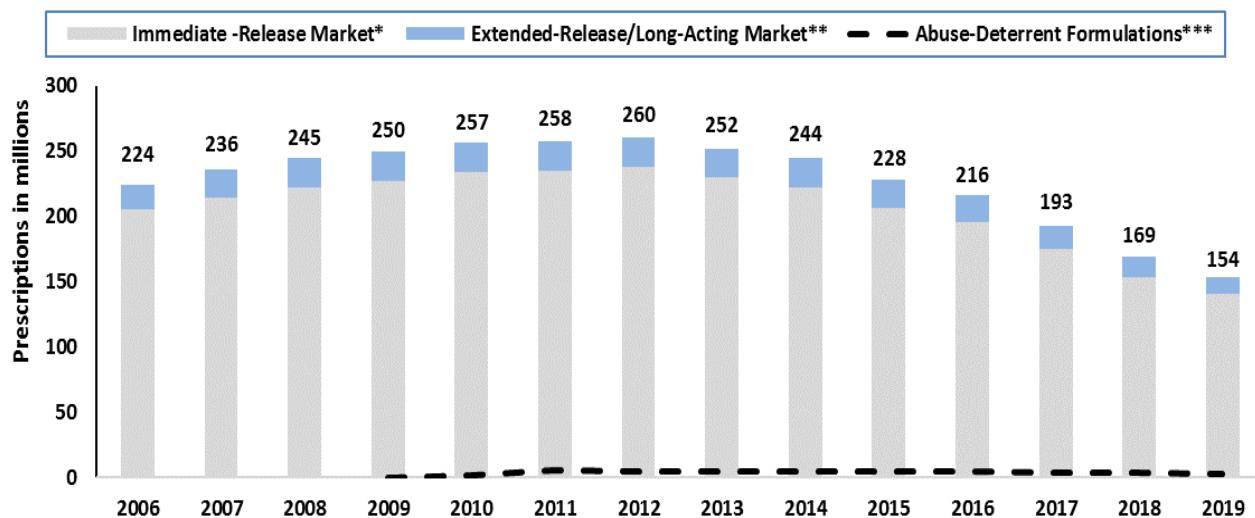
As shown in the figure below, total utilization of opioid analgesics peaked in 2012, with 260 million prescriptions dispensed, then declining 41% by 2019. Immediate-release (IR) formulations accounted for 91%, extended-release/long-acting (ER/LA) formulations accounted

¹¹ <https://www.nap.edu/catalog/24781/pain-management-and-the-opioid-epidemic-balancing-societal-and-individual>

¹² FDA is leveraging a suite of systems approaches. For example, a qualitative framework was used in 2019 to support advisory committee discussions on issues specific to higher dose opioids analgesics (<https://www.fda.gov/advisory-committees/advisory-committee-calendar/june-11-12-2019-joint-meeting-drug-safety-and-risk-management-advisory-committee-and-anesthetic-and>). FDA is also currently developing a system dynamics simulation model, calibrated to US national-level data , which encompasses the range of behavioral aspects of opioid use, misuse, and use disorder, treatment, and overdose (<https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-19-026.html>). When complete, the model will be able to support a wide range of policy analyses related to the opioids system.

for 9%, and ADFs accounted for approximately 2% of the total opioid analgesic prescriptions dispensed in 2019. IR opioid analgesic prescriptions peaked in 2012, with 238 million prescriptions, and the utilization of ER/LA products peaked in 2010, with 23 million prescriptions. As of 2019, 25% of ER/LA opioid analgesic prescriptions were for ADF products. The utilization of ADF formulations peaked in 2011, with 5.6 million prescriptions.. Reformulated oxycodone ER accounted for 73% of dispensed ADF opioid analgesic prescriptions in 2019.

Estimated number of prescriptions dispensed for all opioid analgesics from U.S outpatient retail pharmacies, 2006-2019



Source: IQVIA, National Prescription Audit (NPA) and static data 2006-2011. January 2006-December 2019. Static data extracted March 2017, 2012-2017 data extracted February 2018, 2018 data extracted March 2019, 2019 data extracted Jan 24, 2020

*Immediate-Release formulations include oral solids, oral liquids, rectal, nasal, and transmucosal formulations

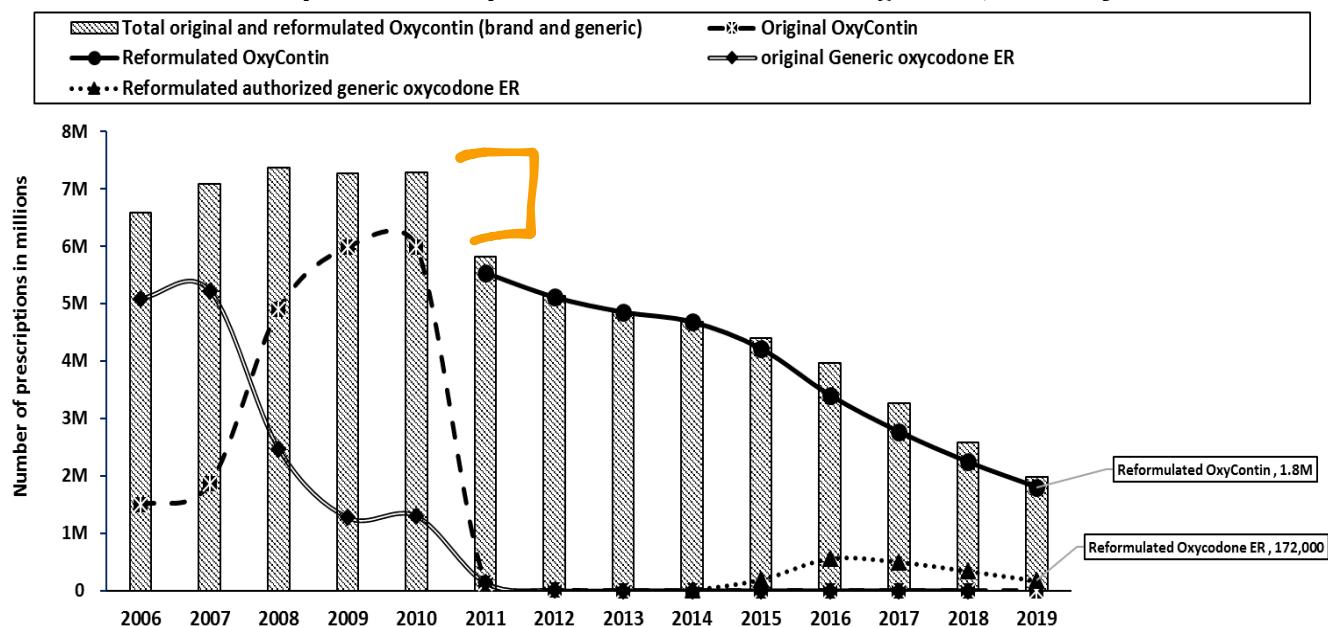
**Extended-Release/Long-Acting formulations include oral solids and transdermal patches

***Abuse-deterrent formulation opioid products include Arymo ER, Embeda ER, Hysingla ER, Morphabond ER, Xtampza ER, OxyContin ER Reformulated (Approval in April 2010), RoxyBond IR

Note: These data include non-injectable opioid analgesics only. Opioid-containing cough-cold products and opioid-containing medication-assisted treatment (MAT) products are not included.

In 2010, distribution of the original formulation of OxyContin ceased and was replaced by reformulated OxyContin. As shown in the figure below, dispensed prescriptions for OxyContin original formulation dropped abruptly from 2010 to 2011 as prescriptions for reformulated OxyContin rose. Of note, original generic oxycodone ER declined from 2007 to 2009, and then dropped further from 2010 to 2011, effectively exiting the market in 2011. Overall ER oxycodone prescription dispensing (original and reformulated, brand and generic) dropped by more than one million prescriptions from 2010 to 2011 and then continued to decline steadily through 2019.

Estimated number of dispensed prescriptions for original and reformulated oxycodone ER products from U.S. outpatient retail pharmacies from 2006 through 2019, annually



Source: IQVIA National Prescription Audit™ (NPA) 2019. Data extracted Feb 2020. File: NPA Oxycodone ER and comparators by prescriptions 2006-2019. 02.15.2020.xlsx

2.2 FDA REVIEW OF POSTMARKETING REQUIREMENT (PMR) STUDIES EVALUATING THE EFFECT OXYCONTIN'S REFORMULATION ON ITS ABUSE AND RELATED ADVERSE OUTCOMES

The four PMR studies that will be discussed at this meeting all examine changes in rates of abuse-related outcomes in post-reformulation compared to pre-reformulation time periods for OxyContin, relative to changes observed in comparator opioid analgesics. The studies use four different sources of data, as described in the table below. The results of these four PMR studies were reviewed by the Division of Epidemiology (DEPI) II and the Division of Biometrics VII (DBVII). [See [Division of Epidemiology Reviews of PMR 3051-2, 3051-2, 3051-3, 3051-4 and Division of Biometrics VII Memorandum](#)].

| Study | Data Source, Setting | Time Periods | Outcomes |
|--------|--|---|---|
| 3051-1 | NAVIPPRO ASI-MV¹: Individuals entering or being assessed for substance use disorder treatment | Pre-period: 3Q2008-2Q2010 Post-period: 1Q2011-4Q2014 | Change in self-reported past 30-day <u>abuse</u> (non-oral and overall) for OxyContin, versus comparators |

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| Study | Data Source, Setting | Time Periods | Outcomes |
|--------|--|---|---|
| 3051-2 | RADARS² Poison Control: Exposure calls to US Poison Centers | Pre-period: 3Q2008-2Q2010 Post-period: 1Q2011-4Q2015 | Change in OxyContin <u>abuse</u> exposure call rates (overall and route-specific), versus comparators |
| 3051-3 | RADARS Treatment Center: Individuals entering opioid use disorder treatment (methadone clinics, other) | Pre-period: 3Q2008-2Q2010 Post-period: 1Q2011-4Q2015 | Change in self-reported past-month <u>abuse</u> (overall only) for OxyContin, versus comparators |
| 3051-4 | Commercial and Medicaid claims: Individuals dispensed OxyContin or comparator opioids | Pre-period: 3Q2008-2Q2010 Post-period: 1Q2011-4Q2015 (- 4Q2012 for Medicaid) | Change in fatal/non-fatal opioid <u>overdose</u> incidence in those dispensed OxyContin, versus comparators |

1. National Addictions Vigilance Intervention and Prevention Program Addiction Severity Index-Multimedia Version
2. Researched Abuse, Diversion and Addiction-Related Surveillance

Overarching considerations in interpreting findings of the PMR studies

As acknowledged in the 2015 Guidance for Industry, the science of ADF assessment is relatively new and continues to evolve. Evaluating the impact of OxyContin's abuse-deterrent formulation in real-world settings has proven challenging for a number of reasons. Many of these were outlined in the FDA Issues Paper accompanying a public scientific workshop FDA convened in July 2017 to discuss methods and data sources for evaluating ADFs in the postmarket setting.¹³

There are a number of overarching methodologic considerations that informed both the design and interpretation of the PMR studies. These issues are also discussed in the DBVII memo and in the individual DEPI reviews of the four PMR studies. Although observational study designs are often used to examine associations, we are interested in the ability to make causal inferences—we want to know if the ADF caused a reduction in abuse and related outcomes. This requires isolation of the effect of the ADF from the changing landscape of opioid use and abuse, as well as from other efforts to combat inappropriate prescribing and abuse of prescription opioids. Causal inference also requires distinguishing the effect of the reformulation from the influence of other sources of confounding and bias in the studies (i.e., other factors, unrelated to the reformulation, that can precipitate changes in observed abuse rates or patterns). For example, the use of non-representative convenience samples can create bias, in that the composition of the study populations change over time in a non-random fashion, complicating comparisons of abuse rates

¹³ <https://www.fda.gov/media/105446/download>

before and after reformulation. Product misclassification, missing data, and changes in survey instruments over time are potential sources of bias in self-reported data. Therefore, the studies include multiple definitions and sensitivity analyses to understand the impact of these factors, resulting in a range of plausible estimates. Additionally, all of the PMR studies employ comparator opioids to better understand background trends and to serve as negative controls, which are intended to approximate the “counterfactual,” or what we expect to have seen in OxyContin abuse trends had it not been reformulated, and then compare that to what we do observe. As there was no single ideal comparator, each study used three primary comparators that were formally compared to OxyContin using statistical models. The studies also included secondary comparators, including heroin, to help further contextualize the results and understand changes in the broader opioid landscape.

Related to causal inference is the question of how best to account for the relationship between drug utilization (i.e., number of prescriptions or tablets dispensed) and abuse rates. Studies have shown that prescription volume correlates with abuse levels—this makes sense, as the drug has to be available to abuse. Although the exact nature of the relationship may not always be straightforward, the number of abuse-related events for a given number of tablets prescribed can be a useful metric for making comparisons across drugs and time periods. However, some of the observed decrease in OxyContin prescribing after the reformulation may have been the result of reduced desirability for abuse and diversion. Although this was likely one factor, it probably does not explain all the decline in OxyContin prescribing between pre- and post-reformulation time periods, as many factors can influence prescribing (e.g., formularies and insurance coverage, cost to patient, REMS, drug company marketing practices). Furthermore, even if all the observed reduction in OxyContin dispensing were due to the abuse-deterrent effect of the reformulation, one would still expect a reduction in levels of abuse for a given amount of drug dispensed (i.e., a reduced likelihood of abuse of tablets dispensed in the community) and that the reduction would be larger than that seen for comparator opioids. Thus, changes in prescribing may be considered both as a mediator (or intermediate step) in the causal pathway from reformulation to reductions in abuse—in which the reformulation reduced abuse through decreased prescribing and community availability of the product—but also as a confounder, where changes in prescribing were due to other factors, confounding the association between introduction of the ADF and changes in abuse rates. Which of these pathways predominates is unclear; failing to adjust for changes in utilization may overestimate the effect of the reformulation, whereas fully adjusting for utilization may underestimate the effect. To address this issue, PMR studies 3051-1 through 3051-3 each analyzed the data using several models, both unadjusted and adjusted for utilization, with the true effect of the reformulation on abuse rates likely lying somewhere within this range of estimates.

The impact of OxyContin’s reformulation on the risk of overdose is an important question, as the sharp rise in prescription opioid overdose was one of the most pressing safety concerns leading FDA to encourage development of ADF opioid analgesics and to determine that original

OxyContin was withdrawn for reasons of safety or effectiveness. However, the reformulation's impact on overdose risk has been one of the most difficult questions to study. Overdose data from death certificates and insurance claims do not generally identify specific drug products or formulations; poison center data vastly under-ascertain fatal drug poisonings (particularly unattended, out-of-hospital overdose deaths) and have limited ability to accurately identify specific products involved in these cases; and due to their inherent limitations, spontaneous adverse event reports cannot be used to estimate incidence or formally compare rates over time. Linkage of insurance claims data to a national mortality database allows estimation of the risk of fatal or non-fatal overdose (using a recently validated algorithm) in patients receiving a particular opioid product. PMR study 3051-4 analyzed three different claims databases, each linked to the National Death Index, to evaluate whether reformulated OxyContin conferred a reduced risk of fatal or non-fatal opioid overdose in patients. However, it is important to note this study was not able to measure any effect on overdose risk in individuals who paid for their opioid medication with cash or obtained their prescription opioids from sources other than their own prescription (e.g., a friend, family member, or dealer), or in individuals who stopped using OxyContin and/or switched to another opioid because of the reformulation. Therefore, PMR study 3051-4 provides only one piece of the story on ADF OxyContin and overdose, but it is an important piece that had not previously been available.



Given the many limitations and complexity of these data, the review team's approach was to qualitatively synthesize data from multiple quantitative analyses, including sensitivity analyses, to draw reasoned conclusions from the totality of the evidence. As described in the DEPI reviews and the DBVII memo, the team drew on fundamental epidemiologic principles around study design, data quality, and causal inference. In addition, DEPI reviewed the published literature to supplement the findings from the PMR studies. The key findings from the literature are described further in Section 2.3, below, and in the full review of the epidemiologic literature ([See Division of Epidemiology Literature Review](#)). The Division of Epidemiology reviews all contain rather detailed executive summaries describing the methodologic considerations, key results, overall interpretation and conclusions for each study.

2.2.1 PMR 3051-1: NAVIPPRO ASI-MV Study ([See Division of Epidemiology Review of PMR Study 3051-1](#))

Study Overview:

PMR study 3051-1 assessed the change in self-reported past 30-day abuse of selected opioids via specific routes (swallowing intact, chewing and swallowing, dissolving and swallowing, snorting, smoking, and injecting) comparing the 2 years before to the 4 years after OxyContin reformulation, in a population of adults evaluated for substance use problems and treatment planning using the ASI-MV® assessment. Comparator opioids are included in this evaluation to

different analyses were conducted, including varying the time period, the definition of OxyContin (i.e., brand OxyContin only, any ER oxycodone), the site inclusion criteria, and the models used to estimate abuse rates and account for changes in drug utilization over time. These varied approaches were used to generate a range of possible estimates and to assess the robustness of the overall study findings.

FDA Review Team Findings:

- Findings were mixed and did not provide compelling evidence that the reformulation meaningfully reduced OxyContin abuse among adults enrolling in OUD treatment.
 - However, the lack of route-specific data limited the ability of this study to detect potential changes in non-oral abuse.
- Polysubstance abuse was common among those abusing OxyContin.
- The reformulation was followed by an increase in heroin abuse, primarily in the privately-funded treatment group (SKIP), although this study was not designed to assess whether the reformulation contributed causally to this increase.
- Adjusted for prescription volume, OxyContin abuse rates remained higher than primary comparator opioids after reformulation; however, such comparisons must be made cautiously due to the inherent limitations of these data.
- The findings from PMR 3051-3 were qualitatively consistent with published studies using this data source in finding decreases in OxyContin abuse rates after reformulation; however, the decreases in OxyContin abuse rates reported in these publications were generally of greater magnitude than what was found in the PMR study and were significantly larger than the change observed for comparators. These differences appear to be related to use of different time periods, regression models, and comparators.

2.2.4 PMR 3051-4: Claims-based Overdose Study ([See Division of Epidemiology Review of PMR Study 3051-4](#))

Study Overview:

PMR study 3051-4 analyzed three administrative claims databases (Medicaid and two commercial claims databases) linked to national mortality data to assess the impact of OxyContin's reformulation on the incidence of fatal or non-fatal opioid overdose (combined) among patients dispensed OxyContin. Analyses compared overdose rates in these patients in the 2 years before to the 5 years after OxyContin reformulation (2 years after in the Medicaid database), with comparisons to changes observed in patients dispensed selected other opioid analgesics. Comparator opioids were used as negative controls to aid in causal inference, and

also provided contextual information on background trends in opioid overdose rates. Due to the complexity of these data, (e.g., many patients dispensed OxyContin concomitantly with intermittent dispensing of other opioid analgesics, and potential for confounding by patient characteristics) a number of different analyses were conducted to better understand the generalizability of study findings and role of potential biases. For example, analyses included the use of several exposure categories that included patients dispensed OxyContin with or without other opioid analgesics, and multiple methods were used to adjust for patient-level characteristics.

FDA Review Team Findings:

- The results of PMR 3051-4 do not demonstrate that the reformulation reduced the risk of opioid overdose in patients dispensed OxyContin, overall.
 - In the commercial claims populations, changes in estimated opioid overdose rates among patients dispensed OxyContin compared to the changes among patients dispensed comparators modestly favored OxyContin, but they were not statistically significantly different from each other. In Medicaid data analyses, results were actually somewhat *unfavorable* to OxyContin.
- When restricted to time that patients had a prescription for OxyContin or comparator *alone* (i.e., without any other opioids), results were somewhat more favorable with respect to the reformulation reducing opioid overdose risk, although the implications and generalizability of this specific finding are not entirely clear, for the following reasons:
 - These results were statistically significant in the commercial insurance claims populations and not in the Medicaid cohort.
 - OxyContin use without concomitant dispensing of any other opioid analgesics was relatively uncommon.
 - It is possible that OxyContin's abuse-deterrent properties did confer a reduced risk of overdose among patients using OxyContin without any other opioid analgesics. However, it is also plausible that patients receiving reformulated OxyContin were at inherently at lower risk of overdose than those who received OxyContin prior to its reformulation, either through changes in prescribing practices (i.e., prescribing lower dosage strengths), or through patient self-selection away from reformulated OxyContin among those seeking to abuse it via non-oral routes. While the latter explanations may be consistent with reformulated OxyContin having an abuse-deterrent effect, it does not necessarily follow that the abuse-deterrent properties conferred a reduced risk of overdose either among those exposed to the product or in those who migrated away

from OxyContin because of its reformulation (e.g., if they shifted to abuse of illicit opioids).

2.3 REVIEW OF OTHER PUBLISHED EPIDEMIOLOGIC LITERATURE ([SEE DIVISION OF EPIDEMIOLOGY LITERATURE REVIEW](#))

Overview of Literature Review:

To supplement and contextualize the formal PMR studies submitted by the application holder and to better understand the broader public health impact of OxyContin's reformulation, the Division of Epidemiology (DEPI) II conducted a comprehensive critical review of peer-reviewed and selected grey literature examining the impact of reformulated OxyContin on opioid use, abuse, morbidity, and mortality. Following a systematic search of the published literature, we identified 78 articles for detailed review and further categorized into three main categories: PMR-related studies (which used the same or similar data sources and methods as the four PMR studies), non-PMR-related original studies, and editorials. **PMR-related published studies were summarized and evaluated as part of the Division of Epidemiology reviews of the related PMR studies 3051-1 through 3051-4.** Six of the PMR-related studies and 13 of the non-PMR related studies were funded by Purdue or a Purdue-affiliated pharmaceutical company.

FDA Review Team Findings:

Our ability to draw firm conclusions from the published literature was limited, although it did provide some valuable information to supplement and contextualize the PMR study findings.

- Published studies indicate that sales of OxyContin declined after its reformulation, in both the U.S. and other countries, although this decline may have occurred due to a variety of reasons.
- Rates of self-reported nonmedical use (i.e., use other than as directed) of OxyContin also declined in the general U.S. population, returning to rates observed several years before the reformulation. It remains unclear to what extent declines in OxyContin prescribing drove declines in the prevalence of its nonmedical use, versus decreases in OxyContin's abuse potential driving reduced demand and prescribing.
- Despite some serious limitations, the totality of evidence from published studies suggests that OxyContin's reformulation reduced its attractiveness for diversion and abuse, particularly non-oral abuse in populations already abusing prescription opioids through tampering and non-oral routes.
- The literature does not provide definitive answers regarding the net public health impact of OxyContin's reformulation in the U.S.

- We identified no reliable, longitudinal evidence regarding the effect of OxyContin's reformulation on the trajectory of opioid use disorder, the likelihood of transitioning from oral to non-oral abuse, the risk of addiction, or the risk of opioid overdose.
- Overall, the literature suggests that while some individuals shifted their use of OxyContin from non-oral to oral routes, others simply substituted different prescription and/or illicit opioids after OxyContin's reformulation. These apparent substitution effects varied across populations, likely reflecting heterogeneity in baseline substance abuse patterns and the availability and cost of other drugs. Polysubstance abuse is common, and drug use patterns are dynamic and likely influenced by many factors, including drug availability, price, and other sociocultural factors.
- Several analyses suggest that OxyContin's reformulation contributed to reductions in rates of fatal overdoses involving prescription opioids in the U.S., but that these declines were offset, or more than offset, by consequent increases in fatal overdoses from illicit opioids; however, the complex mixture of concurrent interventions, secular trends, and geographical heterogeneity in opioid availability and use patterns makes it difficult to determine the precise role of ADF OxyContin in these trends.

2.4 OTHER INFORMATION RELEVANT TO CONSIDERATION OF PUBLIC HEALTH IMPACTS

2.4.1 Polyethylene Oxide (PEO) and excipient harms ([See Division of Pharmacovigilance Memorandum](#))

There are several safety issues that have arisen that relate specifically to the excipient PEO, which is used in reformulated OxyContin and some other ADF opioid analgesic products to make them more difficult to crush and dissolve.

Thrombotic microangiopathy (TMA) with intravenous abuse:

On March 13-14, 2017, FDA convened an Advisory Committee meeting to discuss the postmarketing data relating to another opioid analgesic product, Opana ER (oxymorphone hydrochloride extended-release tablets, Endo Pharmaceuticals), that, like OxyContin, was reformulated with PEO to deter abuse by non-oral routes. As described in the FDA briefing package for the 2017 meeting,¹⁴ one postmarketing safety concern for reformulated Opana ER was the identification of 59 cases of thrombotic microangiopathy (TMA) associated with

¹⁴ <https://www.fda.gov/files/advisory%20committees/published/FDA-Briefing-Information-for-the-March-13-14--2017-Joint-Meeting-of-the-Drug-Safety-and-Risk-Management-Advisory-Committee-and-the-Anesthetic-and-Analgesic-Drug-Products-Advisory-Committee.pdf>

intravenous abuse of this product. Data from animal models have linked PEO of varying molecular weights to acute manifestations of TMA.

Language was subsequently added to the reformulated OxyContin prescribing information in Section 9.2 (Abuse) about this risk:

With parenteral abuse, the inactive ingredients in OXYCONTIN can be expected to result in local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, valvular heart injury, embolism, and death. Cases of thrombotic microangiopathy (a condition characterized clinically by thrombocytopenia and microangiopathic hemolytic anemia) associated with parenteral abuse have been reported.

A recent search of the FDA Adverse Event Reporting System (FAERS) and published medical literature identified only six cases of TMA (all non-fatal) associated with intravenous abuse of reformulated OxyContin. The reports were received over six years (2014-2019), indicating an ongoing, but minimally reported event. All six cases in the series reported intravenous abuse of reformulated OxyContin, and half provided a brief description of the tampering method, all involving thermal manipulation. All patients presented with anemia, thrombocytopenia, evidence of hemolysis, and additional laboratory markers consistent with drug-induced TMA after intravenous use of OxyContin. Our analysis found that these cases appear to be consistent with the risk of TMA currently described in OxyContin labeling. FDA-supported work is ongoing to better understand the various factors that may contribute to the risk of TMA, for example, size of the PEO polymer, manufacturing process, and tampering methods.

Choking, dysphagia, nasal and intestinal obstruction:

In 2011, FDA initiated a safety review evaluating spontaneous adverse event reports it had received of choking, dysphagia, nasal and intestinal obstruction, exacerbation of diverticulitis, and medication residue in the stool associated with the newly reformulated OxyContin ([see Division of Pharmacovigilance 2011 Review](#)). The cases suggested that in some instances, the PEO-containing tablet turns into a “glue-like” substance upon contact with oral/nasal mucosa, causing choking or obstruction. The pills were also noted to not dissolve adequately and in some cases, pass through the GI tract intact without absorption. No serious outcomes were reported except in four patients who had underlying gastrointestinal disorders. This adverse event was subsequently added to the Warnings and Precautions section of the OxyContin label, as follows:

5.11 Difficulty in Swallowing and Risk for Obstruction in Patients at Risk for a Small Gastrointestinal Lumen: There have been post-marketing reports of difficulty in swallowing OXYCONTIN tablets. These reports included choking, gagging, regurgitation and tablets stuck in the throat.... There have been rare post-marketing reports of cases of intestinal obstruction, and exacerbation of diverticulitis, some of which have required medical intervention to remove the tablet. Patients with underlying GI disorders such as

esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying GI disorders resulting in a small gastrointestinal lumen.

2.4.2 CDER's Office of Communications (OCOMM) social science research on prescriber understanding of ADF opioid terminology (See [Office of Communications Memorandum](#))

Findings from previous research conducted by CDER's OCOMM uncovered considerable variability in health care professionals' (HCPs) awareness of, knowledge about, attitudes toward, and experience with ADFs. This lack of awareness and knowledge – as well as potential misunderstandings – about ADFs and the terminology used to describe them have been of significant concern to FDA and are potentially relevant to discussions about the broader public health impact of reformulated OxyContin. OCOMM and other FDA collaborators designed a three-phase research project, which is currently underway, to build on the findings from an earlier project by exploring and assessing ADF-related knowledge, attitudes, and behaviors among opioid analgesic prescribers and dispensers/pharmacists and to explore possible alternative language for describing these products. The mixed-methods approach being undertaken for this project consists of three separate but iterative phases engaging healthcare providers.

To date, the Phase 1 qualitative focus group data collection and analysis have been completed. The following are key findings from this work:

- Prior knowledge of the term 'abuse-deterrant formulation' opioid was uncommon among prescribers and pharmacists.
- OxyContin was the most commonly prescribed ADF
- Most who were unfamiliar with the ADF term guessed incorrectly about what it means. Common misperceptions included:
 - ADFs are formulated to make someone sick when they are using an opioid or when someone takes too high a dose of opioids; similarity to Antabuse was mentioned
 - ADFs do not provide any type of high or euphoric feeling
 - ADF refers to a "policy" or "plan of care"
 - ADFs offer non-narcotic pain relief
 - Single participants also said ADFs had higher addiction potential, had higher abuse potential, were intended to end opioid use, and are a form of physical therapy.
- Some were confused about whether ADFs could be modified at all and about how they work/mechanism of action.

- Some worried prescribing an ADF could lead to feelings of patient dissatisfaction with care or stigmatization
- A few noted they hadn't prescribed ADFs due to perceived ineffectiveness in their ability to prevent misuse, abuse, or addiction.
- Other barriers to use included the need for more information about them before prescribing them, including for data/studies specifically proving their efficacy in reducing abuse and addiction and the extent of those decreases, and about their side effects and mechanisms of action/how they work.
- Across all groups, participants reported limited training and education on ADFs and many suggested additional training would be beneficial.

3 FDA'S OVERALL INTERPRETATION OF THE EVIDENCE

Within the framing of the systems approach described in Section 1, FDA's interpretation of the evidence considers the direct effects of OxyContin's reformulation on its abuse patterns and the risk of overdose associated with its use. We also consider other important public health outcomes to which OxyContin's reformation may have contributed, such as drug substitution behaviors, development or progression of OUD, and harms associated with opioid abuse and OUD, particularly overdose deaths. FDA's interpretation of the evidence also considers the uncertainties that arise from the limitations of the available data and methods, as well as from the complex and evolving landscape of the opioid crisis, including trends in prescribing of opioid analgesics (both conventional and ADF), the availability and potency of illicit opioids, polysubstance use, and the potential for varying effects of the reformulation in different population subgroups. These uncertainties complicate our understanding of the net impact of OxyContin's reformulation as an intervention intended both to improve the safety of a specific opioid analgesic product and to mitigate the harms associated with prescription opioid abuse and the opioid crisis more broadly.

The following conclusions represent the FDA review teams' synthesis of the postmarketing data, guided by a systems approach and based on a critical review of the totality of evidence, including the four required PMR study reports as well as the published literature, the FAERS analysis and ongoing FDA research on prescriber understanding of ADFs and excipient harms.

1. **The totality of evidence from the PMR studies and published literature is fairly compelling that the reformulation of OxyContin has reduced abuse of this product via non-oral routes, including both snorting and injection, although the magnitude of effect cannot easily be quantified and likely varies across populations.**

- This effect has primarily been observed in populations with more advanced substance use disorders, including individuals with moderate to severe addiction who are entering or being assessed for treatment and others who are already tampering with prescription opioids and abusing them through non-oral routes.
- The strongest evidence supporting this conclusion came from PMR 3051-1 (NAVIPPRO ASI-MV study). The conclusion was also supported by weaker, but largely consistent findings from PMR 3051-2 (RADARS Poison Center study) and several published studies conducted in different populations of individuals tampering with prescription opioids or entering treatment with opioids use disorders.

2. Evidence was not robust that the reformulation caused a meaningful reduction in overall OxyContin abuse (i.e., via any route).

- Findings from PMRs 3051-1, 3051-2, and 3051-3, as well as our critical review of published studies contributed to this conclusion.
- This conclusion was based primarily on our inability to disentangle the effect of the ADF from the effect of changes in the opioid analgesic and illicit opioid markets, and from other interventions and secular trends. The lack of a decisive effect of the reformulation on overall OxyContin abuse also likely reflects the predominance of oral abuse and a modest shift from non-oral to oral OxyContin abuse in some populations. Although the FDA guidance for industry notes the importance of considering the impact of the ADF on overall abuse, OxyContin was reformulated primarily to deter abuse by snorting and injecting, and the label states that it is expected to deter abuse by these routes, based on experimental study results.

3. After adjusting for prescription volume, both overall and non-oral abuse rates for OxyContin remained relatively high among the schedule II opioids examined in the post-reformulation period, indicating that, while the reformulation may have improved the safety of OxyContin with respect to non-oral abuse, ADF OxyContin is not necessarily safer than other marketed opioid analgesics with respect to abuse and associated risks.

- It is important to note, however, that such direct cross-sectional comparisons must be interpreted cautiously due to non-representative samples, product misclassification, and missing data.

4. It is unclear whether Oxycontin's reformulation reduced opioid overdoses or had a net public health benefit.

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- The evidence from PMR 3051-4 does not compellingly demonstrate that the reformulation of OxyContin reduced the risk of fatal or non-fatal opioid overdose in patients dispensed OxyContin, overall.
 - Of note, the target population for this study was not an enriched, higher-risk population (e.g., with OUD or abusing prescription opioid via non-oral routes) where effects of the reformulation might be more easily detected if they occurred
- When analyses were restricted to time in which patients received OxyContin *alone*, the findings were somewhat more favorable, although the implications of this are somewhat unclear for several reasons. First, the effect was only seen in the commercial claims cohorts and not in the Medicaid population. Second, OxyContin use without any other opioid analgesics was uncommon. Finally, it is possible that patients receiving OxyContin in the post-reformulation period were at inherently lower risk of overdose, if higher risk patients seeking to abuse it non-orally migrated away from OxyContin, perhaps to other prescription or illicit opioids. Prescribing of the highest dosage strengths of OxyContin also declined, which may confer a lower risk of overdose. Although both of these changes would be consistent with an abuse-deterrent effect, it remains unclear whether the abuse-deterrent properties actually conferred a reduced risk of overdose, either in patients receiving OxyContin or in those who may have avoided OxyContin due to the ADF.
- Multiple studies found that some individuals substituted other prescription or illicit opioids (i.e., heroin) after OxyContin's reformulation; however, these substitution effects appear to vary across populations, likely reflecting heterogeneity in pre-existing drug abuse patterns and available substitutes.
 - These shifts were seen in published studies using a variety of methods, as well as in the PMR studies.
 - Polysubstance abuse is common, especially in individuals with more advanced substance use disorders. There was not clear evidence that OxyContin's reformulation caused heroin-naïve individuals to initiate use, and the shifts from OxyContin to heroin and other opioids may have often occurred in the setting of pre-existing polysubstance abuse including these drugs.
- Several published analyses have suggested that any contribution of OxyContin's reformulation to reductions in fatal prescription opioid overdoses were offset, or more than offset, by consequent increases in fatal illicit opioid overdoses.

- 4**
- While this would be consistent with the substitution effects described in other studies, the direct effect of OxyContin's reformulation on national opioid overdose mortality remains difficult to isolate from the impacts of other interventions (e.g., Florida "pill mill" actions) and secular trends (e.g., availability, price, and purity of heroin).
 - We found no credible information on whether the OxyContin ADF reduces the *initiation* of non-oral abuse (e.g., in patients receiving opioid analgesics for pain or in others abusing prescription opioids but via the oral route), prevents the progression of opioid use disorder, or reduces the incidence of new addiction.
 - Given the limitations of the available data (e.g., poor performance of code-based algorithms to measure abuse and addiction in electronic healthcare data), retrospective studies are likely not capable of rigorously evaluating whether OxyContin's reformulation resulted in a decreased risk of addiction. Answering these questions would likely have required launch of a prospective study in an at-risk population prior to introduction of reformulated OxyContin, and even then, it may have been infeasible to study rigorously.

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Deputy Director for Safety Memorandum to File

Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research
Food and Drug Administration

| | |
|---------------------|---|
| NDA | 022272 |
| Drug names | <i>OxyContin</i> |
| Safety Issue | <i>Abuse-deterrent formulation postmarket requirements-Regulatory History</i> |
| Author name | <i>Judith A. Racoosin, MD, MPH</i> |
| Date | <i>See signature block</i> |

This memo serves to summarize the regulatory history of the postmarket requirements (PMRs) that were required of Purdue at the time reformulated OxyContin was approved for marketing to determine whether the product deterred abuse in the “real world”.

NDA 022272, OxyContin (oxycodone) extended-release tablets, was approved on April 5, 2010.¹ This “reformulated” version of the original OxyContin application (NDA 020553) was developed with excipients intended to deter abuse of the product. At the time of approval, FDA required that postmarketing studies be conducted to determine if the changes to the formulation actually result in a decrease in the risks of misuse and abuse, and their consequences. The following language was included in the April 5, 2010, approval letter:

POSTMARKETING REQUIREMENTS UNDER 505(o)

As you were informed in our December 30, 2009, Complete Response Letter, FDA has determined that you are required to conduct postmarketing studies of OxyContin (Oxycodone Hydrochloride Controlled-Release) Tablets to assess the known serious risks of OxyContin (Oxycodone Hydrochloride Controlled-Release) Tablets, in particular, whether the changes made to the OxyContin (Oxycodone Hydrochloride Controlled-Release) Tablets formulation that are the subject of this application and which are intended to deter misuse and abuse actually result in a decrease in the risks of misuse and abuse, and their consequences.

Specifically, we have determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct epidemiological studies to address whether the changes made to the OxyContin (Oxycodone Hydrochloride Controlled-Release) Tablets formulation that are the subject of this application result in a decrease in misuse and abuse, and their consequences: addiction, overdose, and death.

We acknowledge receipt of your proposal, included in your February 5, 2010, resubmission to this application, that contains brief descriptions of possible postmarketing studies to fulfill this requirement. Because of design and methodology challenges, we continue to be concerned that the proposed studies will not successfully capture the necessary information that will allow us to assess the impact, if any, attributable to the change in the OxyContin (Oxycodone Hydrochloride

¹ http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/022272s000ltr.pdf

P 3

Study Completion: 10/2016
Final Report Submission: 03/2017

3051-4

Determine the change in the incidence of non-fatal and fatal overdose associated with OxyContin exposure relative to the change associated with exposure to appropriate comparators using electronic healthcare data with linkage to an appropriate death registry such as the National Death Index. This study should adhere to the principles as laid out in FDA's "Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data," including but not limited to guidelines regarding validation of outcomes, exposure definition and ascertainment, and measurement of and control for potential confounders.

You will conduct this study according to the following timetable:

Final Protocol Submission: 09/2016
Study Completion: 07/2017
Final Report Submission: 10/2017

Due to the complex study methodology needed to be agreed upon by the Agency and the Applicant, and the novel scientific issues involved, it took longer than anticipated for these protocols to be finalized and for all the studies to be completed.

PMRs 3051-1, -2, and -3 received an "Acknowledge Final Protocol for Postmarketing Requirement" letter on June 28, 2017, and the Final Report Submission milestone was revised to March 31, 2018. The final study reports were submitted for PMRs 3051-1 and -2 on July 31, 2018. Due to newly identified issues with the source data, the final study report for PMR 3051-3 was delayed, and ultimately submitted on April 18, 2019.

With PMR 3051-4, there were additional complexities in finalizing the protocol, including time needed for FDA to obtain advice and information from the Centers for Medicare and Medicaid Services on some aspects of the study relating to use of Medicaid data. PMR 3051-4 received an "Acknowledge Final Protocol for Postmarketing Requirement" letter on September 14, 2018, and the Final Report Submission milestone was revised to August 31, 2019. The final study report for PMR 3051-4 was submitted on August 26, 2019.



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: September 10-11, 2020

To: Members of the Joint Drug Safety and Risk Management (DSaRM)
Advisory Committee and Anesthetic and Analgesic Drug Products
Advisory Committee

From: Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management
(OMEPRM)
Office of Surveillance and Epidemiology (OSE)

Drug Name: OxyContin (oxycodone hydrochloride extended-release tablets)

Subject: Risk Evaluation and Mitigation Strategy (REMS)

In April 2010, a new formulation of OxyContin was approved, its design was to discourage misuse and abuse of the medication. At that time, OxyContin was approved with its own risk evaluation and mitigation strategy (REMS). The REMS consisted of elements to assure safe use (ETASU), and a timetable for submission of assessments. The ETASU included healthcare provider training and Dear Healthcare Professional letters. In addition, a Medication Guide was also required as part of the REMS since OxyContin had serious risks relative to the benefits that may affect a patient's decision to use, or continue to use, OxyContin.

In July 2012, OxyContin became a member of the shared system Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics (ER/LA) REMS. The ER/LA REMS was expanded and modified in September 2018 to include all application holders of immediate-release (IR) opioid analgesics that are expected to be used in the outpatient setting and that are not already covered by another REMS program. With the approval of this modification the ER/LA REMS was renamed the Opioid Analgesic REMS, of which OxyContin is a member. The Opioid Analgesic REMS is one strategy among multiple national and state efforts to reduce the risks of abuse, and misuse, addiction, overdose and deaths due to prescription opioid analgesics by making training available to healthcare providers.

The Opioid Analgesics REMS requires that training be made available to healthcare providers, including prescribers, nurses, and pharmacists, involved in the treatment and monitoring of patients with pain. The FDA believes that all healthcare providers (HCPs) involved in the

management of patients with pain should be educated about the fundamentals of acute and chronic pain management and the risks and safe use of opioids so that when they write or dispense a prescription for an opioid analgesic, or monitor patients receiving these medications, they can help ensure the proper product is selected for the patient and used with appropriate clinical oversight.

Under the Opioid Analgesic REMS, application holders¹ are required to make education programs available to healthcare providers. The application holders are meeting this requirement by providing educational grants to accredited continuing education (CE) providers who offer training to healthcare providers at no or nominal cost. The training must include successful completion of a knowledge assessment and proof of successful program completion.

To be considered compliant with the Opioid Analgesic REMS, the CE courses are required to include the content and messages of a “blueprint” developed by FDA for this purpose. The currently approved FDA Blueprint, *FDA’s Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain*,² focuses on the fundamentals of acute and chronic pain management and provides a contextual framework for the safe prescribing of opioid analgesics. This includes principles related to the acute and chronic pain management; non-pharmacologic treatments for pain; and pharmacologic treatments for pain (both non-opioid analgesic and opioid analgesic). The FDA Blueprint covers basic information about addiction medicine and opioid use disorder. The core messages are directed to prescribers, pharmacists, and nurses, but are also relevant for other healthcare providers who participate in the management of pain.

The Opioid Analgesics REMS also includes a patient counseling guide³ for healthcare providers to assist in properly counseling patients on their responsibilities for using these medicines safely and to provide patients with additional written safety information. The approved labeling for opioid analgesics includes a product-specific one-page Medication Guide to be given to patients each time they receive a prescription of their opioid analgesic medicine. The Medication Guide contains consumer-friendly information on the safe use and disposal of opioid analgesics and instructions for patients to consult their healthcare providers before changing doses, signs of potential overdose and emergency contact instructions, and advice on safe storage to prevent accidental exposure to family members.

Attachments: Appendix X – FDA Blueprint (https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_analgesic_2018_09_18_FDA_Blueprint.pdf)

¹ Application holders refers to all the manufacturers of the new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for opioid analgesics that are subject to the REMS requirements. ANDAs refer to generic drugs. The applicant holders have come together as a consortium and formed the REMS Program Companies (RPC). Throughout this background document, the manufacturers may be referred to as application holders or RPC.

² Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain. The FDA Blueprint contains core messages intended for use by CE providers to develop educational materials to train HCPs under the REMS.

³ https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_Analgesic_2019_11_14_Patient_Counseling_Guide.pdf

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Drug Utilization Review

Date: September 10-2020

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Subject: Utilization of OxyContin Abuse-Deterrent Formulation (ADF)

Drug Name(s): OxyContin (oxycodone extended-release (ER) tablets)

Application Type/Number: Multiple

Applicant/Sponsor: Multiple

OSE RCM #: 2019-1681

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EXECUTIVE SUMMARY

A joint Advisory Committee meeting will be held to discuss the results of post-marketing requirement (PMR) studies submitted by Purdue Pharma L.P. The PMR studies aimed to assess the impact of the reformulation on OxyContin abuse and risk of opioid overdose. To supplement and contextualize the PMR study results and to inform on the broader public health impact of the reformulation, the Division of Epidemiology II conducted a drug utilization review to examine the outpatient retail utilization of abuse-deterrent opioid analgesics, with a focus on single-ingredient oxycodone extended-release (ER) products.

In 2019, an estimated 154 million prescriptions were dispensed for all opioid analgesics from U.S. outpatient retail pharmacies, a decrease of 41% from a peak of 260 million prescriptions dispensed in 2012. Utilization of extended-release/long-acting (ER/LA) opioid analgesics peaked in 2010 at 18.4 million prescriptions and declined by 47% to 9.8 million prescriptions in 2019, with oxycodone ER accounting for 25% of ER/LA prescriptions.

Overall, prescriptions dispensed for oxycodone ER peaked at 7.4 million prescriptions dispensed in 2008 then decreased to 2.4 million prescriptions in 2019. In 2010, distribution of the original formulation of OxyContin and generic oxycodone ER ceased, and reformulated OxyContin became available in the market. As a result, prescriptions for original OxyContin and generic oxycodone ER formulations dropped from 6 million and 1.3 million prescriptions in 2010 to 136,000 and 138,000 prescriptions respectively in 2011. The vast majority of prescriptions dispensed for oxycodone ER was for the reformulated OxyContin at 5.5 million prescriptions dispensed in 2011. The authorized generics for the reformulated oxycodone ER were introduced in 2014, utilization peaked in 2016 with 560,000 prescriptions then steadily declined to 172,000 prescriptions dispensed in 2019. Reformulated OxyContin and its authorized generics accounted for the majority of utilization of abuse-deterrent opioid analgesics, accounting for 73% of prescriptions in 2019.

In terms of average milligrams per prescription (mg/Rx) for oxycodone ER based on the estimated aggregate volume of prescriptions dispensed, the average yearly aggregate of milligrams of oxycodone ER per prescription dispensed decreased from 3,100 mg/Rx in 2009 to 1,700 mg/Rx in 2019. This decline may be due to the overall decrease in the utilization of higher strengths of oxycodone ER formulations. The most common strengths of oxycodone ER tablets were dispensed for 40 mg and 80 mg during the fourth quarter of 2009. However, this trend changed by the fourth quarter of 2019, where oxycodone ER 20 mg accounted for the highest proportions of all strengths.

Mid-level practitioners were the top prescribing specialties of the single-ingredient oxycodone ER TRx in 2019; family practice, internal medicine, general practitioner accounted for the highest proportion of TRx followed by mid-level practitioners in 2009 and 2012. Among specialists, although the total number of TRx dispensed for oxycodone ER decreased during the examined time-periods, the proportion of TRx written by pain medicine/anesthesiologists increased from 14% in 2009 to 22% in 2019.

Our findings show total utilization of oxycodone ER was highest in 2008 followed by a decline of 67% by 2019. The decrease of utilization of oxycodone ER formulation may due to several reasons including the strengthening of warnings on the drug label, expanding patient and prescriber educational campaigns, interventions implemented by federal, state, local governments, recommended limitations on opioid dosages, payer-based dispensing restrictions, prescription drug monitoring programs (PDMP), risk evaluation mitigation strategies (REMS) and issuing guidance for the pharmaceutical industry regarding the development of abuse-deterrent formulations of opioid products in addition to many other interventions.

Competing interventions

1 INTRODUCTION

A joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) will be held on September 10-11, 2020 to discuss the results of post-marketing requirement (PMR) studies submitted by Purdue Pharma L.P (sponsor). The PMR studies aimed to assess the specific impact of the OxyContin reformulation on OxyContin abuse and risk of opioid overdose. To supplement and contextualize the PMR study results submitted by the sponsor and to better understand the broader public health impact of OxyContin's reformulation, the Division of Epidemiology (DEPI) II conducted a drug utilization review to examine the outpatient retail utilization of abuse-deterrent opioid analgesics, with a focus on oxycodone ER formulations to provide background for the Advisory Committee discussion.

2 BACKGROUND AND REGULATORY HISTORY¹

Reformulated OxyContin (oxycodone hydrochloride) is a single-ingredient extended-release (ER) opioid product developed by Purdue Pharma L.P. (sponsor); it was approved for marketing in the U.S. on April 5, 2010. It replaced the original OxyContin formulation approved on December 12, 1995. On August 5, 2010, the sponsor stopped shipping original OxyContin tablets to pharmacies and exclusively started shipping reformulated OxyContin tablets on August 9, 2010. However, pharmacies were still able to dispense their remaining stock of original OxyContin tablets after August 5, 2010. In correspondence dated August 10, 2010, the sponsor notified the U.S Food and Drug Administration (FDA) that it had ceased shipment of original OxyContin.

In October 2014, the sponsor submitted a labeling supplement requesting placement of claims in the label describing a real-world beneficial effect of the ADF of OxyContin. An Advisory Committee meeting was scheduled to be held in July 2015 to discuss the results of post-marketing studies that were submitted in support of the requested label claim. Subsequently, the sponsor submitted a request to withdraw the supplement, citing the need to complete additional analyses.

In April 2015, FDA issued the final *Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry*, outlining the Agency's current thinking on studies that should be conducted to demonstrate that a given opioid formulation has abuse-deterrent properties. The guidance makes recommendations about how those studies should be performed and evaluated and discusses how to describe those studies and their implications in product labeling.

In March 2016, a new PMR letter was issued, formalizing the required studies and timelines. In addition to three studies assessing the impact of the ADF on OxyContin abuse rates, the Agency required a claims-based study linked to mortality data to assess the impact of the reformulation on fatal and non-fatal opioid overdose.

In 2018 and 2019, the sponsor submitted the final study reports for four PMR studies evaluating the effectiveness of the ADF in reducing OxyContin abuse and related outcomes, including fatal and non-fatal overdose, in the post-approval setting. On [September 10-11, 2020 a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk

Management Advisory Committee (DSaRM) will be held to discuss the results of these findings.

3 METHODS AND MATERIALS

¹ Center for Drug Evaluation and Research. (2019, December 21). Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse. Retrieved May 1, 2020, from <https://www.fda.gov/drugs/information-drug-class/timeline-selected-fda-activities-and-significant-events-addressing-opioid-misuse-and-abuse>

3.1 PRODUCTS INCLUDED

Table 1 below shows the oxycodone-containing opioid analgesics, including formulations designed to deter abuse, that are included in this review. Other opioid analgesics defined as schedule-II under the Controlled Substance Act (CSA) (single-ingredient, combination, extended-release/long-acting and immediate-release opioid analgesics, as well as transdermal and suppository formulations) are also included in this review. This review focused on non-injectable opioid analgesics mainly dispensed in the outpatient retail pharmacy setting. We did not include injectable formulations of opioid analgesics, opioid-containing medication-based therapy products and opioid-containing cough/cold products in these analyses.

Table 1²

| Single-Ingredient Oxycodone ER formulations | All other schedule-II opioid analgesics |
|--|--|
| OxyContin | Arymo ER |
| Oxycodone ER | Codeine |
| Xtampza ER | Embeda ER |
| | Fentanyl |
| | Hydrocodone |
| | Hydromorphone |
| | Hysingla ER |
| | Levorphanol |
| | Meperidine |
| | Methadone |
| | Morphabond ER |
| | Morphine |
| | Opium |
| | Oxycodone |
| | Oxymorphone |
| | Roxybond IR |
| | Tapentadol |

3.2 DATA SOURCES USED

² Drug Enforcement Administration. (n.d.). List of Controlled Substances. Retrieved June 15, 2020, from <https://www.deadiversion.usdoj.gov/schedules/>

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

3.2.1 Determining Settings of Care

The IQVIA National Sales Perspectives™ (NSP) database was used to determine the primary setting of care for the utilization of oxycodone ER products based on the estimated number of bottles or packages of these products sold from manufacturers to various settings of care in 2019. Of note, our analysis includes all single-ingredient oxycodone ER products, however, main focus of this review is original and reformulated formulations of OxyContin and its generics.

3.2.2 Prescription Data

The IQVIA, National Prescription Audit (NPA)™ database was used to provide the estimated number of prescriptions and tablets dispensed for OxyContin original, OxyContin reformulated, oxycodone ER original, oxycodone ER reformulated and other opioid analgesics comparators from U.S. outpatient retail pharmacies from 2006 through 2019, annually and quarterly. This database was also used to provide the prescriber specialties for oxycodone ER prescriptions dispensed from U.S. outpatient retail pharmacies for different time-periods (original OxyContin in 2009, after reformulation in 2012, and in 2019).

There was a change in the underlying data and methodology of the proprietary database, IQVIA NPA, to manage prescription claims that are voided or reversed. Prescription volumes dispensed from the retail pharmacies have been historically adjusted back to January 2017, data prior to January 2017 have not been adjusted to the new methodology; therefore, there is a trend break between 2016 and 2017 and any changes over time should be interpreted in the context of the changes in methodology. Of note, in 2018, an estimated 2% of total prescription claims for opioid analgesics dispensed from U.S. retail pharmacies appears to have been voided or reversed

Symphony Health PHAST Prescription Monthly (SHS) database was used to create the “choropleth map”. These maps represent the variability of oxycodone ER utilization across all regions in the U.S. Information on total population in each state was derived from U.S. Census Bureau for 2009, 2012 and 2018.^{3,4,5} The rates were mapped to a color gradient scale based on range and intensity of the oxycodone ER utilization among individual states. The utilization of dispensed prescriptions for oxycodone ER per 10,000 residents was determined by dividing the number of prescriptions dispensed for oxycodone ER in 2009, 2012 and 2018 individually by the census population estimate per state multiplied by 10,000.

4 RESULTS

In 2019, approximately 77% of bottles or packages of oxycodone ER products were sold to the outpatient retail setting; therefore, this review examined the utilization of opioid analgesics from U.S. retail pharmacies.⁶

4.1 PRESCRIPTION DATA

³ U.S. Census Bureau; American Community Survey, 2009 American Community Survey 1-Year Estimates. Accessed January 2020.

⁴ Annual Estimates of the Resident Population by Single Year of Age and Sex for the United States, States, and Puerto Rico Commonwealth: April 1, 2010 to July 1, 2012. Source: U.S. Census Bureau, Population Division. Release Date: June 2013

⁵ Annual Estimates of the Resident Population by Single Year of Age and Sex for the United States, States, and Puerto Rico Commonwealth: April 1, 2010 to July 1, 2018. Source: U.S. Census Bureau, Population Division. Release Date: June 2019

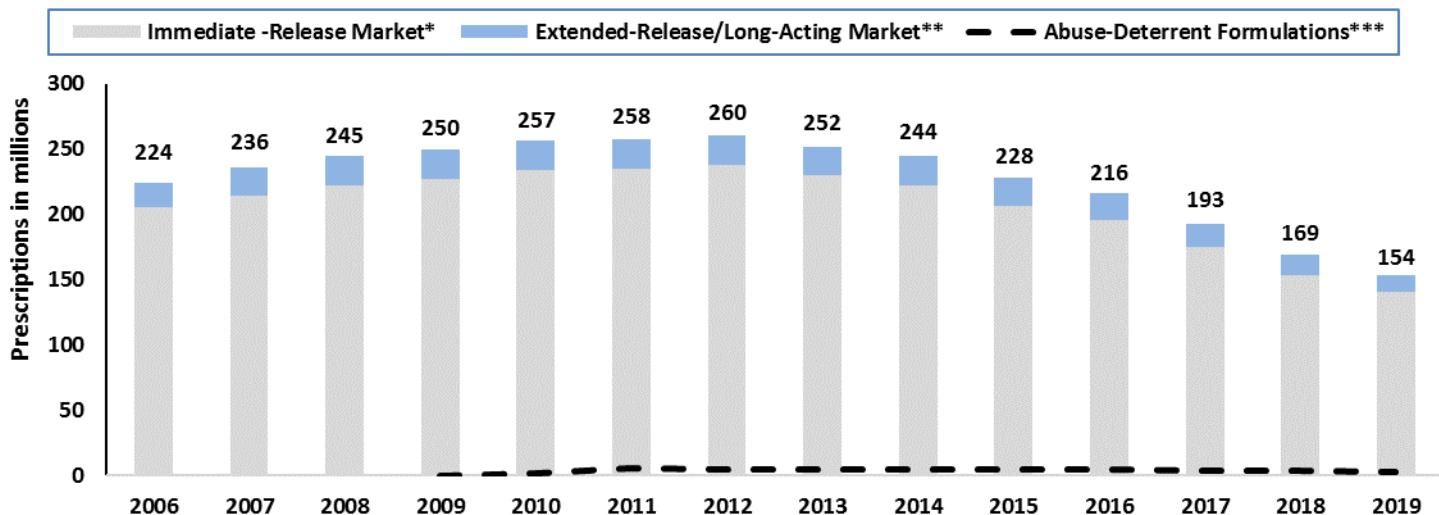
⁶ Source: IQVIA National Sales Perspectives™ 2019. Data extracted February 2020. File: NSP Oxycodone ER distribution 2019.02.24.2020.xlsx

4.1.1 Opioid Analgesics

Figure 1 shows the estimated number of prescriptions dispensed for all opioid analgesics (single and combination products), stratified by formulation (immediate-release, extended-release, and abuse-deterrent) from U.S. outpatient retail pharmacies from January 2006 through December 2019. The total utilization of opioid analgesics peaked in 2012 with 260 million prescriptions then declined by 41% to 154 million prescriptions in 2019. Immediate-release (IR) formulations accounted for 91% and extended-release/long-acting (ER/LA) formulations accounted for 9% of the total opioid analgesic prescriptions dispensed in 2019.

The utilization of IR opioid analgesic prescriptions peaked in 2012 (238 million prescriptions) followed by a 41% steady decline in 2019 (141 million prescriptions). The utilization of ER/LA products was highest (23 million prescriptions) in 2010 with a decline of 43% by 2019 (13 million prescriptions). Abuse-deterrent formulations were introduced to the market in 2009. The utilization of ADF formulations peaked in 2011 (5.6 million prescriptions), followed by a decline of 51% (to 2.7 million prescriptions) in 2019.

Figure 1: Estimated number of prescriptions dispensed for all opioid analgesics from U.S outpatient retail pharmacies, 2006-2019



Source: IQVIA, National Prescription Audit (NPA) and static data 2006-2011. January 2006-December 2019. Static data extracted March 2017, 2012-2017 data extracted February 2018, 2018 data extracted March 2019, 2019 data extracted Jan 24, 2020

*Immediate-Release formulations include oral solids, oral liquids, rectal, nasal, and transmucosal formulations

**Extended-Release/Long-Acting formulations include oral solids and transdermal patches

***Abuse-deterrent formulation opioid products include Arymo ER, Embeda ER, Hysingla ER, Morphabond ER, Xtampza ER, OxyContin ER Reformulated (Approval in April 2010), RoxyBond IR

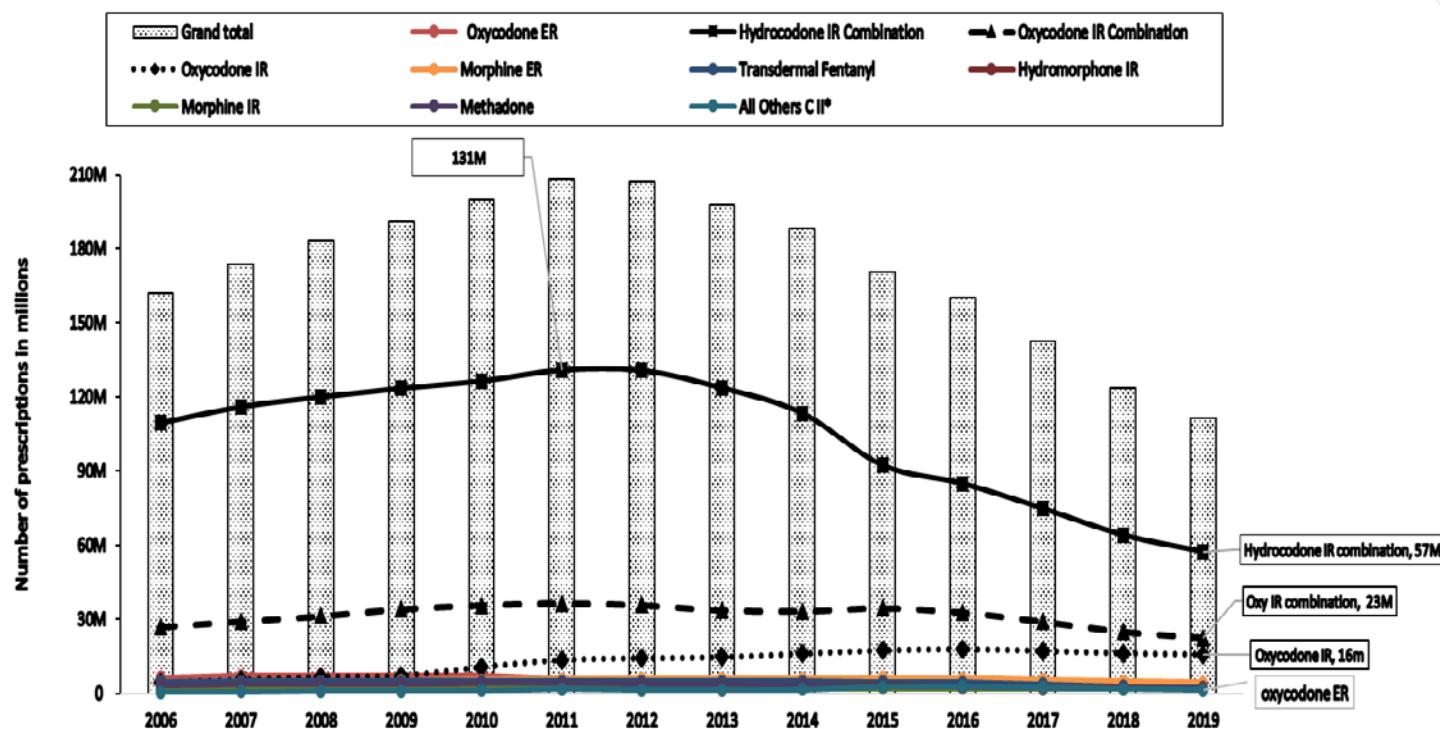
Note: These data include non-injectable opioid analgesics only. Opioid-containing cough-cold products and opioid-containing medication-assisted treatment (MAT) products are not included.

4.1.2 Schedule-II Opioid Analgesics

Figure 2 and Table 2 in Appendix B show the estimated number of dispensed prescriptions for schedule-II opioid analgesics, stratified by molecule from U.S. outpatient retail pharmacies from 2006 through 2019. The utilization of schedule-II opioid analgesics peaked in 2011 with 208 million prescriptions followed by a 47% decline by 2019 (111 million prescriptions). Hydrocodone IR combination products accounted for the highest proportion of use (53%, 57 million prescriptions) followed by the oxycodone IR combination products (21%, 23 million prescriptions) and single-ingredient oxycodone IR (14%, 16 million prescriptions) in 2019.

Hydrocodone IR combination prescriptions declined by 56% from a peak of 131 million prescriptions in 2011 to 57 million prescriptions in 2019. Similar patterns were observed for the oxycodone IR combination products with a 38% decline. In contrast, single-ingredient oxycodone IR increased throughout the study period, from 4 million prescriptions in 2006 to 16 million prescriptions in 2019.

Figure 2: Estimated number of dispensed prescriptions for schedule-II opioid analgesics, stratified by molecule from U.S. outpatient retail pharmacies from 2006 through 2019, annually



Source: IQVIA, National Prescription Audit (NPA) and static data 2006-2014. recent data January 2015-December 2019.

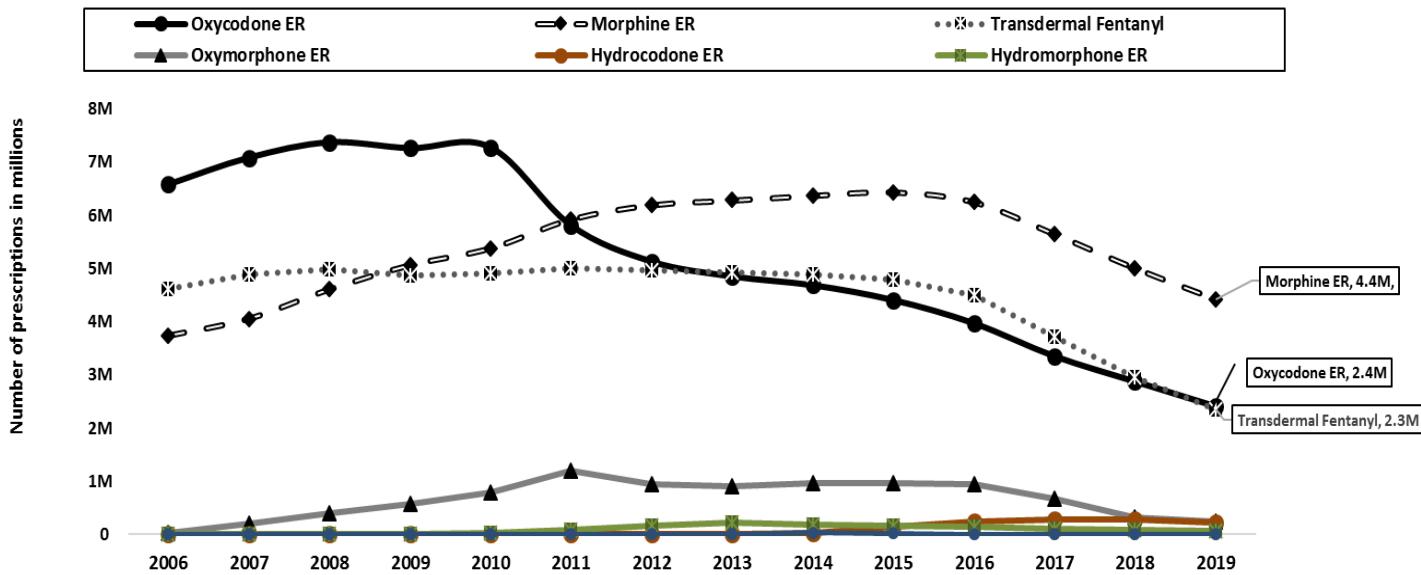
Note: These data include non-injectable opioids only. Opioid-containing cough-cold products and opioid-containing medication-assisted treatment (MAT) products are not included.

4.1.3 Schedule-II Extended-Release/Long-Acting Opioid Analgesics

Figure 3 and Table 3 in Appendix B show the estimated number of prescriptions dispensed for schedule-II ER/LA opioid analgesics, stratified by molecule from U.S. outpatient retail pharmacies from 2006 through 2019. The utilization of ER/LA opioid analgesics peaked in 2010 with 18.4 million prescriptions dispensed then declined by 47% to 9.8 million prescriptions in 2019.

Morphine ER accounted for 46% (4 million prescriptions), followed by oxycodone ER (25%, 2.4 million prescriptions) and transdermal fentanyl (24%, 2.3 million prescriptions) of the estimated total number of prescriptions dispensed for schedule II opioid analgesics in 2019. Oxycodone ER prescriptions decreased by 67% from a peak of 7.4 million prescriptions in 2008. Morphine ER prescriptions peaked to 6.4 million in 2015 and declined by 31% in 2019. The utilization of transdermal fentanyl patches remained consistent from 2006-2016 (4.6-4.9 million prescriptions), but thereafter declined by 53% in 2019.

Figure 3: Estimated number of dispensed prescriptions for schedule-II ER/LA opioid analgesics, stratified by molecule from U.S. outpatient retail pharmacies from 2006 through 2019, annually

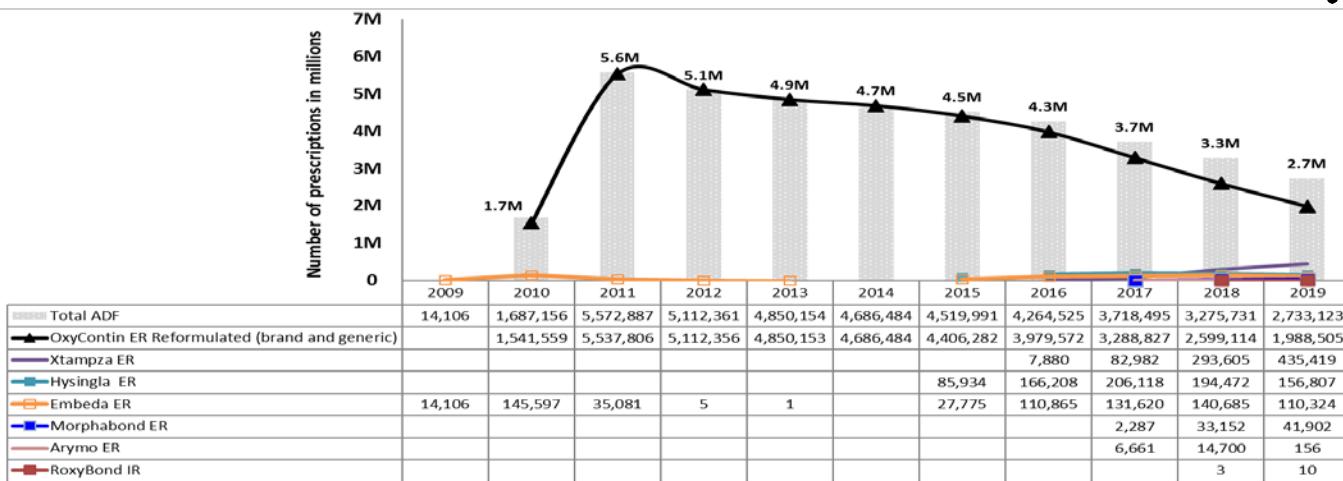


Source: IQVIA, National Prescription Audit (NPA) and static data 2006-2014. recent data January 2014-December 2019.

4.1.4 Abuse-Deterrent Formulations of Opioid Analgesics

Figure 4 shows the estimated number of prescriptions dispensed for abuse-deterrent formulations (ADFs) of opioid analgesics, stratified by product from U.S. outpatient retail pharmacies from 2009 through 2019. An estimated 5.6 million prescriptions were dispensed for abuse-deterrent opioid analgesics which peaked in 2011 then decreased by 51% to approximately 2.7 million prescriptions in 2019. Of these prescriptions, reformulated oxycodone ER accounted for the largest proportion of ADF opioid analgesics with 5.5 million prescriptions in 2011 then decreased by 64% to approximately 2 million prescriptions in 2019. Reformulated oxycodone ER accounted for 73% of dispensed prescriptions in 2019, followed by Xtampza ER (16%), Hysingla ER (6%), Embeda ER (4%) and other ADF products (2% or less).

Figure 4: Estimated number of prescriptions dispensed for abuse-deterrent formulations (ADFs) of opioid analgesics* from U.S. outpatient retail pharmacies from 2009-2019, yearly



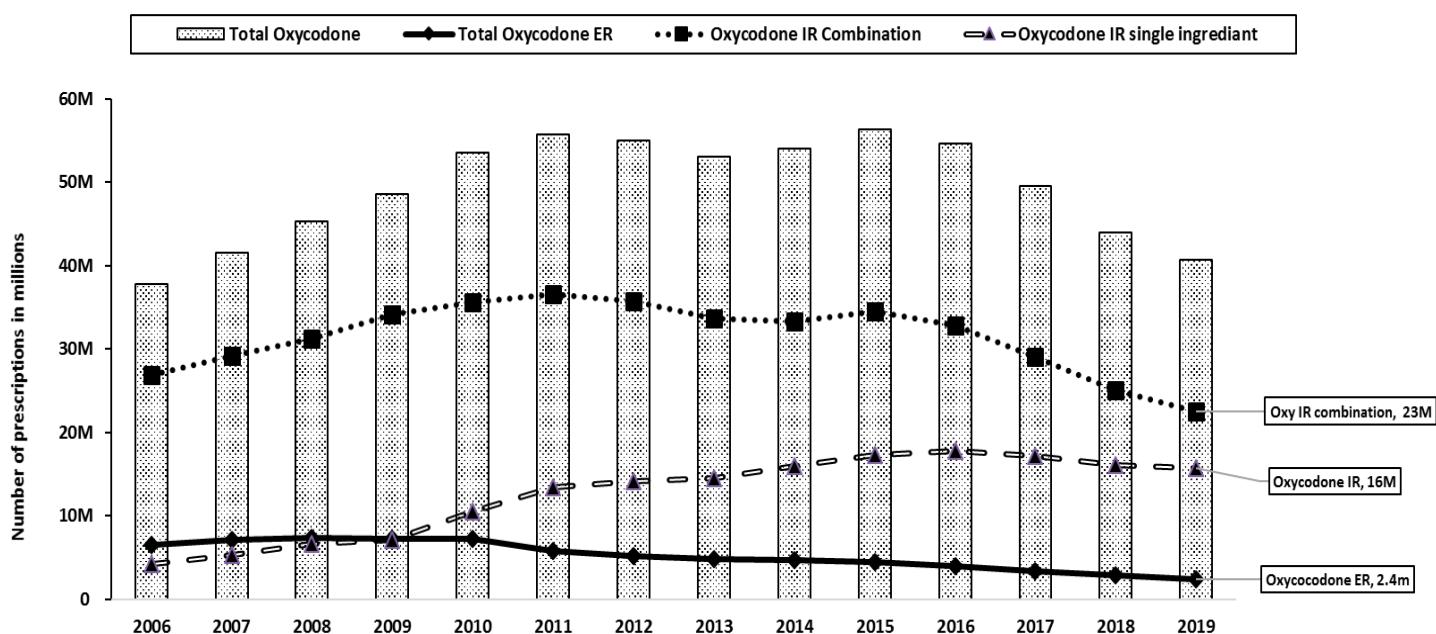
Source: IQVIA, National Prescription Audit (NPA) and static January 2009-December 2019.

Static data extracted March 2017 2012-2017 data extracted February 2018, 2018 data extracted March 2019, 2019 data extracted Jan 24, 2019

4.1.5 All Oxycodone (IR, ER and combination) Products

Figure 5 and Table 4 in Appendix B show the estimated number of prescriptions dispensed for all oxycodone (IR, ER and combination), stratified by product from U.S. outpatient retail pharmacies from 2006 through 2019. During the examined time period, oxycodone IR (single-ingredient and combination) accounted for 94% of the total prescriptions and oxycodone ER accounted for 6% of the total prescriptions. The total utilization of oxycodone IR increased 13% during the examined time-period with the highest proportions of prescriptions dispensed (59% of the total oxycodone prescriptions) in 2019. Single-ingredient oxycodone IR accounted for 41% of the total utilization. The utilization of oxycodone ER decreased 67% from 7.4 million prescriptions in 2008 to 2.4 million prescriptions dispensed in 2019.

Figure 5: Estimated number of prescriptions dispensed for all oxycodone (IR, ER, and combination) products from U.S. outpatient retail pharmacies from 2006-2019, yearly



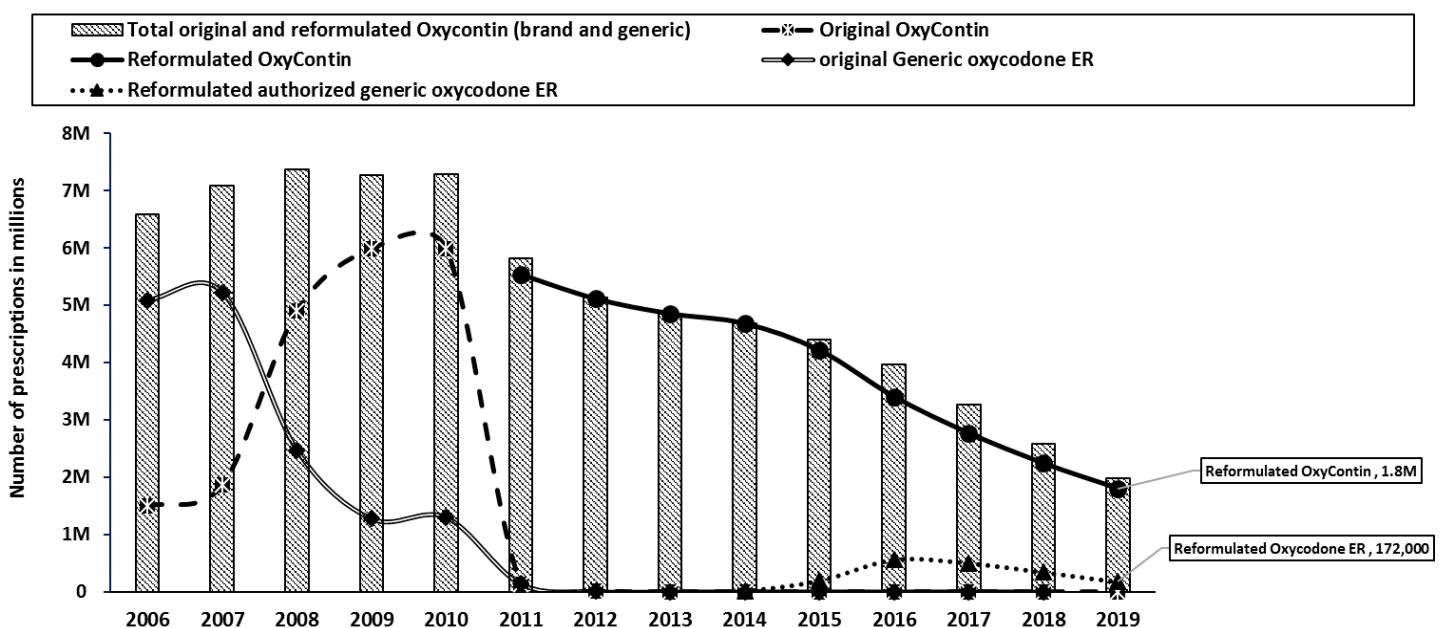
Source: IQVIA National Prescription Audit™ (NPA) 2019. Data extracted Feb 2020. File: NPA Oxycodone ER and comparators by prescriptions 2006-2019. 02.15.2020.xlsx

4.1.6 Oxycodone ER- brand and generics

Figure 6 below and Table 5 in Appendix B show the estimated number of prescriptions dispensed for original OxyContin, reformulated OxyContin, original generic oxycodone ER and reformulated authorized generic oxycodone ER, from U.S. outpatient retail pharmacies from 2006 through 2019.

In August 2010, distribution of the original formulation of OxyContin ceased and reformulated OxyContin became available in the market. As a result, prescriptions for OxyContin original formulation dropped abruptly from 6 million prescriptions in 2010 to 136,000 prescriptions in 2011. The reformulated OxyContin accounted for approximately 5.5 million prescriptions in 2011, however, by 2019, decreased to 1.8 million prescriptions. The reformulated authorized generic oxycodone ER was introduced in 2014, utilization peaked in 2016 with 560,000 prescriptions then steadily declined to 172,000 prescriptions dispensed in 2019.

Figure 6: Estimated number of dispensed prescriptions for original and reformulated oxycodone ER products from U.S. outpatient retail pharmacies from 2006 through 2019, annually



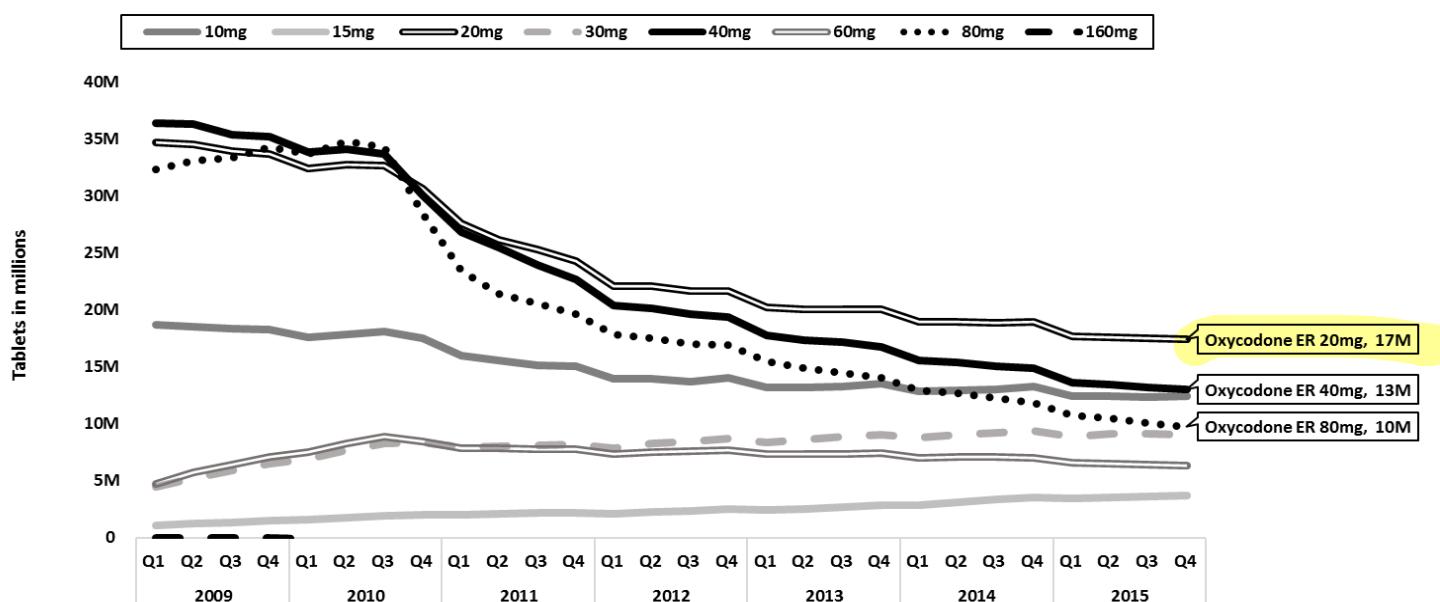
Source: IQVIA National Prescription Audit™ (NPA) 2019. Data extracted Feb 2020. File: NPA Oxycodone ER and comparators by prescriptions 2006-2019. 02.15.2020.xlsx

Figure 7 and Table 6 in Appendix B show the estimated number of tablets dispensed for original and reformulated oxycodone ER formulations from U.S. outpatient retail pharmacies stratified by strength from 2009 through 2015, quarterly. Approximately 72 to 138 million oxycodone ER tablets were dispensed quarterly from 2009 through 2015 with a peak of 138 million tablets in the third quarter of 2010. The highest number of tablets dispensed for the 20mg and 40mg strength was during the first quarter of 2009 with 35 million tablets and 36 million tablets, respectively. The highest number of tablets dispensed for the 80 mg strength was during the second quarter of 2010 with 35 million tablets.

During the fourth quarter of 2015, original and reformulated oxycodone ER 20 mg accounted for the most common strength dispensed (17 million tablets), which is a 50% decrease from its peak (35 million tablets) in the first quarter of 2009. Although, the total utilization of oxycodone ER decreased during the examined time period, the 10mg and 20mg strength remained the most commonly dispensed with 23% (6.4 million) and 26% (7.4 million) of the total tablets dispensed, respectively during the fourth quarter of 2019 (data not shown)⁷; 80mg oxycodone ER tablets accounted for 8% (2.3 million tablets) of the total tablets dispensed during the fourth quarter of 2019.

⁷ IQVIA National Prescription Audit™ (NPA) 2019. Data extracted Feb 2020. File: ADHOC data-Oxycodone ER - units by strengths 2009-2019. 02.18.2020.xlsx

Figure 7: Estimated number of tablets dispensed for original and reformulated oxycodone ER stratified by strength from U.S. outpatient retail pharmacies from 2009 through 2015, quarterly



Source: IQVIA National Prescription Audit™ (NPA) 2019. Data extracted Feb 2020. File: ADHOC data-Oxycodone ER - units by strengths 2009-2019. 02.18.2020.xlsx

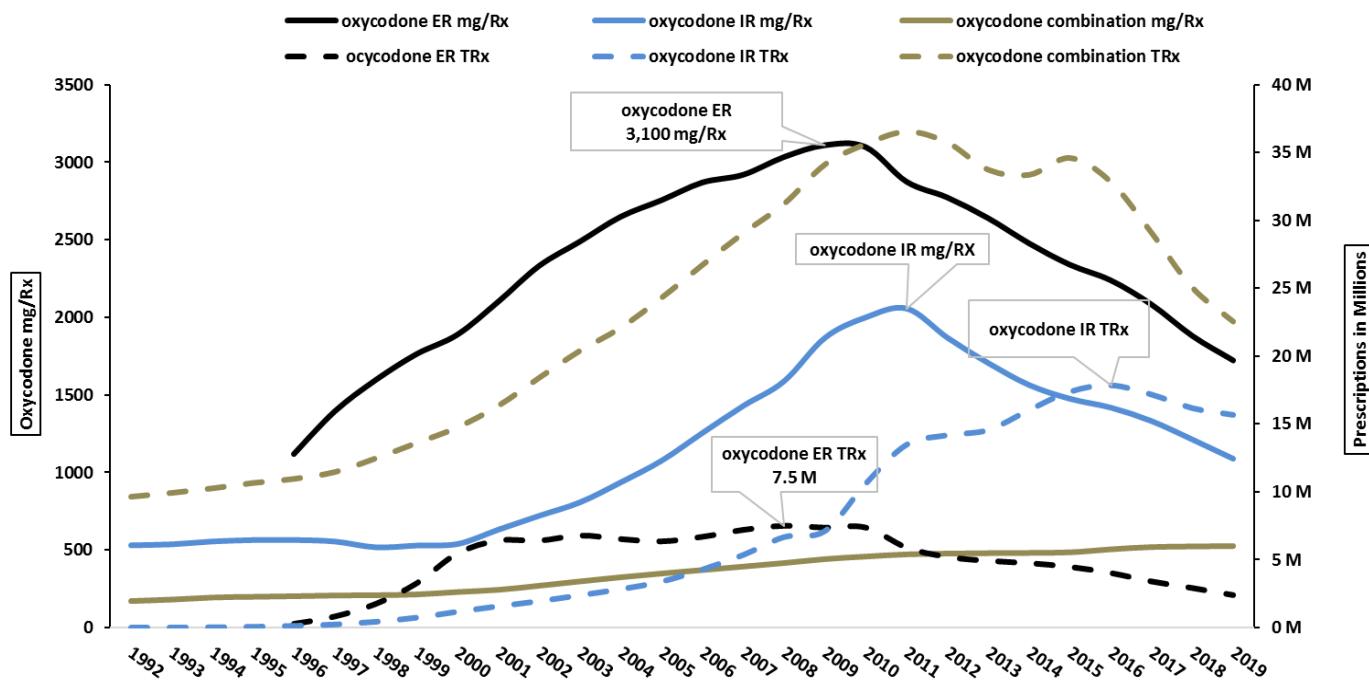
Figure 8 shows the estimated number of dispensed prescriptions and average milligrams per prescription (mg/Rx) for oxycodone (IR, ER, and combination) from U.S. outpatient retail pharmacies from 1992 through 2019, yearly. The aggregate average mg/Rx was calculated based on the estimated total number of mg of oxycodone dispensed per year divided by the aggregate estimated number of prescriptions dispensed per calendar year.

The aggregate average mg/Rx of oxycodone ER prescriptions decreased 45% from its peak of 3,100 mg/Rx in 2009 to 1700 mg/Rx in 2019 and the total number of prescriptions dispensed for oxycodone ER decreased 67% from its peak in 2008 (7.4 million prescription) to 2.4 million prescriptions in 2019.

For single-ingredient oxycodone IR products, the average mg/Rx decreased 47% from its peak of 2,000 mg/Rx in 2011 to 1,100 mg/Rx in 2019 and the total number of prescriptions dispensed decreased 12% from its peak in 2016 (17.9 million prescriptions) to 15.7 million prescriptions in 2019.

The average mg/Rx for combination oxycodone IR products has increased during the examined time to 524 mg/Rx by 2019; however, the total number of prescriptions dispensed for combination oxycodone IR products decreased 38% from its peak in 2011 (36.5 million prescriptions) to 22.6 million prescriptions in 2019.

Figure 8: Estimated number of prescriptions and yearly aggregate average milligram/prescriptions dispensed for oxycodone (IR, ER, and combination) from U.S. outpatient retail pharmacies from 1992 through 2019, yearly



Source: IQVIA National Prescription Audit™. 2019. Data extracted Feb 2020. File: MG Rx and MME graph with 2019 data oxycodone in kilograms 03.25.2020 (002).xlsx

4.2 PRESCRIBER SPECIALTIES

Table 7 shows the top prescriber specialties for oxycodone ER prescriptions dispensed from U.S. outpatient retail pharmacies in 2009 (original), 2012 (after reformulation), and 2019 (recent).

In 2019, mid-level practitioners (physician assistants/nurse practitioners) prescribed approximately 30% of the total oxycodone ER prescriptions dispensed, followed by FP/GP/IM (family practice/general practice/internal Medicine) at 26% and pain-medicine/anesthesiology at 22%. In contrast, FP/GP/IM accounted for the highest proportion of prescriptions followed by mid-level practitioners in 2009 and 2012. Although the number of prescriptions dispensed for oxycodone ER decreased during the examined time-period, the proportion of prescriptions written by pain medicine/ anesthesiologists increased from 14% to 22% of the total prescriptions dispensed in 2019.

P1

Table 7: Top prescriber specialties of Oxycodone ER in 2009 (original), 2012 (after reformulation), and 2019 (recent), based on the estimated number of dispensed prescriptions from U.S. outpatient retail pharmacies

| | 2009 | | 2012 | | 2019 | |
|--|------------------|-------------|------------------|-------------|------------------|---------------|
| | Rx (N) | Share (%) | Rx (N) | Share (%) | Rx (N) | Share (%) |
| Total oxycodone ER | 7,263,121 | 100% | 5,148,478 | 100% | 2,423,605 | 100.0% |
| Physician Assistants/Nurse Practitioners | 662,957 | 9.1% | 749,257 | 14.6% | 716,834 | 29.6% |
| Family Practice/General Practice/Internal Medicine | 3,132,887 | 43.1% | 1,939,505 | 37.7% | 627,461 | 25.9% |
| Pain Medicine/Anesthesiology | 1,039,697 | 14.3% | 844,602 | 16.4% | 530,063 | 21.9% |
| Physical Medicine & Rehab | 630,075 | 8.7% | 489,882 | 9.5% | 249,731 | 10.3% |
| Oncology | 279,665 | 3.9% | 212,015 | 4.1% | 77,983 | 3.2% |
| Neurology | 206,661 | 2.8% | 127,385 | 2.5% | 44,578 | 1.8% |
| Orthopedic Surgery | 305,232 | 4.2% | 210,027 | 4.1% | 31,763 | 1.3% |
| Specialty Unspecified | 150,094 | 2.1% | 94,305 | 1.8% | 11,790 | 0.5% |
| All Others | 855,851 | 11.8% | 481,499 | 9.4% | 133,403 | 5.5% |

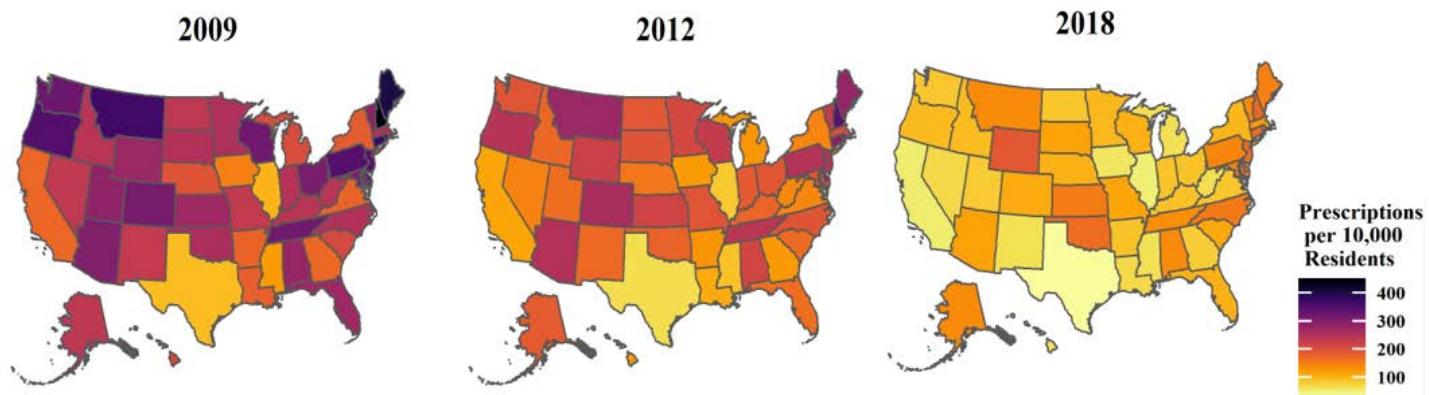
Source: IQVIA National Prescription Audit™. 2019. Data extracted Feb 2020. File: Updated-NPA top 10-Specialty and ADHOC-Oxycodone ER 2015-2019 Retail only Feb-11-2020

4.3 OXYCODONE ER PRESCRIPTIONS PER 10,000 RESIDENTS

Figure 9 below and Table 8 in Appendix B show the number of dispensed prescriptions of oxycodone ER per 10,000 residents from U.S outpatient retail pharmacies stratified by U.S states in 2009, 2012 and 2018. In 2009, oxycodone ER prescriptions ranged from 93-439 prescriptions per 10,000 residents per state. The number of prescriptions dispensed for oxycodone ER were highest in Rhode Island, New Hampshire and Maine in 2009 with over 400 prescriptions per 10,000 residents. In 2012, the oxycodone ER Prescriptions ranged from 83-340 prescriptions per 10,000 residents. The highest prescription to resident ratio remained in Rhode Island, New Hampshire and Maine. By 2018, the utilization of oxycodone ER decreased, ranging from 33-188 prescription per 10,000 residents with the highest prescription to resident ratio in Wyoming, Delaware and New Hampshire.

Geography of
dispensing

Figure 9: Estimated number of Prescriptions dispensed for oxycodone ER per 10,000 residents from U.S. outpatient retail pharmacies in 2009⁸, 2012⁹ and 2018¹⁰



Source: Symphony Health PHAST Prescription Monthly. Data extracted April 2020 File: SHS Oxycodone ER Geo Map by Prescriptions and residents 2009-2012 and 2018. 04.15.2020.xlsx

5 DISCUSSION

This review examined the outpatient retail utilization of oxycodone ER, IR and combination products, schedule-II opioid analgesic and abuse-deterrant opioid analgesics, with a focus on single-ingredient original and reformulated oxycodone ER to provide background for the Advisory Committee discussion.

Findings from our analysis showed the utilization of oxycodone ER decreased by 67% from a peak of 7.4 million prescriptions in 2008 to 2.4 million prescriptions dispensed in 2019. Oxycodone ER accounted for 6% of oxycodone prescriptions and oxycodone IR (single-ingredient and combination) accounted for 94% of oxycodone prescriptions in 2019. Reformulated OxyContin was approved in April 2010 along with a withdrawal of the distribution of original formulation of OxyContin resulting in abrupt drop of prescriptions dispensed for OxyContin original formulation.

In addition to a decline in the number of prescriptions dispensed, the strength and dosage of oxycodone ER prescriptions also decreased in recent years. Similar to the peak in the number of prescriptions dispensed for oxycodone ER in 2008, the aggregate average mg/Rx for oxycodone ER was highest in 2009 at 3,100 mg/Rx before decreasing to 1700 mg/Rx in 2019. This finding is in line with patterns in the most common strengths of oxycodone ER dispensed over time. The most common strengths of oxycodone ER tablets were dispensed for 40 mg and 80 mg during the fourth quarter of 2009. However,

⁸ 2009: U.S. Census Bureau; American Community Survey, 2009 American Community Survey 1-Year Estimates. Accessed January 2020.

⁹ 2012: Annual Estimates of the Resident Population by Single Year of Age and Sex for the United States, States, and Puerto Rico Commonwealth: April 1, 2010 to July 1, 2012: Source: U.S. Census Bureau, Population Division Release Date: June 2013

¹⁰ 2018: Annual Estimates of the Resident Population by Single Year of Age and Sex for the United States, States, and Puerto Rico Commonwealth: April 1, 2010 to July 1, 2018. Source: U.S. Census Bureau, Population Division Release Date: June 2019

this trend changed by the fourth quarter of 2019, where oxycodone ER 20 mg accounted for the highest proportions of all strengths.

Mid-level practitioners were the top-prescribing specialties of the total oxycodone ER prescriptions, followed by FP/GP/IM (Family Practice/General Practice/Internal Medicine) in 2019. Of note, FP/GP/IM accounted for the highest proportion of prescriptions followed by mid-level practitioners in 2009 and 2012. This change in the type of providers writing for oxycodone is likely due to the changes increasing prescriptive authority for mid-level practitioners as well as the increasing number of mid-level practitioners providing care. Changes include the American Medical Association (AMA) nurse practitioner prescriptive authority in 2017 that allows prescriptive authority to nurse practitioners for drugs falling into schedule II¹¹. In addition, although the number of prescriptions dispensed for oxycodone ER decreased during the examined time-period (2009, 2012 and 2019), the proportion of prescriptions written by pain medicine/anesthesiologists increased for the total prescriptions dispensed in 2019.

Although the decline in utilization of oxycodone ER began after 2008 and continued after reformulation, there were changes in the patterns of oxycodone ER such as the decrease in mg/Rx and lower utilization of the higher strength formulations. The decrease of utilization of oxycodone ER formulation may be due to several reasons including the strengthening of warnings on the drug label, expanding patient and prescriber educational campaigns, interventions implemented by federal, state, local governments, recommended limitations on opioid dosages, payer-based dispensing restrictions, prescription drug monitoring programs (PDMP), risk evaluation mitigation strategies (REMS) and issuing guidance for the pharmaceutical industry regarding the development of abuse-deterrent formulations of opioid products in addition to many other interventions.¹²

6 CONCLUSION

After the introduction of ADFs in 2009, utilization of oxycodone ER prescriptions decreased 67% by 2019. Similarly, in terms of dosing, the peak of average mg of oxycodone/prescription of oxycodone ER was observed in 2009 with 3100mg/Rx followed by a decline to 1700mg/Rx in 2019. The most common strengths of oxycodone ER tablets were dispensed for 40 mg and 80 mg during the fourth quarter of 2009. By the fourth quarter of 2019 oxycodone ER 20 mg accounted for the highest proportions of all strengths.

¹¹ Nurse Practitioner Prescriptive Authority. (n.d.). Retrieved from <https://nursinglicensemap.com/resources/nurse-practitioner-prescriptive-authority/>

¹² Chai, Grace. "New Opioid Analgesic Approvals and Outpatient Utilization of Opioid Analgesics in the United States, 1997 through 2015." *Anesthesiology | ASA Publications*, 1 May 2018, [anesthesiology.pubs.asahq.org/article.aspx?articleid=2675976](https://pubs.asahq.org/article.aspx?articleid=2675976).

7 APPENDIX A DRUG UTILIZATION DATABASE DESCRIPTIONS

IQVIA National Sales Perspectives™ (NSP)

The IQVIA 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 nonretail markets. Volume is expressed in terms of sales dollars, eashes, 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. The manufacturer sales distribution data do not provide an estimate of direct patient use but do provide a national estimate of units sold from the manufacturer to various retail and non-retail settings of care. The amount of product purchased by these settings of care may be a possible surrogate for use if we assume that facilities purchase drugs in quantities reflective of actual patient use.

IQVIA National Prescription Audit™ (NPA)

The IQVIA 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 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 3.7 billion prescription claims per year, captured from a sample of the universe of approximately 58,900 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 92% 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 60 – 86% (varies by class and geography) of mail service pharmacies and approximately 75 – 83% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month. Due to the changing pharmaceutical marketplace, IQVIA has implemented changes to its prescription database to manage prescription voids, reversals, and abandonments that span multiple weeks. Beginning in January 2019, IQVIA has projected published prescription volumes dispensed from the retail pharmacies based on sold date, instead of date of adjudication (i.e., fill date). Projected estimates have been adjusted and restated in the database to January 2017, data prior to 2017 remain unadjusted. As a result, a trend break occurs between 2016 and 2017 prescription volumes dispensed from the retail pharmacies, any changes over time must be interpreted in the context of the changes in the underlying data and methodology.

Dispensed prescription estimates are nationally projected based on a sample of prescriptions claims from mail-order/ specialty and retail pharmacies. Summarization of these projected estimates across time periods and/or settings of care may lead to differences in prescription count due to rounding attributable to the projection methodology utilized. No statistical tests were performed on these estimates to determine statistically significant changes over time. Therefore, all changes over time should be considered approximate, and may be due to random error.

Findings from this review should be interpreted within the context of the known limitations of the databases used. Dispensed prescription estimates are nationally projected based on a sample of

prescriptions claims from U.S. retail pharmacies. Summarization of these projected estimates across time periods and/or products may lead to differences in prescription count due to rounding attributable to the projection methodology utilized. Moreover, the utilization patterns of opioid analgesics in the retail setting might not represent the utilization patterns in other settings of care such as inpatient and clinic settings, which were not examined in this review.

PHAST™ Prescription Monthly

PHAST Prescription Monthly is a syndicated view of U.S. retail and mail order pharmacy prescription activity, updated on a monthly basis. PHAST Prescription Monthly covers over 65,000 pharmacies in the sample including retail, mail order, specialty and other non-retail outlets. The dispensed prescriptions in the sample represent approximately 92% of all U.S. retail prescriptions (cash, Medicaid, commercial) as well as 69% of all U.S. mail order prescriptions. The retail and mail order prescriptions are projected to the national level.

8 APPENDIX B DRUG UTILIZATION TABLES

Table 2: Estimated number of dispensed prescriptions for schedule-II opioid analgesics, stratified by molecule from U.S. outpatient retail pharmacies from 2006 through 2019, annually

| | 2006 | | 2007 | | 2008 | | 2009 | | 2010 | | 2011 | | 2012 | |
|-------------------------------------|--------------------|-------------|--------------------|-------------|--------------------|-------------|--------------------|-------------|--------------------|-------------|--------------------|-------------|--------------------|-------------|
| | Rx (N) | Share (%) |
| Total Oxycodone ER | 6,580,531 | 100% | 7,084,898 | 100% | 7,373,310 | 100% | 7,263,667 | 100% | 7,281,009 | 100% | 5,811,684 | 100% | 5,131,465 | 100% |
| Oxycontin Original | 1,492,308 | 22.7% | 1,870,454 | 26.4% | 4,905,290 | 66.5% | 5,990,029 | 82.5% | 5,984,113 | 82.2% | 135,709 | 2.3% | 14,002 | 0.3% |
| Oxycontin Reformulated | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | 5,537,806 | 95.3% | 5,112,356 | 99.6% |
| Oxycodone ER Original | 5,088,223 | 77.3% | 5,214,444 | 73.6% | 2,468,020 | 33.5% | 1,273,638 | 21.3% | 1,296,896 | 17.8% | 138,169 | 2.4% | 5,107 | 0.1% |
| Oxycodone ER Reformulated | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Xtampza ER | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Other Opioid C II Analgesics | 155,553,040 | 100% | 166,782,957 | 100% | 175,600,653 | 100% | 183,573,025 | 100% | 192,401,829 | 100% | 202,158,019 | 100% | 201,792,766 | 100% |
| Hydrocodone IR Combination | 109,458,295 | 70.4% | 116,028,774 | 69.6% | 120,045,910 | 68.4% | 123,560,313 | 67.3% | 126,486,873 | 65.7% | 130,931,707 | 64.8% | 130,755,781 | 64.8% |
| Oxycodone IR Combination | 26,880,965 | 17.3% | 29,168,003 | 17.5% | 31,294,342 | 17.8% | 34,173,202 | 18.6% | 35,660,363 | 18.5% | 36,546,292 | 18.1% | 35,737,524 | 17.7% |
| Oxycodone IR | 4,277,980 | 2.8% | 5,347,486 | 3.2% | 6,650,239 | 3.8% | 7,097,660 | 3.9% | 10,576,205 | 5.5% | 13,427,054 | 6.6% | 14,108,130 | 7.0% |
| Morphine ER | 3,738,260 | 2.4% | 4,058,238 | 2.4% | 4,612,829 | 2.6% | 5,067,499 | 2.8% | 5,386,291 | 2.8% | 5,930,760 | 2.9% | 6,198,303 | 3.1% |
| Transdermal Fentanyl | 4,619,907 | 3.0% | 4,886,973 | 2.9% | 4,987,252 | 2.8% | 4,866,117 | 2.7% | 4,912,480 | 2.6% | 4,997,384 | 2.5% | 4,961,133 | 2.5% |
| Hydromorphone IR | 1,541,318 | 1.0% | 1,790,722 | 1.1% | 2,052,870 | 1.2% | 2,408,979 | 1.3% | 2,595,238 | 1.3% | 2,912,786 | 1.4% | 3,086,274 | 1.5% |
| Morphine IR | 1,204,302 | 0.8% | 1,295,979 | 0.8% | 1,431,924 | 0.8% | 1,581,532 | 0.9% | 1,687,895 | 0.9% | 1,793,771 | 0.9% | 1,845,083 | 0.9% |
| Methadone* | 3,425,724 | 2.2% | 3,637,978 | 2.2% | 3,760,772 | 2.1% | 3,863,991 | 2.1% | 3,935,176 | 2.0% | 3,938,607 | 1.9% | 3,725,332 | 1.8% |
| Oxymorphone ER | 21,375 | <0.1% | 196,975 | 0.1% | 400,138 | 0.2% | 582,710 | 0.3% | 786,827 | 0.4% | 1,196,953 | 0.6% | 939,908 | 0.5% |
| Hydrocodone ER | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Oxymorphone IR | 8,927 | <0.1% | 62,409 | <0.1% | 113,167 | 0.1% | 165,094 | 0.1% | 180,894 | 0.1% | 239,560 | 0.1% | 163,380 | 0.1% |
| Hydromorphone ER | 1 | <0.1% | 1 | <0.1% | -- | -- | 2 | <0.1% | 27,011 | <0.1% | 95,823 | <0.1% | 170,654 | 0.1% |
| Transmucosal Fentanyl | 375,986 | 0.2% | 309,419 | 0.2% | 251,210 | 0.1% | 205,926 | 0.1% | 166,576 | 0.1% | 147,322 | 0.1% | 101,264 | 0.1% |
| Acetaminophen/Oxycodone ER | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| All Others C II | -- | -- |
| | 2013 | | 2014 | | 2015 | | 2016 | | 2017 | | 2018 | | 2019 | |
| | Rx (N) | Share (%) |
| Total Oxycodone ER | 4,851,762 | 100% | 4,686,915 | 100% | 4,406,612 | 100% | 3,970,627 | 100% | 3,351,303 | 100% | 2,875,446 | 100% | 2,408,210 | 100% |
| Oxycontin Original | 1,327 | <0.1% | 293 | <0.1% | 227 | <0.1% | 83 | <0.1% | 33 | <0.1% | 39 | <0.1% | 14 | <0.1% |
| Oxycontin Reformulated | 4,850,153 | 100% | 4,679,869 | 100% | 4,214,781 | 95.6% | 3,404,029 | 85.7% | 2,769,866 | 82.7% | 2,243,041 | 78.0% | 1,803,717 | 74.9% |
| Oxycodone ER Original | 282 | <0.1% | 138 | <0.1% | 103 | <0.1% | 76 | <0.1% | 24 | <0.1% | 1 | <0.1 | -- | -- |
| Oxycodone ER Reformulated | -- | -- | 6,615 | 0.1% | 191,604 | 4.3% | 558,934 | 14.1% | 499,580 | 14.9% | 340,981 | 11.9% | 172,160 | 7.1% |
| Xtampza ER | -- | -- | -- | -- | -- | -- | 7,880 | 0.2% | 82,982 | 2.5% | 293,605 | 10.2% | 435,419 | 18.1% |
| Other Opioid C II Analgesics | 192,907,539 | 100% | 183,651,757 | 100% | 165,937,370 | 100% | 156,287,903 | 100% | 139,190,290 | 100% | 120,667,622 | 100% | 108,866,618 | 100% |
| Hydrocodone IR Combination | 123,656,888 | 64.1% | 113,397,454 | 61.7% | 92,347,145 | 55.7% | 84,899,055 | 54.3% | 74,796,375 | 53.7% | 64,041,349 | 53.1% | 57,269,463 | 52.6% |
| Oxycodone IR Combination | 33,718,084 | 17.5% | 33,337,954 | 18.2% | 34,573,991 | 20.8% | 32,819,232 | 21.0% | 29,065,659 | 20.9% | 25,026,512 | 20.7% | 22,561,496 | 20.7% |
| Oxycodone IR | 14,513,238 | 7.5% | 15,972,555 | 8.7% | 17,317,048 | 10.4% | 17,801,720 | 11.4% | 17,135,194 | 12.3% | 16,136,935 | 13.4% | 15,691,229 | 14.4% |
| Morphine ER | 6,288,088 | 3.3% | 6,375,570 | 3.5% | 6,441,121 | 3.9% | 6,256,262 | 4.0% | 5,651,221 | 4.1% | 5,008,279 | 4.2% | 4,426,406 | 4.1% |
| Transdermal Fentanyl | 4,923,139 | 2.6% | 4,881,447 | 2.7% | 4,791,686 | 2.9% | 4,502,576 | 2.9% | 3,724,634 | 2.7% | 2,963,377 | 2.5% | 2,346,870 | 2.2% |
| Hydromorphone IR | 3,044,891 | 1.6% | 3,031,568 | 1.7% | 3,011,224 | 1.8% | 2,790,646 | 1.8% | 2,452,803 | 1.8% | 2,112,413 | 1.8% | 1,915,093 | 1.8% |
| Morphine IR | 1,869,195 | 1.0% | 1,892,574 | 1.0% | 1,888,174 | 1.1% | 1,873,243 | 1.2% | 1,798,190 | 1.3% | 1,737,889 | 1.4% | 1,646,865 | 1.5% |
| Methadone* | 3,484,537 | 1.8% | 3,242,281 | 1.8% | 2,846,882 | 1.7% | 2,591,013 | 1.7% | 2,241,870 | 1.6% | 1,918,665 | 1.6% | 1,646,190 | 1.5% |
| Oxymorphone ER | 901,307 | 0.5% | 960,933 | 0.5% | 968,029 | 0.6% | 947,081 | 0.6% | 667,401 | 0.5% | 324,858 | 0.3% | 238,006 | 0.2% |
| Hydrocodone ER | -- | -- | 35,093 | 0.0% | 149,957 | 0.1% | 240,748 | 0.2% | 274,804 | 0.2% | 275,302 | 0.2% | 227,124 | 0.2% |
| Oxymorphone IR | 186,550 | 0.1% | 212,113 | 0.1% | 212,759 | 0.1% | 209,437 | 0.1% | 168,141 | 0.1% | 117,095 | 0.1% | 93,322 | 0.1% |
| Hydromorphone ER | 226,452 | 0.1% | 185,035 | 0.1% | 160,632 | 0.1% | 138,126 | 0.1% | 115,219 | 0.1% | 96,703 | 0.1% | 72,200 | 0.1% |
| Transmucosal Fentanyl | 95,170 | <0.1 | 95,992 | 0.1% | 90,556 | 0.1% | 62,892 | <0.1% | 38,272 | <0.1% | 23,177 | <0.1% | 14,109 | <0.1% |
| Acetaminophen/Oxycodone ER | -- | -- | 31,188 | <0.1 | 19,355 | <0.1% | 6,994 | <0.1% | 2,622 | <0.1% | 13 | <0.1% | 4 | <0.1% |
| All Others C II | -- | -- | -- | -- | 1,117,300 | 0.6% | 1,218,764 | 0.8% | 1,098,769 | 0.8% | 908,245 | 0.8% | 732,354 | 0.7% |

Source: IQVIA National Prescription Audit™ 2019. Data extracted Feb 2020. File: NPA Oxycodone ER and comparators by prescriptions 2006-2019. 02.15.2020.xlsx

*Immediate molecules include will be oral solids, liquids, rectal, transmucosal and nasal products.

Table 3: Estimated number of dispensed prescriptions for schedule-II ER/LA opioid analgesics, stratified by molecule from U.S. outpatient retail pharmacies from 2006 through 2019, annually

| | 2006 | | 2007 | | 2008 | | 2009 | | 2010 | | 2011 | | 2012 | |
|----------------------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|
| | Rx (N)) | Share (%) |
| Total ER-LA | 14,960,074 | 100% | 16,227,085 | 100% | 17,373,529 | 100% | 17,779,995 | 100% | 18,393,618 | 100% | 18,032,604 | 100% | 17,401,463 | 100% |
| Oxycodone ER | 6,580,531 | 44.0% | 7,084,898 | 43.7% | 7,373,310 | 42.4% | 7,263,667 | 40.9% | 7,281,009 | 39.6% | 5,811,684 | 32.2% | 5,131,465 | 29.5% |
| Morphine ER | 3,738,260 | 25.0% | 4,058,238 | 25.0% | 4,612,829 | 26.6% | 5,067,499 | 28.5% | 5,386,291 | 29.3% | 5,930,760 | 32.9% | 6,198,303 | 35.6% |
| Transdermal Fentanyl | 4,619,907 | 30.9% | 4,886,973 | 30.1% | 4,987,252 | 28.7% | 4,866,117 | 27.4% | 4,912,480 | 26.7% | 4,997,384 | 27.7% | 4,961,133 | 28.5% |
| Oxymorphone ER | 21,375 | 0.1% | 196,975 | 1.2% | 400,138 | 2.3% | 582,710 | 3.3% | 786,827 | 4.3% | 1,196,953 | 6.6% | 939,908 | 5.4% |
| Hydrocodone ER | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Hydromorphone ER | 1 | <0.1% | 1 | <0.1% | -- | -- | 2 | <0.1% | 27,011 | 0.1% | 95,823 | 0.5% | 170,654 | 1.0% |
| Acetaminophen/Oxycodone ER | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| | 2013 | | 2014 | | 2015 | | 2016 | | 2017 | | 2018 | | 2019 | |
| | Rx (N)) | Share (%) |
| Total ER-LA | 17,190,748 | 100% | 17,156,181 | 100% | 16,937,392 | 100% | 16,062,414 | 100% | 13,787,204 | 100% | 11,543,978 | 100% | 9,718,820 | 100% |
| Oxycodone ER | 4,851,762 | 28.2% | 4,686,915 | 27.3% | 4,406,612 | 26.0% | 3,970,627 | 24.7% | 3,351,303 | 24.3% | 2,875,446 | 24.9% | 2,408,210 | 24.8% |
| Morphine ER | 6,288,088 | 36.6% | 6,375,570 | 37.2% | 6,441,121 | 38.0% | 6,256,262 | 38.9% | 5,651,221 | 41.0% | 5,008,279 | 43.4% | 4,426,406 | 45.3% |
| Transdermal Fentanyl | 4,923,139 | 28.6% | 4,881,447 | 28.5% | 4,791,686 | 28.3% | 4,502,576 | 28.0% | 3,724,634 | 27.0% | 2,963,377 | 25.7% | 2,346,870 | 24.1% |
| Oxymorphone ER | 901,307 | 5.2% | 960,933 | 5.6% | 968,029 | 5.7% | 947,081 | 5.9% | 667,401 | 4.8% | 324,858 | 2.8% | 238,006 | 2.4% |
| Hydrocodone ER | -- | -- | 35,093 | 0.2% | 149,957 | 0.9% | 240,748 | 1.5% | 274,804 | 2.0% | 275,302 | 2.4% | 227,124 | 2.3% |
| Hydromorphone ER | 226,452 | 1.3% | 185,035 | 1.1% | 160,632 | 0.9% | 138,126 | 0.9% | 115,219 | 0.8% | 96,703 | 0.8% | 72,200 | 0.7% |
| Acetaminophen/Oxycodone ER | -- | -- | 31,188 | 0.2% | 19,355 | 0.1% | 6,994 | 0.1% | 2,622 | <0.1% | 13 | <0.1% | 4 | <0.1% |

Source: IQVIA National Prescription Audit™ 2019. Data extracted Feb 2020. File: NPA Oxycodone ER and comparators by prescriptions 2006-2019. 02.15.2020.xlsx

Table 4: Estimated number of prescriptions dispensed for all oxycodone (IR, ER, and combination) products* from U.S. outpatient retail pharmacies from 2006-2019, yearly

| | 2006 | | 2007 | | 2008 | | 2009 | | 2010 | | 2011 | | 2012 | |
|---------------------------------------|-------------------|--------------|-------------------|--------------|-------------------|--------------|-------------------|--------------|-------------------|--------------|-------------------|--------------|-------------------|--------------|
| | Rx (N) | Share (%) |
| Total Oxycodone (ER,IR) | 37,739,476 | 100% | 41,600,387 | 100% | 45,317,891 | 100% | 48,534,529 | 100% | 53,517,577 | 100% | 55,785,030 | 100% | 54,977,119 | 100% |
| Total Oxycodone IR | 31,158,945 | 82.6% | 34,515,489 | 83.0% | 37,944,581 | 83.7% | 41,270,862 | 85.0% | 46,236,568 | 86.4% | 49,973,346 | 89.6% | 49,845,654 | 90.7% |
| Combination oxycodone IR | 26,880,965 | 86.3% | 29,168,003 | 84.5% | 31,294,342 | 82.5% | 34,173,202 | 82.8% | 35,660,363 | 77.1% | 36,546,292 | 73.1% | 35,737,524 | 71.7% |
| Single ingredient Oxycodone IR | 4,277,980 | 13.7% | 5,347,486 | 15.5% | 6,650,239 | 17.5% | 7,097,660 | 17.2% | 10,576,205 | 22.9% | 13,427,054 | 26.9% | 14,108,130 | 28.3% |
| Single ingredient Oxycodone ER | 6,580,531 | 17.4% | 7,084,898 | 17.0% | 7,373,310 | 16.3% | 7,263,667 | 15.0% | 7,281,009 | 13.6% | 5,811,684 | 10.4% | 5,131,465 | 9.3% |
| | 2013 | | 2014 | | 2015 | | 2016 | | 2017 | | 2018 | | 2019 | |
| | Rx (N) | Share (%) |
| Total Oxycodone (ER,IR) | 53,083,084 | 100% | 53,997,424 | 100% | 56,297,651 | 100% | 54,591,579 | 100% | 49,552,156 | 100% | 44,038,893 | 100% | 40,660,935 | 100% |
| Total Oxycodone IR | 48,231,322 | 90.9% | 49,310,509 | 91.3% | 51,891,039 | 92.2% | 50,620,952 | 92.7% | 46,200,853 | 93.2% | 41,163,447 | 93.5% | 38,252,725 | 94.1% |
| Combination oxycodone IR | 33,718,084 | 69.9% | 33,337,954 | 67.6% | 34,573,991 | 66.6% | 32,819,232 | 64.8% | 29,065,659 | 62.9% | 25,026,512 | 60.8% | 22,561,496 | 59.0% |
| Single ingredient Oxycodone IR | 14,513,238 | 30.1% | 15,972,555 | 32.4% | 17,317,048 | 33.4% | 17,801,720 | 35.2% | 17,135,194 | 37.1% | 16,136,935 | 39.2% | 15,691,229 | 41.0% |
| Single ingredient Oxycodone ER | 4,851,762 | 9.1% | 4,686,915 | 8.7% | 4,406,612 | 7.8% | 3,970,627 | 7.3% | 3,351,303 | 6.8% | 2,875,446 | 6.5% | 2,408,210 | 5.9% |

Source: IQVIA National Prescription Audit™ 2019. Data extracted Feb 2020. File: NPA Oxycodone ER and comparators by prescriptions 2006-2019. 02.15.2020.xlsx

Table 5: Estimated number of dispensed prescriptions for original and reformulated single-ingredient oxycodone ER products from U.S. outpatient retail pharmacies from 2006 through 2019, annually

| | 2006 | | 2007 | | 2008 | | 2009 | | 2010 | | 2011 | | 2012 | |
|---------------------------|------------------|-------------|------------------|-------------|------------------|-------------|------------------|-------------|------------------|-------------|------------------|-------------|------------------|-------------|
| | Rx (N) | Share (%) |
| Total Oxycodone ER | 6,580,531 | 100% | 7,084,898 | 100% | 7,373,310 | 100% | 7,263,667 | 100% | 7,281,009 | 100% | 5,811,684 | 100% | 5,131,465 | 100% |
| Original Oxycontin | 1,492,308 | 22.7% | 1,870,454 | 26.4% | 4,905,290 | 66.5% | 5,990,029 | 82.5% | 5,984,113 | 82.2% | 135,709 | 2.3% | 14,002 | 0.3% |
| Reformulated OxyContin | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | 5,537,806 | 95.3% |
| Original Oxycodone ER | 5,088,223 | 77.3% | 5,214,444 | 73.6% | 2,468,020 | 33.5% | 1,273,638 | 21.3% | 1,296,896 | 17.8% | 138,169 | 2.4% | 5,107 | 0.1% |
| Reformulated Oxycodone ER | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| | 2013 | | 2014 | | 2015 | | 2016 | | 2017 | | 2018 | | 2019 | |
| | Rx (N) | Share (%) |
| Total Oxycodone ER | 4,851,762 | 100% | 4,686,915 | 100% | 4,406,612 | 100% | 3,963,122 | 100% | 3,269,503 | 100% | 2,584,062 | 100% | 1,975,891 | 100% |
| Original Oxycontin | 1,327 | <0.1% | 293 | <0.1% | 227 | <0.1% | 83 | <0.1% | 33 | <0.1% | 39 | <0.1% | 14 | <0.1% |
| Reformulated OxyContin | 4,850,153 | 100% | 4,679,869 | 100% | 4,214,781 | 95.6% | 3,404,029 | 85.9% | 2,769,866 | 84.7% | 2,243,041 | 86.8% | 1,803,717 | 91.3% |
| Original Oxycodone ER | 282 | <0.1% | 138 | <0.1% | 103 | <0.1% | 76 | <0.1% | 24 | <0.1% | 1 | <0.1% | -- | -- |
| Reformulated Oxycodone ER | -- | -- | 6,615 | 0.1% | 191,604 | 4.3% | 558,934 | 14.1% | 499,580 | 15.3% | 340,981 | 13.2% | 172,160 | 8.7% |

Source: IQVIA National Prescription Audit™ 2019. Data extracted Feb 2020. File: NPA Oxycodone ER and comparators by prescriptions 2006-2019. 02.15.2020.xlsx

Table 6: Estimated number of tablets dispensed for original and reformulated oxycodone ER from U.S. outpatient retail pharmacies stratified by strength from 2009 through 2015, quarterly

| Q1 2009 | | Q2 2009 | | Q3 2009 | | Q4 2009 | | Q1 2010 | | Q2 2010 | | Q3 2010 | | Q4 2010 | | Q1 2011 | | Q2 2011 | | Q3 2011 | | Q4 2011 | | Q1 2012 | | Q2 2012 | | |
|--------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|------------|-------------|------------|-------------|------------|-------|
| Tablets (N) | Share(%) | Tablets (N) | Share(%) | Tablets (N) | Share(%) | Tablets (N) | Share(%) | Tablets (N) | Share(%) | Tablets (N) | Share(%) | Tablets (N) | Share(%) | Tablets (N) | Share(%) | Tablets (N) | Share(%) | Tablets (N) | Share(%) | Tablets (N) | Share(%) | Tablets (N) | Share(%) | Tablets (N) | Share(%) | Tablets (N) | Share(%) | |
| Total oxycodone ER | 132,505,805 | 100% | 134,802,018 | 100% | 134,801,788 | 100% | 136,654,349 | 100% | 133,738,164 | 100% | 137,311,178 | 100% | 137,795,575 | 100% | 125,561,460 | 100% | 111,678,695 | 100% | 106,483,233 | 100% | 103,023,327 | 100% | 99,874,203 | 100% | 91,575,635 | 100% | 91,760,339 | 100% |
| 10mg | 18,680,818 | 14.1% | 18,567,406 | 13.8% | 18,362,041 | 13.6% | 18,281,516 | 13.4% | 17,614,967 | 13.2% | 17,859,341 | 13.0% | 18,105,341 | 13.1% | 17,515,022 | 13.9% | 16,005,448 | 14.3% | 15,580,710 | 14.6% | 15,183,847 | 14.7% | 15,048,308 | 15.1% | 13,934,445 | 15.2% | 13,919,112 | 15.2% |
| 15mg | 1,050,869 | 0.8% | 1,207,329 | 0.9% | 1,334,892 | 1.0% | 1,488,899 | 1.1% | 1,581,449 | 1.2% | 1,756,149 | 1.3% | 1,915,036 | 1.4% | 2,021,613 | 1.6% | 2,014,404 | 1.8% | 2,072,004 | 1.9% | 2,134,926 | 2.1% | 2,149,742 | 2.2% | 2,129,150 | 2.3% | 2,247,260 | 2.4% |
| 20mg | 34,743,426 | 26.2% | 34,530,151 | 25.6% | 33,984,048 | 25.2% | 33,730,274 | 24.7% | 32,454,747 | 24.3% | 32,780,751 | 23.9% | 30,696,833 | 24.4% | 27,595,212 | 24.7% | 26,164,883 | 24.6% | 25,301,353 | 24.6% | 24,316,770 | 24.3% | 22,133,419 | 24.2% | 22,082,121 | 24.1% | | |
| 30mg | 4,479,393 | 3.4% | 5,254,306 | 3.9% | 5,887,840 | 4.4% | 6,529,547 | 4.8% | 6,933,644 | 5.2% | 7,675,931 | 5.6% | 8,316,961 | 6.0% | 8,322,998 | 6.6% | 7,968,290 | 7.1% | 7,991,254 | 7.3% | 8,087,844 | 7.9% | 8,216,571 | 8.2% | 7,845,201 | 8.6% | 8,271,963 | 9.0% |
| 40mg | 36,472,543 | 27.5% | 36,375,563 | 27.0% | 35,446,589 | 26.3% | 35,203,605 | 25.8% | 33,872,582 | 25.3% | 34,152,347 | 24.9% | 33,695,516 | 24.4% | 30,062,723 | 23.9% | 26,834,010 | 24.0% | 25,464,081 | 22.7% | 23,961,620 | 23.3% | 20,383,309 | 22.3% | 20,158,301 | 22.0% | | |
| 60mg | 4,745,604 | 3.6% | 5,709,349 | 4.2% | 6,382,473 | 4.7% | 7,073,594 | 5.2% | 7,544,048 | 5.6% | 8,300,162 | 6.0% | 8,914,899 | 6.5% | 8,439,668 | 6.7% | 7,823,578 | 7.0% | 7,823,414 | 7.3% | 7,788,913 | 7.6% | 7,787,079 | 7.8% | 7,328,254 | 8.0% | 7,539,184 | 8.2% |
| 80mg | 32,352,607 | 24.4% | 33,157,402 | 24.6% | 33,403,768 | 24.8% | 34,346,774 | 25.1% | 33,736,660 | 25.2% | 34,786,493 | 25.3% | 34,269,326 | 24.8% | 28,502,501 | 22.7% | 23,437,753 | 21.0% | 21,386,886 | 20.1% | 20,564,823 | 20.0% | 19,672,558 | 19.7% | 17,823,856 | 19.5% | 17,542,398 | 19.1% |
| 160mg | 543 | <0.1% | 513 | <0.1% | 137 | <0.1% | 140 | <0.1% | 70 | <0.1% | -- | -- | -- | -- | -- | -- | 101 | <0.1% | -- | -- | -- | -- | -- | 71 | <0.1% | -- | -- | |
| Total oxycodone ER | 90,607,744 | 100% | 90,989,388 | 100% | 84,884,401 | 100% | 84,082,151 | 100% | 83,845,318 | 100% | 83,697,522 | 100% | 79,041,597 | 100% | 79,188,320 | 100% | 78,799,210 | 100% | 78,927,041 | 100% | 73,363,622 | 100% | 73,097,627 | 100% | 72,257,047 | 100% | 71,828,740 | 100% |
| 10mg | 13,735,607 | 15.2% | 14,067,362 | 15.5% | 13,181,444 | 15.5% | 13,183,319 | 15.7% | 13,254,236 | 15.8% | 13,575,163 | 16.2% | 12,841,608 | 16.2% | 12,920,640 | 16.3% | 12,999,081 | 16.5% | 13,324,134 | 16.9% | 12,451,803 | 17.0% | 12,439,963 | 17.0% | 12,361,825 | 17.1% | 12,456,498 | 17.3% |
| 15mg | 2,381,386 | 2.6% | 2,487,634 | 2.7% | 2,421,756 | 2.9% | 2,549,808 | 3.0% | 2,695,751 | 3.2% | 2,837,717 | 3.4% | 2,875,486 | 3.6% | 3,109,727 | 3.9% | 3,350,941 | 4.3% | 3,556,296 | 4.5% | 3,424,515 | 4.7% | 3,511,835 | 4.8% | 3,624,689 | 5.0% | 3,725,655 | 5.2% |
| 20mg | 21,713,100 | 24.0% | 21,716,640 | 23.9% | 20,228,323 | 23.8% | 20,101,575 | 23.0% | 20,043,373 | 23.9% | 20,034,723 | 23.9% | 18,950,538 | 24.0% | 18,952,899 | 24.0% | 18,896,500 | 24.0% | 18,943,734 | 24.0% | 17,663,322 | 24.1% | 17,634,174 | 24.1% | 17,512,038 | 24.2% | 17,427,750 | 24.3% |
| 30mg | 8,457,747 | 9.3% | 8,696,076 | 9.6% | 8,391,456 | 9.9% | 8,594,325 | 10.2% | 8,838,064 | 10.5% | 9,033,879 | 10.8% | 8,779,202 | 11.1% | 9,024,403 | 11.4% | 9,176,915 | 11.6% | 9,342,997 | 11.8% | 8,913,544 | 12.1% | 9,102,994 | 12.5% | 9,095,899 | 12.6% | 9,079,383 | 12.6% |
| 40mg | 19,663,729 | 21.7% | 19,406,623 | 21.3% | 17,790,129 | 21.0% | 17,356,876 | 20.6% | 17,148,991 | 20.5% | 16,734,712 | 20.0% | 15,588,291 | 19.1% | 15,387,245 | 19.4% | 15,093,465 | 19.2% | 14,855,640 | 18.8% | 13,618,155 | 18.6% | 13,461,938 | 18.4% | 13,199,342 | 18.3% | 13,015,243 | 18.1% |
| 60mg | 7,624,365 | 8.4% | 7,728,269 | 8.5% | 7,372,462 | 8.7% | 7,373,693 | 8.8% | 7,387,168 | 8.8% | 7,401,824 | 8.8% | 7,040,758 | 8.9% | 7,095,383 | 9.0% | 7,055,678 | 9.0% | 7,022,187 | 8.9% | 6,543,459 | 8.9% | 6,491,818 | 8.9% | 6,424,822 | 8.9% | 6,371,327 | 8.9% |
| 80mg | 17,031,810 | 18.8% | 16,892,782 | 18.6% | 15,502,831 | 18.3% | 14,922,555 | 17.7% | 14,079,505 | 16.8% | 12,965,713 | 16.4% | 12,668,023 | 16.6% | 12,226,630 | 15.3% | 11,882,054 | 15.1% | 10,748,824 | 14.7% | 10,454,906 | 14.3% | 10,038,442 | 13.9% | 9,752,883 | 13.6% | | |
| 160mg | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | | | |

Source: IQVIA, National Prescription Audit™ (NPA). 2009-2019. Extracted Feb 2016. File: ADHOC data-Oxycodone ER - units by strengths 2009-2019. 02.18.2020.xls

Table 8: Estimated number of prescriptions dispensed for oxycodone ER per 10,000 residents from U.S. outpatient retail pharmacies in 2009⁹, 2012¹⁰ and 2018¹¹ (50 contiguous)

| | 2009 | | | 2012 | | | 2018 | | |
|----------------------|----------------------|------------|---------------------------------------|----------------------|------------|---------------------------------------|----------------------|------------|---------------------------------------|
| | Prescriptions (N) | Population | Prescriptions per 10,000 residents | Prescriptions (N) | Population | Prescriptions per 10,000 residents | Prescriptions (N) | Population | Prescriptions per 10,000 residents |
| Alabama | 130,857 | 4,708,708 | 277 | 102,958 | 4,822,023 | 213 | 67,151 | 4,887,871 | 137 |
| Alaska | 16,528 | 608,473 | 236 | 13,567 | 731,449 | 185 | 10,122 | 737,438 | 137 |
| Arizona | 197,971 | 6,595,778 | 300 | 163,212 | 6,553,255 | 249 | 83,765 | 7,171,646 | 110 |
| Arkansas | 51,061 | 2,889,450 | 176 | 37,836 | 2,949,131 | 128 | 26,299 | 3,013,825 | 87 |
| California | 636,085 | 36,961,664 | 172 | 433,086 | 38,041,430 | 113 | 206,229 | 39,557,045 | 52 |
| Colorado | 155,063 | 5,024,748 | 310 | 135,173 | 5,187,582 | 260 | 61,453 | 5,095,564 | 107 |
| Connecticut | 130,714 | 3,518,288 | 371 | 104,723 | 3,590,347 | 291 | 60,111 | 3,572,665 | 168 |
| Delaware | 30,539 | 885,122 | 345 | 26,987 | 917,092 | 294 | 16,555 | 967,171 | 171 |
| District of Columbia | 16,102 | 599,657 | 268 | 13,022 | 632,323 | 205 | 7,680 | 702,455 | 109 |
| Florida | 504,796 | 18,537,960 | 272 | 316,205 | 19,317,568 | 163 | 220,734 | 21,299,325 | 103 |
| Georgia | 167,597 | 9,829,211 | 170 | 121,903 | 9,919,945 | 122 | 84,434 | 10,519,475 | 80 |
| Hawaii | 27,097 | 1,295,178 | 209 | 17,047 | 1,392,313 | 122 | 8,602 | 1,420,491 | 60 |
| Idaho | 37,544 | 1,545,801 | 242 | 27,260 | 1,595,728 | 170 | 16,481 | 1,754,208 | 93 |
| Illinois | 130,426 | 12,910,409 | 101 | 106,928 | 12,875,255 | 83 | 63,461 | 12,741,080 | 49 |
| Indiana | 158,015 | 6,423,113 | 246 | 121,518 | 6,537,334 | 185 | 58,851 | 6,691,878 | 87 |
| Iowa | 44,308 | 3,007,857 | 147 | 37,637 | 3,074,186 | 122 | 18,267 | 3,156,145 | 57 |
| Kansas | 76,310 | 2,818,747 | 270 | 62,266 | 2,885,905 | 215 | 43,943 | 2,911,505 | 150 |
| Kentucky | 104,083 | 4,314,113 | 241 | 75,097 | 4,380,415 | 173 | 39,649 | 4,468,402 | 88 |
| Louisiana | 80,768 | 4,492,076 | 179 | 50,007 | 4,601,893 | 108 | 32,423 | 4,659,978 | 69 |
| Maine | 52,783 | 1,318,301 | 400 | 37,456 | 1,329,192 | 281 | 19,505 | 1,338,404 | 145 |
| Maryland | 174,055 | 5,699,478 | 305 | 114,701 | 5,884,563 | 104 | 89,037 | 6,042,718 | 147 |
| Massachusetts | 165,614 | 6,593,387 | 251 | 134,626 | 6,646,144 | 202 | 84,992 | 6,902,149 | 123 |
| Michigan | 202,721 | 9,069,727 | 203 | 125,075 | 9,883,360 | 126 | 63,766 | 9,995,915 | 63 |
| Minnesota | 133,167 | 5,266,215 | 252 | 112,720 | 5,379,130 | 209 | 54,576 | 5,611,179 | 97 |
| Mississippi | 35,748 | 2,951,996 | 121 | 26,750 | 2,984,926 | 89 | 18,779 | 2,986,530 | 62 |
| Missouri | 137,593 | 5,987,580 | 229 | 116,070 | 6,021,988 | 192 | 69,906 | 6,126,452 | 114 |
| Montana | 35,636 | 7,949,080 | 365 | 27,637 | 1,005,141 | 274 | 14,599 | 1,062,305 | 137 |
| Nebraska | 34,975 | 1,796,622 | 194 | 28,923 | 1,855,525 | 155 | 19,833 | 1,929,268 | 102 |
| Nevada | 62,080 | 2,643,085 | 234 | 39,037 | 2,758,931 | 144 | 21,145 | 3,034,302 | 69 |
| New Hampshire | 58,013 | 1,324,575 | 437 | 44,956 | 1,320,718 | 340 | 23,128 | 1,356,458 | 170 |
| New Jersey | 298,061 | 8,707,740 | 343 | 218,915 | 8,864,590 | 246 | 148,390 | 8,908,520 | 166 |
| New Mexico | 46,392 | 2,009,671 | 230 | 35,523 | 2,085,538 | 170 | 13,247 | 2,095,428 | 63 |
| New York | 360,887 | 19,541,453 | 184 | 279,487 | 19,570,261 | 142 | 191,089 | 19,542,209 | 98 |
| North Carolina | 234,186 | 9,380,884 | 249 | 189,070 | 9,752,073 | 193 | 159,120 | 10,383,020 | 153 |
| North Dakota | 15,323 | 646,844 | 236 | 13,327 | 699,628 | 190 | 6,558 | 760,077 | 86 |
| Ohio | 356,382 | 11,542,645 | 308 | 221,272 | 11,544,225 | 191 | 102,530 | 11,689,442 | 87 |
| Oklahoma | 94,681 | 3,087,050 | 256 | 67,503 | 3,814,820 | 176 | 65,299 | 3,943,079 | 105 |
| Oregon | 133,079 | 3,825,657 | 347 | 95,475 | 3,899,353 | 244 | 39,964 | 4,190,713 | 95 |
| Pennsylvania | 434,041 | 12,604,767 | 344 | 314,597 | 12,763,536 | 246 | 180,508 | 12,807,060 | 140 |
| Rhode Island | 46,315 | 1,053,200 | 430 | 32,118 | 1,050,292 | 305 | 13,292 | 1,057,315 | 125 |
| South Carolina | 94,661 | 4,561,242 | 207 | 79,280 | 4,723,723 | 167 | 55,756 | 5,084,127 | 109 |
| South Dakota | 20,240 | 812,383 | 249 | 16,177 | 833,354 | 194 | 10,220 | 882,235 | 115 |
| Tennessee | 199,698 | 6,296,254 | 317 | 154,678 | 6,456,243 | 230 | 90,261 | 6,770,010 | 133 |
| Texas | 232,244 | 24,782,302 | 93 | 170,436 | 26,059,203 | 65 | 96,703 | 28,701,845 | 33 |
| Utah | 79,598 | 2,784,572 | 285 | 46,978 | 2,855,287 | 164 | 25,514 | 3,161,105 | 80 |
| Vermont | 17,968 | 621,760 | 288 | 14,439 | 626,011 | 230 | 8,716 | 626,299 | 139 |
| Virginia | 138,000 | 7,882,590 | 176 | 116,509 | 8,185,867 | 142 | 73,078 | 8,517,685 | 85 |
| Washington | 215,214 | 6,664,195 | 322 | 133,381 | 6,897,012 | 193 | 63,357 | 7,355,591 | 84 |
| West Virginia | 43,898 | 1,810,777 | 241 | 26,051 | 1,855,413 | 140 | 11,674 | 1,805,832 | 64 |
| Wisconsin | 179,769 | 5,054,774 | 317 | 131,369 | 5,726,398 | 229 | 60,284 | 5,813,568 | 103 |
| Wyoming | 14,901 | 544,270 | 273 | 12,704 | 576,412 | 220 | 10,915 | 577,737 | 188 |

Source: Symphony Health PHAST Prescription Monthly. Data extracted April 2020 File: SHS Oxycodone ER Geo Map by prescriptions and residents 2009-2012 and 2018. 04.15.2020.xlsx

Department of Health and Human Services Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

OxyContin® Postmarketing Requirement (PMR) 3051-4 Final Study Report

Date: August 7th, 2020

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Subject: Review of OxyContin PMR 3051-4 final study report –
Changes in Fatal and Non-fatal Overdose among Individuals Dispensed OxyContin after its Reformulation with Abuse-deterrent Properties – A Healthcare Database Analysis with Linkage to the National Death Index

Drug Name(s): OxyContin (oxycodone hydrochloride extended-release)

Application Type/Number: NDA 022272/IND 029038

Applicant/sponsor: Purdue Pharma L.P.

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ABBREVIATIONS:

-2y/2y Two-year period before (3Q2008-2Q2010) compared to the two-year period after the introduction of reformulated OxyContin (1Q2011 to 4Q2012) excluding the transition period

-2y/5y Two-year period before (3Q2008-2Q2010) compared to the five-year period after the introduction of reformulated OxyContin (1Q2011- 3Q2015), excluding the transition period

ADF Abuse-deterrent formulation

aRR Adjusted rate ratio

BOE Basis of eligibility

CI Confidence interval

CMS Centers for Medicare and Medicaid Services

ER Extended-release

FDA United States Food and Drug Administration

FFS Fee-for-Service

HIRD HealthCore Integrated Research Database®

ICD-9-CM International Classification of Diseases, Ninth Revision, Clinical Modification

ICD-10-CM International Classification of Diseases, Tenth Revision, Clinical Modification

IR Immediate-release

IRR Incidence rate ratio

LA Long-acting

MAX Medicaid Analytical eXtract

N/A Not applicable

NDI National Death Index

NOS Not otherwise specified

OUD Opioid use disorder

PMR Postmarketing requirement

PPV Positive predictive value

PS Propensity score

REMS Risk evaluation and mitigation strategy

RORR Ratio of rate ratios

RR Rate ratio

SAP Statistical analysis plan

SD Standard deviation

SE Single-entity

TD Transdermal

EXECUTIVE SUMMARY

Postmarketing requirement (PMR) study 3051-4 is one of four studies the United States Food and Drug Administration (FDA) required of the sponsor, Purdue Pharma, to evaluate the impact of OxyContin's reformulation on its abuse. Specifically, PMR study 3051-4 aimed to assess the impact of the reformulation on overdose rates among patients dispensed OxyContin. This study included data from three administrative claim databases and required new linkages to mortality data to capture fatal overdose. In conjunction with the other PMR studies (3051-1, 2, and 3) and other relevant information, the findings of this study can be used to help inform the overarching question of whether OxyContin's reformulation meaningfully reduced its abuse and associated harms, like overdose.

Overview of study methods:

In brief, the study assessed the change in any fatal or non-fatal opioid overdose rates (hereafter, overdose rates) among patients dispensed OxyContin, comparing the two years before (3Q2008-2Q2010, hereafter pre-period) to the five years after OxyContin's reformulation (1Q2011-3Q2015, hereafter post-period)ⁱ, excluding a market transition period (3Q2010-4Q2010) immediately following the marketing of reformulated OxyContin. The study included analyses in three separate administrative claims databases to evaluate the consistency of results across databases and patient populations: 1) HealthCore Integrated Research Database® (hereafter, HIRD), 2) MarketScan Commercial and Medicare Supplemental Claims and Encounters database (hereafter, MarketScan), and 3) Medicaid Analytic eXtract (MAX): National Medicaid Database (hereafter, Medicaid). These databases were linked to the National Death Index (NDI) to capture fatal opioid overdoses.

Outside of the fatal opioid overdoses captured in NDI, all opioid overdose outcomes were identified using a validated code-based diagnostic algorithm developed for use in administrative claims databases. In a published portability study, the opioid overdose algorithm that differentiated intentionality did not perform reliably across other claims databases, most notably in Tennessee's Medicaid data. Because of the superior performance of the any opioid overdose (unintentional and intentional) algorithm compared to the intentional opioid overdose algorithm, we considered results using the any opioid overdose algorithm to be primary, and these are the focus of this review. FDA views the unintentional opioid overdose analyses in PMR study 3051-4 to be exploratory.

The study included information on overdose rates among those dispensed other opioid analgesics to aid in causal inference. Three primary comparators (extended-release [ER] morphine tablets or capsules, transdermal fentanyl, and methadone tablets or capsules) were used as negative controls (i.e., "counterfactuals") for OxyContin, intended to approximate expected changes in overdose rates among those dispensed OxyContin in the absence of the reformulation; several secondary comparators were also included to provide additional context.

ⁱ Two years after OxyContin reformulation were available in Medicaid database (1Q2011-4Q2012) at time of analysis

Preliminary analyses of utilization data found that a large majority of patients dispensed OxyContin received overlapping prescriptions for other opioid analgesics. Immediate-release (IR) opioid analgesics were the most commonly dispensed with OxyContin, particularly IR formulations of hydrocodone and oxycodone. Concomitance with other opioid analgesics complicates our ability to make causal inferences about the effect of OxyContin's reformulation. Therefore, overdose rates associated with OxyContin and comparators were calculated using several different exposure group definitions. The main cohort included exposure time in which patients received OxyContin or the comparator either with or without concomitant opioid analgesics. Additional analyses used cohorts that included time in which the patient received concomitant IR opioid analgesics only and also more restricted cohorts that only included time in which the patient received OxyContin or the comparator without any concomitant opioid analgesics.

Treatment episodes in the pre- and post-periods were defined as continuous patient-level opioid analgesic exposure periods (in person-months), calculated using the drug dispensing dates and the estimated number of days dispensed in patients' administrative pharmacy claims. Unadjusted and adjusted overdose incidence rates and 95% confidence intervals (CI) were modeled using Poisson regression. Adjusted analyses included demographic characteristics, clinical characteristics, and other comorbidities ascertained using administrative claims.

Investigators calculated overdose rate ratios (RR) by comparing the overdose rates of the pre- and post-periods for OxyContin and each of the comparator opioid analgesic exposure groups ($RR = [\text{overdose incidence rate post-period}] / [\text{overdose incidence rate pre-period}]$). A ratio of rate ratios (RORR) was then used to compare the changes in overdose rates between the pre- and post-periods comparing patients dispensed OxyContin to those dispensed a comparator opioid analgesic ($RORR = [\text{comparator RR}] / [\text{OxyContin RR}]$). In these types of difference in difference models, an $RORR > 1$ reflects a more favorable pre-post change in overdose rates among those dispensed OxyContin relative to any changes in overdose rates in patients dispensed a comparator; in this context, favorable could mean a greater pre-post reduction or a smaller increase in overdose rates among those dispensed OxyContin relative to those dispensed a comparator, or even no change in overdose rates among those dispensed OxyContin but an increase in overdose rates among those dispensed a comparator. An $RORR < 1$ indicates a more favorable change for among those dispensed a comparator. A random-effects meta-analysis was also used to compute meta-analyzed (combined) RRs and RORRs for the two commercial databases (MarketScan and HIRD).

Due to the inherent uncertainties associated with these data and their interpretation, multiple analyses were conducted to assess robustness of the study findings. For example, the analytic cohorts were restricted to incident use periods only. Using an incident user cohort can help minimize biases that result from including those with experience using the drug but it also substantially reduces sample size and power. Investigators also conducted additional analyses stratified by fee-for-service (FFS) and managed care Medicaid plan types to ensure that data capture and results were consistent across coverage plans. Finally, to explore additional methods for adjusting for relevant characteristics of patients with opioid analgesic use, the investigators used propensity score weighted Poisson regression models for some analyses.

Summary of results:

Summary of eligible patients and descriptive analyses

Approximately 25% of the total U.S. Medicaid membership during the study period was eligible after applying the data usability criteria; all eligible patients dispensed an opioid analgesic of interest were linkable to NDI (N=445,118). In the commercial claims databases, ~40% of the eligible patients dispensed an opioid analgesic of interest were linkable to NDI in MarketScan (N=288,645), while ~60% of the eligible patients linkable to NDI in HIRD (N=201,801).

Overall, the mean ages were older in commercial claims populations compared to the Medicaid population. The Medicaid population had higher proportions of patients with nearly all comorbidities compared to the commercial claims populations, but in aggregate (across the entire study period) there were no substantial differences in measured clinical characteristics comparing those dispensed OxyContin and those dispensed primary comparators in any of the databases.

The sponsor's pre-study preliminary analyses found some notable changes in patient characteristics across the study period. There were geographic shifts in the population of patients dispensed OxyContin in MarketScan, but not Medicaid. In MarketScan, median age and arthritisⁱⁱ and chronic pain diagnoses all increased among patients dispensed OxyContin; there were also minor increases in substance use disorder diagnoses. There were large declines in the number of higher strength tablets dispensed over the period — notably the 80 milligram tablets.

Changes in opioid overdose rates among patients dispensed OxyContin

In the commercial claims combined incident and prevalent user cohorts (see Table 1), there were modest reductions in opioid overdose rates among patients dispensed OxyContin with or without other opioid analgesics concomitantly, and when restricted to person-time dispensed OxyContin with any immediate-release (IR) opioid analgesic concomitantly. These reductions were not seen in the Medicaid cohort. None of the adjusted overdose rate ratios for these cohorts were statistically significant. When restricted to person-time dispensed OxyContin alone (with no other opioid analgesics), there were larger reductions in opioid overdose rates among OxyContin recipients across all databases, but the changes were only statistically significant in one database (HIRD).

ⁱⁱ "Arthritis" includes arthropathies, osteoarthritis and musculoskeletal pain

Table 1: Adjusted overdose rate ratios among those dispensed OxyContin across databases, by concomitancy with other opioid analgesics

| OxyContin exposure group | Medicaid | | | MarketScan | | | HIRD | | |
|--|-------------------------------------|--------------------------------|--------------------------|-------------------------------------|--------------------------------|--------------------------|-------------------------------------|--------------------------------|--------------------------|
| | Pre-period rate per 1,000 PMs (ref) | Post-period rate per 1,000 PMs | Adjusted rate ratio (CI) | Pre-period rate per 1,000 PMs (ref) | Post-period rate per 1,000 PMs | Adjusted rate ratio (CI) | Pre-period rate per 1,000 PMs (ref) | Post-period rate per 1,000 PMs | Adjusted rate ratio (CI) |
| Any OxyContin use ⁱ | 1.80 | 1.86 | 1.00 (0.89-1.12) | 0.82 | 0.80 | 0.90 (0.75-1.08) | 0.93 | 0.85 | 0.84 (0.65-1.09) |
| Concomitant use ⁱⁱ with any IR opioid analgesic | 1.89 | 2.02 | 1.04 (0.91-1.19) | 0.93 | 0.96 | 0.95 (0.77-1.17) | 0.93 | 0.75 | 0.74 (0.54-1.02) |
| OxyContin use alone | 1.65 | 1.42 | 0.85 (0.68-1.06) | 0.60 | 0.44 | 0.72 (0.50-1.04) | 0.91 | 0.48 | 0.52 (0.32-0.83)* |

(FDA generated table using data from PMR 3051-4 study report)

Key: *= statistically significant ($p<0.05$); ⁱ=excludes periods dispensed OxyContin or primary comparator concomitantly; ⁱⁱ=includes only periods dispensed an IR opioid analgesics concomitantly, excluding periods dispensed OxyContin or primary comparator opioid analgesics concomitantly; person-months (PMs); confidence interval (CI); adjusted for variables in section 3.4.5; for all databases, the pre-period is two years before the reformulation, but the post-period for Medicaid analyses is two years after the reformulation and the post-period for MarketScan/HIRD analyses is five years after the reformulation

Overall, the incident only cohorts were smaller with substantially reduced aggregate exposure time across databases compared to analyses from combined cohorts. Overdose rate ratios using incident only cohorts were generally similar to those of the combined cohort but were not statistically significant for any of the OxyContin exposure groups.

Overdose rate changes for OxyContin compared to primary comparators

In Medicaid analyses, with the exception of fentanyl, the adjusted ratio of rate ratios (RORR) favored the comparators (i.e., $RORR < 1$) over OxyContin among patients with or without other opioid analgesics dispensed concomitantly, but the RORR was only statistically significant for methadone (see Table 2). Adjusted RORRs also favored comparators when restricted to person-time dispensed any IR opioid analgesic concomitantly, with statistically significant RORRs for ER morphine and methadone. In the commercial claims analyses (MarketScan and HIRD), the adjusted RORRs all generally favored OxyContin when looking at those dispensed the comparators with or without other opioid analgesics concomitantly, or when restricted to person-time dispensed with an IR opioid analgesic concomitantly, but no RORR was statistically significant for any comparator. Meta-analyzed comparative results from the commercial claims databases were generally consistent with results of the commercial claims analyzed separately, except that the RORRs were statistically significant for methadone (favoring OxyContin) when analyzed separately.

When restricted to person-time dispensed OxyContin or comparators alone, all adjusted RORRs favored OxyContin, but only in the commercial claims databases were some adjusted RORRs statistically significant: ER morphine in the HIRD data, and fentanyl and methadone in the MarketScan data. Meta-analyzed results from the commercial claims databases were also generally consistent with results when analyzed separately, except that all RORRs were statistically significant (favoring OxyContin) when meta-analyzed.

Table 2: Adjusted ratios of rate ratios among those dispensed primary comparators compared to those dispensed OxyContin, by database and concomitancy with other opioid analgesics

| Opioid analgesic exposure group | Exposure period category | Medicaid | MarketScan | HIRD |
|---------------------------------|--|--|--|--|
| | | Adjusted ratio of rate ratio (CI) ⁱⁱⁱ | Adjusted ratio of rate ratio (CI) ⁱⁱⁱ | Adjusted ratio of rate ratio (CI) ⁱⁱⁱ |
| ER morphine | (with or without concomitant opioid analgesic use periods) | 0.91 (0.80-1.04) | 1.12 (0.86-1.46) | 1.09 (0.78-1.53) |
| | | 1.05 (0.90-1.22) | 1.19 (0.93-1.53) | 1.04 (0.73-1.49) |
| | | 0.85 (0.74-0.98)* | 1.32 (0.97-1.79) | 1.20 (0.83-1.74) |
| Fentanyl | (with or without concomitant opioid analgesic use periods) | 0.84 (0.72-0.99)* | 1.00 (0.74-1.35) | 1.01 (0.66-1.56) |
| | | 0.98 (0.83-1.17) | 1.09 (0.81-1.45) | 1.17 (0.74-1.83) |
| | | 0.80 (0.67-0.96)* | 1.08 (0.73-1.59) | 1.19 (0.73-1.92) |
| Methadone | (with or without concomitant opioid analgesic use periods) | 1.17 (0.90-1.52) | 1.62 (0.97-2.72) | 2.20 (1.18-4.10)* |
| | | 1.27 (0.95-1.69) | 1.68 (1.02-2.78)* | 1.40 (0.73-2.70) |
| | | 1.03 (0.79-1.33) | 1.94 (1.14-3.29)* | 1.76 (0.98-3.17) |

(FDA generated table using data from PMR 3051-4 study report)

Key: *= statistically significant ($p<0.05$); ⁱ=excludes periods dispensed OxyContin or primary comparator concomitantly; ⁱⁱ=includes only periods dispensed an IR opioid analgesic concomitantly, excluding periods dispensed OxyContin or primary comparator opioid analgesics concomitantly; ⁱⁱⁱ= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); person-months (PMs); confidence interval (CI); adjusted for variables in section 3.4.5; reference for this table is OxyContin adjusted rate ratio (see Table 1); for all databases, the pre-period is two years before the reformulation, but the post-period for Medicaid analyses is two years after the reformulation and the post-period for MarketScan/HIRD analyses is five years after the reformulation

The adjusted RORR point estimates using the incident user only cohort were generally similar to those using the combined cohort, but the RORRs were not statistically significant, with the exception of methadone which was statistically significant (favoring OxyContin) among patients with or without other opioid analgesics dispensed concomitantly. When the Medicaid analyses were stratified by plan type (FFS or managed

care),ⁱⁱⁱ some adjusted RORR estimates were qualitatively different from each other, notably for fentanyl, but RORRs in both cohorts were mostly not significant.

The RORR estimates using the unintentional opioid overdose algorithm were similar to the RORR estimates using the primary any opioid overdose algorithm. Overall, the number of fatal overdoses was much lower than non-fatal overdose, and the proportion of overdoses that were fatal did not change across time periods, either for OxyContin or any comparator group.

Methodological considerations:

Patient characteristics and sample selection

PMR study 3051-4 assessed opioid overdose rates among patients directly dispensed opioid analgesics through traditional channels of distribution and reimbursed by Medicaid or commercial insurance. While important to study with respect to the impact of the reformulation, patients who receive an insurance-reimbursed prescription for opioid analgesics may not be representative of the populations where non-oral abuse and overdose are most common. This type of patient-based study population receiving prescription opioid analgesics paid for by health insurance may be at an inherently lower risk for opioid abuse and overdose than individuals who obtain prescription opioids using cash (who are not included in commercial claims data) or through diversion (i.e., from other sources like friends or illicit channels). Those who obtain opioids from sources other than their own prescription may be particularly at risk for abuse and overdose via non-oral routes which are *a priori* expected to be affected the most by OxyContin's reformulation.

Many otherwise eligible patients could not be included in PMR study 3051-4 due to lack of data linkage capability and other data quality issues, but these exclusions likely did not bias the comparative analyses. In MarketScan and HIRD, not all eligible opioid-analgesic-dispensed patients could be linked to the NDI; however, demographic characteristics and comorbidities were similar when comparing those who were linkable to those who were not. In Medicaid, only a minority of all beneficiaries had data deemed usable, but there did not appear to be meaningful differences in the results of stratified analyses by Medicaid coverage type.

Sensitivity analyses were conducted using an incident user cohort to help minimize potential selection biases resulting from including prevalent (ongoing) users. Prevalent users had to survive long enough to be included in the study and thus may be at a potentially lower risk for the outcome, although it is also possible that the likelihood of the outcome increases with greater exposure time. Nevertheless, because of the way "incident" use was defined in this study, incident and prevalent users were fairly comparable, as both can have prior experience with non-study opioid analgesics and can contribute multiple treatment episodes. Despite the greater statistical uncertainty in the incident user only analyses, the point estimates using the combined user cohort (incident and prevalent) and incident user only cohort were very similar.

ⁱⁱⁱ This was only conducted using the unintentional opioid overdose algorithm

Challenges with exposure and outcome measurement in administrative claims data

Drug exposure can be difficult to accurately characterize in claims-based observational studies, particularly for opioid analgesics. While opioid analgesic drugs can be taken routinely like antihypertensives, they are also taken as needed or sporadically. This variability in use patterns creates uncertainty with respect to measuring exposure time and defining time at risk for the outcome, and therefore many assumptions are needed to calculate exposure time. For example, the actual use patterns by the patient may not be well represented by the days' supply, which is a variable input by the pharmacist based on a combination of factors. The dose taken by the patient may also not be captured well in claims data, but this can be an important risk factor for overdose. Neither daily dose nor tablet strength were included in comparative analyses in this study.

Because of the potential for lagged outcomes in this study, overdose rates associated with some opioid analgesics may be underestimated. In this study, leftover opioid analgesic tablets from the previous dispensing were ignored in exposure time calculations, excluding what could have been additional "at risk" exposure time. At the same time, "stockpiled" leftover drug and frequent changes in opioid analgesic regimens create challenges in accurately allocating exposure time, and thus correctly attributing overdose outcomes to a particular dispensed opioid analgesic. Furthermore, unobservable factors may affect drug continuation, for example, prescriber concerns about aberrant behaviors and risk of overdose. This type of informative censoring can also bias relative comparisons between opioid analgesic and time periods.

Finally, without reliable ascertainment of intentionality, route-specific information, or information on the specific opioid(s) involved in an overdose, PMR study 3051-4 was unable to examine specific subsets of overdose cases likely most relevant to understanding the impact of the reformulation (i.e., unintentional overdose involving non-oral abuse of OxyContin). While it is unknown what opioid(s) specifically precipitated each overdose in this study, the event is attributed to the last opioid analgesic the patient was dispensed, and therefore, some inaccurate attribution of overdoses to specific opioid analgesics is likely (e.g., a patient overdoses on multiple drugs, including heroin, after being dispensed ER morphine).

Adjusting for potential confounders

D 3 Ti

a) Risk factors for overdose

Without sufficient adjustment for all important confounders it is difficult to say whether observed changes in overdose rates for OxyContin (relative to comparators) were due to the effect of the reformulation on overdose risk in patients receiving the drug, or shifts in the risk profiles of patients receiving the drug. Preliminary data suggested that there were indeed some differences in the patients dispensed OxyContin comparing the pre- and post-periods, including potentially relevant comorbidities. It is unclear, however, whether confounding was adequately addressed in this study.

Risk factors like opioid use disorder (OUD) and prior overdose were considered for adjustment in the models but doing so comes with challenges. The sponsor viewed OUD as a potential mediator in the causal pathway between opioid analgesic dispensing and

overdose, and thus, did not adjust for it in primary models. However, while the proportion of patients with OUD diagnosis codes was relatively similar when comparing those dispensed OxyContin to the primary comparators in aggregate (across the entire study period), it is not clear whether there was differential prescribing of specific opioid analgesics to patients with OUD diagnosis codes by period, as those data were not provided. Any systematic differential opioid analgesic prescribing by OUD diagnosis and study period could bias results considerably. At the same time, OUD diagnosis codes in claims data are not a reliable indicator of the presence or absence of OUD, which limits their utility as a covariate in this study.

Prior opioid overdose was found to be, by far, the strongest risk factor for subsequent overdose. The prevalence of prior opioid overdose was relatively balanced when comparing those dispensed OxyContin to the primary comparators in aggregate, but it was included in all adjusted models as a time-varying covariate to account for its strong association with the outcome of interest. Time-varying covariates can introduce time-varying confounding and bias associations, but from the sponsor's perspective it was nevertheless important to account for the within-person correlation from patients' contributing multiple overdose events over the study period. Given the study design and the definition/algorithm's demonstrated validity, including a time-varying "any prior overdose" variable is appropriate.

The sponsor argued that other potentially important risk factors like major depressive disorder, alcohol use disorder, or other substance use disorders are also better operationalized as mediators in the causal pathway rather than adjusted for as confounders. The sponsor did not submit any data to support this position. To be mediators these conditions would have to occur as a result of starting a specific opioid analgesic therapy, but many of the conditions are common and likely to be present before treatment initiation. In other words, these types of variables may be confounders, or even effect modifiers, of the association between the OxyContin reformulation and overdose.

Concomitant benzodiazepine use is a known risk factor for opioid overdose, but it was not adjusted for in any primary analyses as the sponsor again viewed this as a potential mediator. Overall, benzodiazepine use was comparable in patients dispensed OxyContin and other comparator opioid analgesics in aggregate (across the entire study period), but to better understand the potential impact of benzodiazepine use on study results, FDA requested additional analyses. Subsequently submitted data suggest that any benzodiazepine dispensing changes from the pre- to post-periods were likely nondifferential by opioid analgesic and that adjusting for baseline benzodiazepine use did not meaningfully impact results in HIRD and Medicaid. Nor was benzodiazepine use found to be a statistically significant effect modifier. Given these results, and the relative balance in benzodiazepine dispensing rates across opioid analgesic exposure groups and time periods, relative comparisons between opioid analgesics were likely not substantially biased by concomitant benzodiazepine use. Nonetheless, because benzodiazepines and opioids are often obtained through means other than one's own (insurance reimbursed) prescription, it is unknown whether there was actual differential use of other substances across time periods or comparators.

b) Adequacy of adjusted models in controlling for confounding

To account for differences in the patient populations before and after the reformulation and to mitigate the impact of confounding, some Poisson models used covariate adjustment, while others were weighted by the propensity score (PS),^{iv} but the results were not substantively different from unadjusted results. This may be due, in part, to limited and incomplete adjustment for some important potential confounders, as discussed above. Adequately adjusting for confounders in claims-based analyses is often challenged by incomplete data (e.g., current alcohol and substance use, socioeconomic status), and a lack of validated diagnosis codes known to accurately reflect important medical conditions (e.g., OUD). Nonetheless, adjusted analyses that control for patient characteristics, including demographic information and certain conditions that are more reliably captured using claims-based diagnosis codes, are still preferable to unadjusted analyses, however limited.

Even after adjusting for measurable potential confounders, it is likely that channeling bias was still relevant in this study, and this type of selection bias can be particularly challenging to address using administrative claims data alone. Because the reformulation was specifically designed to deter tablet manipulation for the purposes of abuse, it is possible that prescribers differentially prescribed (“channeled”) reformulated OxyContin to patients they perceived to have a higher risk of abusing the drug. This could introduce imbalances in the overdose risk profile of patients comparing the two periods, potentially attenuating any true benefit of the reformulation.

An alternative scenario must also be considered, however, wherein patients seeking to abuse OxyContin “self-selected” *not* to receive the product after reformulation, requesting and receiving different opioid analgesics without abuse-deterring properties, or transitioning to non-prescribed opioids (e.g., heroin or diverted prescription opioids), thus creating a *lower* risk cohort of OxyContin users following reformulation. In this scenario, results would show a more favorable impact of the reformulation on overdose risk. The overall decline in OxyContin dispensing, and particularly of the 80 milligram tablets, may in part reflect such a migration away from OxyContin by individuals seeking to abuse it by non-oral routes. Although it is unclear to what extent that ultimately explains the decreased dispensing, it does at least indicate some significant changes in prescribing patterns for OxyContin that could substantially affect the risk profile of patients receiving the product.

Interpretation of PMR Study 3051-4 Findings:

Effect of OxyContin’s reformulation on overdose rates among those dispensed any OxyContin (i.e., with or without other opioid analgesics concomitantly):

The results of PMR 3051-4 do not demonstrate that the reformulation reduced the risk of opioid overdose in patients dispensed OxyContin, overall (i.e., including exposure with or without other opioid analgesics). A conclusion that OxyContin’s reformulation actually reduced opioid overdose risk in these patients would be supported by robust and statistically significant reductions in overdose rates that were temporally associated with the intervention, largely consistent across databases, and unlikely to be explained by either

^{iv} Note this was only using the unintentional overdose outcome

systematic or random error. In HIRD, the overdose rates among OxyContin recipients appeared to decrease modestly immediately after the reformulation but the decline was not sustained, and there was no discernable decline in overdose rates among those dispensed OxyContin in either the Medicaid or MarketScan databases. Small changes are more likely to be completely explained by residual confounding, particularly when we are not confident that confounding was adequately controlled for, given the limited adjustment for some potentially important covariates and limited ability to measure others. Furthermore, most changes across time periods were not statistically significant, indicating that random chance cannot be ruled out as an explanation either.

To account for potential confounding by calendar time (i.e., secular trends), changes in opioid overdose rates among those dispensed OxyContin should also differ meaningfully from any changes observed in those dispensed comparator opioid analgesics. In the commercial claims populations, changes in opioid overdose rates among patients dispensed OxyContin compared to the changes among patients dispensed primary comparators modestly favored OxyContin, but they were not significantly different from each other. In fact, the results of Medicaid data analyses among users of any OxyContin or OxyContin with IR opioid analgesics concomitantly were actually *unfavorable* to OxyContin with respect to changes in overdose rates after the reformulation, in that reductions in overdose rates among those dispensed ER morphine and methadone were observed but there was no change among those dispensed OxyContin.

Concomitant dispensing and switching from one opioid analgesic to another creates challenges in disentangling the marginal effect of one opioid analgesic on overdose risk in the context of multiple concurrent opioid analgesic exposures, but the use of multiple opioid analgesics concurrently was more the rule than the exception in these populations. Although it complicates causal inference, studying the effect of the reformulation in settings in which the drug is most commonly used (i.e., with other opioid analgesics) is still important. One possible explanation for the lack of an observed effect in this cohort is that the reformulation actually had little or no effect on overall opioid overdose because opioid analgesic use and abuse patterns are complex and dynamic, in some cases including both prescription and illicit opioids. Opioid analgesic concomitancy patterns in patients dispensed OxyContin also changed over the study period, with increased concomitant prescribing overall and changes in the types of opioid analgesics used with OxyContin. It is therefore perhaps not unexpected that changing a single product's formulation did not appear to result in an overall reduction in opioid overdose.

Although this study did not show that the reformulation reduced overdose risk in insured patients receiving OxyContin, the findings also do not preclude this possibility. While certainly important to study, this study cohort may not reflect the population most likely to abuse or experience an overdose involving OxyContin. It is possible that effects of reformulation might have been detected in higher risk groups,^v including those obtaining OxyContin from sources other than their own prescription or using cash to purchase prescription opioid analgesics, and those abusing opioids by non-oral routes. However,

^v PMR study 3051-1 and study 3051-3 targeted higher risk groups like those being specifically assessed for opioid treatment, but overdose outcomes were not assessed in those studies

these groups are generally not distinguishable in data sources capable of linking a specific drug exposure to overdose outcomes, while controlling for other confounding factors.

Effect of OxyContin's reformulation on overdose rates among those dispensed OxyContin alone (i.e., without other opioid analgesics concomitantly):

When restricting analyses to patients dispensed OxyContin or comparators alone, results were somewhat more favorable with respect to the impact of the reformulation on opioid overdose risk, although this was true only in the commercial claims populations, and not in Medicaid. The implications and generalizability of this finding are not entirely clear. Analyses that only include patients using one opioid analgesic product at a time are simpler from a causal inference perspective, as noted above, but OxyContin use without the concomitant dispensing of any other opioid analgesics—primarily IR opioid analgesics—is much less common than dispensing of OxyContin with at least intermittent use of other opioid analgesics and represents a relatively small subset of OxyContin use in real-world settings.

Bi-annual overdose rate data were not provided for this smaller cohort so it was not possible to determine the exact timing of declines in overdose rates relative to the reformulation. While the results were more favorable with respect to the impact of the reformulation, they were not entirely consistent across databases, or across comparators, and there was greater uncertainty in the estimates due to the reduced exposure time. When restricted to person-time dispensed OxyContin alone, reductions in opioid overdose rates were modest and only significant in one commercial claims database (HIRD). Overall, changes in opioid overdose rates when restricted to person-time dispensed OxyContin alone differed favorably from changes in comparators, to varying degrees. Statistical significance varied across comparators in the two commercial claims databases, and the differences were not significant in Medicaid. When the results of the commercial claims databases were combined using meta-analytic methods, the point estimates were generally similar to those from analyses conducted separately in each database, but the comparative results were all statistically significant using meta-analysis. At the same time, these results must be interpreted with caution as only two databases (effectively two separate “studies”) were combined, and between-study heterogeneity could not be properly evaluated.

It is possible that OxyContin's reformulation reduced the risk of overdose in patients who received this product without any other opioid analgesics, at least among patients with commercial insurance. Given the potential for residual confounding in these analyses, however, it is also important to consider alternative explanations for these findings. It is possible that patients receiving reformulated OxyContin were inherently at lower risk of overdose than those who received original OxyContin. Some “non-exchangeability” of the cohorts would remain if there were important unmeasured differences between these groups. Such differences could be due to increased prescriber awareness of risk of OxyContin abuse in general (e.g., due to the 2010 OxyContin REMS provider communications), or changes in patient selection related specifically to OxyContin's abuse-deterrent properties.

Differences could also be related to patient “self-selection;” for example, if individuals seeking to abuse OxyContin non-orally stopped abusing OxyContin, some perhaps instead seeking out other opioids, either prescription or illicit, when OxyContin was reformulated.

If this was the case, then post-period OxyContin user cohort might have had a lower risk of overdose. Although this latter explanation would be consistent with reformulated OxyContin having an abuse-deterrent effect, it does not necessarily show that the abuse-deterrent properties conferred a reduced risk of overdose among those exposed to the product, or that those who stopped using OxyContin because of its reformulation (and were therefore not included in the reformulated OxyContin exposure group) were less likely to experience an overdose. In addition, the distribution of dispensed OxyContin tablet strengths skewed lower in the post-period, which could have contributed to the observed declines in overdose rates when restricted to person-time dispensed OxyContin alone relative to comparators, independent of any risks associated with non-oral abuse specifically or the direct ability of the abuse-deterrent properties to reduce these risks. Again, the changes in OxyContin dosage strengths dispensed could reflect some abuse-deterrent effect of the reformulation, with individuals who seek high-strength tablets to manipulate for the purposes of abuse migrating away from OxyContin after its reformulation. It is unclear, though, whether lower overdose rates in a cohort receiving lower doses of OxyContin can reasonably be interpreted as the “abuse-deterrent” properties reducing the risk of overdose.

Conclusions:

The results of PMR 3051-4 do not demonstrate that the reformulation reduced the risk of opioid overdose in patients dispensed OxyContin, overall. When restricted to person-time dispensed OxyContin or comparators *alone* (i.e., without other opioid analgesics), results were somewhat more favorable with respect to the reformulation reducing opioid overdose risk, although this was true only in the commercial claims populations and not the Medicaid cohort. The implications and generalizability of this specific finding are not entirely clear, however, in part because OxyContin use without concomitant dispensing of any other opioid analgesics was relatively uncommon. The interpretation of this finding is further complicated by the potential for unmeasured differences between the prescribed patient populations in the pre- and post-reformulation periods. It is possible that OxyContin’s abuse-deterrent properties did confer a reduced risk of overdose among patients using the product without any other opioid analgesics. However, it is also plausible that patients receiving OxyContin alone in the post-reformulation period were inherently at a lower risk of overdose than those who received OxyContin alone during the pre-period, either through changes in OxyContin prescribing practices, or through “self-selection” away from reformulated OxyContin among patients seeking to abuse it via non-oral routes. While the latter explanation may be consistent with reformulated OxyContin having an abuse-deterrent effect, it does not necessarily follow that the abuse-deterrent properties conferred a reduced risk of overdose among those exposed to the product or that those who migrated away from OxyContin because of its reformulation actually had a lower risk of overdose.

1 INTRODUCTION

Postmarketing requirement (PMR) study 3051-4 is one of four studies the United States Food and Drug Administration (FDA) required of the sponsor, Purdue Pharma, LP (hereafter, the sponsor) to evaluate the impact of OxyContin's reformulation on its abuse and overdose. Specifically, PMR study 3051-4 aimed to assess the impact of the reformulation on risk of overdose among patients dispensed OxyContin. OxyContin (oxycodone hydrochloride, controlled release; New Drug Application [NDA] 022272) was reformulated with physicochemical properties that were intended to deter tablet manipulation for the purposes of abuse primarily via insufflation and injection. The reformulation incorporated a high molecular weight polymer (polyethylene oxide) matrix with the intention of making the tablet more difficult to manipulate for the purposes of non-oral misuse or abuse. Based on review of *in vitro* and clinical study data, in 2013 FDA concluded that reformulated OxyContin had "abuse-deterrent" characteristics, and the label^{vi} was updated with its current language:

"The in vitro data demonstrate that OXYCONTIN has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the in vitro data, also indicate that OXYCONTIN has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OXYCONTIN by these routes, as well as by the oral route, is still possible."

Observational studies, including PMR study 3051-4, were required to provide further information on the ability of reformulated OxyContin to deter abuse and reduce abuse-related harms in the postmarket setting. Study 3051-4 used three sources of administrative claims data to measure changes in the rates of overdose among patients dispensed OxyContin, comparing the pre-reformulation period of OxyContin marketing to the post-reformulation period, relative to comparable opioid analgesic drugs marketed during that time. The three additional required studies evaluated changes from the pre- to post-reformulation in: 1) opioid abuse in a sentinel population of adults who were assessed for substance use disorder and treatment planning, using data from the NAVIPPRO® ASI-MV surveillance system (PMR 3051-1); 2) opioid abuse exposure calls to US poison control centers, using data from the RADARS® Poison Control Program (PMR 3051-2); 3) opioid abuse in a sentinel population of adults entering methadone and non-methadone treatment for opioid use disorder, using data from the RADARS Treatment Center Program (PMR 3051-3).

In 2014, the sponsor submitted postmarket studies to support a "real-world" abuse-deterrence labeling claim; these studies were reviewed by the Division of Epidemiology (DEPI) and the Division of Biometrics (DB7), and an Advisory Committee (AC) meeting was scheduled for July 2015 to discuss the studies findings' in a public forum. In June 2015, the sponsor withdrew their labeling supplement and the AC meeting was cancelled. In 2016, FDA issued formal PMR letters to ensure timely study completion and to allow FDA to provide input on study design and methods. With respect to PMR study 3051-4, this study was not a part of the initial 2014 submission and was formally required in the

^{vi} OxyContin label (revised 08/2015):

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022272s027lbl.pdf

2016 PMR letter to address a need for an evaluation of the impact of reformulation on non-fatal and fatal overdose associated with OxyContin dispensing.

Unlike the other PMR studies (3051-1,2,3), PMR study 3051-4 required new linkages to mortality data and use of validated claims-based algorithms to ascertain opioid overdose outcomes. In 2016, FDA recommended major modifications to PMR study 3051-4, including, but not limited to, analyzing data from patients with concurrent use of other opioid analgesics in addition to OxyContin, and adding a Medicaid database. FDA also provided input on the protocol and analysis plan to assess the usability of Medicaid data. In 2019, the sponsor submitted the final study report incorporating FDA's recommendations, including a formal assessment of Medicaid data usability by state.

The objective of this review was to determine whether data from PMR study 3051-4 support that OxyContin's reformulation reduced fatal and non-fatal opioid overdose risk among patients dispensed the product.

In conjunction with the other PMR studies (3051-1, 2, and 3) and other relevant information, the findings of this study can be used to help inform the overarching question of whether OxyContin's reformulation meaningfully reduced its abuse and associated harms. While each study can alone provide important information on the potential impact of the reformulation, it is ultimately necessary to evaluate the totality of evidence from all sources to answer this question.

2 REVIEW METHODS AND MATERIALS

To prepare this review document, DEPI reviewed:

- PMR study 3051-4 final study report (EPI8034ORF) - "Changes in Fatal and Non-fatal Overdose among Individuals Dispensed OxyContin® after its Reformulation with Abuse-deterrent Properties – A Healthcare Database Analysis with Linkage to the National Death Index" (received August 2019)
 - Study protocol
 - Statistical analysis plan
 - Study results, including all appendices
- Sponsor submitted responses to information requests:
 - Received March 3, 2017
 - Received March 9, 2017
 - Received December 12, 2019
 - Received January 31, 2020
 - Received March 26, 2020
 - Received April 1, 2020

In brief, this review document provides a summary and interpretation of PMR study 3051-4 methods and main findings, including a discussion of relevant methodological issues and how these impact inferences that can be made based on the study's results. The findings of this review will be used to inform the broader question of whether OxyContin's reformulation was effective in reducing abuse and associated harms. DEPI also conducted a review of the literature to identify published studies using administrative claims data that may provide context or supplemental information to aid in the interpretation of PMR study

3051-4 ([see background document: OSE Literature Review](#)). Two such studies were identified, and these were reviewed for any additional information that could inform our interpretation of the findings of PMR study 3051-4.

To determine whether OxyContin's reformulation reduced overdose rates among patients dispensed the product, PMR study 3051-4 findings were evaluated using FDA's Guidance for Industry, "Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data,"^{vii} and fundamental guiding principles of epidemiology, including principles for making causal inferences from observational data.

3 PMR STUDY 3051-4 METHODS

3.1 STUDY OVERVIEW

In PMR study 3051-4, investigators analyzed three administrative claims databases (Medicaid and two commercial claims databases) linked to national mortality data to assess the impact of OxyContin's reformulation on the incidence of fatal or non-fatal opioid overdose ("overdose") among patients dispensed OxyContin. Analyses compared overdose rates in these patients in the two years before (3Q2008-2Q2010) to the five years after (1Q2011-3Q2015) OxyContin reformulation (two years after OxyContin reformulation in Medicaid database [1Q2011-4Q2012]), excluding a transition period (3Q2010-4Q2010). The change in overdose rates among patients dispensed OxyContin was compared to the change observed in patients dispensed selected other opioid analgesics. These comparators were intended to provide contextual information on opioid overdose trends unrelated to the reformulation and to aid in causal inference. Due to the complexity of these data, (e.g., many patients dispensed OxyContin concomitantly with intermittent dispensing of other opioid analgesics, and potential for confounding by patient characteristics) a number of different analyses were conducted to better understand the generalizability of study findings and role of potential biases. For example, some analyses included the use of several exposure categories that included patients dispensed OxyContin with or without other opioid analgesics. In separate analyses, alternative methods were used to adjust for patient-level characteristics. Primary PMR study 3051-4 analyses were conducted in three different administrative claims databases to look for consistency in findings across databases and patient populations.

3.2 STUDY OBJECTIVES

Primary objectives as stated in the protocol:

- 1) Assess the changes in the rates of unintentional overdose among those dispensed OxyContin, two years before the reformulation versus (vs.) five years after the reformulation (-2 years[y]/5y)
- 2) Assess the changes in rates of unintentional overdose among those dispensed OxyContin vs. primary comparator opioid analgesics (-2y/5y)

^{vii} FDA's Guidance for Industry: <https://www.fda.gov/media/79922/download>

- 3) Assess the changes in rates of unintentional overdose among those dispensed OxyContin vs. secondary comparator opioid analgesics (-2y/5y)

Secondary objectives as stated in the protocol:

- 1) Assess the changes in rates of unintentional and suicide-related (intentional) overdose separately among those dispensed OxyContin vs. primary comparator opioid analgesics (-2y/5y)
- 2) Assess the changes in rates of unintentional overdose among patients continuously dispensed OxyContin from the pre- to post-period vs. those continuously dispensed primary comparator opioid analgesics from the pre- to post-period (-2y/5y)
- 3) Describe temporal trends in overdose rates between 2008 and 2015 among those dispensed OxyContin, and primary and secondary comparator opioid analgesics
- 4) Compare the characteristics of individuals dispensed OxyContin or primary comparator opioids, overall, and stratified by ability to link to the National Death Index (NDI)

3.3 OVERARCHING METHODOLOGICAL CONSIDERATIONS

There are several aspects of the PMR 3051-4 study design and methods that were intended to address concerns with the data quality and potential biases. A number of preliminary descriptive analyses were also conducted to help inform the study design and analytic approach.

Use of multiple claims databases: Three separate administrative claims databases were used in PMR study 3051-4 to broaden the patient population under study and evaluate the consistency of findings in multiple patient populations and data environments. Two databases were commercial claims databases, including only individuals with private insurance, and the other was the Medicaid Analytic eXtract database, including those with subsidized government insurance (see Section 3.4.1.2) and potentially different risk profiles based on their higher prevalence of certain comorbidities.

Use of comparator drugs as negative controls: Three primary comparators (extended-release [ER] morphine, transdermal [TD] fentanyl, and methadone) were used as negative controls, “counterfactuals,” for OxyContin, approximating the expected changes in overdose rates among patients dispensed OxyContin had it not been reformulated. The comparators were chosen to reflect a diverse set of ER or long-acting (LA) opioid analgesic products with comparable market share and regulatory requirements (see Section 3.4.3). The primary comparators’ in this study have long marketing histories as ER/LA opioid analgesics suggesting that they may be subject to the same longer-term secular trends in patient selection, prescribing practices, abuse profile, and overdose risk as OxyContin. Using comparators can help to account for larger secular trends in the outcome, and published data suggest that there are likely secular trends in opioid overdose that are important to consider. For instance, following sustained annual increases from 1999 to roughly 2011, the rate of increase of opioid overdose deaths involving prescription opioids (natural and semisynthetic) has slowed since 2011, whereas those from heroin and

synthetic opioids (i.e., illicit fentanyl analogs) have increased dramatically.^{viii} These data reflect overdoses in the entire US population and may not reflect trends within the cohorts studied in PMR study 3051-4, but they underscore the importance of controlling for secular trends when making inferences about any changes in overdose rates over time. In addition, changing commercial and state Medicaid coverage policies during the study period could differentially affect population risk profiles and overdose risk across study time periods.

Dispensing trends for OxyContin: The sponsor conducted two analyses (see Appendix 8.1) in response to an information request sent by the Agency in 2017 requesting data on opioid analgesic switching patterns around the time of the reformulation, and the prevalence of OxyContin's use concomitantly with other opioid analgesics. The findings are briefly summarized here:

- **Opioid analgesic switching patterns:** Among patients dispensed original OxyContin, 61% switched to reformulated OxyContin in the MarketScan commercial insurance database, 19% switched to other opioid analgesics, 6% continued to receive original OxyContin, and 14% had no further opioid analgesic claims observed by 3 months after OxyContin reformulation. In the Medicaid database, 65% switched to reformulated OxyContin, 17% switched to other opioid analgesics, 8% continued to receive original OxyContin, and 10% had no further opioid analgesic claims observed. More than 80% of those who switched went on to initiate a generic immediate release (IR) opioid analgesic in both databases. The most common other opioid analgesic that OxyContin users switched to was IR oxycodone (49%). Roughly 42% and 57% of generic ER oxycodone users were subsequently dispensed reformulated OxyContin within 3 months of a defined index prescription date^{ix} around when generic ER oxycodone marketing ceased in the commercially-insured and Medicaid populations, respectively. Of note, this analysis did not assess whether these switching and discontinuation patterns (i.e., from OxyContin to other opioid analgesics or discontinuation of opioid analgesics) were different from patterns before the reformulation or attributable specifically to OxyContin's reformulation.
- **Concomitant opioid analgesic use:** In the MarketScan commercial insurance database from 2008 to 2015, only ~10% to ~14% of patients dispensed OxyContin were dispensed OxyContin alone (i.e., without other opioid analgesics) for the duration of their OxyContin dispensing in a given year, while ~80% to ~87% were dispensed OxyContin concomitantly with other opioid analgesics, often mixing periods of both concomitant dispensing and dispensing alone. In the Medicaid database from 2008 to 2012, ~28% to ~34% of patients dispensed OxyContin were only dispensed OxyContin alone for the duration of their OxyContin use in a given year, while ~66% to ~71% were dispensed OxyContin concomitantly with other opioid analgesics, also often mixing periods of both concomitant dispensing and dispensing alone. In both databases, IR opioid analgesics were the most commonly

^{viii} Hedegaard H, Miniño AM, Warner M. Drug overdose deaths in the United States, 1999–2018. NCHS Data Brief, no 356. Hyattsville, MD: National Center for Health Statistics. 2020

^{ix} Defined as an active ER oxycodone dispensing on October 1, 2010, or an ER oxycodone dispensing between October 1, 2010 and March 31, 2011.

dispensed with OxyContin among the drugs analyzed, particularly IR formulations of hydrocodone and oxycodone.

- There were some notable changes in patient characteristics comparing before and after the reformulation (See Appendix 8.1). There were geographic shifts among patients dispensed OxyContin in MarketScan, but not Medicaid, with increases in the Northeast and South and declines in North Central, U.S. Age skewed older comparing periods in MarketScan, but not in Medicaid. Arthritis^x and chronic pain diagnoses also increased considerably among patients dispensed OxyContin comparing periods in MarketScan, and there were minor increases in diagnoses of substance use disorder^{xi}; this was not as clear in Medicaid because the data provided on comorbidities was very limited. Additionally, there were large declines in number of higher strength tablets dispensed over the period analyzed in both MarketScan and Medicaid — notably the 80 milligram tablets.
- Based on the concomitant use data, overdose rates were assessed separately among all OxyContin users, or those with or without other opioid analgesics dispensed concomitantly (including those dispensed IR opioid analgesics, specifically), and specifically during time dispensed OxyContin alone, or without other opioid analgesics dispensed concomitantly. Using multiple distinct exposure groups helps to reflect the various ways patients are dispensed opioid analgesics and improves the generalizability of the study's findings. Comparative analyses of patients using only one opioid analgesic product at a time are simpler from a causal inference perspective, but this does not appear to be the most common treatment practice with respect to OxyContin. At the same time, consistent effects across all exposure groups would suggest a more robust impact of the reformulation on overdose rates and would facilitate a more straightforward interpretation of the study's findings.

Medicaid data usability: Because of the differences in how administrative claims data from fee-for-service (FFS) and comprehensive managed care Medicaid coverage types are collected and reported for patient-level healthcare encounters, separate analyses were conducted to assess the usability (i.e., “completeness”) of data from the different plan types across all available states and years (See sub-study methods and results in Appendix 8.3). Based on the results of this evaluation, for PMR study 3051-4 Medicaid overdose analyses the sponsor included only data in a given state/year determined to be usable based on measures of “continuity” and “connectivity” of administrative claims using criteria derived from Li et al.^{xii} (See section 3.4.1.2 and Appendix 8.3). Primary results were assembled using a combined cohort of FFS and comprehensive managed care patients in states/years deemed usable, but stratified analyses by coverage type were also conducted as sensitivity analyses.

^x “Arthritis” includes arthropathies, osteoarthritis and musculoskeletal pain

^{xi} “Substance use disorder” excludes opioid use disorder

^{xii} Li et al. (2017) Internal validation of Medicaid Analytic eXtract (MAX) data capture for comprehensive managed care plan enrollees from 2007 to 2010. *Pharmacoepidemiology and Drug Safety*: 1-10; <https://doi.org/10.1002/pds.4365>

Validated outcome ascertainment: Opioid overdose outcomes were identified using the code-based diagnostic algorithm developed for use in administrative claims databases and validated as part of the extended-release/long-acting opioid analgesic (ER/LA OA) PMR study 3033-6, conducted by the Opioid Product Consortium (OPC) (see Section 3.4.6).^{xiii} The results of PMR study 3033-6 are described in Green et al,^{xiv} along with additional algorithm portability assessments (i.e., their ability to perform consistently across databases) which showed that the “any opioid overdose” algorithm (unintentional and intentional; fatal and non-fatal) was consistently superior in accurately ascertaining cases to the intentional opioid overdose algorithm (fatal and non-fatal) across several claims databases, most notably in TennCare (Tennessee Medicaid data). **Therefore, FDA now views the “any opioid overdose” analyses in PMR study 3051-4 as primary, and while they were originally planned as primary objectives, the unintentional opioid overdose analyses are now viewed as exploratory due to this algorithm’s poorer performance in the validation and database portability studies.**

Adjusting for patient differences across periods: Opioid overdose incidence rate ratios were adjusted for patient demographic characteristics, clinical characteristics, and other comorbidities (see Section 3.4.5) using both standard multivariate adjustment, and propensity score weighted Poisson models to help mitigate the potential confounding from important differences in patient-level characteristics in the pre- and post-reformulation periods, or across groups receiving different opioid analgesics. Changes in prescribing practices could bias results if higher risk (with respect to abuse and overdose), or lower risk, patients were “channeled” onto specific opioid analgesics differentially across the study period.

3.4 STUDY METHODS

3.4.1 Design & Setting

3.4.1.1 Study Design

Retrospective, pre- versus post-intervention cohort study

3.4.1.2 Electronic healthcare databases

HealthCore Integrated Research Database (hereafter, HIRD)

HIRD is an administrative healthcare claims database with data on commercially-insured individuals. HIRD includes longitudinal (since 2006) medical and pharmacy claims data from over 50 million commercial and Medicare Advantage Anthem health plan members.

IBM (formerly Truvon Health) MarketScan Commercial and Medicare Supplemental Claims and Encounters database (hereafter, MarketScan)

^{xiii} ER/LA opioid PMR letter: <https://www.fda.gov/media/95546/download>; ClinicalTrials.gov Identifier: NCT02667197, <https://clinicaltrials.gov/ct2/show/NCT02667197>

^{xiv} Green CA, et al. (2019) Identifying and classifying opioid-related overdoses: A validation study. *Pharmacoepidemiol Drug Saf*;28: 1127–1137. <https://doi.org/10.1002/pds.4772>

MarketScan is an administrative healthcare claims database with data on commercially-insured individuals with employer-based health insurance, and their covered family members. Marketscan included longitudinal medical and pharmacy claims data for over 100 million individuals over the study period.

Medicaid Analytic eXtract (MAX): National Medicaid Database (hereafter, Medicaid)

Medicaid MAX is an administrative healthcare claims database available through the Centers for Medicare and Medicaid Services (CMS) with data on individuals with subsidized government insurance. At the time of analysis, these Medicaid data covered beneficiaries in all 50 states and Washington D.C. through 2012 (28 states through 2013), including all medical and pharmacy claims for beneficiaries covered by both FFS and comprehensive managed care Medicaid plans.

For all Medicaid analyses, the sponsor only retained data for patients a given combination of state, year, and basis of eligibility (BOE) group that was determined to be usable, or essentially “complete,” based on operationalized measures of “continuity”^{xv} and “connectivity”^{xvi} for patients’ administrative claims over time using criteria derived from Li et al.^{xvii} (2017) (See sub-study results in Appendix 8.3):

- For managed care members, there were 12 states that had all data included in the study (all years 2008-2012 for both the adult and disabled populations), while 19 states did not have any years included for either the adult or disabled populations. The other 19 states (and Washington, DC) had a subset of their years included for either the adult and/or disabled BOE groups.
- For FFS patients, there were six states that had all years excluded for the adult population, and two states that had all years excluded for the disabled population. There were 20 states that had all years included in both the adult and disabled populations, and for the other 35 states and Washington DC, most of their data were included.

In sum, approximately 25% of the Medicaid beneficiary population (~24 million of ~95 million) were eligible for this study after applying the data usability criteria from Li et al.

National Death Index (NDI)

All databases were linked to the NDI to ascertain mortality status and cause of death among patients dispensed opioid analgesics. The NDI, maintained by National Center for Health Statistics (NCHS), is a central computerized index of death record information comprised of data from state vital statistics offices.

^{xv} “Continuity” is defined by medical treatment that continues after a patient switches from FFS to managed care coverage

^{xvi} “Connectivity” is defined by medical treatment that is expected given a specific diagnosis among patients in either FFS or managed care

^{xvii} Li et al. (2017) Internal validation of Medicaid Analytic eXtract (MAX) data capture for comprehensive managed care plan enrollees from 2007 to 2010. *Pharmacoepidemiology and Drug Safety*: 1-10; <https://doi.org/10.1002/pds.4365>

3.4.1.3 Time period definitions

2-year baseline (3Q2008-2Q2010), hereafter pre-period: reflects a baseline period with relatively stable utilization of OxyContin^{xviii}

6-month transition (3Q2010-4Q2010): excluded from analyses as it represents the transition period (i.e., a period that includes the introduction of reformulated OxyContin to the market, and the decreasing supply and availability of the original OxyContin formulation)

5-years post-reformulation (1Q2011-3Q2015), hereafter post-period: provides an estimate of the sustained effect after the reformulation. The last quarter of 2015 was excluded to avoid the use of un-validated ICD-10-CM overdose codes when the US switched from ICD-9 to ICD-10 billing codes.

- **Two-years post-reformulation for Medicaid (1Q2011 to 4Q2012) analyses:** The Medicaid data did not have complete information available from 2013 – 2015 for all states so the post-period was truncated.

3.4.2 Study Population

Inclusion criteria applied to all analyses:

- Individuals aged 16-74 years (aged 16-64 years in Medicaid)
- At least one pharmacy dispensing of an eligible oral or transdermal (TD) opioid analgesic between July 1, 2008 and September 30, 2015
- At least three months of continuous health plan eligibility (prior to an eligible opioid analgesic dispensing)
- Population that is linkable to the NDI (except for Secondary Objective 4)

Patients with prior opioid overdose were included in the study. Approximately 40% of the HIRD, and 66% of MarketScan populations were **not** linkable to the NDI; these patients were excluded.

For the Medicaid population, only treatment episodes from state, year, and BOE groups for FFS and managed care members deemed eligible based on criteria defined by Li et al. were included

3.4.3 Comparators

Primary comparators

These primary comparators were intended to serve as negative controls for OxyContin, reflecting background trends and approximating expected changes in OxyContin overdose rates in the absence of the reformulation but subject to the same secular trends and various public health efforts (i.e., the “counterfactual” scenario). As there is no single ideal comparator, three comparators were chosen to reflect a diverse set of ER or long-acting (LA) opioid analgesic products with market share and settings of use that were similar to

^{xviii} Does not include the large changes in brand versus generic ER oxycodone prescriptions observed in early 2008 after the reinstatement of the OxyContin patent

OxyContin's and that were subject to the same regulatory actions (e.g., ER/LA Opioid Risk Evaluation and Mitigation Strategies) as OxyContin.

- **ER morphine tablets or capsules:** an ER prescription opioid analgesic drug used in chronic pain settings. ER morphine was not reformulated and had a large, relatively stable market share over the study period. While all the primary comparators have some utility, ER morphine may represent the best direct opioid analgesic to compare to OxyContin, with a relative potency and total number of patients dispensed over the study period fairly similar to those of OxyContin.
- **TD fentanyl (hereafter, fentanyl):** an ER prescription opioid analgesic drug with a long marketing history and used in chronic pain settings. Fentanyl had relatively stable utilization over the study period. The time period for this study largely predates the emergence of illicit fentanyl in the black market, and the subsequent rise in fentanyl-related deaths. It bears mentioning that TD fentanyl underwent a market transition from majority reservoir to matrix TD formulations over the study period, which could have impacted overdose risk associated with these products.
- **Methadone tablets or capsules:** a long-acting prescription opioid analgesic drug that is used in chronic pain settings and was not reformulated. Methadone had gradually declining use but no major fluctuations in utilization over the study period.

Secondary comparators

Secondary comparators were included to provide contextual information to assist the interpretation of observed changes in overdose rates for OxyContin and primary comparators. Secondary comparators included the following, along with the main reasons for not being selected as primary comparators:

- **ER oxymorphone tablets:** reformulated during the post-period, low market share during the study period
- **SE/IR oxycodone tablets:** not an ER/LA opioid analgesic, often used in acute pain settings
- **IR hydromorphone tablets:** not an ER/LA opioid analgesic, often used in acute pain settings

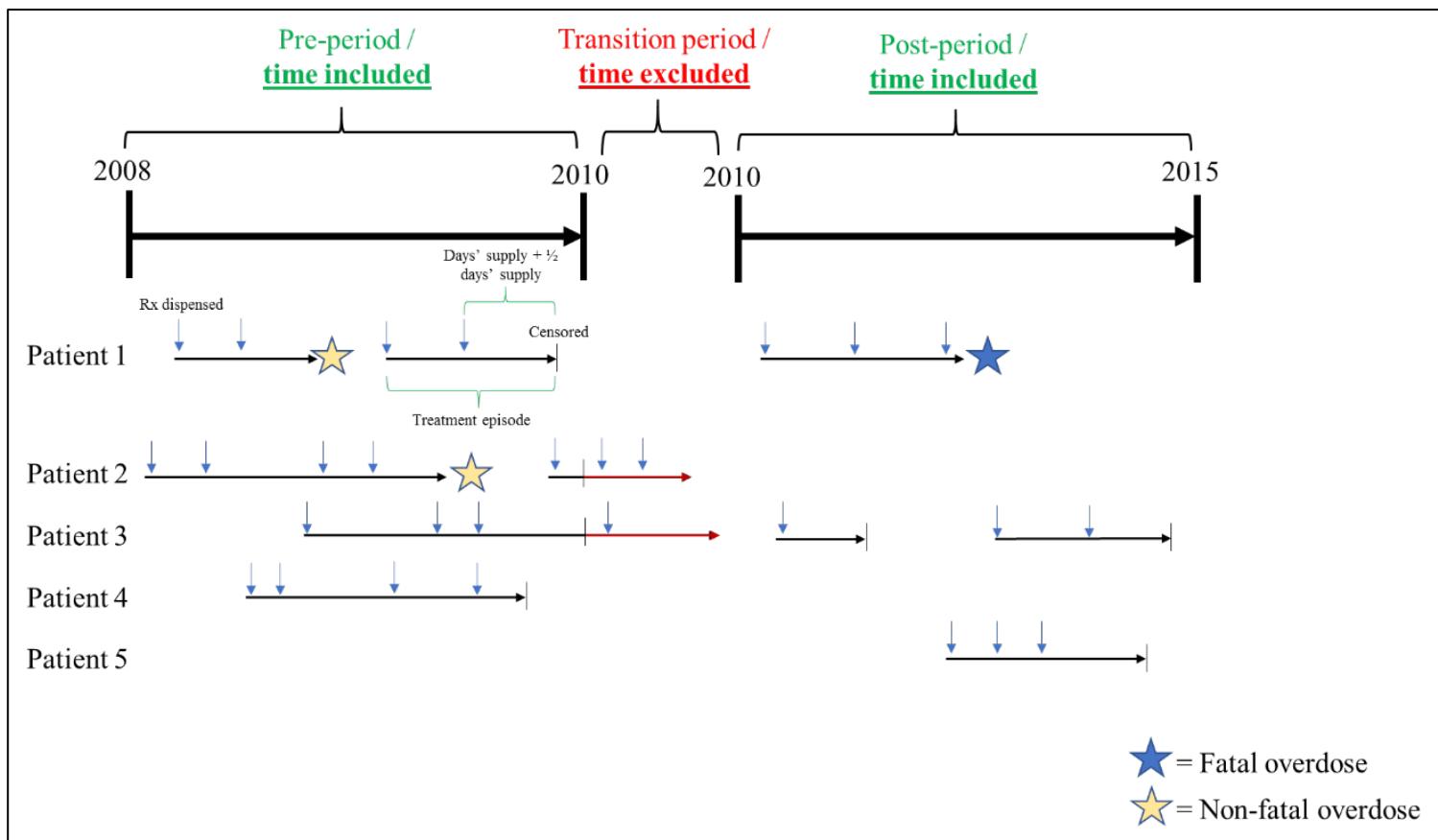
With the exception of single-entity immediate-release (SE/IR) oxycodone, the secondary comparators have lower utilization and more severe fluctuations in their utilization during the study period. SE/IR oxycodone could serve as a direct comparator given it is the same active moiety, but as an IR formulation, patient populations and prescribing practices may be quite different from OxyContin, particularly with regard to opioid analgesic co-prescribing. SE/IR oxycodone is frequently dispensed with OxyContin (see Appendix 8.1) further complicating its use as a comparator.

3.4.4 Exposure Time

Treatment episodes in the pre- and post-periods were defined as continuous patient-level opioid analgesic exposure periods (in person-time [months]) (see Figure 1), calculated using the drug dispensing dates and the number of days dispensed in patients' administrative pharmacy claims. The number of days dispensed is an estimate entered by

the dispensing pharmacist and may be influenced by the prescriber instructions, insurance reimbursement, or other unknown factors. Continuous opioid analgesic exposure time within a treatment episode began on the date of first dispensing of the opioid analgesic and ended at the exhaustion of days' supply plus half of the days' supply of the last dispensing of the opioid analgesic in that treatment episode, including the day of dispensing as an exposed day. Continuous opioid analgesic exposure time ended if there was one or more patient days of discontinuity in opioid analgesic "exposed" time; a treatment episode was censored if an individual discontinued an opioid analgesic of interest, initiated another study opioid analgesic (depending on the analyses), had the outcome of interest (fatal or non-fatal overdose), died, terminated their health plan, or reached the end of a study period (e.g., end of pre-period, post-period, or transition period).

Figure 1: Exposure time schematic



(FDA generated figure)

Key: Prescription (Rx); horizontal arrows that are black denote opioid analgesic exposure time periods (i.e., treatment episodes) that would theoretically be included in analyses; horizontal arrows that are red denote time that would not be included as it overlapped the transition period; vertical arrows denote prescription dispensed; note, all overdoses were included (fatal or non-fatal) in final analyses

If an individual obtained a new dispensing of the same opioid analgesic prior to exhausting the days' supply of a prior prescription of that opioid analgesic, the episode was extended using the newest prescription days' supply plus half days' supply. Any overlap between the days' supply of the two prescriptions was ignored. This means that exposure time did

not account for indefinite “stockpiling” of medications. When there was a dispensing of a different opioid analgesic (i.e., opioid analgesic switch) before the end of the days’ supply for the previous dispensing, a new treatment episode was created at the first dispensing of the new opioid analgesic, but this new episode also included any overlapping days’ supply of the previous opioid analgesic dispensing, thus it would be concomitant use (of the new opioid analgesic with the old opioid analgesic) until the older prescription ran out.

Exposure groups:

Treatment episodes were categorized by opioid analgesic concomitancy to reflect the various ways patients are dispensed opioid analgesics, and to look for consistency of effect across exposure groups. As described above (Section 3.3 and Appendix 8.5), the sponsor conducted analyses on opioid analgesic switching patterns and concomitancy among patients dispensed OxyContin around the time of the reformulation. Based on these findings, analyses were conducted separately for the following mutually exclusive exposure groups:

- those involving the dispensing an opioid analgesic with or without concomitant opioid analgesics;
- those involving the dispensing of only one opioid analgesic (i.e., no concomitant use);
- those involving the dispensing of several opioid analgesics concomitantly

O OxyContin dispensing

1. Any OxyContin use: Time dispensed OxyContin, regardless of other opioid analgesic dispensing (including comparators)
2. Any OxyContin use (without concomitant primary comparator): Time dispensed OxyContin, excluding periods dispensed primary comparators concomitantly
3. OxyContin use without a concomitant opioid analgesic (CO): Time dispensed OxyContin only, censored at dispensing of another opioid analgesic (comparators or any other)
4. OxyContin with concomitant IR opioid analgesic: Time dispensed OxyContin and any IR opioid analgesic concomitantly, excluding periods dispensed primary comparator concomitantly
5. OxyContin with a CO: Time dispensed OxyContin and an IR or ER opioid analgesic concomitantly, excluding periods dispensed primary comparator concomitantly
 - These data were not included in this review. The vast majority of concomitant use was with IR opioid analgesics (#4), therefore the results of these analyses were nearly identical to the results for #4.

O Any primary comparator (PC) dispensing

1. Any PC use: Time dispensed a PC, regardless of other opioid analgesic dispensing (including comparators)
2. Any PC use (excluding periods with OxyContin or other PC): Time dispensed a PC, excluding periods dispensed OxyContin or any other PC concomitantly

3. PC use without a CO: Time dispensed a PC only, censored at dispensing of another opioid analgesic (comparators or any other)
4. PC with concomitant IR: Time dispensed a PC and any IR opioid analgesic concomitantly, excluding periods dispensed OxyContin or any other PC concomitantly
5. PC with a CO: Time dispensed a PC and an IR or ER opioid analgesic concomitantly, excluding periods dispensed of OxyContin or any other PC concomitantly
 - These data are not presented. The vast majority of concomitant use is with IR opioid analgesics (#4), therefore the results of these analyses are nearly identical.

- **Any secondary comparator (SC) dispensing**

1. Any SC use (excluding periods with OxyContin, PC, or other SCs): Time dispensed a SC, excluding periods dispensed OxyContin or any PC or SC concomitantly, permitting dispensing of any non-comparators concomitantly
2. SC use without a CO: Time dispensed with a SC only, censored at dispensing of another opioid analgesic (comparators or any other)
3. SC with a CO: Time dispensed a SC and an IR or ER opioid analgesic concomitantly, excluding periods dispensed OxyContin or any PC or SC concomitantly
 - These data are not presented in this review. The results of these analyses were nearly identical to those from #1.

Primary analyses included both treatment episodes defined as existing (prevalent) and new (incident) use episodes analyzed together (i.e., any patient meeting inclusion criteria); this was done to improve statistical power given the rare outcome of overdose. Sensitivity analyses stratified by prevalent and incident use treatment episodes were also conducted (See section 3.4.7.2). For these analyses, “incident use” was defined as having had no recorded dispensing of any study opioid analgesic in at least three months (i.e., 92 days of data coverage) prior to the start of a treatment episode. The population of “incident users” could have taken other opioid analgesics not listed in Section 3.2.3, so patients were not necessarily “new” to recent opioid analgesic use (e.g., patients could have used IR hydrocodone prior to the index date). An individual could re-enter the cohort as an “incident user” at later points in the study if they met the incident use criteria at the beginning of their new treatment episode.

For Secondary Objective 2, which examined overdose rates among patients continuously dispensed OxyContin (without a PC) or a PC opioid analgesic (without OxyContin or other PC) from the pre-period through the post-period, all pre-period treatment episodes that were initially eligible for Primary Objective 2 were included; however, for the post-period, only treatment episodes from the patients who were still dispensed the study opioid analgesic at the end of the pre-period, and continuously dispensed the same opioid analgesic through the transition period, and into the post-period were included in the cohort. Since patient inclusion in these analyses was based on post-reformulation information, patients with continuous opioid analgesic use must have survived without a

fatal overdose through the pre-period and transition period to be included. Secondary Objective 2 analyses were considered exploratory.

3.4.5 Covariates

Demographic characteristics, clinical characteristics, and other comorbidities were ascertained for each treatment episode using patients' administrative claims, including diagnosis codes from their inpatient and outpatient service claims (See Table 3). These variables were selected based on their availability in the data, and their potential relevancy as a confounder with respect to their association with the choice of opioid analgesic dispensed and the outcome of opioid overdose. The primary clinical covariates (Table 3, comorbidities I) were selected because they were for chronic conditions with diagnosis codes that were expected to be consistently noted for a given patient across the study period; this is important as patients may contribute multiple treatment episodes. Additional variables (Table 3, comorbidities II) were included only in propensity score (PS) weighted analyses (See Section 3.4.7.2) limited to "incident use" periods. The sponsor deemed these additional variables (Table 3, comorbidities II) as potential intermediate ("downstream") variables (or mediators) in the causal pathway (i.e., clinical characteristics potentially caused by the opioid analgesic dispensed) that may obscure the "true" causal effect.

Benzodiazepine use was also deemed an intermediate variable in the causal pathway by the sponsor, and thus was excluded from all analyses; FDA requested the sponsor re-analyze the data with baseline benzodiazepine use (within three months of treatment initiation) as a covariate in the fully-adjusted models and the results were submitted in their April 1, 2020, information request response. FDA also requested the sponsor explore its role as a potential effect modifier in those analyses, testing for statistically significant interactions between baseline benzodiazepine use and opioid analgesic exposure group across the databases, and conducting stratified analyses where necessary.

As noted in section 3.4.2, patients with eligible treatment episodes after a non-fatal overdose were included in analyses. Because patients could have had an overdose and become eligible again, and because past overdose is highly predictive of future overdose, the sponsor also used a time-updated variable for "history of overdose event/poisoning" in adjusted analyses to account for within-person correlation.

The lookback period was three months (i.e., 92 days) prior to each treatment episode for all covariates, except for certain demographic characteristics which were assessed at the first opioid analgesic dispensing (e.g., geographic region), and other select covariates which used a six-month lookback period (these are noted in the table below).

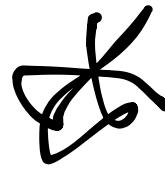


Table 3: Variables in statistical models

| Variables used in all fully-adjusted statistical models | | Additional variables used only in propensity score analyses (sensitivity analyses) |
|--|--|--|
| Demographic / descriptive characteristics | Comorbidities / clinical characteristics I | Comorbidities / clinical characteristics II |
| Age | Abdominal pain | Alcohol use disorder |
| Gender | Amputation | Generalized anxiety disorder |
| Geographic region (commercial databases) | Arthritis, arthropathies, osteoarthritis, and musculoskeletal pain | Attention deficit hyperactive disorder (ADHD) |
| United States (US) state residence (Medicaid database) | Back pain | Bipolar disorder |
| Calendar year of index date | Chronic pain | Major depressive disorder |
| Plan type (Health Maintenance Organization [HMO], preferred provider organization [PPO], consumer driver health insurance [CDHP]/high deductible health plan [HDHP]) | Fibromyalgia | History of attempted suicide |
| Medicaid coverage type (fee-for-service [FFS], managed care [CMC]) | Headache | Post-traumatic stress disorder |
| Medicaid basis of eligibility (basis of eligibility [BOE]) group (disabled, adult) | Malignancy | Sleep disorder |
| | Multiple sclerosis | Somatoform disorder |
| | Neuropathic pain | Opioid Use Disorder |
| | Peripheral vascular disease | Non-OUD Substance Use Disorder |
| | Stroke | Borderline personality disorder |
| | Liver disease | All-cause office visits in last six months |
| | Renal disease | All cause emergency department visits in last six months |
| | Chronic Obstructive Pulmonary Disease (COPD) | All cause hospitalizations in last six months |
| | Impaired respiratory function | Distinct medication classes in last six months |
| | Deyo-Charlson-comorbidity index | Prior use of Tramadol (ER or IR) |
| | History of overdose/ poisoning* | |
| | Prior use of opioid analgesic (none, extended-release [ER] opioid only, immediate-release [IR] opioid only, ER + IR opioids) | |

(FDA generated table)

Key: *=time-updated variable at each treatment episode since patients with previous overdose could be included if they were subsequently dispensed an opioid analgesic; extended-release (ER); immediate-release (IR); opioid use disorder (OUD)

3.4.6 Outcome Measures

Opioid overdose outcomes were identified using the code-based diagnostic algorithm developed for use in administrative claims databases and validated as part of the extended-release/long-acting opioid analgesic (ER/LA OA) PMR study 3033-6, conducted by the Opioid Product Consortium (OPC)^{xix}; the algorithm also relied on database linkages to the NDI to capture fatal opioid overdose events.

The OPC published the results of PMR study 3033-6^{xx} and additional algorithm portability assessments they conducted independently, including testing the algorithms in Tennessee

^{xix} ER/LA opioid PMR letter: <https://www.fda.gov/media/95546/download>; ClinicalTrials.gov Identifier: NCT02667197: <https://clinicaltrials.gov/ct2/show/NCT02667197>

^{xx} Green CA, et al. (2019) Identifying and classifying opioid-related overdoses: A validation study. *Pharmacoepidemiol Drug Saf*;28: 1127–1137. <https://doi.org/10.1002/pds.4772>

Medicaid data (TennCare). That study demonstrated the any opioid overdose algorithm (unintentional and intentional; fatal and non-fatal) was superior to the intentional opioid overdose algorithm (fatal and non-fatal), with consistently high sensitivity, specificity, positive predictive value, and F scores across databases (See Table 4). The sponsor conducted a partial portability assessment of the algorithms (See Appendix 8.2) as part of PMR 3051-4, evaluating their performance in only the HIRD database where they had access to medical records, and the performance metrics they provided were generally consistent with those presented Green et al.

Because of the superior performance of the any overdose algorithm and the limited portability of the intentional overdose algorithm, particularly in the Tennessee Medicaid data, FDA views the any opioid overdose analyses in PMR study 3051-4 as primary, and analyses differentiating between intentional and unintentional are viewed as exploratory.

Table 4: Performance of the any opioid overdose algorithm and the intentional opioid overdose algorithm from PMR study 3051-4 and Green et al.

| Measure | Kaiser Permanente Northwest | | HIRD* | | Kaiser Permanente Washington | | Optum Integrated Database | | Tennessee Medicaid data (TennCare) | |
|---------------------------|-----------------------------|-----------------------------|---------------------|-----------------------------|------------------------------|-----------------------------|---------------------------|-----------------------------|------------------------------------|-----------------------------|
| | Any opioid overdose | Intentional opioid overdose | Any opioid overdose | Intentional opioid overdose | Any opioid overdose | Intentional opioid overdose | Any opioid overdose | Intentional opioid overdose | Any opioid overdose | Intentional opioid overdose |
| Sensitivity | 97.2 | 70.5 | n/a | 66.0 | 100.0 | 74.1 | 96.9 | 63.2 | 99.2 | 44.9 |
| Specificity | 84.6 | 90.2 | n/a | 96.4 | 89.2 | 86.7 | 100.0 | 91.0 | 92.4 | 87.1 |
| Positive Predictive Value | 87.4 | 78.9 | 85.0 | 88.6 | 84.1 | 74.1 | 100.0 | 81.1 | 91.9 | 64.5 |
| Negative Predictive Value | 96.5 | 85.5 | n/a | n/a | 100 | 86.7 | 96.9 | 80.1 | 99.2 | 75.1 |
| F-Score | 0.92 | 0.74 | n/a | n/a | 0.92 | 0.74 | 0.98 | 0.67 | 0.95 | 0.53 |

(FDA generated table from PMR 3051-4 study report and Green et al)

Key: *=These results were provided in the PMR study 3051-4 portability sub-study; all data (but HIRD) were abstracted from Green et al (2019); F-score is a measure of a test's accuracy

In PMR study 3051-4, an overdose was included as an outcome if it occurred during an eligible treatment episode. Thus, patients could have several non-fatal overdose events throughout the study period if they had several eligible treatment episodes and overdoses.

Of note, all overdose algorithms used in PMR 3051-4 include fatal and non-fatal overdoses involving any opioid, including prescription products and/or illicit opioids such as heroin and illicitly manufactured fentanyl.

Primary outcome in PMR study 3051-4

- Any opioid overdose: Intentional or unintentional, fatal or non-fatal opioid overdose

Exploratory outcomes in PMR study 3051-4

- Unintentional fatal or non-fatal opioid overdose
- Intentional fatal or non-fatal opioid overdose

3.4.7 Statistical Analyses

3.4.7.1 Primary Methods

Primary metrics and statistical models

Unadjusted and adjusted overdose incidence rates and 95% confidence intervals (CI) were modeled using Poisson regression, with person-time (i.e., opioid analgesic exposure time) included as an *offset*, and pre- versus post-reformulation overdose rate ratios (RR) were calculated for OxyContin and comparator opioid analgesic exposure groups, as defined in Section 3.4.4 above. The regression models used repeated-measures Generalized Estimating Equations (GEE) with an independent covariance matrix to account for the correlation between a given patient's multiple eligible treatment episodes; the robust ("sandwich") variance estimator was used to calculate 95% CIs. The expanded model was specified as follows:

$$\ln(Events_i) = \beta_0 + \beta_{oxy}Z_{oxy} + \beta_{pp}Z_{pp} + \beta_{RoR}Z_{pp}Z_{oxy} + \bar{\beta}_c \bar{z}_c + \ln(PersonTime_i)$$

The subscript i refers to each (mutually exclusive) block of person-time defined by opioid analgesic exposure group, pre- or post-reformulation period, and covariates. The indicator variable Z_{oxy} takes on the values 0 for OxyContin (1 to n for comparator opioid analgesics); Z_{pp} takes on the values 1 for the post-reformulation period (0 for pre-reformulation period). $\bar{\beta}_c \bar{z}_c$ represents the full set of covariates.

Overdose RRs comparing the overdose rates of the pre- and post-periods were calculated for OxyContin and each of the comparator opioid analgesic exposure groups ($RR = [\text{overdose incidence rate post-period}] / [\text{overdose incidence rate pre-period}]$). A ratio of rate ratios (RORR) was used to compare the changes in overdose rates between the pre- and post-periods comparing patients dispensed OxyContin to those dispensed a comparator opioid analgesic ($RORR = [\text{comparator RR}] / [\text{OxyContin RR}]$). In these types of difference in difference models,^{xxi} the RORR is represented by the interaction (β_{RoR}) between time period (binary variable: pre- or post-period) and opioid analgesic exposure group (with OxyContin as the reference drug group). An $RORR > 1$ reflects a more favorable change in overdose rates among those dispensed OxyContin comparing the periods before and after the reformulation relative to any changes in overdose rates for patients dispensed a comparator; in this context, favorable could mean a greater reduction or a smaller increase in overdose rates among those dispensed OxyContin comparing periods relative to those dispensed a comparator, or no change in overdose rates among those dispensed OxyContin but increasing overdose rates among those dispensed a comparator. An $RORR < 1$ indicates a more favorable change for among those dispensed a comparator.

^{xxi} Wing C et al. (2018) Designing Difference in Difference Studies: Best Practices for Public Health Policy Research. Annual Review of Public Health; 39: 453-469.

Meta-analytic methods

Analyses were undertaken separately in the three databases, and results are presented separately in the study report; however, DerSimonian and Laird^{xxii} random-effects meta-analysis was also used to compute meta-analyzed (combined) RRs and RORRs for the two commercial databases (MarketScan and HIRD). The Medicaid population was not included in these analyses given *a priori* differences in this population compared to the commercially-insured populations and the shorter post-reformulation period available in the Medicaid data.

PMR 3051-4 final study report only included meta-analyzed results for the unintentional overdose (exploratory outcome), which are not shown in this review, but the updated the meta-analyzed results (April 2020 information request response) using the any overdose outcome are described.

3.4.7.2 Sensitivity analyses

1) Incident user only cohort

In a subset of analyses, cohorts were restricted to incident use periods, with “incident” defined as having had no recent (within three months) dispensing of any study opioid analgesic (See Section 3.2.4); separately, prevalent only users were also analyzed (these data are not included in this review). Restricting to incident user only patient cohorts can help minimize selection biases that result from including ongoing users that, by definition, have had some experience with the study drug, and have not had the outcome, or are potentially less susceptible for the outcome. In the case of opioid analgesic use and overdose, it is also possible that the converse is true, in that the likelihood of the outcome increases with exposure time. Selection biases can also be introduced when adjusting for variables after initiation, particularly those that may have been impacted by treatment selection. The results of analyses using the incident user only cohort were compared to the results of analyses using the combined (incident and prevalent user) cohort to better understand the effect of potential selection biases.

2) Fee-for-service versus comprehensive managed care

State-based Medicaid programs generally involve a mix of fee-for-service (FFS) or comprehensive managed care insurance coverage plans, with states transitioning between models over time (See Appendix 8.3). Administrative insurance claims data from Medicaid FFS-covered patients are collected differently than managed care patients, and the state-specific shifts in primary coverage type can challenge longitudinal studies relying on consistent data capture over time. Consistent with the primary analyses using only states/years/basis of eligibility (BOE) combinations with useable (i.e., “complete”) FFS or managed care Medicaid data, as a sensitivity analyses the sponsor also conducted stratified analyses to look for differences by coverage type.

^{xxii} Borenstein M. et al. (2010) A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods*, 1: 97-111. DerSimonian R, and Laird N (1986) Meta-analysis in clinical trials. *Control Clin Trials*, 7: 177-88. DerSimonian R, and Laird N (2015) Meta-analysis in clinical trials revisited. *Contemp Clin Trials*, 45: 139-45

3) Propensity score (PS) weighted analyses

Sensitivity analyses using propensity scores were conducted to explore additional methods for adjusting for relevant characteristics of patients with opioid analgesic use that are more strongly associated with one period (pre- or post-period) over another, and to mitigate the potential for confounding with respect to OxyContin prescribing, or the prescribing of the comparator drugs, around the time of the reformulation.

Overdose rate ratios were estimated using PS-weighted Poisson regression models of only incident user cohorts to best reflect the probability of initiation. In these analyses, the post-period cohort was weighted to match the covariate (demographic, clinical characteristics, and comorbidities) distribution of the pre-period cohort. Each data partner fit separate PS models (i.e., logistic regression models) to estimate the probability that an incident treatment episode was from the post-period versus the pre- period for those involving OxyContin and for those involving each comparator. Weights based on these fitted probabilities were assigned to individual treatment episodes (weight of 1 for treatment episodes in the pre-period; weight of $PS_i / 1-PS_i$ for the post-period). Propensity score distributions were evaluated, and extreme weights were trimmed (non-overlapping distributions). Covariate balance after PS-weighting was assessed using standardized mean differences, using <0.10 difference in prevalence as a threshold for defining “balance”.

4 STUDY RESULTS

Notes on terminology:

- FDA has defined the term “*abuse*” as the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. FDA recognizes that this term has been identified as potentially stigmatizing to individuals with substance use disorders. This is in no way our intent; rather, we are using the term abuse as it has been previously defined specifically by FDA to describe a specific set of behaviors, or as it is used in the study(ies) we are reviewing.

In this review, unless otherwise specified, “*overdose rates*” are defined as “*rates of combined any (unintentional or intentional) fatal or non-fatal opioid overdose*”. In a validation study using medical record review to estimate the predictive performance of claims-based opioid overdose algorithms, the algorithm to ascertain any opioid overdose (intentional or unintentional; fatal or non-fatal) was superior to the algorithm differentiating between intentional and unintentional overdose (See Section 3.4.6). Therefore, FDA views analyses using any opioid overdose as primary.

- When describing overdose rates in different exposure groups—for example, those that include only time in which patients were dispensed OxyContin (or a comparator), without other opioid analgesics concomitantly—we may use the following terminology for simplicity in text, tables, and figures: “*among patients dispensed OxyContin (or comparator) alone*” or “*OxyContin use alone*. Overdose rates and rate ratios are computed using person-time of exposure, not the number of patients; therefore, a patient can theoretically contribute time to multiple different exposure groups during

the study period. This does not mean that these patients were only *ever* dispensed OxyContin alone, but rather that the patients contributed exposure time to the analysis for this exposure cohort.

- When using the term “*significant*” or “*significance*” we are referring to statistical significance, not necessarily clinical or public health significance.

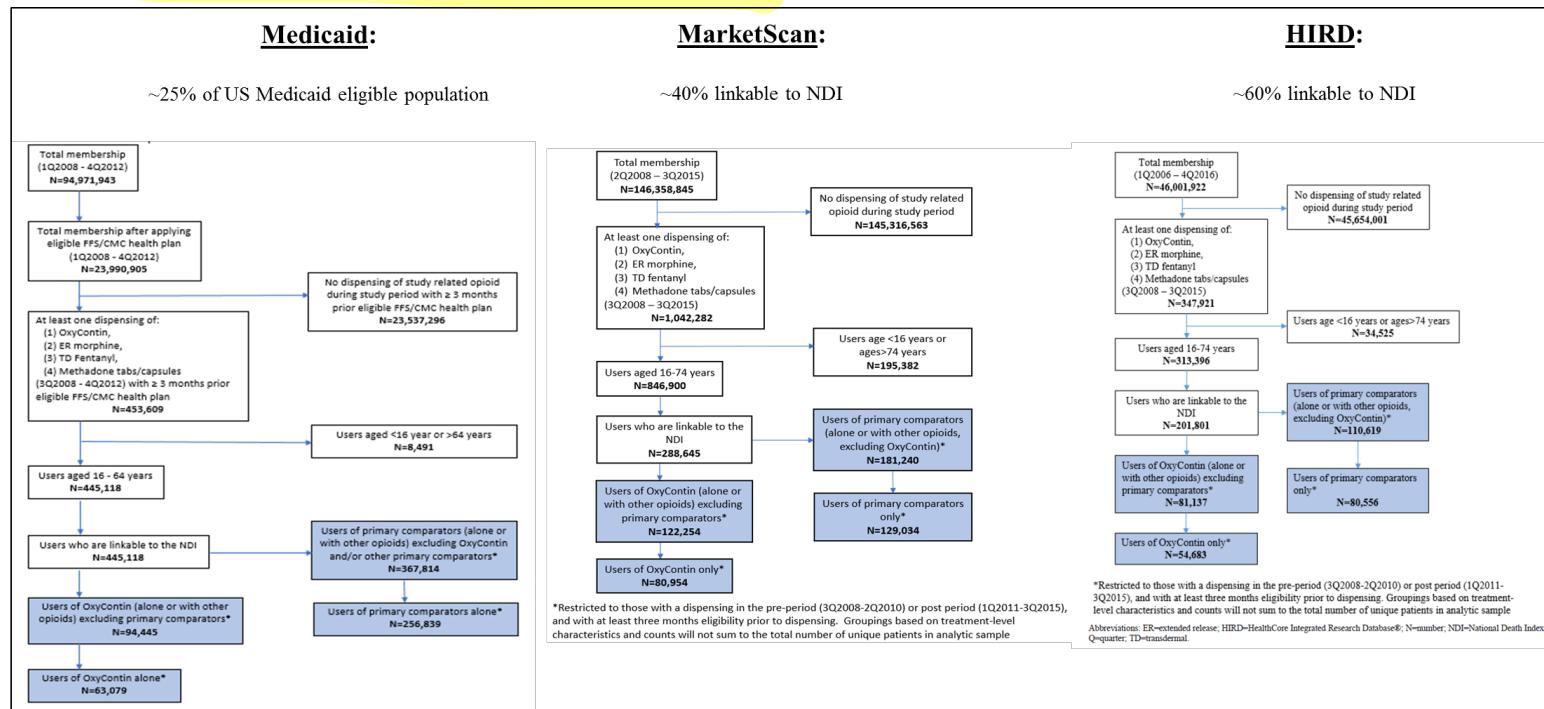
4.1 DESCRIPTIVE COHORT SUMMARY

4.1.1 Study Cohort Summary

Figure 2 shows the total number of available patients in each database, and the total number of excluded patients after applying linkage and inclusion/exclusion criteria; the numbers at the bottom of the flowcharts (blue boxes) reflect the final analytic sets for primary objectives. In Medicaid, ~25% (N= 23,990,905) of the total Medicaid membership during the study period was eligible after applying the Li et al. criteria (data usability criteria); all eligible patients dispensed an opioid analgesic of interest were linkable to NDI (N=445,118), with 94,445 patients dispensed OxyContin alone or with other opioid analgesics over the study period.

In the commercial claims databases, ~40% of the eligible patients dispensed an opioid analgesic of interest were linkable to NDI in MarketScan (N=288,645), while ~60% of the eligible patients were linkable to NDI in HIRD (N=201,801). MarketScan had the most patients dispensed OxyContin alone or with other opioid analgesics over the study period (N=122,254), and HIRD had the least (N=81,137).

Figure 2: Cohort flowcharts of included patients, by database



(Sponsor figure taken from PMR 3051-4 study report; reformatted by FDA)

Table 5 shows summary demographic and clinical characteristics of patients dispensed OxyContin (excluding the use of primary comparators) and patients dispensed any primary comparators (excluding the use of OxyContin) in aggregate, combining the pre- and post-periods. Mean exposure time contributed per patient was slightly longer among those dispensed primary comparator opioid analgesics compared to those dispensed OxyContin, particularly in the commercial claims databases. At the same time, the mean exposure time per treatment episode (irrespective of the patient) was similar among those dispensed primary comparator opioid analgesics compared to those dispensed OxyContin (see Appendix 8.4.1-8.4.3), ranging from 1.4 to 2.1 months. A slightly larger proportion of patients dispensed OxyContin were male compared to those dispensed primary comparator opioid analgesics, but the mean ages were similar within databases. Overall, the mean ages were older in commercial claims databases compared to the Medicaid population.

There were no substantial differences in clinical characteristics comparing those dispensed OxyContin and those dispensed primary comparators (see Table 5 and Appendix 8.4.1-8.4.3). Of note, the proportions of those with a history of overdose and opioid type dependence (ICD 9 code: 304.0x) were slightly larger among those dispensed primary comparators; data were not provided by period. Prior benzodiazepine dispensing was also similar comparing exposure groups across databases. In Medicaid (see Appendix 8.7) rates of benzodiazepine dispensing across opioid analgesic exposure groups were largely the same comparing the pre- and post-periods, while in HIRD (see Appendix 8.7) rates of benzodiazepine dispensing decreased similarly from the pre- to post-periods across nearly all opioid analgesic exposure groups. Overall, the Medicaid population had more comorbidities compared to those of the commercial claims databases across opioid analgesic exposure groups.

Table 5: Demographic and clinical characteristics summary for those dispensed OxyContin and other primary comparator opioid analgesics, by database

| Variable | Value | Any OxyContin* | | | Any Primary Comparator Opioids^ | | |
|--|----------------------------|-----------------|-----------------|-----------------|---------------------------------|-----------------|-----------------|
| | | Medicaid | MarketScan | HIRD | Medicaid | MarketScan | HIRD |
| Patients | | 94,445 | 122,254 | 81,137 | 367,814 | 181,240 | 110,619 |
| Total person-time per patient in months | Mean (SD) | 7.8 (10.0) | 6.0 (10.3) | 6.1 (11.4) | 8.1 (10.3) | 8.0 (11.9) | 9.5 (13.9) |
| Treatment Episodes | | 522,775 | 561,703 | 378,441 | 2,039,232 | 975,389 | 654,462 |
| Gender | Female | 295,875 (56.6%) | 285,366 (50.8%) | 189,986 (50.2%) | 1,241,520 (60.9%) | 560,051 (57.4%) | 382,769 (58.5%) |
| | Male | 226,900 (43.4%) | 276,337 (49.2%) | 188,455 (49.8%) | 797,712 (39.1%) | 415,338 (42.6%) | 271,693 (41.5%) |
| Age (years) | Mean (SD) | 46.7 (10.5) | 53.1 (12.0) | 51.4 (12.2) | 46.9 (10.6) | 54.6 (11.6) | 53.4 (11.9) |
| DCI | Mean (SD) | 2.0 (2.8) | 2.0 (3.1) | 1.7 (2.8) | 2.0 (2.8) | 2.4 (3.3) | 2.0 (3.0) |
| Clinical and comorbidity characteristics | Abdominal Pain | 99,797 (19.1%) | 80,535 (14.3%) | 55,554 (14.7%) | 436,472 (21.4%) | 179,919 (18.4%) | 120,612 (18.4%) |
| | Chronic pain | 104,311 (20.0%) | 65,463 (11.7%) | 63,456 (16.8%) | 427,644 (21.0%) | 143,661 (14.7%) | 138,170 (21.1%) |
| | Neuropathic pain | 16,857 (3.2%) | 14,164 (2.5%) | 10,627 (2.8%) | 70,734 (3.5%) | 32,678 (3.4%) | 26,043 (4.0%) |
| | COPD | 102,942 (19.7%) | 64,556 (11.5%) | 49,926 (13.2%) | 401,863 (19.7%) | 129,161 (13.2%) | 104,775 (16.0%) |
| | Major depression disorder | 88,372 (16.9%) | 62,556 (11.1%) | 58,692 (15.5%) | 378,331 (18.6%) | 128,661 (13.2%) | 119,470 (18.3%) |
| | History of overdose | 2,657 (0.5%) | 1,428 (0.3%) | 1,110 (0.3%) | 15,485 (0.8%) | 3,801 (0.4%) | 3,160 (0.5%) |
| | Opioid type dependence | 30,472 (5.8%) | 9,560 (1.7%) | 11,343 (3.0%) | 119,537 (5.9%) | 18,777 (1.9%) | 23,706 (3.6%) |
| | Non-opioid drug dependence | 32,589 (6.2%) | 7,963 (1.4%) | 8,840 (2.3%) | 119,625 (5.9%) | 15,083 (1.5%) | 19,215 (2.9%) |
| | Benzodiazepines | 97,110 (18.6%) | 86,631 (15.4%) | 60,818 (16.1%) | 368,051 (18.1%) | 154,579 (15.8%) | 109,074 (16.7%) |

Frequency (percent) presented unless otherwise specified

*Any use of OxyContin excluding concomitant primary comparator opioid use.

[^]Any use of any of the primary comparators (ER morphine, TD fentanyl, or methadone) excluding concomitant OxyContin or other primary comparator use.

Abbreviations: DCI=Deyo-Charlson Index; HIRD=HealthCore Integrated Research Database; SD=standard deviation; COPD=Chronic Obstructive Pulmonary Disease.

(Sponsor table taken from PMR 3051-4 study report)

When comparing NDI-linkable patients to “un-linkable” patients in the commercial claims databases (see Appendix 8.4.2 and 8.4.3) among all patients dispensed opioid analgesics, the patients were largely similar with respect to the demographic and clinical characteristics.

Table 6 shows unadjusted opioid overdose incidence rate ratios (IRRs)^{xxiii} for some relevant comorbidities using all patients dispensed any opioid analgesic. Across databases, IRRs comparing those with prior opioid overdose to those without prior overdose were very high, substantially higher than other comorbidities with elevated statistically significant IRRs. Of note, the sponsor only provided these IRR data (Table 6), so IRRs for other relevant comorbidities are unknown.

^{xxiii} IRRs were calculated without regard to pre- or post-period, meaning all exposure time was combined for all opioid analgesics across the study period

Table 6: Incidence rate ratios for select variables, by database

| Preceding characteristics | HIRD | | | MarketScan | | | Medicaid | | |
|-------------------------------|-------|-------|-------|------------|-------|-------|----------|-------|-------|
| | IRR | LCL | UCL | IRR | LCL | UCL | IRR | LCL | UCL |
| Large Risk Elevation | | | | | | | | | |
| Opioid overdose | 29.27 | 20.39 | 42.02 | 19.02 | 14.76 | 24.53 | 14.64 | 13.19 | 16.24 |
| Modest Risk Elevation | | | | | | | | | |
| Stroke | 1.54 | 1.10 | 2.16 | 1.34 | 1.03 | 1.74 | 1.28 | 1.11 | 1.48 |
| COPD | 1.50 | 1.29 | 1.75 | 1.28 | 1.12 | 1.46 | 1.33 | 1.25 | 1.41 |
| Impaired respiratory function | 1.44 | 1.18 | 1.76 | 1.61 | 1.38 | 1.88 | 1.50 | 1.39 | 1.61 |
| Chronic pain | 1.48 | 1.28 | 1.70 | 1.48 | 1.31 | 1.66 | 1.37 | 1.30 | 1.44 |
| Reduced Risk | | | | | | | | | |
| Malignancy | 0.61 | 0.42 | 0.88 | 0.65 | 0.52 | 0.82 | 0.73 | 0.66 | 0.82 |

Abbreviations: HIRD=HealthCore Integrated Research Database; COPD=Chronic Obstructive Pulmonary Disease, LCL=lower confidence interval; UCL=upper confidence limit; IRR=incidence rate ratio.

All characteristics are as noted on claims diagnoses in the preceding 92 days.

(Sponsor table taken from PMR 3051-4 study report)

Across all opioid analgesic exposure groups, ~10% of patients with an opioid overdose had multiple, distinct non-fatal overdoses during follow-up of the study, but no data were provided on whether this disproportionately involved one opioid analgesic exposure group or another.

4.1.2 Overdose Rate Trends Over Time

Figure 3 shows the bi-annual overdose rates (per 1,000 person-months) among patients dispensed OxyContin and other opioid analgesic comparators in the Medicaid data across the study period (note the shorter study period with these analyses: *July 2008 - December 2012*). Like all the other opioid analgesic comparators with the exception of ER oxymorphone, bi-annual overdose rates among patients dispensed OxyContin were relatively stable throughout the study period, with perhaps a slight decline immediately after the transition period. Overall, rates among patients dispensed OxyContin were lower than those for all of the other opioid analgesic comparator groups.

Figure 3: Overdose rates over the study period in Medicaid data two years before versus two years after the reformulation (-2y/2y), by opioid analgesic exposure group

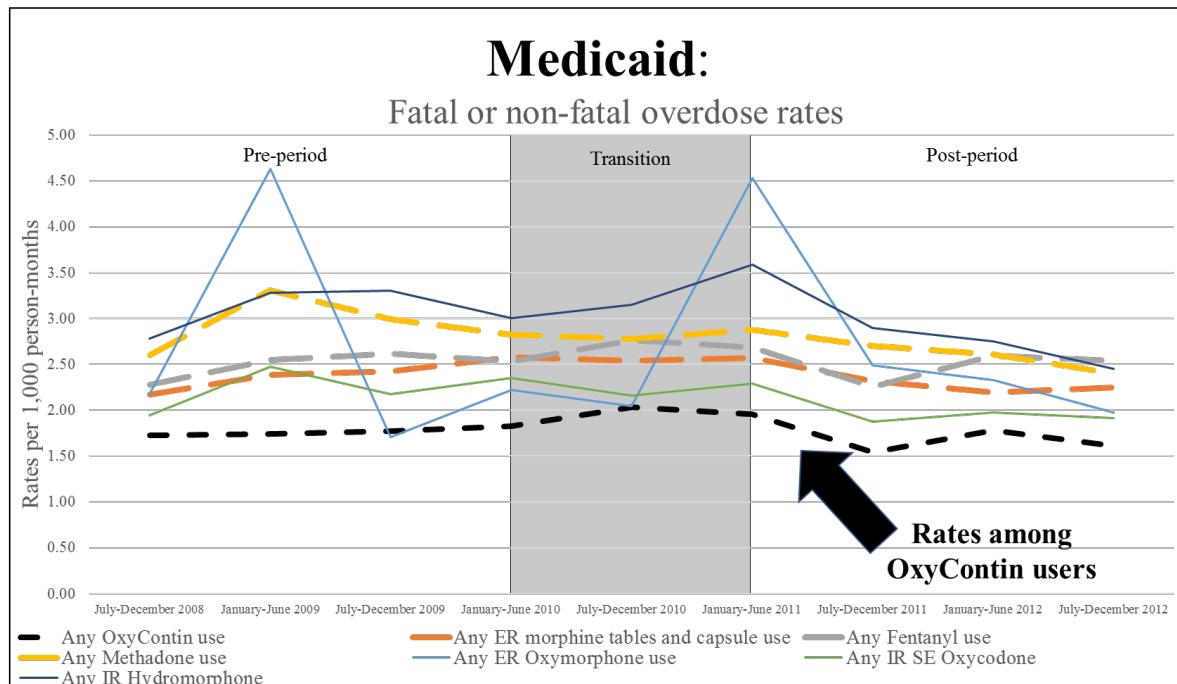
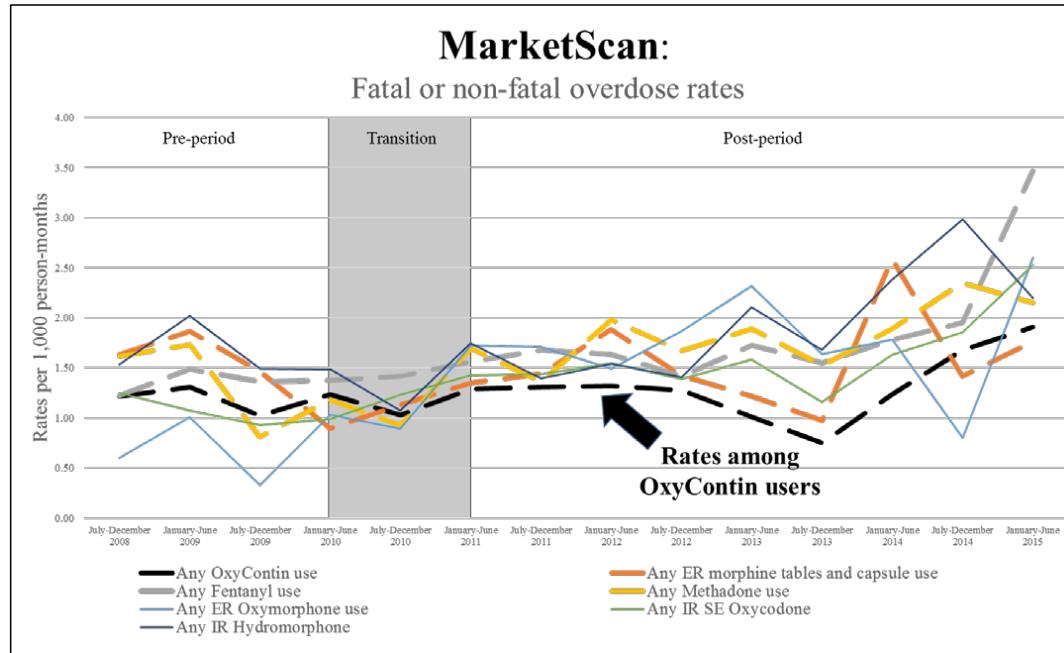


Figure 4 shows the overdose rates (per 1,000 person-months) among patients dispensed OxyContin and other opioid analgesic comparators in the MarketScan data across the study period. Bi-annual overdose rates among patients dispensed OxyContin were also relatively stable around the time of reformulation, and similar to that of other opioid analgesic comparator groups. While there was no discernable decline in overdose rates among patients dispensed OxyContin immediately after the reformulation, there was an apparent decline in 2013, followed by a large increase in 2014. This increase at the end of the study period was seen for multiple opioid analgesic comparator groups

Figure 4: Overdose rates over the study period in MarketScan data two years before versus five years after the reformulation (-2y/5y), by opioid analgesic exposure group

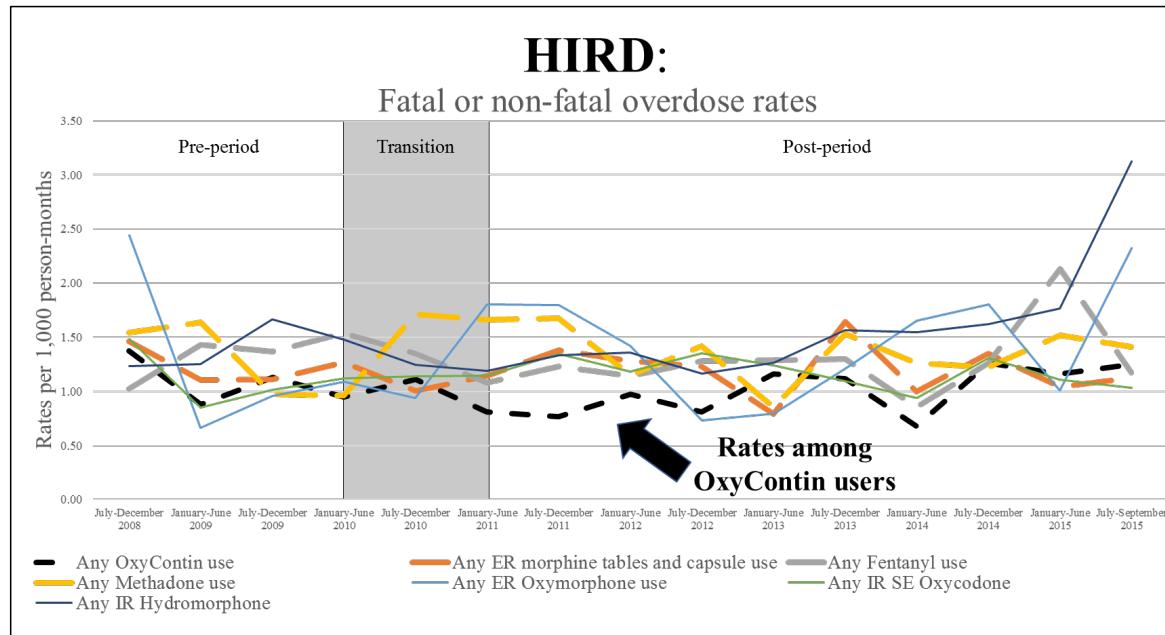


(FDA generated figure using data from PMR 3051-4 study report)

Key: immediate-release (IR); extended-release (ER); single-entity (SE); vertical line represents approximate date of reformulated OxyContin's initial marketing; the dashed (thicker) lines are for primary comparators; the solid (thinner) lines are for secondary comparators; grey box is the market transition period; **note:** the figure does not include data from 3Q2015 as these rates were based off of only a limited number of patients meeting criteria (must have had a opioid analgesic prescription before the beginning of 3Q2015)

Figure 5 shows the overdose rates (per 1,000 person-months) among patients dispensed OxyContin and other opioid analgesic comparators in the HIRD data across the study period. Bi-annual overdose rate trends among patients dispensed OxyContin were largely similar to those of the other opioid analgesic comparator groups in the pre-period. Rates in patients dispensed OxyContin appeared to decline following the transition period and then fluctuated throughout the post-period, returning to levels similar to those seen in the pre-period.

Figure 5: Overdose rates over the study period in HIRD data, by opioid analgesic exposure group (-2y/5y)



(FDA generated figure using data from PMR 3051-4 study report)

Key: immediate-release (IR); extended-release (ER); single-entity (SE); vertical line represents approximate date of reformulated OxyContin's initial marketing; the dashed (thicker) lines are for primary comparators; the solid (thinner) lines are for secondary comparators; grey box is the market transition period; note: the figure does not include data from 3Q2015 as these rates were based off of only a limited number of patients meeting criteria (must have had a opioid analgesic prescription before the beginning of 3Q2015)

4.2 OVERDOSE RATES COMPARING PRE- AND POST-REFORMULATION PERIODS

4.2.1 Overdose Rates Among Those Dispensed OxyContin^{xxiv}

Table 7 shows the total number of overdoses, the total amount of person-time, the overdose rates (per 1,000 person-months) in the pre- and post-periods, and the rate ratios comparing periods among those dispensed any OxyContin^{xxv} (with or without other opioid analgesics) in the Medicaid data. The information in the table is further stratified by time dispensed only OxyContin (without any other opioid analgesics concomitantly) and time dispensed OxyContin with any concomitant opioid analgesics.

The majority of exposure time among those dispensed OxyContin was time dispensed OxyContin with other opioid analgesics concomitantly, both in the pre- (65%) and post-periods (75%). Small reductions in adjusted overdose rates were observed across OxyContin exposure groups, but none were statistically significant.

Table 7: Medicaid data – overdose rates and rate ratios among those dispensed OxyContin, by concomitancy with other opioid analgesics (-2y/5y)

| OxyContin dispensing | Pre-reformulation period (ref) | | | Post-reformulation period | | | Unadjusted rate ratio (CI) | Adjusted rate ratio (CI) |
|------------------------------------|--------------------------------|--------------------------------|-----------------------------------|--------------------------------|--------------------------------|-----------------------------------|----------------------------|--------------------------|
| | Overdoses (fatal or non-fatal) | Person months of exposure time | Rate per 1,000 person months (CI) | Overdoses (fatal or non-fatal) | Person months of exposure time | Rate per 1,000 person months (CI) | | |
| Any use | 800 | 414,793 | 1.93 (1.79-2.08) | 733 | 373,766 | 1.96 (1.80-2.13) | 1.02 (0.91-1.14) | 0.95 (0.84-1.08) |
| Only use | 236 | 143,156 | 1.65 (1.44-1.89) | 131 | 92,079 | 1.42 (1.19-1.71) | 0.86 (0.69-1.08) | 0.83 (0.64-1.08) |
| With concomitant opioid analgesics | 564 | 271,637 | 2.08 (1.89-2.28) | 602 | 281,687 | 2.14 (1.95-2.35) | 1.03 (0.91-1.17) | 0.95 (0.82-1.10) |

(FDA generated table using data from the April 1, 2020, information request response)

Key: *= statistically significant ($p<0.05$); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5; “Any use” includes person-time among all patients dispensed OxyContin, including those with or without concomitant dispensing of other opioid analgesics; “Only use” includes person-time among patients dispensed OxyContin alone, without concomitant dispensing of other opioid analgesics; “With concomitant opioid analgesics” includes person-time among patients dispensed OxyContin with concomitant dispensing of other opioid analgesics; **note:** “any use” is the total, meaning it combines “only use” periods and “with concomitant opioid analgesics” periods

Table 8 shows the total number of overdoses, the total amount of person-time, and the overdose rates (per 1,000 person-months) in the pre- and post-periods, and the rate ratios comparing periods among those dispensed any OxyContin in the HIRD data.; table 8 also stratifies by time dispensed only OxyContin and time dispensed OxyContin with any concomitant opioid analgesics.

^{xxiv} These analyses had only been conducted in the Medicaid and HIRD databases at the time of this FDA review. FDA expects MarketScan data to be provided at a later date.

^{xxv} Because these were not comparative analyses, this group also includes concomitant use with primary or secondary comparators.

The majority of exposure time among those dispensed OxyContin was time dispensed OxyContin with other opioid analgesics concomitantly, both in the pre- (66%) and post-periods (73%). Like in Medicaid, reductions in overdose rates were observed across OxyContin exposure groups, but only when analyses were restricted to time dispensed OxyContin without other opioid analgesics were they of a large magnitude and statistically significant (adjusted rate ratio [aRR] = 0.51, 95% confidence interval [CI]: 0.32-0.81).

Table 8: HIRD data – overdose rates and rate ratios among those dispensed OxyContin, by concomitancy with other opioid analgesics (-2y/5y)

| OxyContin dispensing | Pre-reformulation period (ref) | | | Post-reformulation period | | | Unadjusted rate ratio (CI) | Adjusted rate ratio (CI) |
|------------------------------------|--------------------------------|--------------------------------|-----------------------------------|--------------------------------|--------------------------------|-----------------------------------|----------------------------|--------------------------|
| | Overdoses (fatal or non-fatal) | Person months of exposure time | Rate per 1,000 person months (CI) | Overdoses (fatal or non-fatal) | Person months of exposure time | Rate per 1,000 person months (CI) | | |
| Any use | 205 | 188,219 | 1.09 (0.91-1.30) | 319 | 331,823 | 0.96 (0.79-1.17) | 0.88 (0.68-1.15) | 0.84 (0.66-1.08) |
| Only use | 58 | 63,959 | 0.91 (0.62-1.32) | 43 | 90,142 | 0.48 (0.34-0.67) | 0.53 (0.32-0.87)* | 0.51 (0.32-0.81)* |
| With concomitant opioid analgesics | 147 | 124,260 | 1.18 (0.97-1.44) | 276 | 241,681 | 1.14 (0.91-1.43) | 0.97 (0.72-1.30) | 0.92 (0.70-1.21) |

(FDA generated table using data from PMR 3051-4 study report)

Key: *= statistically significant ($p<0.05$); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5; “Any use” includes person-time among all patients dispensed OxyContin, including those with or without concomitant dispensing of other opioid analgesics; “Only use” includes person-time among patients dispensed OxyContin alone, without concomitant dispensing of other opioid analgesics; “With concomitant opioids analgesic” includes person-time among patients dispensed OxyContin with concomitant dispensing of other opioid analgesics; **note:** “any use” is the total, meaning it combines “only use” periods and “with concomitant opioid analgesics” periods

4.2.2 Overdose Rates Among Those Dispensed OxyContin and Primary Comparators

4.2.2.1 Medicaid data

Table 9 shows overdose rates and rate ratios among those dispensed OxyContin and primary comparators, stratified by concomitancy with other opioid analgesics in the Medicaid cohort. Ratio of rate ratios (RORRs) are also provided to compare pre- vs. post-period opioid overdose rate ratios for OxyContin to those of primary comparators (RORR = [comparator RR] / [OxyContin RR]). In the pre- and post-periods, overdose rates were highest among those dispensed methadone with or without other opioid analgesics concomitantly, and lowest among those dispensed OxyContin with or without other opioid analgesics concomitantly. This was the same when restricted to person-time dispensed the comparator opioid analgesic alone (without other opioid analgesics concomitantly).

Among those dispensed OxyContin with or without other opioid analgesics concomitantly, there was no change in overdose rates comparing periods. For those dispensed comparators, ER morphine (adjusted RR = 0.91, CI: 0.85-0.98) and methadone (adjusted RR=0.85, CI: 0.78-0.93) did have statistically significant reductions comparing periods after covariate adjustment. While the RORRs favored those two comparators over OxyContin (i.e., RORR < 1, representing a more favorable change in opioid overdose rates

among those dispensed the comparator relative to those dispensed OxyContin), only the unadjusted and adjusted RORRs for methadone were statistically significant.

When restricted to person-time dispensed OxyContin alone, the reduction in overdose rates was not statistically significant. For this exposure group, although all RORRs were greater than one (favoring OxyContin), none were statistically significant.

Table 9: Medicaid data – overdose rates, rate ratios, and ratio of rate ratios among those dispensed OxyContin and primary comparators, by concomitancy with other opioid analgesics (-2y/2y)

| Opioid analgesic | Exposure period category | Pre-reformulation period (ref) | | | Post-reformulation period | | | Unadjusted rate ratio (CI) | Adjusted rate ratio (CI) | Unadjusted ratio of rate ratio (CI) ⁱⁱ | Adjusted ratio of rate ratio (CI) ⁱⁱ |
|------------------|--|--------------------------------|--------------------------------|-----------------------------------|--------------------------------|--------------------------------|-----------------------------------|----------------------------|--------------------------|---|---|
| | | Overdoses (fatal or non-fatal) | Person months of exposure time | Rate per 1,000 person months (CI) | Overdoses (fatal or non-fatal) | Person months of exposure time | Rate per 1,000 person months (CI) | | | | |
| OxyContin | Any use ⁱ | 693 | 384,417 | 1.80 (1.66-1.95) | 651 | 349,899 | 1.86 (1.70-2.03) | 1.03 (0.92-1.16) | 1.00 (0.89-1.12) | ref | ref |
| ER morphine | (with or without concomitant opioid analgesic use periods) | 1,562 | 581,045 | 2.69 (2.53-2.85) | 2,013 | 803,822 | 2.50 (2.38-2.63) | 0.93 (0.86-1.01) | 0.91 (0.85-0.98)* | 0.90 (0.79-1.04) | 0.91 (0.80-1.04) |
| Fentanyl | | 862 | 337,179 | 2.56 (2.38-2.75) | 987 | 359,083 | 2.75 (2.56-2.95) | 1.08 (0.97-1.19) | 1.05 (0.95-1.15) | 1.04 (0.89-1.22) | 1.05 (0.90-1.22) |
| Methadone | | 1,350 | 421,755 | 3.20 (2.99-3.42) | 1,334 | 477,538 | 2.79 (2.62-2.98) | 0.87 (0.80-0.96)* | 0.85 (0.78-0.93)* | 0.85 (0.73-0.98)* | 0.85 (0.74-0.98)* |
| OxyContin | Use alone | 236 | 143,156 | 1.65 (1.44-1.89) | 131 | 92,079 | 1.42 (1.19-1.71) | 0.86 (0.69-1.08) | 0.85 (0.68-1.06) | ref | ref |
| ER morphine | (without concomitant opioid analgesic use periods) | 409 | 180,388 | 2.27 (2.04-2.52) | 482 | 211,101 | 2.28 (2.07-2.52) | 1.01 (0.87-1.16) | 1.00 (0.87-1.15) | 1.17 (0.89-1.53) | 1.17 (0.90-1.52) |
| Fentanyl | | 245 | 111,001 | 2.21 (1.93-2.53) | 254 | 105,633 | 2.40 (2.11-2.74) | 1.09 (0.90-1.32) | 1.08 (0.89-1.30) | 1.26 (0.94-1.70) | 1.27 (0.95-1.69) |
| Methadone | | 652 | 220,697 | 2.95 (2.67-3.27) | 610 | 235,976 | 2.59 (2.36-2.83) | 0.88 (0.77-1.00)* | 0.88 (0.77-1.00)* | 1.01 (0.78-1.32) | 1.03 (0.79-1.33) |

(FDA generated table using data from PMR 3051-4 study report)

Key: *= statistically significant ($p<0.05$); ⁱ=excludes periods dispensed OxyContin or primary comparator concomitantly; ⁱⁱ= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); person-months (PMs); extended-release (ER); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

FDA requested that the sponsor re-analyze adjusted analyses to also include baseline benzodiazepine dispensing as a covariate in the model, and the results were nearly identical to the primary adjusted analyses when baseline benzodiazepine dispensing was not included in the model (See Appendix 8.7). FDA also requested that the sponsor explore the role of baseline benzodiazepine dispensing as an effect modifier. In those analyses, the interactions were not statistically significant for any opioid analgesic exposure group (See Appendix 8.7). Stratified analyses based on the presence of baseline benzodiazepine dispensing were also similar to each other.

When using the opioid overdose algorithm that differentiates by intentionality in exploratory analyses (See Appendix 8.6), unintentional overdose adjusted RORRs results were overall similar to those using the any overdose outcome.

4.2.2.2 MarketScan data

Table 10 shows overdose rates and rate ratios among those dispensed OxyContin and primary comparators, stratified by concomitancy with other opioid analgesics in the MarketScan cohort; RORRs are also provided. In the pre- and post-periods, overdose rates among those dispensed OxyContin with or without other opioid analgesics concomitantly, and when restricted to person-time dispensed OxyContin alone, were the lowest but still relatively similar to the other opioid analgesics.

Among those dispensed OxyContin with or without other opioid analgesics concomitantly, reductions in overdose rates comparing periods were not statistically significant. Unadjusted overdose rates for those dispensed fentanyl (RR = 1.23, CI: 1.02-1.47) and methadone (RR = 1.31, CI: 1.01-1.70) had statistically significant increases comparing the periods, but not after adjusting for covariates. The RORRs all favored OxyContin, but none were statistically significant.

When restricted to person-time dispensed OxyContin alone, reductions in overdose rates were observed but were also not statistically significant. Unadjusted and adjusted RORRs all favored OxyContin, and all were statistically significant with the exception of the adjusted RORR for ER morphine.

Table 10: MarketScan data – overdose rates, rate ratios, and ratio of rate ratios among those dispensed OxyContin and primary comparators, by concomitancy with other opioid analgesics (-2y/5y)

| Opioid analgesic | Exposure period category | Pre-reformulation period (ref) | | | Post-reformulation period | | | Unadjusted rate ratio (CI) | Adjusted rate ratio (CI) | Unadjusted ratio of rate ratio (CI) ⁱⁱ | Adjusted ratio of rate ratio (CI) ⁱⁱ |
|------------------|--|--------------------------------|--------------------------------|-----------------------------------|--------------------------------|--------------------------------|-----------------------------------|----------------------------|--------------------------|---|---|
| | | Overdoses (fatal or non-fatal) | Person months of exposure time | Rate per 1,000 person months (CI) | Overdoses (fatal or non-fatal) | Person months of exposure time | Rate per 1,000 person months (CI) | | | | |
| OxyContin | Any use ⁱ | 220 | 268,476 | 0.82 (0.70-0.96) | 367 | 459,907 | 0.80 (0.71-0.89) | 0.97 (0.81-1.18) | 0.90 (0.75-1.08) | ref | ref |
| ER morphine | (with or without concomitant opioid analgesic use periods) | 194 | 190,891 | 1.02 (0.86-1.20) | 430 | 378,948 | 1.13 (1.01-1.28) | 1.12 (0.91-1.37) | 1.01 (0.83-1.23) | 1.15 (0.87-1.51) | 1.12 (0.86-1.46) |
| Fentanyl | | 206 | 216,440 | 0.95 (0.82-1.11) | 436 | 373,612 | 1.17 (1.06-1.29) | 1.23 (1.02-1.47)* | 1.07 (0.90-1.27) | 1.26 (0.97-1.64) | 1.19 (0.93-1.53) |
| Methadone | | 101 | 102,965 | 0.98 (0.80-1.21) | 229 | 177,857 | 1.29 (1.10-1.51) | 1.31 (1.01-1.70)* | 1.19 (0.93-1.52) | 1.35 (0.98-1.86) | 1.32 (0.97-1.79) |
| OxyContin | Use alone | 58 | 97,454 | 0.60 (0.46-0.78) | 62 | 140,826 | 0.44 (0.34-0.57) | 0.74 (0.51-1.08) | 0.72 (0.50-1.04) | ref | ref |
| ER morphine | (without concomitant opioid analgesic use periods) | 41 | 64,175 | 0.64 (0.47-0.87) | 93 | 115,790 | 0.80 (0.64-1.00) | 1.26 (0.86-1.83) | 1.16 (0.81-1.68) | 1.70 (1.00-2.89)* | 1.62 (0.97-2.72) |
| Fentanyl | | 50 | 77,764 | 0.64 (0.48-0.86) | 108 | 124,640 | 0.87 (0.71-1.05) | 1.35 (0.95-1.91) | 1.21 (0.85-1.70) | 1.82 (1.09-3.04)* | 1.68 (1.02-2.78)* |
| Methadone | | 40 | 53,956 | 0.74 (0.54-1.03) | 101 | 88,928 | 1.14 (0.91-1.41) | 1.53 (1.04-2.26) | 1.39 (0.95-2.02) | 2.07 (1.21-3.56)* | 1.94 (1.14-3.29)* |

(FDA generated table using data from PMR 3051-4 study report)

Key: * = statistically significant ($p < 0.05$); ⁱ=excludes periods dispensed OxyContin or primary comparator concomitantly; ⁱⁱ= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); person-months (PMs); extended-release (ER); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

When using the opioid overdose algorithm that differentiates by intentionality in exploratory analyses (See Appendix 8.6), RORR results for unintentional overdose were overall similar to those using the any overdose outcome.

4.2.2.3 HIRD data

Table 11 shows overdose rates and rate ratios among those dispensed OxyContin and primary comparators, stratified by concomitancy with other opioid analgesics in the HIRD cohort; RORRs are also provided. As in MarketScan, in the pre- and post-periods, overdose rates among those dispensed OxyContin with or without other opioid analgesics concomitantly, and when restricted to person-time dispensed OxyContin alone, were generally lower but still similar to rates among those dispensed other opioid analgesics.

Among those dispensed OxyContin with or without other opioid analgesics concomitantly, reductions were not statistically significant. This was also true for the primary opioid analgesic comparators. The RORRs all favored OxyContin but were not statistically significant.

When restricted to person-time dispensed OxyContin alone, there was a statistically significant reduction (adjusted RR = 0.52, CI: 0.32-0.83) in overdose rates comparing periods; however, while all RORRs favored OxyContin, RORRs were only statistically significant for ER morphine.

Table 11: HIRD data – overdose rates, rate ratios, and ratio of rate ratios among those dispensed OxyContin and primary comparators, by concomitancy with other opioid analgesics (-2y/5y)

| Opioid analgesic | Exposure period category | Pre-reformulation period (ref) | | | Post-reformulation period | | | Unadjusted rate ratio (CI) | Adjusted rate ratio (CI) | Unadjusted ratio of rate ratio (CI) ⁱⁱ | Adjusted ratio of rate ratio (CI) ⁱⁱ |
|------------------|--|--------------------------------|--------------------------------|-----------------------------------|--------------------------------|--------------------------------|-----------------------------------|----------------------------|--------------------------|---|---|
| | | Overdoses (fatal or non-fatal) | Person months of exposure time | Rate per 1,000 person months (CI) | Overdoses (fatal or non-fatal) | Person months of exposure time | Rate per 1,000 person months (CI) | | | | |
| OxyContin | Any use ⁱ | 164 | 176,145 | 0.93 (0.77-1.13) | 268 | 314,899 | 0.85 (0.69-1.04) | 0.91 (0.69-1.21) | 0.84 (0.65-1.09) | ref | ref |
| ER morphine | (with or without concomitant opioid analgesic use periods) | 133 | 121,089 | 1.10 (0.91-1.32) | 328 | 293,756 | 1.12 (0.96-1.30) | 1.02 (0.80-1.29) | 0.91 (0.73-1.14) | 1.11 (0.77-1.60) | 1.09 (0.78-1.53) |
| Fentanyl | (with or without concomitant opioid analgesic use periods) | 160 | 132,254 | 1.21 (0.97-1.51) | 293 | 250,060 | 1.17 (1.02-1.35) | 0.97 (0.75-1.25) | 0.88 (0.69-1.12) | 1.06 (0.72-1.55) | 1.04 (0.73-1.49) |
| Methadone | (with or without concomitant opioid analgesic use periods) | 100 | 86,429 | 1.16 (0.93-1.45) | 224 | 169,022 | 1.33 (1.08-1.63) | 1.15 (0.86-1.53) | 1.01 (0.77-1.32) | 1.25 (0.84-1.87) | 1.20 (0.83-1.74) |
| OxyContin | Use alone | 58 | 63,959 | 0.91 (0.62-1.32) | 43 | 90,142 | 0.48 (0.34-0.67) | 0.53 (0.32-0.87)* | 0.52 (0.32-0.83)* | ref | ref |
| ER morphine | (without concomitant opioid analgesic use periods) | 33 | 40,538 | 0.81 (0.57-1.16) | 81 | 82,527 | 0.98 (0.76-1.27) | 1.21 (0.78-1.87) | 1.13 (0.74-1.73) | 2.29 (1.18-4.45)* | 2.20 (1.18-4.10)* |
| Fentanyl | (without concomitant opioid analgesic use periods) | 47 | 45,981 | 1.02 (0.71-1.47) | 62 | 79,376 | 0.78 (0.60-1.02) | 0.76 (0.49-1.20) | 0.72 (0.47-1.11) | 1.45 (0.73-2.89) | 1.40 (0.73-2.70) |
| Methadone | (without concomitant opioid analgesic use periods) | 58 | 46,873 | 1.24 (0.93-1.65) | 107 | 83,859 | 1.28 (0.92-1.76) | 1.03 (0.70-1.52) | 0.91 (0.63-1.31) | 1.96 (1.04-3.71) | 1.76 (0.98-3.17) |

(FDA generated table using data from PMR 3051-4 study report)

Key: *= statistically significant ($p<0.05$); ⁱ=excludes periods dispensed OxyContin or primary comparator concomitantly; ⁱⁱ= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); person-months (PMs); extended-release (ER); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

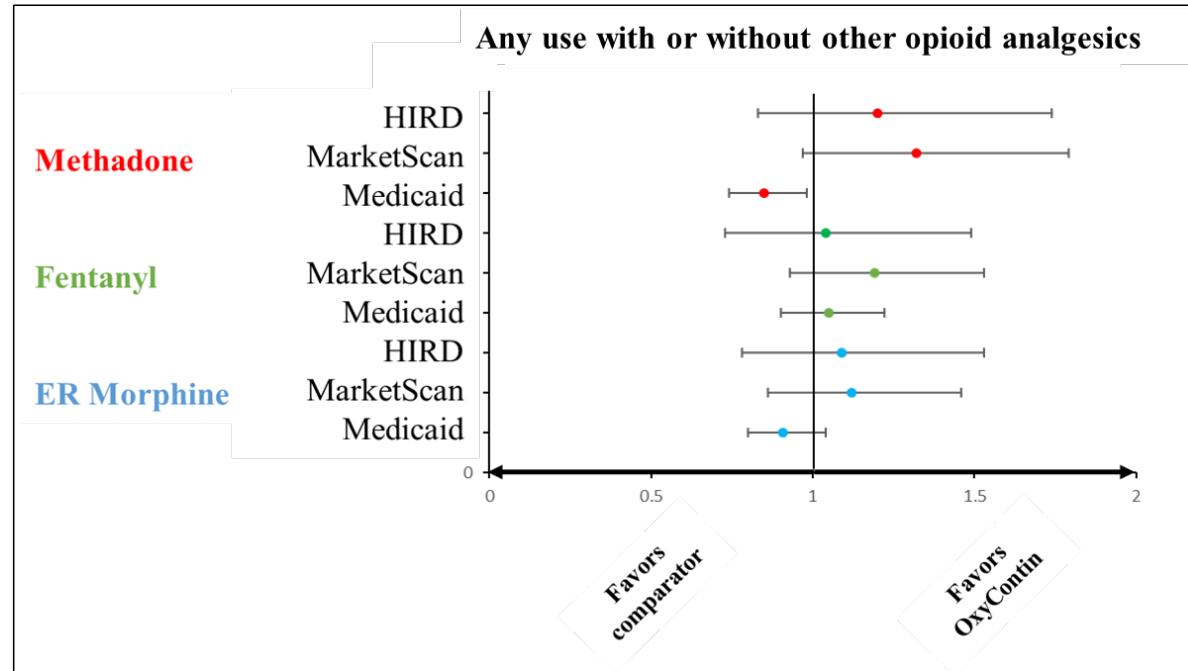
When baseline benzodiazepine dispensing was included as a covariate in the adjusted model the results were also nearly identical to the primary adjusted analyses when baseline benzodiazepine dispensing was not included in the model (See Appendix 8.7). Like in the Medicaid cohort, baseline benzodiazepine dispensing did not appear to be an effect modifier, with no statistically significant interactions for any opioid analgesic exposure group, both in analyses with other opioid analgesics concomitantly, and those without other opioid analgesics concomitantly (See Appendix 8.7).

When using the opioid overdose algorithm that differentiates by intentionality in exploratory analyses (See Appendix 8.6), unintentional overdose adjusted RORR results were overall similar to those using the any overdose outcome.

Figures 6.A and 6.B visually depict only the adjusted RORRs from Tables 8-10 (above), by database and concomitancy with other opioid analgesics. Overall, the RORRs are more favorable to OxyContin when analyses are restricted to exposure time in which a patient was dispensed a single opioid analgesic alone (Figure 6.B) compared to when analyses include exposure time with and without other opioid analgesics (i.e., among all patients using OxyContin) dispensed concomitantly (Figure 6.A).

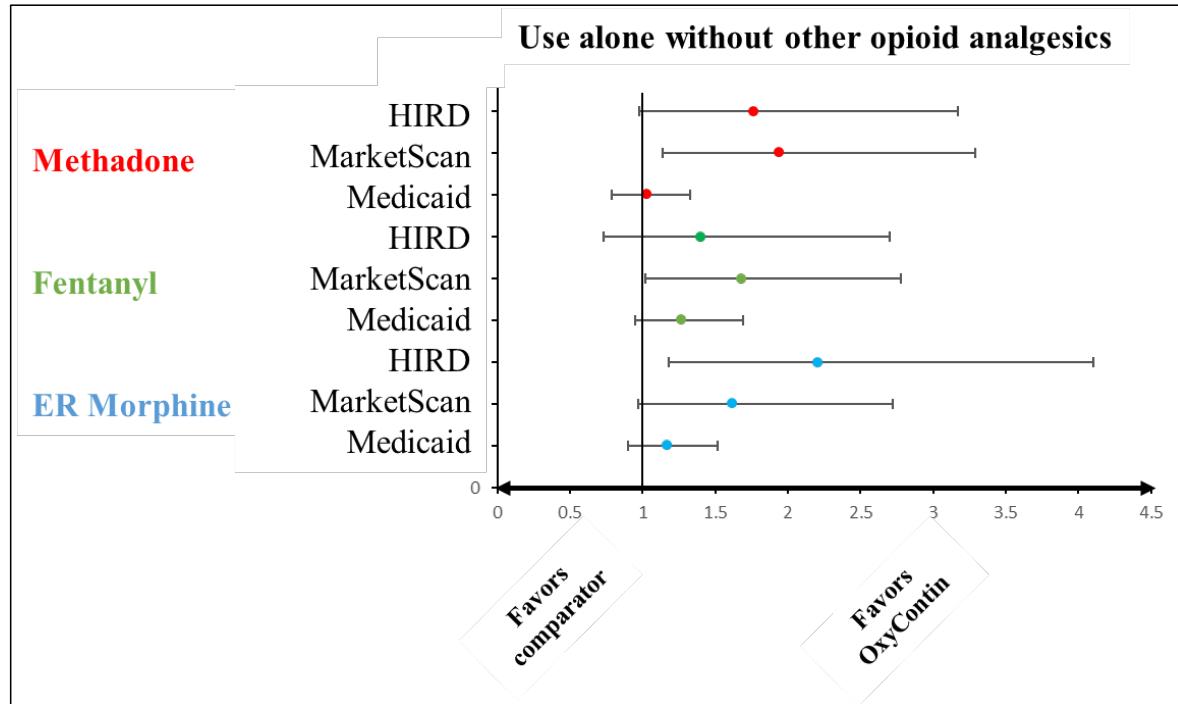
Figure 6.A and 6.B: Adjusted ratios of rate ratios – pre- versus post-period change in opioid overdose rates in patients dispensed primary comparator opioid analgesics compared to the change in patients dispensed OxyContin: with or without concomitant opioid analgesics (A) and without concomitant opioid analgesics (B)

6A:



(FDA generated figure using data from PMR 3051-4 study report)

6B:



(FDA generated figure using data from PMR 3051-4 study report)

Key: extended-release (ER); X-axis is adjusted ratios of rate ratios (RORR); null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); horizontal lines are 95% confidence interval

4.2.2.4 Meta-analyzed commercial claims data

Table 12 shows RORRs for primary comparators, by concomitancy with other opioid analgesics, using meta-analytic methods to generate “combined” RORR results for the commercial claims databases (MarketScan and HIRD). Overall the results were generally consistent with those from analyses conducted in the commercial claims databases separately. Among those dispensed OxyContin with or without other opioid analgesics concomitantly, RORRs for all comparators favored OxyContin, but only the RORRs for methadone were statistically significantly. When restricted to person-time dispensed OxyContin alone, RORRs for all primary comparators were statistically significantly, favoring OxyContin.

Table 12: Meta-analyzed data – Commercial claims *combined* overdose ratio of rate ratios among those dispensed OxyContin and primary comparators, by concomitancy with other opioid analgesics (-2y/5y)

| Opioid analgesic | Exposure period category | Meta-analysis: Commercial claims databases [^] | |
|---|---|---|---|
| | | Unadjusted ratio of rate ratio (CI) ⁱⁱ | Adjusted ratio of rate ratio (CI) ⁱⁱ |
| Any OxyContin ⁱ (reference) | | | |
| ER morphine | Any use ⁱ (with or without concomitant opioid analgesic use periods) | 1.13 (0.91-1.41) | 1.11 (0.90-1.37) |
| Fentanyl | | 1.19 (0.96-1.48) | 1.14 (0.93-1.40) |
| Methadone | | 1.31 (1.02-1.68)* | 1.27 (1.00-1.61)* |
| OxyContin alone (reference) | | | |
| ER morphine | Use alone (without concomitant opioid analgesic use periods) | 1.91 (1.26-2.89)* | 1.84 (1.24-2.74)* |
| Fentanyl | | 1.68 (1.12-2.53)* | 1.57 (1.06-2.34)* |
| Methadone | | 2.02 (1.34-3.06)* | 1.86 (1.25-2.75)* |

(FDA generated table using data from PMR 3051-4 study report)

Key: *=statistically significant ($p<0.05$); [^]=MarketScan and HIRD only; ⁱ=excludes periods dispensed OxyContin or primary comparator concomitantly; ⁱⁱ= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); extended-release (ER); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

4.2.2.5 OxyContin or comparators dispensed concomitantly with an immediate-release opioid analgesic only

Table 13 and Figure 7 shows RORRs comparing overdose rate changes among those dispensed comparator opioid analgesics with any IR opioid analgesic concomitantly to those dispensed OxyContin with any IR opioid analgesic concomitantly across databases. In Medicaid, all RORRs favored comparators, but only RORRs for ER morphine and methadone were statistically significant. The results from the commercial claims databases

were entirely different, with nearly all RORRs favoring OxyContin, but none statistically significant.

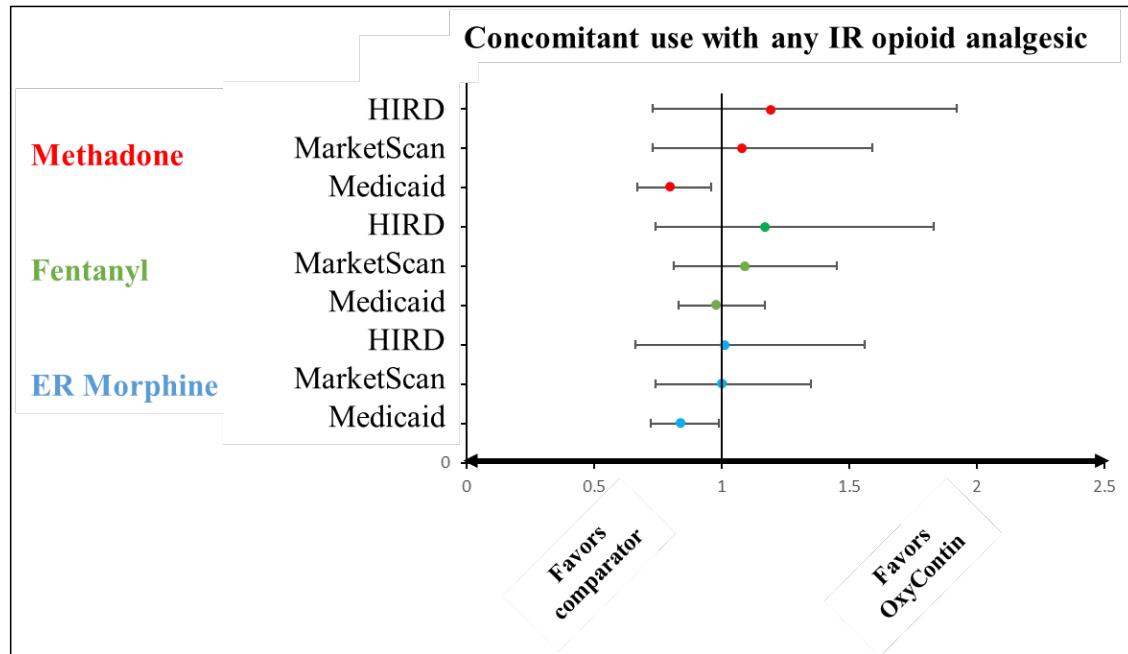
Table 13: Unadjusted and adjusted overdose rate ratios and ratios of rate ratios among those dispensed primary comparators concomitantly with any IR opioid analgesic compared to those dispensed OxyContin concomitantly with any IR opioid analgesic, by database

| Opioid analgesic ⁱ | Medicaid | | MarketScan | | HIRD | |
|--|---|---|---|---|---|---|
| | Unadjusted ratio of rate ratio (CI) ⁱⁱ | Adjusted ratio of rate ratio (CI) ⁱⁱ | Unadjusted ratio of rate ratio (CI) ⁱⁱ | Adjusted ratio of rate ratio (CI) ⁱⁱ | Unadjusted ratio of rate ratio (CI) ⁱⁱ | Adjusted ratio of rate ratio (CI) ⁱⁱ |
| OxyContin with concomitant IR opioid analgesic | ref | | | | | |
| ER morphine with concomitant IR opioid analgesic | 0.84 (0.71-0.99)* | 0.84 (0.72-0.99)* | 1.02 (0.74-1.41) | 1.00 (0.74-1.35) | 1.03 (0.65-1.62) | 1.01 (0.66-1.56) |
| Fentanyl with concomitant IR opioid analgesic | 0.98 (0.82-1.18) | 0.98 (0.83-1.17) | 1.16 (0.86-1.57) | 1.09 (0.81-1.45) | 1.19 (0.74-1.90) | 1.17 (0.74-1.83) |
| Methadone with concomitant IR opioid analgesic | 0.81 (0.67-0.97)* | 0.80 (0.67-0.96)* | 1.10 (0.73-1.66) | 1.08 (0.73-1.59) | 1.21 (0.72-2.03) | 1.19 (0.73-1.92) |

(FDA generated table using data from PMR 3051-4 study report)

Key: *= statistically significant ($p < 0.05$); ⁱ=excludes periods dispensed OxyContin or primary comparator concomitantly; ⁱⁱ= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); person-months (PMs); extended-release (ER); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

Figure 7: Adjusted ratios of rate ratios – pre- versus post-period change in opioid overdose rates in patients dispensed primary comparators concomitantly with any IR opioid analgesic compared to those dispensed OxyContin concomitantly with any IR opioid analgesic, by database



(FDA generated figure using data from PMR 3051-4 study report)

Key: X-axis is adjusted ratios of rate ratios (RORR); null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); horizontal lines are 95% confidence interval; extended-release (ER)

4.2.2.6 Overdose death in the pre- and post-periods

Table 14 shows the total number of overdose deaths, and the proportion of fatal overdoses among the total number of overdoses in the pre and post-periods, by database and opioid analgesic comparator. Of note, counts less than or equal to 10 were suppressed in the PMR 3051-4 study report, therefore, proportions of fatal overdose could not be calculated for these periods. Overall, the number of fatal overdoses was considerably lower than non-fatal overdoses for OxyContin and the comparators, but there do not appear to be meaningful changes comparing periods in the proportion of fatal overdose among all overdose for OxyContin and the comparators.

Table 14: Fatal overdose cases by period and opioid analgesic comparators

| Opioid analgesic | Exposure period category | Medicaid | | MarketScan | | HIRD | |
|------------------|--|--------------------------|---------------------------|--------------------------|---------------------------|--------------------------|---------------------------|
| | | Pre-reformulation period | Post-reformulation period | Pre-reformulation period | Post-reformulation period | Pre-reformulation period | Post-reformulation period |
| OxyContin | | 124 (18%) | 94 (14%) | 24 (11%) | 56 (15%) | ≤10 | ≤10 |
| ER morphine | Any use ⁱ | 184 (12%) | 274 (14%) | 30 (15%) | 67 (16%) | ≤10 | 11 (3%) |
| Fentanyl | (with or without concomitant opioid analgesic use periods) | 135 (16%) | 144 (15%) | 25 (12%) | 75 (17%) | ≤10 | ≤10 |
| Methadone | | 191 (14%) | 218 (16%) | 15 (15%) | 58 (25%) | ≤10 | 15 (7%) |
| OxyContin | Use alone | 41 (17%) | 16 (12%) | ≤10 | ≤10 | ≤10 | ≤10 |
| ER morphine | 61 (15%) | 66 (14%) | ≤10 | 15 (16%) | ≤10 | ≤10 | |
| Fentanyl | 41 (17%) | 32 (13%) | ≤10 | 18 (17%) | ≤10 | ≤10 | |
| Methadone | 89 (14%) | 95 (16%) | ≤10 | 33 (33%) | ≤10 | ≤10 | |

(FDA generated table using data from PMR 3051-4 study report)

Key: ⁱ=excludes periods dispensed OxyContin or primary/secondary comparator concomitantly; extended-release (ER); When counts were less than or equal 10 (denoted in table as ≤10), the number of fatal overdoses was suppressed in the study report, so the proportion of fatal overdoses among all overdoses could not be calculated

4.2.3 Overdose Rates Among Those Dispensed OxyContin and Other Secondary Comparators

Table 15 shows overdose rate ratios and RORRs for secondary comparators, stratified by concomitancy with other opioid analgesics and database. Of note, MarketScan analyses were only conducted using the unintentional overdose algorithm to ascertain overdose outcomes, therefore, these analyses are considered exploratory (See Appendix 8.4.2).

In Medicaid, overdose rate reductions were observed among those dispensed SE IR oxycodone with or without other opioid analgesics concomitantly, and alone, but this was not seen in the HIRD database. Results for the other secondary comparators were more consistent across databases, and overdose rate ratios were mostly not statistically significant. All the RORRs generally favored OxyContin when it was compared to the secondary comparators, but the RORRs were only statistically significant for SE IR oxycodone in HIRD.

Table 15: Unadjusted and adjusted overdose rate ratio and ratio of rate ratios among those dispensed OxyContin and other secondary comparators, by database and concomitancy with other opioid analgesics^{xxvi}

| Opioid analgesic | Exposure period category | Medicaid | | | | HIRD | | | |
|------------------|---|----------------------------|--------------------------|--|--|----------------------------|--------------------------|--|--|
| | | Unadjusted rate ratio (CI) | Adjusted rate ratio (CI) | Unadjusted ratio of rate ratio (CI) ⁱ | Adjusted ratio of rate ratio (CI) ⁱ | Unadjusted rate ratio (CI) | Adjusted rate ratio (CI) | Unadjusted ratio of rate ratio (CI) ⁱ | Adjusted ratio of rate ratio (CI) ⁱ |
| OxyContin | | 0.92 (0.80-1.06) | 0.88 (0.76-1.01) | ref | | 0.66 (0.49-0.90)* | 0.61 (0.46-0.82)* | ref | |
| ER Oxymorphone | Any use ⁱ (with or without concomitant opioid analgesic use periods) | 0.98 (0.74-1.30) | 1.01 (0.77-1.32) | 1.06 (0.77-1.45) | 1.15 (0.85-1.55) | 0.99 (0.54-1.82) | 0.81 (0.47-1.40) | 1.50 (0.77-2.95) | 1.32 (0.71-2.44) |
| SE IR Oxycodone | | 0.89 (0.81-0.98)* | 0.88 (0.81-0.97)* | 0.97 (0.82-1.15) | 1.01 (0.85-1.19) | 1.12 (0.82-1.54) | 0.99 (0.73-1.35) | 1.70 (1.09-2.63)* | 1.62 (1.07-2.44)* |
| IR Hydromorphone | | 0.90 (0.76-1.06) | 0.89 (0.76-1.04) | 0.98 (0.78-1.22) | 1.02 (0.82-1.25) | 0.92 (0.61-1.39) | 0.81 (0.55-1.19) | 1.39 (0.83-2.32) | 1.32 (0.82-2.11) |
| OxyContin | | 0.86 (0.69-1.08) | 0.84 (0.67-1.04) | ref | | 0.53 (0.32-0.87)* | 0.51 (0.32-0.81)* | ref | |
| ER Oxymorphone | Use alone (without concomitant opioid analgesic use periods) | 1.03 (0.67-1.57) | 1.09 (0.72-1.63) | 1.19 (0.74-1.93) | 1.30 (0.82-2.06) | 1.13 (0.37-3.44) | 1.13 (0.41-3.13) | 2.15 (0.63-7.28) | 2.24 (0.73-6.86) |
| SE IR Oxycodone | | 0.90 (0.80-1.00)* | 0.90 (0.81-1.01) | 1.04 (0.81-1.34) | 1.08 (0.85-1.38) | 1.14 (0.78-1.66) | 1.02 (0.71-1.48) | 2.16 (1.15-4.05)* | 2.02 (1.12-3.64)* |
| IR Hydromorphone | | 0.98 (0.80-1.21) | 0.96 (0.79-1.18) | 1.14 (0.84-1.55) | 1.15 (0.86-1.55) | 0.94 (0.57-1.55) | 0.80 (0.50-1.27) | 1.79 (0.89-3.64) | 1.58 (0.84-2.97) |

(FDA generated table using data from PMR 3051-4 study report)

Key: *= statistically significant ($p<0.05$); ⁱ=excludes periods dispensed OxyContin or primary/secondary comparator concomitantly; ⁱⁱ= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); person-months (PMs); extended-release (ER); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

Of note, the exposure time was much lower for secondary comparators ER oxymorphone and IR hydromorphone compared to OxyContin in both the pre- and post-periods and across databases (See Appendix 8.5), particularly when further restricted to use without other opioid analgesics concomitantly.

4.2.4 Sensitivity and Exploratory Analyses

4.2.4.1 Results comparing incident user cohort to the combined (incident and prevalent)

^{xxvi} FDA is waiting for sponsor submission of MarketScan results using the any overdose outcome (intentional and unintentional)

user cohorts

Table 16 shows the total number of overdoses, the total amount of person-time, and the overdose rates in the pre- and post-periods among those dispensed OxyContin in the Medicaid database, stratified by combined (incident and prevalent patients) and incident^{xxvii} only patient cohorts, and opioid analgesic concomitancy. Unadjusted and adjusted rate ratios are also provided.

The exposure time was ~70% lower in the pre-period and ~75% lower in the post-period among those dispensed OxyContin with or without other opioid analgesics in the incident only cohort compared to the combined cohort; unadjusted and adjusted rate ratios were similar comparing the incident cohort and combined cohort, and neither were statistically significant.

When restricted to person-time dispensed OxyContin alone in the incident only cohort compared to the combined cohort, the exposure time was ~64% lower in the pre-period and ~68% lower in the post-period. Also, unadjusted and adjusted rate ratio were qualitatively different comparing the incident cohort and combined cohort, but neither were statistically significant.

Table 16: Medicaid data - overdose rates (and exposure time) and overdose rate ratios among those dispensed OxyContin in the combined (incident and prevalent) and incident only cohorts by concomitancy with other opioid analgesics (-2y/2y)

| OxyContin cohort | Cohort | Pre-reformulation period (ref) | | | Post-reformulation period | | | Unadjusted rate ratio (CI) | Adjusted rate ratio (CI) |
|-----------------------------------|-----------------------------------|--------------------------------|--------------------------------|-----------------------------------|--------------------------------|--------------------------------|-----------------------------------|----------------------------|--------------------------|
| | | Overdoses (fatal or non-fatal) | Person months of exposure time | Rate per 1,000 person months (CI) | Overdoses (fatal or non-fatal) | Person months of exposure time | Rate per 1,000 person months (CI) | | |
| Any OxyContin ⁱ | Combined (Incident and prevalent) | 693 | 384,417 | 1.80 (1.66-1.95) | 651 | 349,899 | 1.86 (1.70-2.03) | 1.03 (0.92-1.16) | 1.00 (0.89-1.12) |
| | Incident only | 198 | 113,884 | 1.74 (1.51-2.01) | 153 | 87,758 | 1.74 (1.47-2.06) | 1.00 (0.81-1.25) | 0.98 (0.79-1.22) |
| OxyContin use alone ⁱⁱ | Combined (Incident and prevalent) | 236 | 143,156 | 1.65 (1.44-1.89) | 131 | 92,079 | 1.42 (1.19-1.71) | 0.86 (0.69-1.08) | 0.85 (0.68-1.06) |
| | Incident only | 69 | 51,166 | 1.35 (1.06-1.72) | 42 | 29,192 | 1.44 (1.05-1.98) | 1.07 (0.72-1.59) | 1.08 (0.73-1.61) |

(FDA generated table using data from PMR 3051-4 study report)

Key: *= statistically significant ($p<0.05$); ⁱ=Any OxyContin use (with or without concomitant opioid analgesics) excluding periods dispensed OxyContin or primary comparator concomitantly; ⁱⁱ= when restricted to person-time dispensed OxyContin alone (without concomitant opioid analgesics); Confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

Table 17 shows the total number of overdoses, the total amount of person-time, the overdose rates and rate ratios among those dispensed OxyContin in the MarketScan database, stratified by combined and incident only patient cohorts, and opioid analgesic concomitancy. Among those dispensed OxyContin with or without other opioid analgesics, the exposure time in the incident only cohort was ~72% lower in the pre-period and ~81%

^{xxvii} No use of any opioid comparator in the prior 3 months, but patients could have been dispensed non-comparator opioids during that period and patients could be included as incident multiple times throughout the study period

lower in the post-period, compared to the combined cohort; however unadjusted and adjusted rate ratios were similar comparing the incident cohort and combined cohort, and neither was statistically significant.

When restricted to person-time dispensed OxyContin alone, the incident only cohort had ~68% lower exposure time in the pre-period and ~78% lower in the post-period, compared to the combined cohort. Again, unadjusted and adjusted rate ratios were similar comparing the incident only and combined cohorts, and neither was statistically significant.

Table 17: MarketScan data - overdose rates (and exposure time) and overdose rate ratios among those dispensed OxyContin in the combined (incident and prevalent) and incident only cohorts by concomitancy with other opioid analgesics (-2y/5y)

| OxyContin cohort | Cohort | Pre-reformulation period (ref) | | | Post-reformulation period | | | Unadjusted rate ratio (CI) | Adjusted rate ratio (CI) |
|-----------------------------------|-----------------------------------|--------------------------------|--------------------------------|-----------------------------------|--------------------------------|--------------------------------|-----------------------------------|----------------------------|--------------------------|
| | | Overdoses (fatal or non-fatal) | Person months of exposure time | Rate per 1,000 person months (CI) | Overdoses (fatal or non-fatal) | Person months of exposure time | Rate per 1,000 person months (CI) | | |
| Any OxyContin ⁱ | Combined (Incident and prevalent) | 220 | 268,476 | 0.82 (0.70-0.96) | 367 | 459,907 | 0.80 (0.71-0.89) | 0.97 (0.81-1.18) | 0.90 (0.75-1.08) |
| | Incident only | 57 | 75,220 | 0.76 (0.53-1.08) | 52 | 88,378 | 0.59 (0.44-0.78) | 0.78 (0.49-1.22) | 0.71 (0.45-1.12) |
| OxyContin use alone ⁱⁱ | Combined (Incident and prevalent) | 58 | 97,454 | 0.60 (0.46-0.78) | 62 | 140,826 | 0.44 (0.34-0.57) | 0.74 (0.51-1.08) | 0.72 (0.50-1.04) |
| | Incident only | 18 | 31,262 | 0.58 (0.35-0.94) | ≤10 | 30,769 | 0.26 (0.11-0.61) | 0.45 (0.17-1.20) | 0.44 (0.17-1.17) |

(FDA generated table using data from PMR 3051-4 study report)

Key: *= statistically significant ($p<0.05$); ⁱ=Any OxyContin use (with or without concomitant opioid analgesics) excluding periods dispensed OxyContin or primary comparator concomitantly; ⁱⁱ= when restricted to time OxyContin alone (without concomitant opioid analgesics); Confidence interval (CI); adjusted for variables in section 3.4.5

Table 18 shows the total number of overdoses, the total amount of person-time, the overdose rates and rate ratios among those dispensed OxyContin in the HIRD database, stratified by combined and incident only patient cohorts, and opioid analgesic concomitancy. Among those dispensed OxyContin with or without other opioid analgesics, the exposure time was ~46% lower in the pre-period and ~73% lower in the post-period in the incident only cohort compared to the combined cohort; unadjusted and adjusted rate ratios were similar comparing the incident cohort and combined cohort, and neither was statistically significant.

When restricted to person-time dispensed OxyContin alone in the incident only cohort compared to the combined cohort, the exposure time was ~35% lower in the pre-period and ~67% lower in the post-period. Also, unadjusted and adjusted rate ratios were similar comparing the incident cohort and combined cohort, but only statistically significant when using the combined cohort.

Table 18: HIRD data - overdose rates (and exposure time) and overdose rate ratios among those dispensed OxyContin in the combined (incident and prevalent) and incident only cohorts by concomitancy with other opioid analgesics (-2y/5y)

| OxyContin cohort | Cohort | Pre-reformulation period (ref) | | | Post-reformulation period | | | Unadjusted rate ratio (CI) | Adjusted rate ratio (CI) |
|-----------------------------------|-----------------------------------|--------------------------------|--------------------------------|-----------------------------------|--------------------------------|--------------------------------|-----------------------------------|----------------------------|--------------------------|
| | | Overdoses (fatal or non-fatal) | Person months of exposure time | Rate per 1,000 person months (CI) | Overdoses (fatal or non-fatal) | Person months of exposure time | Rate per 1,000 person months (CI) | | |
| Any OxyContin | Combined (Incident and prevalent) | 164 | 176,145 | 0.92 (0.77-1.13) | 268 | 314,899 | 0.85 (0.69-1.04) | 0.91 (0.69-1.21) | 0.84 (0.65-1.09) |
| | Incident only | 85 | 95,484 | 0.89 (0.67-1.18) | 61 | 86,036 | 0.71 (0.54-0.93) | 0.80 (0.54-1.18) | 0.76 (0.51-1.12) |
| OxyContin use alone ⁱⁱ | Combined (Incident and prevalent) | 58 | 63,959 | 0.91 (0.62-1.33) | 43 | 90,142 | 0.48 (0.34-0.67) | 0.53 (0.32-0.87)* | 0.52 (0.32-0.83)* |
| | Incident only | 37 | 41,461 | 0.89 (0.53-1.50) | 17 | 29,741 | 0.57 (0.34-0.97) | 0.64 (0.37-1.34) | 0.60 (0.28-1.28) |

(FDA generated table using data from PMR 3051-4 study report)

Key: *= statistically significant ($p<0.05$); ⁱ=Any OxyContin use (with or without concomitant opioid analgesics) excluding periods dispensed OxyContin or primary comparator concomitantly; ⁱⁱ= when restricted to person-time dispensed OxyContin alone (without concomitant opioid analgesics); Confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

Table 19 shows adjusted RORRs for primary comparators using the combined (incident and prevalent patients) and incident only cohorts, stratified by concomitancy with other opioids analgesics and database.

The adjusted RORRs were similar and not statistically significant for analyses using the combined cohort and the incident only cohort for ER morphine with or without other opioid analgesics concomitantly, and fentanyl with or without other opioid analgesics concomitantly. For methadone with or without other opioid analgesics concomitantly, the RORR using the incident only cohort in MarketScan was considerably larger than when using the combined cohort, but results were generally similar in the other databases.

When restricted to person-time dispensed OxyContin alone, the adjusted RORRs were qualitatively different comparing cohorts in Medicaid for ER morphine and methadone, but results were rather similar between cohorts in the other databases for all primary comparators.

Table 19: Adjusted ratio of rate ratios among those dispensed primary comparators using the combined cohort (incident and prevalent users) and incident user only cohort, by database and concomitancy with other opioid analgesics

| Opioid analgesic ⁱ | Exposure period category | Medicaid | | MarketScan | | HIRD | |
|---|---|--|--|--|--|--|--|
| | | Combined cohort: Adjusted ratio of rate ratio (CI) ⁱⁱ | Incident only: Adjusted ratio of rate ratio (CI) ⁱⁱ | Combined cohort: Adjusted ratio of rate ratio (CI) ⁱⁱ | Incident only: Adjusted ratio of rate ratio (CI) ⁱⁱ | Combined cohort: Adjusted ratio of rate ratio (CI) ⁱⁱ | Incident only: Adjusted ratio of rate ratio (CI) ⁱⁱ |
| Any OxyContin ⁱ (reference) | | | | | | | |
| ER morphine | Any use ⁱ | 0.91 (0.80-1.04) | 0.89 (0.70-1.13) | 1.12 (0.86-1.46) | 1.27 (0.74-2.17) | 1.09 (0.78-1.53) | 1.45 (0.88-2.39) |
| Fentanyl | (with or without concomitant opioid analgesic use periods) | 1.05 (0.90-1.22) | 1.13 (0.86-1.48) | 1.19 (0.93-1.53) | 1.36 (0.79-2.34) | 1.04 (0.73-1.49) | 1.10 (0.66-1.84) |
| Methadone | | 0.85 (0.74-0.98)* | 0.83 (0.64-1.07) | 1.32 (0.97-1.79) | 2.17 (1.11-4.26)* | 1.20 (0.83-1.74) | 1.40 (0.84-2.35) |
| OxyContin alone (reference) | | | | | | | |
| ER morphine | Use alone | 1.17 (0.90-1.52) | 0.77 (0.50-1.21) | 1.62 (0.97-2.72) | 2.24 (0.72-6.96) | 2.20 (1.18-4.18)* | 1.99 (0.83-4.76) |
| Fentanyl | (without concomitant opioid analgesic use periods) | 1.27 (0.95-1.77) | 1.16 (0.71-1.89) | 1.68 (1.02-2.78)* | 1.58 (0.53-4.75) | 1.40 (0.73-2.70) | 1.34 (0.53-3.43) |
| Methadone | | 1.06 (0.81-1.40) | 0.76 (0.49-1.18) | 1.94 (1.14-3.29)* | 3.43 (0.97-12.10) | 1.76 (0.98-3.17) | 1.55 (0.67-3.61) |

(FDA generated table using data from PMR 3051-4 study report)

Key: * = statistically significant ($p < 0.05$); ⁱ=excludes periods dispensed OxyContin or primary comparator concomitantly; ⁱⁱ= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); confidence interval (CI); combined cohort includes incident and prevalent patients; adjusted for variables in section 3.4.5

Of note, similar to what was observed among those dispensed OxyContin (Tables 15-17, above), exposure time was much lower among primary comparators when analyses were restricted to the incident only cohort (See Appendix 8.5), particularly when further restricted to time dispensed alone (without other opioid analgesics concomitantly).

4.2.4.2 Medicaid data: fee-for-service versus managed care plans

Table 20 shows adjusted overdose rate ratios among those dispensed OxyContin and primary comparators, and RORRs, in the Medicaid database stratified by Medicaid plan type and by concomitancy with other opioid analgesics. Of note, these Medicaid analyses were only conducted using the unintentional overdose algorithm to ascertain overdose outcomes, therefore, these analyses are considered exploratory.

Comparing the results from those with fee-for-service (FFS) plans to those with managed care plans, some differences were observed. Among those dispensed OxyContin with or without other opioid analgesics concomitantly, all adjusted RORRs for primary comparators favored OxyContin in the FFS cohort, while in the managed care cohort, all RORRs for primary comparators favored the comparators, with varying statistical significance. When restricted to person-time dispensed OxyContin alone, the adjusted

RORRs for ER morphine were similar comparing cohorts, but this was not true for fentanyl and methadone.

Table 20: Unintentional overdose rate ratio and adjusted ratio of rate ratios among those dispensed OxyContin and primary comparators in the Medicaid data, by plan type and concomitancy with other opioid analgesics

| Opioid analgesic | Exposure period category | Fee-For-Service | | Managed Care | |
|------------------|---|------------------------------|---|--------------------------|---|
| | | Adjusted rate ratio (CI) | Adjusted ratio of rate ratio (CI) ⁱⁱ | Adjusted rate ratio (CI) | Adjusted ratio of rate ratio (CI) ⁱⁱ |
| OxyContin | Any use ⁱ (with or without concomitant opioid analgesic use periods) | 0.81 (0.68-0.95)* | ref | 1.18 (0.98-1.42) | ref |
| ER morphine | | 0.90 (0.80-1.01) | 1.11 (0.91-1.37) | 0.99 (0.89-1.09) | 0.84 (0.68-1.03) |
| Fentanyl | | 1.03 (0.90-1.18) | 1.28 (1.03-1.59)* | 0.99 (0.84-1.16) | 0.84 (0.66-1.07) |
| Methadone | | 0.81 (0.70-0.94)* | 1.01 (0.81-1.26) | 0.91 (0.81-1.03) | 0.77 (0.62-0.96)* |
| OxyContin | Use alone (without concomitant opioid analgesic use periods) | 0.80 (0.59-1.09) | ref | 0.91 (0.61-1.34) | ref |
| ER morphine | | 0.91 (0.73-1.13) | 1.13 (0.78-1.64) | 1.04 (0.84-1.29) | 1.15 (0.73-1.79) |
| Fentanyl | | 1.21 (0.95-1.54) | 1.51 (1.02-2.22)* | 0.78 (0.55-1.12) | 0.86 (0.51-1.46) |
| Methadone | | 0.78 (0.64-0.95)* | 0.97 (0.68-1.40) | 0.97 (0.80-1.18) | 1.07 (0.69-1.65) |

(FDA generated table using data from PMR 3051-4 study report)

Key: *= statistically significant ($p<0.05$); ⁱ=excludes periods dispensed OxyContin or primary comparator concomitantly; ⁱⁱ= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

4.2.4.3 Propensity score analyses

Table 21 shows adjusted unintentional overdose rate ratios among those dispensed OxyContin and primary comparators, and RORRs, from the propensity-score (PS)-weighted analyses, across databases. Of note, these analyses were only conducted using the unintentional overdose algorithm to ascertain overdose outcomes; therefore, these analyses are considered exploratory.

The results of the PS-weighted analyses among patients dispensed OxyContin with or without other opioid analgesics concomitantly were generally consistent with the main results based on multivariable modeling, except that no RORR was statistically significant in the PS-weighted analyses.

Table 21: PS-weighted unintentional overdose rate ratio and adjusted ratio of rate ratios (RORRs) among those dispensed OxyContin and primary comparators, by database

| Opioid analgesic ⁱ | Medicaid | | MarketScan | | IIRD | |
|-------------------------------|--------------------------|---|--------------------------|---|--------------------------|---|
| | Adjusted rate ratio (CI) | Adjusted ratio of rate ratio (CI) ⁱⁱ | Adjusted rate ratio (CI) | Adjusted ratio of rate ratio (CI) ⁱⁱ | Adjusted rate ratio (CI) | Adjusted ratio of rate ratio (CI) ⁱⁱ |
| Any OxyContin | 0.90 (0.69-1.17) | ref | 0.73 (0.44-1.20) | ref | 0.64 (0.41-0.99)* | ref |
| Any ER morphine | 0.89 (0.78-1.02) | 0.99 (0.74-1.33) | 0.89 (0.65-1.22) | 1.22 (0.67-2.22) | 1.03 (0.72-1.49) | 1.61 (0.92-2.82) |
| Any fentanyl | 1.09 (0.90-1.33) | 1.22 (0.88-1.69) | 0.91 (0.65-1.28) | 1.25 (0.68-2.29) | 0.75 (0.50-1.11) | 1.16 (0.64-2.11) |
| Any methadone | 0.88 (0.74-1.04) | 0.98 (0.72-1.33) | 1.49 (0.86-2.58) | 2.05 (0.98-4.27) | 0.93 (0.64-1.35) | 1.45 (0.82-2.57) |

(FDA generated table using data from PMR 3051-4 study report)

Key: *= statistically significant ($p<0.05$); ⁱ=including use with or without other opioid analgesics concomitantly, but excluding periods dispensed OxyContin or primary comparator concomitantly; ⁱⁱ= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); propensity score (PS); confidence interval (CI); reference (ref); variables used in the PS-weighting are noted in section 3.4.5

4.2.4.4 Analyses among those dispensed OxyContin or comparators continuously from pre- to post-periods

Table 22 shows the *unintentional*^{xxviii} overdose rate ratios among patients dispensed OxyContin or primary comparators with or without other opioid analgesics concomitantly who had continuous dispensings from the pre-period continuing into the post-period. Across all databases, reductions in unintentional overdose were observed among those dispensed OxyContin, but in adjusted analyses rate ratios were not statistically significant. Reductions in unintentional overdose were also observed across all comparators and databases, with statistically significant rate ratios among those dispensed ER morphine in Medicaid and IIRD, and statistically significant rate ratios among those dispensed fentanyl and methadone in Medicaid.

^{xxviii} Of note, these analyses were only conducted using the unintentional overdose algorithm therefore they are considered exploratory (see Section 3.4.6)

Table 22: Unadjusted and adjusted unintentional overdose rate ratio among those dispensed OxyContin and primary comparators with or without other opioid analgesics concomitantly and with “continuous use” from the pre- to post-reformulation periods, by database

| Opioid analgesic ⁱ | Medicaid | | MarketScan | | HIRD | |
|-------------------------------|-----------------------------|-----------------------------|----------------------------|--------------------------|-----------------------------|-----------------------------|
| | Unadjusted rate ratio (CI) | Adjusted rate ratio (CI) | Unadjusted rate ratio (CI) | Adjusted rate ratio (CI) | Unadjusted rate ratio (CI) | Adjusted rate ratio (CI) |
| Any OxyContin | 0.76 (0.60-0.97)* | 0.86 (0.68-1.10) | 0.72 (0.38-1.37) | 0.75 (0.41-1.37) | 0.68 (0.38-1.24) | 0.79 (0.45-1.39) |
| Any ER morphine | 0.62 (0.53-0.74)* | 0.73 (0.62-0.87)* | 0.56 (0.25-1.22) | 0.61 (0.29-1.31) | 0.33 (0.17-0.63)* | 0.33 (0.17-0.65)* |
| Any fentanyl | 0.63 (0.50-0.79)* | 0.76 (0.60-0.97)* | 0.74 (0.37-1.50) | 0.81 (0.41-1.61) | 0.59 (0.36-0.97)* | 0.71 (0.45-1.13) |
| Any methadone | 0.48 (0.39-0.59)* | 0.55 (0.45-0.67)* | 0.68 (0.32-1.47) | 0.68 (0.34-1.34) | 0.51 (0.29-0.88)* | 0.56 (0.32-0.98) |

(FDA generated table using data from PMR 3051-4 study report)

Key: *= statistically significant ($p < 0.05$); ⁱ=excludes periods dispensed OxyContin or primary comparator concomitantly; person-months (PMs); extended-release (ER); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

4.3 SPONSOR'S INTERPRETATION OF PMR 3051-4 RESULTS

“The 2010 reformulation of OxyContin to a product with physicochemical barriers to deter injection or insufflation was not associated with a substantial decline in the overall incidence of unintentional opioid overdose in OxyContin users, beyond what might have been expected from secular trends seen in comparator opioids. However, when attention was restricted to person-time during which there was no use of concomitant opioids, the OxyContin reformulation was associated with an unequivocal decline in overdose rates during only OxyContin use as compared to during the use of only comparators, particularly in the commercially insured databases. There was a more modest decline among the Medicaid population.”

Note: The sponsor's interpretation in the PMR 3051-4 study report was based on the unintentional overdose outcome findings, which FDA considers to be exploratory due to its inferior performance in algorithm validation studies relative to the “any” opioid overdose algorithm.

5 DISCUSSION

5.1 FDA SUMMARY OF PMR STUDY 3051-4 FINDINGS

Changes in opioid overdose rates among patients dispensed OxyContin

In the commercial claims combined incident and prevalent user cohorts (see Table 23), there were modest reductions in opioid overdose rates among patients dispensed OxyContin with or without other opioid analgesics concomitantly, and when restricted to person-time dispensed OxyContin with any immediate-release (IR) opioid analgesic

concomitantly. These reductions were not seen in the Medicaid cohort. None of the adjusted overdose rate ratios for these cohorts were statistically significant. When restricted to person-time dispensed OxyContin alone (with no other opioid analgesics), there were larger reductions in opioid overdose rates among OxyContin recipients across all databases, but the changes were only statistically significant in one database (HIRD).

Table 23: Adjusted overdose rate ratios among those dispensed OxyContin across databases, by concomitancy with other opioid analgesics

| OxyContin exposure group | Medicaid | | | MarketScan | | | HIRD | | |
|--|-------------------------------------|--------------------------------|--------------------------|-------------------------------------|--------------------------------|--------------------------|-------------------------------------|--------------------------------|--------------------------|
| | Pre-period rate per 1,000 PMs (ref) | Post-period rate per 1,000 PMs | Adjusted rate ratio (CI) | Pre-period rate per 1,000 PMs (ref) | Post-period rate per 1,000 PMs | Adjusted rate ratio (CI) | Pre-period rate per 1,000 PMs (ref) | Post-period rate per 1,000 PMs | Adjusted rate ratio (CI) |
| Any OxyContin use ⁱ | 1.80 | 1.86 | 1.00 (0.89-1.12) | 0.82 | 0.80 | 0.90 (0.75-1.08) | 0.93 | 0.85 | 0.84 (0.65-1.09) |
| Concomitant use ⁱⁱ with any IR opioid analgesic | 1.89 | 2.02 | 1.04 (0.91-1.19) | 0.93 | 0.96 | 0.95 (0.77-1.17) | 0.93 | 0.75 | 0.74 (0.54-1.02) |
| OxyContin use alone | 1.65 | 1.42 | 0.85 (0.68-1.06) | 0.60 | 0.44 | 0.72 (0.50-1.04) | 0.91 | 0.48 | 0.52 (0.32-0.83)* |

(FDA generated table using data from PMR 3051-4 study report)

Key: *= statistically significant ($p<0.05$); ⁱ=excludes periods dispensed OxyContin or primary comparator concomitantly; ⁱⁱ=includes only periods dispensed an IR opioid analgesic concomitantly, excluding periods dispensed OxyContin or primary comparator use concomitantly; person-months (PMs); confidence interval (CI); adjusted for variables in section 3.4.5; For all databases, the pre-period is two years before the reformulation, but the post-period for Medicaid analyses is two years after the reformulation and the post-period for MarketScan/HIRD analyses is five years after the reformulation

Overall, the incident only cohorts were smaller samples with substantially reduced aggregate exposure time across databases compared to analyses from combined cohorts. Overdose rate ratios using incident only cohorts were generally similar to those of the combined cohort, but not statistically significant for any of the OxyContin exposure groups.

Overdose rate changes for OxyContin compared to changes for primary comparators

In Medicaid analyses, with the exception of fentanyl, the adjusted ratio of rate ratios (RORR) favored the comparators (i.e., $RORR < 1$) over OxyContin among patients with or without other opioid analgesics dispensed concomitantly, but the RORR was only statistically significant for methadone (see Table 24). Adjusted RORRs also favored comparators when restricted to person-time dispensed any IR opioid analgesic concomitantly, with statistically significant RORRs for ER morphine and methadone. In the commercial claims analyses (MarketScan and HIRD), the adjusted RORRs all generally favored OxyContin when looking at those dispensed the comparators with or

without other opioid analgesics concomitantly, or when restricted to person-time dispensed with an IR opioid analgesic concomitantly, but no RORR was statistically significant for any comparator. Meta-analyzed comparative results from the commercial claims databases were generally consistent with results of the commercial claims analyzed separately, except that the RORRs were statistically significant for methadone (favoring OxyContin) when analyzed separately.

When restricted to person-time dispensed OxyContin or comparators alone, all adjusted RORRs favored OxyContin, but only in the commercial claims databases were some adjusted RORRs statistically significant: ER morphine in the HIRD data, and fentanyl and methadone in the MarketScan data. Meta-analyzed results from the commercial claims databases were also generally consistent with results when analyzed separately, except that all RORRs were statistically significant (favoring OxyContin) when meta-analyzed.

Table 24: Adjusted ratio of rate ratios among those dispensed primary comparators compared to those dispensed OxyContin, by database and concomitancy with other opioid analgesics

| Opioid analgesic exposure group | Exposure period category | Medicaid | MarketScan | HIRD |
|---------------------------------|---|--|--|--|
| | | Adjusted ratio of rate ratio (CI) ⁱⁱⁱ | Adjusted ratio of rate ratio (CI) ⁱⁱⁱ | Adjusted ratio of rate ratio (CI) ⁱⁱⁱ |
| ER morphine | (with or without concomitant opioid analgesic use periods) | 0.91 (0.80-1.04) | 1.12 (0.86-1.46) | 1.09 (0.78-1.53) |
| | | 1.05 (0.90-1.22) | 1.19 (0.93-1.53) | 1.04 (0.73-1.49) |
| | | 0.85 (0.74-0.98)* | 1.32 (0.97-1.79) | 1.20 (0.83-1.74) |
| Fentanyl | Concomitant IR opioid analgesic use ⁱⁱ (with concomitant IR opioid analgesic use periods) | 0.84 (0.72-0.99)* | 1.00 (0.74-1.35) | 1.01 (0.66-1.56) |
| | | 0.98 (0.83-1.17) | 1.09 (0.81-1.45) | 1.17 (0.74-1.83) |
| | | 0.80 (0.67-0.96)* | 1.08 (0.73-1.59) | 1.19 (0.73-1.92) |
| Methadone | Use alone (without concomitant opioid analgesic use periods) | 1.17 (0.90-1.52) | 1.62 (0.97-2.72) | 2.20 (1.18-4.10)* |
| | | 1.27 (0.95-1.69) | 1.68 (1.02-2.78)* | 1.40 (0.73-2.70) |
| | | 1.03 (0.79-1.33) | 1.94 (1.14-3.29)* | 1.76 (0.98-3.17) |

(FDA generated table using data from PMR 3051-4 study report)

Key: *= statistically significant ($p<0.05$); ⁱ=excludes periods dispensed OxyContin or primary comparator concomitantly; ⁱⁱ=includes only periods dispensed an IR opioid analgesic concomitantly, excluding periods dispensed OxyContin or primary comparator opioid analgesic concomitantly; ⁱⁱⁱ= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); person-months (PMs); confidence interval (CI); adjusted for variables in section 3.4.5; reference for this table is OxyContin adjusted rate ratio (see Table 1); adjusted for variables in section 3.4.5; for all databases, the pre-period is two years before the reformulation, but the post-period for Medicaid analyses is two years after the reformulation and the post-period for MarketScan/HIRD analyses is five years after the reformulation

The adjusted RORR point estimates using the incident user only cohort were generally similar to those using the combined cohort, but the RORRs were not statistically significant, with the exception of methadone which was statistically significant (favoring OxyContin) among patients with or without other opioid analgesics dispensed concomitantly. When the Medicaid analyses were stratified by plan type (FFS or managed care),^{xxix} some adjusted RORR estimates were qualitatively different from each other, notably for fentanyl, but RORRs in both cohorts were mostly not significant.

The RORR estimates using the unintentional opioid overdose algorithm were similar to the RORR estimates using the primary any opioid overdose algorithm. Overall, the number of fatal overdoses was much lower than non-fatal overdose, and the proportion of overdoses that were fatal did not change across time periods, either for OxyContin or any comparator group.

5.2 PUBLISHED LITERATURE

DEPI identified two relevant publications in the scientific literature that used electronic healthcare databases to evaluate changes in overdose rates after the OxyContin reformulation (See Appendix 8.8 for summary table); one publication (Coplan et al., 2016)¹ was authored by the sponsor. Coplan et al. describes the results for the original 10 studies/analyses conducted by the sponsor to support potential postmarket labeling claims for OxyContin. One of the analyses assessed the overdose rates among those dispensed OxyContin one year before versus three years after the reformulation using MarketScan claims data, and similar methods to PMR study 3051-4. Opioid overdose rates (based on diagnosis codes) among those dispensed OxyContin decreased 34% (95% CI: 7 to 53%) comparing the pre- and post-periods, from 0.42 to 0.28 per 100 person-years, and that change was statistically significantly different ($p<0.027$) to that of ER morphine (+17%, CI: -19 to 69%). The RRs in Coplan et al. are relatively consistent with what was observed in MarketScan for PMR study 3051-4, but the percent reductions for OxyContin in PMR study 3051-4 were not statistically significant comparing pre- and post-periods, nor were the RORRs for ER morphine. Different from PMR study 3051-4, Coplan et al. used only overdoses captured in the administrative claims (without mortality linkage) and shorter pre- and post-periods, and analyses did not adjust for differences in patient characteristics between periods. It is unclear whether Coplan's analyses included or excluded person-time in which other opioid analgesics were used concomitantly with OxyContin. Given the more rigorous methods used in PMR study 3051-4, with a longer time period and more complete capture of overdose events (including both fatal or nonfatal), it is not unexpected that the percent changes observed for OxyContin in PMR study 3051-4 would be more attenuated than what was observed in Coplan et al.

The other relevant published study, Larochelle et al. (2015), aimed to evaluate how opioid analgesic dispensing and overdose rates were impacted by two changes in the opioid analgesic market: the withdrawal of propoxyphene (11/2010), and the introduction of reformulated OxyContin (8/2010). Larochelle et al. used Optum commercial claims data to assess rates of opioid analgesic dispensing and prescription opioid overdose (based on

^{xxix} This was only conducted using the unintentional opioid overdose algorithm

diagnosis codes) before and after the interventions using an interrupted time series design. Analyses did not differentiate between opioid analgesics, and all eligible patients in the data were included regardless of whether they had been dispensed opioid analgesics. In the two years after both opioid analgesic market changes, the total opioid analgesic dispensing rate in milligrams of morphine-equivalent dose (MED) per member per quarter decreased by 19% from the expected rate; ER oxycodone decreased by 39% from the expected rate (absolute change: -11.3 mg MED per member per quarter [95% CI, -12.4 to -10.1]). For overdose, the estimated rate (per 100,000 members per quarter) attributed to prescription opioid analgesics decreased by 20% (absolute change: -1.10 per 100,000 members per quarter [95% CI, -1.47 to -0.74]), and heroin overdose increased by 23% (absolute change: 0.26 per 100,000 members per quarter [95% CI: -0.01 to 0.53]). Like Coplan et al., only overdoses treated in emergency departments and hospitals that would generate claims were captured, thus excluding most overdose fatalities. Larochelle et al. contend that the overall reduction in rates of opioid analgesic dispensing and prescription opioid overdose was associated with both market changes, and also notes the need to address increasing heroin overdose. With no differentiation between type of opioid analgesic dispensed in overdose rates in Larochelle et al., it was not possible to directly compare their results to those of PMR study 3051-4.

5.3 METHODOLOGICAL CONSIDERATIONS FOR CAUSAL INTERPRETATIONS

5.3.1 Patient Characteristics and Sample Selection

PMR study 3051-4 assessed opioid overdose rates among patients directly dispensed opioid analgesics through traditional channels of distribution and reimbursed by Medicaid or commercial insurance. While important to study with respect to the impact of the reformulation, patients who receive an insurance-reimbursed prescription for opioid analgesics may not be representative of the populations where non-oral abuse and overdose are most common. This type of patient-based study population receiving prescription opioid analgesics paid for by health insurance may be at an inherently lower risk for opioid abuse and overdose than individuals who obtain prescription opioid analgesics using cash or through diversion (i.e., from other sources like friends or illicit channels). Those who obtain opioid analgesics from sources other than their own prescription may be particularly at risk for abuse and overdose via non-oral routes, which are *a priori* expected to be impacted the most by OxyContin's reformulation based on the pre-market data suggesting that crushing tablets for non-oral use was made more difficult. MarketScan and HIRD data also include patients with primarily employer-based health insurance, potentially selecting for those with lower overdose risk. Medicaid data, on the other hand, include patients with a higher prevalence of important comorbidities, such as opioid use disorder (OUD) and respiratory impairment (see Table 4), with perhaps challenging socioeconomic circumstances. However, as active patients with regular healthcare encounters, it is likely their overdose risk is still lower than what would be expected in an enriched population sample selected because of having OUD or the use of opioids via non-oral routes.

Many otherwise eligible patients could not be included in PMR study 3051-4 due to lack of data linkage capability and other data quality issues, but these exclusions likely did not bias the comparative analyses. The generalizability of study findings was also likely not

impacted by these exclusions as the sample of patients dispensed opioid analgesics and person-time of exposure were large in all three databases. In MarketScan, ~60% of the eligible opioid-analgesic-using patients could not be linked to the NDI (~40% in HIRD) for full outcome ascertainment, which did dramatically reduce available exposure time and statistical power to compare rates of opioid overdose, particularly in comparative analyses of opioid analgesics with lower utilization rates. Importantly, demographic characteristics and comorbidities were similar when comparing those who were linkable to those who were not. In Medicaid, only ~25% of all beneficiaries had data deemed usable (i.e., “complete”) for this study, with both fee-for-service (FFS) and, to a greater extent, comprehensive managed care members being affected. Nevertheless, there did not appear to be differential inclusion by patient characteristics in the commercial claims databases with respect to linkage to NDI (see Appendix 8.4.2 and 8.4.3), nor did there appear to be meaningful differences in the results of stratified analyses by Medicaid coverage type (see Table 19)^{xxx}. Also, since Medicaid data were excluded at that state/year-level and not patient-level, patients were not differentially excluded based on opioid analgesic exposure or clinical characteristics.

Sensitivity analyses were conducted using an incident user cohort to help minimize potential selection biases resulting from including prevalent (ongoing) users; however, despite the substantially reduced exposure time in the incident user only analyses (see Tables 15-17 and Appendix 8.5), the results using the combined user cohort (incident and prevalent) and incident user only cohort were very similar. PMR study 3051-4 did not use a traditional definition of incident use. In this study, incident users of a particular drug could not have had prior dispensing of any study opioid analgesics within the previous three months, but patients could have had recent dispensing of non-study opioid analgesics, including commonly used opioid analgesics like IR hydrocodone, and patients could contribute “incident” time in subsequent treatment episodes over the study period if they met the criteria again. Prevalent users with experience with the study drug had to survive long enough to be included in the study, and thus may be at a potentially lower risk for the outcome (otherwise known as the “depletion of susceptibles” bias). Therefore, inclusion of prevalent users in PMR study 3051-4 can introduce selection bias, but with an effect that is difficult to predict since it is also possible that the likelihood of the outcome *increases* with greater exposure time. Selection biases can also be introduced by adjusting for variables that are impacted by treatment selection after initiation. This is of particular concern in analyses that include prevalent users, as baseline characteristics are measured after initiation of the opioid analgesic for that exposure period. Nevertheless, because of the way “incident” use was defined in PMR study 3051-4, incident and prevalent users were more or the less comparable, as both can have prior experience with non-study opioid analgesics, and both can contribute multiple treatment episodes during the study period. Overall, patient characteristics associated with incident only versus prevalent only treatment episodes were very similar to each other, which also helps mitigate some concerns with using a combined cohort.

^{xxx} Note this was only using the unintentional overdose outcome

5.3.2 Challenges with Exposure and Outcome Measurement in Administrative Claims Data

Drug exposure is difficult to measure and characterize in claims-based observational studies, particularly for opioid analgesics. While opioid analgesic drugs can be taken routinely like antihypertensives, they are also taken as needed or sporadically for acute conditions, acute exacerbations of chronic conditions, or for intermittent chronic pain. Opioid analgesics can be taken alone, or in combination with other opioid analgesics, for example where a long-acting product is used for sustained pain management and a short-acting product used for breakthrough pain. The variability in use patterns creates uncertainty with respect to measuring exposure time and defining time at risk for the outcome. Unlike many drugs for chronic conditions, opioid analgesic prescriptions are not used in uniform, regular, or predictable ways, and therefore, many assumptions made to generate exposure time may be inaccurate. For instance, PMR study 3051-4 calculated exposed days by using prescription dispensing date, days' supply, and tablets dispensed. However, the treatment instructions from the prescriber or the actual use patterns by the patient may not be well represented by the days' supply which is a variable input by the pharmacist based on a combination of factors. Similarly, while tablet strength is typically available, daily morphine equivalent dose (MED) can be challenging to define based on the prescription data, particularly when multiple opioid analgesics are prescribed concomitantly but taken in different ways. Any differential change in mean MED and/or dispensed tablet strengths by study opioid analgesic and period could bias overdose rate comparative analyses with respect to overdose risk. Data were not provided on MED or tablet strength dispensing rates among those dispensed OxyContin or comparators comparing the pre- versus post-periods; these data would be useful in assessing the potential for changes in the user cohorts, particularly the proportion of patients receiving the highest dosage strengths, which may be more likely to be diverted and abused.^{xxxii}

Carefully defining exposed periods and measuring exposure time is critical, as outcomes occurring outside of those periods would not be captured despite their being potentially associated with a recent opioid analgesic dispensing. The sponsor assumed no indefinite “stockpiling,” meaning leftover opioid analgesic tablets from the previous dispensing were ignored in exposure time calculations, excluding what could have been additional “at risk” exposure time. Because of the potential for lagged outcomes in this study, where events occur outside of the exposure time window but may still be related to prior opioid analgesic exposures (i.e., leftover drug), relevant outcomes may be systematically missed using a narrower exposure definition, under-ascertaining the “true” overdose rates associated with these drugs. The exposure time definition in this PMR study 3051-4 included an extension period of half of the days’ supply of the last prescription in which an outcome could still be captured. However, if “stockpiling” differed by opioid analgesic or across time periods, this could bias relative changes in overdose rates by differentially shortening exposed time, but more granular opioid-analgesic-specific data were not provided to explore these potential differences. When comparing OxyContin to primary comparators (in aggregate) combining the pre- and post-periods (see Appendix 8.4.1-8.4.3), mean exposure time per

^{xxxii} Rigg KK, Kurtz SP, Surratt HL (2012) Patterns of prescription medication diversion among drug dealers. *Drugs (Abingdon Engl)*; 19(2): 144–155

individual treatment episode was roughly equivalent suggesting relative parity in measured exposure time and comparative analyses not meaningfully impacted by disproportionate amounts of exposure time per episode. Also of concern but difficult to address, claims-based pharmacy dispensing data do not include prescriptions paid for with cash, and therefore, these prescriptions would not be included in exposure time calculations. In another commercial insurance population, approximately 8% of opioid analgesics were paid for with cash.^{xxxii}

In general, because of the potential for unattributed outcomes and missing cash payments, a less restrictive definition of when an episode ends (i.e., accounting for “stockpiling”) may be preferred over the narrower definition. At the same time, there are also trade-offs with using a less restrictive definition in accurately allocating exposure time when comparing drugs that are often substituted for one another (as is the case for PMR study 3051-4), and with respect to causal inference in that more distal prescription dispensing may be inaccurately associated with more recent outcomes. Regardless of the assumptions made on exposure time calculations, there are factors motivating prescribing decisions that are unobservable in these data but that can have meaningful impact on comparative results. One particular issue in this study stems from prescribers potentially discontinuing an opioid analgesic prescription over concerns about aberrant behaviors and risk of overdose. This would effectively censor exposure time in the higher risk patients and may mitigate overdose rates differentially by opioid analgesic product; this type of informative censoring can also bias relative comparisons between opioid analgesic and periods.

Without reliable ascertainment of intentionality, route-specific information, or any information on the opioid(s) involved, PMR study 3051-4 was unable to examine specific subsets of overdose cases likely most relevant to understanding the overall impact of the reformulation (i.e., unintentional overdose involving non-oral abuse of OxyContin). This study used a validated algorithm to ascertain any opioid overdose events in administrative claims and mortality data; however, these databases do not have information on either the route (i.e., oral, inhalation, injection) or specific opioid(s) involved in the overdose event, making evaluating the impact of the reformulation even more challenging. The greatest impact of the reformulation would be expected in overdoses involving product manipulation (i.e., crushing, dissolving) and non-oral routes, the specific routes it was designed to deter, but these data are not available in claims or mortality database linkages. Additionally, while it is unknown what opioid(s) specifically precipitated the overdose in this study, the overdose event is attributed to the last opioid analgesic(s) the patient was dispensed, and therefore, some inaccurate attribution of overdoses to specific opioid analgesic groups is likely (e.g., a patient overdoses on heroin when they are prescribed ER morphine). Because opioids obtained through other means, including those outside of traditional prescribing channels (e.g., bought illegally on the black market), heroin, or other non-opioid prescription or illicit drugs that may have contributed to the overdose are unknown, it is not clear whether there was differential use of these substances across time periods and across patients receiving different opioid analgesics that could have impacted comparative analyses. The specificity of the primary outcome was also limited because the

^{xxxii} Walker AM et al. (2017) Possible Opioid Shopping and its Correlates. The Clinical Journal of Pain; 33 (11): 976-982.

opioid overdose algorithm that differentiated intentionality did not perform reliably across other claims databases, most notably in the TennCare (Tennessee's Medicaid data). While the "any opioid overdose" outcome may indeed be the most appropriate outcome in this study given that opioid overdose is a rare outcome where intent is not always easily determined, unintentional opioid overdose analyses were originally planned as primary objectives. However, in light of the portability data from Green et al.^{xxxiii}, FDA views the unintentional opioid overdose analyses in PMR study 3051-4 to be exploratory.

5.3.3 Adjusting for potential confounders

5.3.3.1 Risk factors for overdose

Without sufficient adjustment for *all* important confounders it is difficult to say whether observed changes in overdose rates were due to the effect of the reformulation on overdose risk in patients receiving the drug or simply a shift in the risk profile of patients receiving the drug. Preliminary data suggested that there were indeed differences in the patients dispensed OxyContin comparing the pre- and post-periods, including potentially relevant comorbidities. It is unclear, however, whether confounding was adequately addressed in this study.

Risk factors like opioid use disorder (OUD) and prior overdose were considered for adjustment in the models, but doing so comes with challenges, particularly when using administrative claims data. The sponsor contends (in their December 2019 information request response) that OUD is actually better operationalized as a mediator in the causal pathway between opioid analgesic dispensing and overdose, where model adjustment would thus not be appropriate. While the proportion of patients with OUD diagnosis codes when the pre- and post-periods were combined was similar when comparing those dispensed OxyContin to the primary comparators (in aggregate), it is not clear whether there was actually differential prescribing of specific opioid analgesic to patients with OUD diagnosis codes in the pre- versus post-periods as those data were not provided. Any systematic differential opioid analgesic prescribing by OUD diagnosis and study period could bias results considerably. Including prevalent users further complicates adjusting for baseline OUD, as these may be measured after opioid analgesic initiation. Furthermore, because patients can be "incident users" multiple times in this study, an incident user only analysis still cannot fully address its potential role as a confounder. At the same time, the sensitivity and positive predictive value of OUD diagnosis codes in claims data are inadequate,^{xxxiv} which limits their utility in claims-based analyses, including their use as a covariate in statistical models. Therefore, while the data provided by the sponsor do not support their position that OUD is a mediator, it is reasonable to not adjust for an OUD variable based solely on the presence of diagnosis codes, as it is not a reliable indicator of true OUD. Including OUD defined by codes in the model would not adequately address

^{xxxiii} Green CA, et al. (2019) Identifying and classifying opioid-related overdoses: A validation study. *Pharmacoepidemiol Drug Saf*; 28: 1127–1137. <https://doi.org/10.1002/pds.4772>

^{xxxiv} Carrell DS, et al. (2020) Measuring problem prescription opioid use among patients receiving long-term opioid analgesic treatment: development and evaluation of an algorithm for use in EHR and claims data, *Journal of Drug Assessment*, 9:1, 97-105, DOI: 10.1080/21556660.2020.1750419

confounding by OUD and may consequently introduce additional unforeseen biases of relative comparisons.

As for prior opioid overdose, the prevalence was relatively balanced when comparing those dispensed OxyContin to the primary comparators (in aggregate across entire study period), but it was included in all adjusted models as a time-varying covariate to account for its strong association with the outcome of interest (see Table 5). Time-varying covariates can introduce time-varying confounding and bias associations, but from the sponsor's perspective it was important to account for the within-person correlation from patients' contributing multiple overdose events (~10% of patients across all three databases) over the study period. FDA concurs that including a time-varying prior overdose variable is appropriate given the definition/algorithm's validity in administrative claims data, but also given that it is highly predictive of future overdose and that the PMR 3051-4 study design includes multiple treatment episodes per patient where the outcome can occur.

The sponsor argued that other potentially important risk factors like major depressive disorder, alcohol use disorder, or other substance use disorders are also better operationalized as mediators in the causal pathway, but again, the sponsor did not submit any data to support this position. To be mediators these conditions would have to occur as a result of starting a specific opioid analgesic therapy, but many of the conditions are common and likely to be present before treatment initiation in many patients. In other words, these types of variables may be confounders, or effect modifiers, of the association between OxyContin reformulation and overdose.

Concomitant benzodiazepine use is a known risk factor for opioid overdose, but it was not adjusted for in any primary analyses as the sponsor again viewed this as a potential mediator. Overall, benzodiazepine use was relatively rare and comparable across study opioid analgesics in all three databases (see Table 4 and Appendix 8.4.1-8.4.3), with the prevalence of any benzodiazepine dispensing similar across study opioid analgesics when combining the pre- and post-periods, but slightly higher in Medicaid compared to the commercial claims databases. In both the HIRD and Medicaid databases (see Appendix 8.4.2 and 8.4.3), the majority of patients dispensed opioid analgesics were not dispensed benzodiazepines; rates of benzodiazepine dispensing across study opioid analgesics were largely the same comparing the pre- and post-periods in Medicaid, while rates across nearly all study opioid analgesics decreased from the pre- to post-periods in HIRD. These data suggest that any benzodiazepine dispensing changes from the pre- to post-periods were likely nondifferential by opioid analgesic. To better understand the potential impact of benzodiazepine use on study results, FDA recommended that the sponsor explore the effect of benzodiazepine dispensing as a confounder, and separately as an effect modifier. In their subsequent re-analysis of the data, the sponsor found that additionally adjusting for baseline benzodiazepine use (as a covariate in the model) did not meaningfully impact results in HIRD and Medicaid, and that benzodiazepine use was not a statistically significant effect modifier (interaction $p>0.05$) (see Appendix 8.7). Given these results, and the relative balance in benzodiazepine dispensing rates across opioid analgesic exposure groups overall, and across time periods, relative comparisons between opioid analgesics are likely not substantially biased by any changes in concomitant benzodiazepine use. Nonetheless, because benzodiazepines and opioid analgesics are often obtained through means other than one's own (insurance reimbursed) prescription, it is

unknown whether there was actual differential use of other substances across time periods or comparators.

5.3.3.2 Adequacy of adjusted models in controlling for confounding

To account for differences in the patient populations before and after the reformulation and mitigate the impact of confounding, some Poisson models were adjusted by demographic and clinical characteristics, while others were weighted by the propensity score (PS),^{xxxv} but the results were not substantively different from unadjusted results. Adjusting for pre-versus post-period changes in the composition of the patient populations can help minimize bias with respect to relative comparisons within and between opioid analgesics if the propensity for exposure, or risk of outcome shifts based on the patient characteristics. However, the results of adjusted analyses in PMR study 3051-4 were similar and only minimally attenuated, if at all, compared to the crude, unadjusted results. This may be due, in part, to limited and incomplete adjustment for some important potential confounders, as discussed above. Adequately adjusting for confounders in these types of claims-based analyses is often challenged by incomplete data (e.g., smoking status, current alcohol and illicit substance use, socioeconomic status), and a lack of validated diagnosis codes known to accurately reflect important medical conditions (e.g., OUD). Including time-varying covariates in the model (e.g., prior overdose) can help with time-varying confounding, but it can also introduce additional time-varying confounding if other important time-varying exposures are not adequately controlled for. This may not be the case in PMR study 3051-4, but only one variable was ultimately incorporated as a time-varying exposure. Nonetheless, adjusted analyses that control for patient characteristics, including demographic information and certain conditions that are more reliably captured using claims-based diagnosis codes, are still preferable to unadjusted analyses, however limited. Unadjusted analyses can be fraught as they inherently assume complete exchangeability in patient populations over the study period across opioid analgesics.

Still, even after adjusting for measurable potential confounders in PMR study 3051-4, it is likely that channeling bias (a type of selection bias), is still relevant. Because the reformulation was specifically designed to deter tablet manipulation for the purposes of abuse, it is possible that prescribers differentially prescribed (“channeled”) reformulated OxyContin to patients they perceived to have a higher risk of misusing the drug. This channeling of patients to one opioid analgesic over another would introduce imbalances in the overdose risk profile of patients comparing the two periods, potentially attenuating any true benefit of the reformulation. This type of bias is prevalent in pharmacoepidemiology studies in general, and it can be particularly challenging to address using administrative claims data alone. In some respects, the sponsor had already been marketing original OxyContin as the “safer” alternative to other opioid analgesics with respect to abuse due to its ER properties for many years prior to its reformulation.^{xxxvi} Therefore, the true extent

^{xxxv} Unintentional overdose algorithm only (exploratory outcome)

^{xxxvi} New York Times, published May 10th, 2007, “In guilty plea, OxyContin maker to pay \$600 million”: <https://www.nytimes.com/2007/05/10/business/11drug-web.html?auth=login-email&login=email>; The United States Attorney’s Office, Western District of Virginia, John L. Brownlee, News release May 10th, 2007: https://media.defense.gov/2007/May/10/2001711223/-1/-1/purdue_fredrick_1.pdf

of this type of differential channeling by study period is unclear, and it is possible its effect when comparing study periods is ultimately negligible.

An alternative scenario must also be considered, however, wherein patients seeking to abuse OxyContin “self-selected” *not* to receive the abuse-deterrent product, requesting and receiving different opioid analgesics without abuse-deterrent properties, or transitioning to non-prescribed opioids (e.g., heroin), thus creating a *lower* risk cohort of OxyContin users following reformulation. In this scenario, results would show a more favorable impact of the reformulation on overdose risk. The overall decline in dispensing, and particularly of the 80 milligram tablets (See Appendix 8, and background document: OSE Drug Utilization Review), may in part reflect such a migration away from OxyContin by people wishing to divert and/or abuse it. Although it is unclear to what extent that ultimately explains the decreased dispensing, it does at least suggest some significant changes in prescribing patterns for OxyContin. Changes in prescribing patterns may also be due to multiple factors, including changes in insurance coverage or formularies (i.e., reimbursement) that would not necessarily bias relative comparisons, but this information was not available in PMR study 3051-4.



5.4 OVERALL INTERPRETATION OF PMR STUDY 3051-4 FINDINGS

When interpreting PMR study 3051-4 results, one overarching concern is the potential for inappropriately attributing observed changes in overdose rates to the reformulation when the changes were, in fact, caused by other factors. The use of comparators, adjustment for confounders, and various sensitivity analyses to assess bias can help to determine whether causal inference is warranted and to better understand the uncertainty surrounding any observed overdose rate changes; however, with respect to PMR study 3051-4, any assertions of a direct effect of the reformulation must be appropriately qualified. A *quantitative* interpretation of a direct effect on overdose rates is not appropriate given the study design and described data limitations, but *qualitatively* attributing some unknown, but “non-zero,” effect of the reformulation could be, if supported by the totality of findings. Importantly, this study was not designed to evaluate overdose rates in those who may obtain OxyContin through cash payments or channels other than their own prescription, nor was it able to specifically evaluate overdose involving product manipulation or non-oral routes.

Effect of OxyContin’s reformulation on overdose rates among those dispensed any OxyContin (i.e., with or without other opioid analgesics concomitantly):

The results of PMR 3051-4 do not demonstrate that the reformulation reduced the risk of opioid overdose in patients dispensed OxyContin, overall (i.e., including exposure with or without other opioid analgesics). Our interpretation is based on results using the “any opioid overdose” (fatal and non-fatal; intentional and unintentional) outcome algorithm, although these results were similar, overall, to those using the unintentional overdose outcome algorithm, which showed inferior performance in validation studies.

A conclusion that OxyContin’s reformulation actually reduced opioid overdose risk in these patients would be supported by robust and statistically significant reductions in overdose rates that were temporally associated with the intervention, largely consistent across databases, and unlikely to be explained by either systematic (i.e., bias and

confounding) or random (i.e., chance) error. In HIRD, the overdose rates among OxyContin recipients appeared to decrease modestly immediately after the reformulation (transition period) but the decline was not sustained, and there was no discernable decline in overdose rates among those dispensed OxyContin in either the Medicaid or MarketScan databases. Observed pre-post changes in the overdose rates among those dispensed OxyContin were of relatively small magnitude, and small changes are more likely to be completely explained by residual confounding, particularly when we are not confident that confounding was adequately controlled for, given the limited adjustment for some potentially important covariates and limited ability to measure others. Furthermore, most changes across time periods were not statistically significant, indicating that random chance cannot be ruled out as an explanation either.

To account for potential confounding by calendar time (i.e., secular trends), changes in opioid overdose rates among those dispensed OxyContin should *also* differ meaningfully from any changes observed in those dispensed comparator opioid analgesics. In the commercial claims populations, changes in opioid overdose rates among patients dispensed OxyContin compared to the changes among patients dispensed primary comparators modestly favored OxyContin, but they were not significantly different from each other. In fact, the results of Medicaid analyses among patients dispensed any OxyContin or OxyContin with IR opioid analgesics concomitantly were actually *unfavorable* to OxyContin with respect to changes in overdose rates after the reformulation, in that reductions in overdose rates among those dispensed ER morphine and methadone were observed but there was no change among those dispensed OxyContin.

Concomitant dispensing and switching from one opioid analgesic to another creates challenges in disentangling the marginal effect of one opioid analgesic on overdose risk in the context of multiple concurrent opioid analgesic exposures, but the use of multiple opioid analgesics concurrently was more the rule than the exception in these populations. Although it complicates causal inference, studying the effect of the reformulation in settings in which the drug is most commonly used (i.e., with other opioid analgesics) is still important. One possible explanation for the lack of an observed effect in this cohort is that the reformulation actually had little or no effect on overall opioid overdose, in part because opioid analgesic use and abuse patterns are complex and dynamic, in some cases including both prescription and illicit opioids. Opioid analgesic concomitancy patterns in patients dispensed OxyContin also changed over the study period, with increased concomitant prescribing overall and changes in the types of opioid analgesics used with OxyContin (see Appendix 8.1). It is therefore perhaps not unexpected that changing a single product's formulation did not appear to result in an overall reduction in opioid overdose.

Although PMR study 3051-4 does not convincingly show that the reformulation reduced overdose risk in insured patients receiving OxyContin, the findings also do not prove that the reformulated had no effect on overdose risk or preclude this possibility. While certainly important to study, this study cohort may not reflect the population most likely to abuse or experience an overdose involving OxyContin. The effects of the reformulation might be more easily detected in higher risk groups where its impact may be greatest, including those obtaining OxyContin from sources other than their own prescription or using cash to purchase prescription opioids, and those abusing opioids by non-oral routes. However, these groups are generally not distinguishable in data sources capable of linking a specific

drug exposure to overdose outcomes, while controlling for other confounding factors. It is possible that studying lower risk patient populations, coupled with the lack of information on route of administration and the opioid(s) involved in the overdose, limited the ability to detect some true effect of the reformulation on overdose risk in individuals exposed to the product.^{xxxvii}

Effect of OxyContin's reformulation on overdose rates among those dispensed OxyContin alone (i.e., without other opioid analgesics concomitantly):

When restricting analyses to patients dispensed OxyContin or comparators alone, results were somewhat more favorable with respect to the impact of the reformulation on opioid overdose risk, although this was true only in the commercial claims populations (not Medicaid), and the implications and generalizability of this finding are not entirely clear. Analyses that only include patients using one opioid analgesic product at a time are simpler from a causal inference perspective, as noted above, but OxyContin use without the concomitant dispensing of any other opioid analgesics—primarily IR opioid analgesics—is much less common than dispensing of OxyContin with at least intermittent use of other opioid analgesics (see Appendix 8.1) and represents a relatively small subset of OxyContin use in real-world settings.

While the results were more favorable with respect to the impact of the reformulation, they were not entirely consistent across databases, or across comparators, and there was greater uncertainty in the estimates due to the reduced exposure time. When restricted to person-time dispensed OxyContin alone, observed reductions in opioid overdose rates were modest and only statistically significant in one commercial claims database (HIRD). Overall, changes in opioid overdose rates when restricted to person-time dispensed OxyContin alone differed favorably from changes in comparators, to varying degrees. None of the differences were statistically significantly in Medicaid, however, and statistical significance varied across comparators in the two commercial claims databases where the differences were larger. When the results of the commercial claims databases were combined using meta-analytic methods, the associations were generally consistent with the results of analyses conducted separately in each database, but the comparative results were all statistically significant using meta-analysis. At the same time, these results must be interpreted with caution as only two databases (effectively two separate “studies”) were combined, and between-study heterogeneity could not be properly evaluated ([See background document: OB Statistical Review Memo](#)).

Given the potential for residual confounding in these analyses, it is also important to consider alternative explanations for these findings. It is possible that OxyContin's reformulation reduced the risk of overdose in patients who received this product without any other opioid analgesics, at least among patients with commercial insurance. It is also possible, however, that patients receiving reformulated OxyContin were inherently at lower risk of overdose than those who received original OxyContin. This “non-exchangeability” of the cohorts would remain if there were important unmeasured differences between these groups. Such differences could be due to increased prescriber

^{xxxvii} PMR study 3051-1 and study 3051-3 targeted higher risk groups like those being specifically assessed for opioid treatment, but overdose outcomes were not assessed in those studies

awareness of risk of OxyContin abuse in general (e.g., due to the 2010 OxyContin REMS provider communications), or changes in patient selection related specifically to OxyContin’s abuse-deterrent properties.

Differences could also be related to patient “self-selection,” for example, if individuals seeking to abuse OxyContin non-orally stopped abusing OxyContin, perhaps instead seeking out other opioids, either prescription or illicit, when OxyContin was reformulated. If this was the case, then post-period OxyContin user cohort might have had a lower risk of overdose. Although this latter explanation would be consistent with reformulated OxyContin having an abuse-deterrent effect, it does not necessarily show that the abuse-deterrent properties conferred a reduced risk of overdose among those exposed to the product, or that those who stopped using OxyContin because of its reformulation (and were therefore not included in the reformulated OxyContin exposure group) were less likely to experience an overdose. In addition, the distribution of dispensed OxyContin tablet strengths skewed lower in the post-period ([See Appendix 8.1, and background document: OSE Drug Utilization Review](#)), which could have contributed to the observed declines in overdose rates when restricted to person-time dispensed OxyContin alone relative to comparators, independent of any risks associated with non-oral abuse specifically or the direct ability of the abuse-deterrent properties to reduce these risks. Again, the changes in OxyContin dosage strengths dispensed could reflect some abuse-deterrent effect of the reformulation, with individuals who seek high-strength tablets to manipulate for the purposes of abuse migrating away from OxyContin after its reformulation, but it is unclear whether subsequent decreases in overdose rates in a cohort receiving lower doses of OxyContin can reasonably be interpreted as the “abuse-deterrent” properties reducing the risk of overdose.

6 CONCLUSION

The results of PMR 3051-4 do not demonstrate that the reformulation reduced the risk of opioid overdose in patients dispensed OxyContin, overall. When restricted to person-time dispensed OxyContin or comparators *alone* (i.e., without other opioid analgesics), results were somewhat more favorable with respect to the reformulation reducing opioid overdose risk, although this was true only in the commercial claims populations and not the Medicaid cohort. The implications and generalizability of this specific finding are not entirely clear, however, in part because OxyContin use without concomitant dispensing of any other opioid analgesics was relatively uncommon. The interpretation of this finding is further complicated by the potential for unmeasured differences between the prescribed patient populations in the pre- and post-reformulation periods. It is possible that OxyContin’s abuse-deterrent properties did confer a reduced risk of overdose among patients using the product without any other opioid analgesics. However, it is also plausible that patients receiving OxyContin alone in the post-reformulation period were inherently at a lower risk of overdose than those who received OxyContin alone during the pre-period, either through changes in OxyContin prescribing practices, or through “self-selection” away from reformulated OxyContin among patients seeking to abuse it via non-oral routes. While the latter explanation may be consistent with reformulated OxyContin having an abuse-deterrent effect, it does not necessarily follow that the abuse-deterrent properties conferred

a reduced risk of overdose among those exposed to the product or that those who migrated away from OxyContin because of its reformulation actually had a lower risk of overdose.

7 REFERENCES

1. Coplan PM, Chilcoat HD, Butler SF, et al. (2016) The Effect of an Abuse-Deterrent Opioid Formulation (OxyContin) on Opioid Abuse- Related Outcomes in the Postmarketing Setting. *Clinical Pharmacology & Therapeutics*; 100 (3): 275-286.
2. Laroche MR, Zhang F, Ross-Degnan D, et al. (2015) Rates of Opioid Dispensing and Overdose After Introduction of Abuse-Deterrent Extended-Release Oxycodone and Withdrawal of Propoxyphene. *JAMA Intern Med*; 175 (6): 978-987.

8 APPENDICES

8.1 SPONSOR RESPONSE'S TO FDA INFORMATION REQUESTS FROM 2016

Sponsor response from March 3rd, 2017:

“Responses to FDA Information Request email dated November 23, 2016 on the protocol for OxyContin® NDA 022272 PMR 3051-4 (Fatal and Non-Fatal Overdose – A Healthcare Database Analysis with Linkage to the National Death Index): Question #3 Responses on Switching Patterns Around the Time of OxyContin’s Reformulation”

Figure 1: MarketScan data - Switching to reformulated OxyContin or other opioids among patients with a dispensing for OxyContin that covered the date reformulated OxyContin was introduced to the market (*opioid dispensing within 3 months after 8/10/2010) (MarketScan, N=22,153)

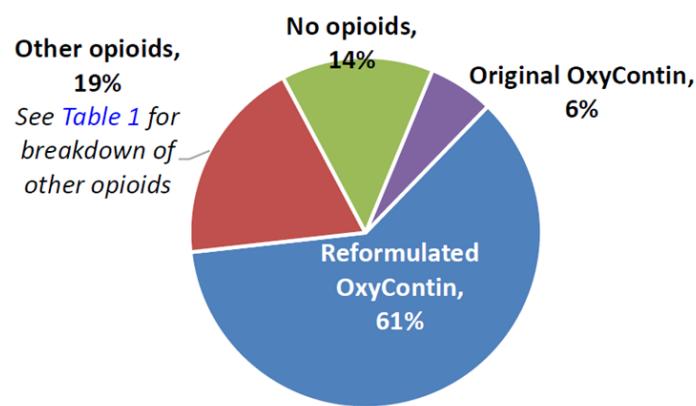


Figure 2: Medicaid data - Switching to reformulated OxyContin or other opioids among patients with a dispensing for OxyContin that covered the date reformulated OxyContin was introduced to the market (*opioid dispensing within 3 months after 8/10/2010) (Medicaid, N=3,020)

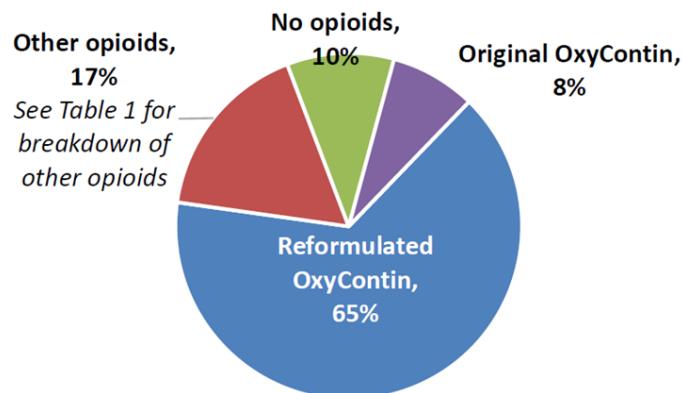


Table 1: Type of opioid switched to among patients dispensed other (Non-OxyContin) opioids

| | Commercial N=4,276 | Medicaid N=515 |
|---------------|-----------------------|-------------------|
| | N (%) | N (%) |
| Generic ER/LA | 1,448 (34%) | 163 (32%) |
| Generic IR | 3,467 (81%) | 442 (86%) |
| Brand ER/LA | 480 (11%) | 55 (11%) |
| Brand IR | 360 (8%) | 50 (10%) |

Note: total exceeds 100% because patients could have more than one opioid type

Table 2: Most common opioids switched to by tablet strength

| Commercial N=4,276 | | | Medicaid N=515 | | |
|--------------------------------------|-------|-----|--|-------|-----|
| | N (%) | | | N (%) | |
| Opioid and Tablet Strength | N | % | Opioid and Tablet Strength | N | % |
| IR oxycodone 30mg | 731 | 17% | IR Oxycodone Hydrochloride 30 MG | 65 | 13% |
| IR hydrocodone APAP 325mg-10mg | 516 | 12% | IR Acetaminophen/oxycodone Hydrochloride 325 MG-10 MG | 56 | 11% |
| ER oxycodone 80mg | 457 | 11% | IR Tramadol Hydrochloride 50 MG | 54 | 10% |
| IR oxycodone APAP 325mg-10mg | 395 | 9% | IR Acetaminophen/oxycodone Hydrochloride 325 MG-5 MG | 53 | 10% |
| IR oxycodone 15mg | 345 | 8% | IR Acetaminophen/hydrocodone Bitartrate 325 MG-10 MG | 45 | 9% |
| IR hydrocodone APAP 500mg-5mg | 261 | 6% | IR Oxycodone Hydrochloride 5 MG | 43 | 8% |
| IR oxycodone 5mg | 246 | 6% | ER Oxycodone Hydrochloride 80 MG | 42 | 8% |
| IR oxycodone APAP 325mg-5mg | 243 | 6% | IR Acetaminophen/hydrocodone Bitartrate 500 MG-5 MG | 42 | 8% |
| IR tramadol 50mg | 223 | 5% | IR Oxycodone Hydrochloride 15 MG | 36 | 7% |
| IR hydrocodone APAP 750mg-7.5mg | 222 | 5% | ER Methadone Hydrochloride 10 MG | 29 | 6% |
| IR hydrocodone APAP 500mg-10mg | 194 | 5% | IR Acetaminophen/oxycodone Hydrochloride 325 MG-10 MG | 25 | 5% |
| ER oxymorphone 40mg (brand) | 182 | 4% | ER Morphine Sulfate 60 MG | 25 | 5% |
| Methadone 10mg | 176 | 4% | ER Oxycodone Hydrochloride 40 MG | 21 | 4% |
| IR oxycodone APAP 325mg-10mg (brand) | 148 | 3% | IR Acetaminophen/hydrocodone Bitartrate 325 MG-5 MG | 20 | 4% |
| Buprenorphine/naloxone 8mg-2mg | 146 | 3% | IR Acetaminophen/hydrocodone Bitartrate 325 MG-7.5 MG | 19 | 4% |
| ER oxycodone 20mg | 138 | 3% | IR Hydromorphone Hydrochloride 4 MG | 19 | 4% |
| ER oxycodone 40mg | 122 | 3% | IR Acetaminophen/hydrocodone Bitartrate 500 MG-10 MG | 18 | 3% |
| ER morphine 30mg | 106 | 2% | ER Morphine Sulfate 30 MG | 18 | 3% |
| Fentanyl patch 100mcg/h | 100 | 2% | IR Acetaminophen/oxycodone Hydrochloride 325 MG-7.5 MG | 16 | 3% |
| IR hydrocodone APAP 750mg-7.5mg | 99 | 2% | IR Acetaminophen/hydrocodone Bitartrate 500 MG-7.5 MG | 16 | 3% |
| Fentanyl patch 50mcg/h | 93 | 2% | IR Fentanyl Citrate 0.05 MG/1 ML | 13 | 3% |
| IR hydromorphone 4mg | 89 | 2% | ER Oxymorphone Hydrochloride 40 MG | 13 | 3% |
| ER morphine 60mg | 85 | 2% | ER Morphine Sulfate 15 MG | 13 | 3% |
| ER oxymorphone 20mg (brand) | 64 | 1% | ER Morphine Sulfate 100 MG | 11 | 2% |
| Fentanyl patch 25mcg/h | 62 | 1% | IR Acetaminophen/oxycodone Hydrochloride 650 MG-10 MG | 10 | 2% |

Note: total exceeds 100% because patients could have more than one opioid/dose

IR=immediate release; ER=extended release; APAP=acetaminophen; MG=milligrams

Table 3: Patterns of opioid use three and six months after an index generic ER oxycodone prescription between October 1, 2010 and March 31, 2011

| | Commercial N=5,963 | | Medicaid N=452 | |
|--------------------------|-----------------------|-------------|-------------------|-----------|
| | 3 months | 6 months | 3 months | 6 months |
| OxyContin ⁽¹⁾ | 2,533 (42%) | 2,792 (47%) | 257 (57%) | 286 (63%) |
| Other Opioids | 1,238 (21%) | 1,442 (24%) | 92 (20%) | 109 (24%) |
| No Opioids | 1,391 (23%) | 1,552 (26%) | 43 (10%) | 53 (12%) |
| Generic ER oxycodone | 801 (13%) | 177 (3%) | 60 (13%) | 4 (1%) |

⁽¹⁾ represents all OxyContin, original or reformulated, but given the timing the large majority would have been reformulated OxyContin

Sponsor response from March 3rd, 2017:

“Responses to FDA Information Request email dated November 23, 2016 on the protocol for OxyContin® NDA 022272 PMR 3051-4 (Fatal and Non-Fatal Overdose – A Healthcare Database Analysis with Linkage to the National Death Index): Question #1 Responses on Descriptive Information on Proposed Analytic Cohort”

Table 4: Opioid analgesics analyzed

| Opioid Group | Opioids Included |
|---|--|
| Comparator opioid analgesics | <ul style="list-style-type: none"> • Extended-release (ER) morphine • ER hydromorphone • ER oxymorphone • Immediate-release (IR) single-entity (SE) oxycodone • IR morphine^a • IR hydrocodone acetaminophen • IR hydromorphone • Methadone |
| Other non-comparator opioid analgesics | <ul style="list-style-type: none"> • IR oxycodone acetaminophen • IR oxymorphone • Fentanyl (all formulations) • IR tapentadol • Codeine • Meperidine • Propoxyphene • ER hydrocodone • ER tapentadol • Levorphanol • Buprenorphine^b |

^a IR morphine included as a comparator opioid analgesic in MarketScan commercial analysis but not in Medicaid analysis

^b Excludes Suboxone, Subutex and associated generics.

Table 5: Demographics of patients dispensed OxyContin (MarketScan data)

| | 2H2008-1H2009 | 2H2009-1H2010 | 2H2010 | 2011 | 2012 | 2013 | 2014 | 1Q2015-3Q2015 |
|--|----------------|---------------|--------------|--------------|--------------|--------------|--------------|---------------|
| Number of patients ^a | 70,808 | 71,796 | 44,436 | 67,708 | 64,753 | 51,584 | 51,929 | 29,028 |
| Age, Years Mean (SD) | 48.2 (10.9) | 48.4 (11.1) | 49 (10.6) | 48.8 (11.2) | 48.8 (11.3) | 49 (11.3) | 49.3 (11.2) | 49.8 (10.9) |
| Age, Years Median (Range) | 50 (16-64) | 50 (16-64) | 51 (16-64) | 51 (16-64) | 51 (16-64) | 52 (16-64) | 52 (16-64) | 53 (16-64) |
| Age Categorized, n (%) | | | | | | | | |
| 16-24 | 2,616 (4%) | 2,759 (4%) | 1,362 (3%) | 2,878 (4%) | 2,856 (4%) | 2,298 (4%) | 2,153 (4%) | 1,008 (3%) |
| 25-34 | 6,585 (9%) | 6,563 (9%) | 3,701 (8%) | 5,817 (9%) | 5,677 (9%) | 4,285 (8%) | 4,211 (8%) | 2,194 (8%) |
| 35-44 | 13,112 (18.5%) | 13,032 (18%) | 7,744 (17%) | 11,398 (17%) | 10,902 (17%) | 8,589 (17%) | 8,553 (16%) | 4,713 (16%) |
| 45-54 | 24,988 (35%) | 24,574 (34%) | 15,590 (35%) | 22,652 (33%) | 20,910 (32%) | 16,318 (32%) | 16,100 (31%) | 8,906 (31%) |
| 55-64 | 23,507 (33%) | 24,868 (35%) | 16,039 (36%) | 24,963 (37%) | 24,408 (38%) | 20,094 (39%) | 20,912 (43%) | 12,207 (42%) |
| Gender, n (%) | | | | | | | | |
| Male | 34,885 (49%) | 35,466 (49%) | 21,960 (49%) | 33,304 (49%) | 32,410 (50%) | 25,607 (50%) | 25,805 (50%) | 14,218 (49%) |
| Female | 35,923 (51%) | 36,330 (51%) | 22,476 (51%) | 34,404 (51%) | 32,343 (50%) | 25,977 (50%) | 26,124 (50%) | 14,810 (51%) |
| Geographic region, n (%) | | | | | | | | |
| Northeast | 10,130 (14%) | 10,935 (15%) | 7,125 (16%) | 12,001 (18%) | 12,763 (20%) | 9,899 (19%) | 12,036 (23%) | 6,125 (21%) |
| North Central | 19,612 (28%) | 19,268 (27%) | 11,506 (26%) | 17,110 (25%) | 15,640 (24%) | 11,632 (23%) | 10,282 (20%) | 5,458 (19%) |
| South | 24,804 (35%) | 25,325 (35%) | 15,544 (35%) | 22,008 (33%) | 20,700 (32%) | 15,730 (30%) | 18,267 (35%) | 12,152 (42%) |
| West | 14,379 (20%) | 14,919 (21%) | 10,078 (23%) | 14,797 (22%) | 14,307 (22%) | 12,731 (25%) | 9,669 (19%) | 5,232 (18%) |
| Unknown | 1,883 (3%) | 1,349 (2%) | 183 (<1%) | 1,792 (3%) | 1,343 (2%) | 1,592 (3%) | 1,675 (3%) | 61 (<1%) |

^aTotal number of patients based on patients with an OxyContin dispensing in each calendar year with no carry-over of prescriptions spanning multiple years (ie, prescriptions truncated at the end of the time period)

Table 6: Prevalence of relevant diagnoses among patients dispensed OxyContin (MarketScan data)

| | 2H2008-1H2009 (n=70,808) | 2H2009-1H2010 (n=71,796) | 2H2010 (n=44,436) | 2011 (n=67,708) | 2012 (n=64,753) | 2013 (n=51,584) | 2014 (n=51,929) | 1Q2015-3Q2015 (n=29,028) |
|-------------------------------------|-----------------------------|-----------------------------|----------------------|--------------------|--------------------|--------------------|--------------------|-----------------------------|
| Diagnosis, n (%) | | | | | | | | |
| Abdominal pain | 5,134 (7%) | 5,181 (7%) | 3,152 (7%) | 5,067 (7%) | 4,902 (8%) | 3,883 (8%) | 4,178 (8%) | 2,383 (8%) |
| Amputation | 593 (<1%) | 622 (<1%) | 393 (<1%) | 704 (1%) | 728 (1%) | 588 (1%) | 738 (1%) | 506 (2%) |
| Arthritis ^a | 25,802 (36%) | 28,177 (39%) | 16,939 (38%) | 30,607 (45%) | 30,588 (47%) | 24,654 (48%) | 25,987 (50%) | 14,398 (50%) |
| Back pain | 32,726 (46%) | 33,854 (47%) | 22,016 (50%) | 30,736 (45%) | 30,147 (47%) | 24,086 (47%) | 25,099 (48%) | 15,671 (54%) |
| Chronic pain | 5,135 (7%) | 6,544 (9%) | 4,963 (11%) | 7,330 (11%) | 8,273 (13%) | 6,990 (14%) | 8,747 (17%) | 6,258 (22%) |
| Fibromyalgia | 4,773 (7%) | 5,397 (8%) | 3,581 (8%) | 5,001 (7%) | 5,016 (8%) | 4,044 (8%) | 4,626 (9%) | 3,022 (10%) |
| Headache | 5,222 (7%) | 5,556 (8%) | 3,450 (8%) | 5,228 (8%) | 5,262 (8%) | 4,071 (8%) | 4,500 (9%) | 2,675 (9%) |
| Malignancy | 8,210 (12%) | 8,159 (11%) | 4,903 (11%) | 8,455 (12%) | 8,245 (13%) | 6,539 (13%) | 6,808 (13%) | 3,911 (13%) |
| Multiple sclerosis | 482 (<1%) | 521 (<1%) | 346 (<1%) | 484 (<1%) | 480 (<1%) | 353 (<1%) | 359 (<1%) | 219 (<1%) |
| Neuropathic pain | 7,869 (11%) | 8,438 (12%) | 5,471 (12%) | 8,264 (12%) | 8,255 (13%) | 6,563 (13%) | 7,442 (14%) | 4,798 (17%) |
| Major depression | 7,205 (10%) | 7,767 (11%) | 4,879 (11%) | 7,705 (11%) | 8,158 (13%) | 6,162 (12%) | 6,933 (13%) | 4,163 (14%) |
| Generalized anxiety | 3,706 (5%) | 4,360 (6%) | 2,897 (7%) | 4,836 (7%) | 5,622 (9%) | 4,718 (9%) | 6,226 (12%) | 4,049 (14%) |
| Bipolar disorder | 900 (1%) | 928 (1%) | 606 (1%) | 860 (1%) | 849 (1%) | 664 (1%) | 721 (1%) | 428 (1%) |
| Substance use disorder ^b | 857 (1%) | 1,107 (2%) | 720 (2%) | 967 (1%) | 985 (2%) | 851 (2%) | 972 (2%) | 761 (3%) |

^aArthritis, arthropathies, osteoarthritis and musculoskeletal pain

^bSubstance use disorder excludes opioid dependence/addiction

Table 7: Opioid utilization patterns among patients dispensed OxyContin (MarketScan data)

| | 2H2008-1H2009 (n=70,808) | 2H2009-1H2010 (n=71,796) | 2H2010 (n=44,436) | 2011 (n=67,708) | 2012 (n=64,753) | 2013 (n=51,584) | 2014 (n=51,929) | 1Q2015-3Q2015 (n=29,028) |
|---------------------------------|-----------------------------|-----------------------------|----------------------|--------------------|--------------------|--------------------|--------------------|-----------------------------|
| # prescriptions dispensed, mean | 4.71 | 4.66 | 3.40 | 4.40 | 4.35 | 4.37 | 4.31 | 4.02 |
| # days dispensed, mean | 133.91 | 131.35 | 95.47 | 121.55 | 118.81 | 119.2 | 116.92 | 109.8 |
| # tablets dispensed, mean | 389.23 | 373.39 | 267.13 | 332.84 | 328.23 | 407.19 | 325.05 | 328.26 |
| Total # prescription dispensed | 333,446 | 334,373 | 151,163 | 298,053 | 281,361 | 225,244 | 223,893 | 116,808 |
| 10 mg | 59,896 | 58,905 | 25,929 | 60,056 | 59,533 | 49,164 | 52,142 | 26,671 |
| 15 mg | 3,702 | 5,533 | 3,282 | 7,206 | 8,635 | 8,486 | 11,655 | 6,934 |
| 20 mg | 95,597 | 86,297 | 39,488 | 82,336 | 76,002 | 58,705 | 58,338 | 30,315 |
| 30 mg | 15,770 | 22,167 | 12,610 | 25,407 | 27,099 | 24,668 | 27,455 | 16,761 |
| 40 mg | 81,825 | 80,029 | 33,703 | 60,352 | 54,065 | 40,429 | 36,054 | 17,540 |
| 60 mg | 15,270 | 21,992 | 11,670 | 20,890 | 21,218 | 17,914 | 17,771 | 9,587 |
| 80 mg | 61,377 | 59,450 | 24,481 | 41,806 | 34,809 | 25,878 | 20,478 | 9,000 |
| 160 mg | 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total # tablets dispensed | 27,560,455 | 26,808,087 | 11,870,202 | 22,536,212 | 21,254,167 | 21,004,270 | 16,879,726 | 9,528,628 |
| 10 mg | 3,984,643 | 3,652,835 | 1,575,582 | 3,432,195 | 3,471,279 | 3,548,520 | 3,178,597 | 1,766,567 |
| 15 mg | 242,918 | 365,434 | 213,852 | 474,041 | 590,843 | 742,707 | 832,420 | 600,340 |
| 20 mg | 7,349,620 | 6,420,793 | 2,866,969 | 5,768,009 | 5,432,677 | 5,385,618 | 4,263,155 | 2,471,278 |
| 30 mg | 1,118,953 | 1,581,340 | 906,956 | 1,801,877 | 2,016,251 | 2,373,664 | 2,204,643 | 1,453,792 |
| 40 mg | 7,254,714 | 6,934,140 | 2,885,581 | 5,107,369 | 4,515,733 | 4,170,675 | 2,949,052 | 1,499,629 |
| 60 mg | 1,200,231 | 1,753,143 | 918,396 | 1,667,344 | 1,709,289 | 1,824,256 | 1,460,956 | 830,276 |
| 80 mg | 6,408,616 | 6,100,402 | 2,502,866 | 4,285,377 | 3,518,095 | 2,958,830 | 1,990,903 | 906,746 |
| 160 mg | 760 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Table 8: Number of patients dispensed OxyContin, by opioid concomitancy (MarketScan data)

| | 2H2008-1H2009 | 2H2009-1H2010 | 2H2010 | 2011 | 2012 | 2013 | 2014 | 1Q2015-3Q2015 |
|---|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Number (%) | | | | | | | | |
| OxyContin alone for the duration of OxyContin dispensed prescriptions in that year ^a | 9,990 (14%) | 10,675 (14%) | 7,346 (15%) | 7,938 (11%) | 7,142 (10%) | 5,645 (10%) | 5,294 (10%) | 3,389 (11%) |
| OxyContin dispensed concurrently with comparator opioids in that year ^b | 46,123 (65%) | 49,131 (65%) | 30,695 (64%) | 49,365 (69%) | 48,597 (70%) | 38,559 (70%) | 38,714 (70%) | 21,309 (68%) |
| A mixture of OxyContin alone and OxyContin concurrent with comparator opioids ^c | 39,253 (85%) | 41,481 (84%) | 24,115 (79%) | 41,678 (84%) | 40,886 (84%) | 32,337 (84%) | 32,545 (84%) | 17,290 (81%) |
| OxyContin dispensed concurrently with comparator opioids only | 6,870 (15%) | 7,650 (16%) | 6,580 (21%) | 7,687 (16%) | 7,711 (16%) | 6,222 (16%) | 6,169 (16%) | 4,019 (19%) |
| OxyContin dispensed concurrently with non-comparator opioids in that year | 14,695 (21%) | 15,591 (21%) | 9,676 (21%) | 14,758 (21%) | 13,426 (19%) | 11,031 (20%) | 11,084 (20%) | 6,698 (21%) |
| Total ^d | 70,808 | 75,397 | 47,717 | 72,061 | 69,165 | 55,235 | 55,092 | 31,396 |
| Mean Person time (Days) | | | | | | | | |
| OxyContin alone for the duration of OxyContin use in that year ^a | 127.0 | 117.4 | 86.2 | 110.2 | 101.5 | 102.9 | 99.5 | 93.0 |
| OxyContin dispensed concurrently with comparator opioids in that year ^b | 133.9 | 133.1 | 94.1 | 124.0 | 121.7 | 122.9 | 121.6 | 112.5 |
| A mixture of OxyContin alone and OxyContin concurrent with comparator opioids ^c | 141.8 | 140.3 | 98.5 | 130.9 | 127.6 | 129.0 | 127.1 | 117.7 |
| OxyContin alone | 50.3 | 48.5 | 33.3 | 43.7 | 41.5 | 39.8 | 38.4 | 32.9 |
| OxyContin dispensed concurrently with comparator opioids | 91.5 | 91.8 | 65.1 | 87.3 | 86.1 | 89.2 | 88.7 | 84.8 |
| OxyContin dispensed concurrently with non-comparator opioids | 88.6 | 93.9 | 77.9 | 86.6 | 90.3 | 91.6 | 92.3 | 90.3 |
| OxyContin dispensed concurrently with non-comparator opioids in that year | 108.2 | 107.8 | 83.3 | 97.6 | 98.6 | 97.5 | 100.2 | 101.4 |
| Total | 127.6 | 125.7 | 90.7 | 117.1 | 115.1 | 115.8 | 115.2 | 108.0 |

^a OxyContin alone indicates OxyContin dispensed without other opioids as defined in Table 2 above (ie, neither comparator nor non-comparator opioid analgesics).

^b OxyContin and comparator opioids concurrently, with or without non-comparator opioids

^c Reflects the number of patients/person-time for patients who did not exclusively use OxyContin alone, but had periods of use of OxyContin alone as well as periods of use of OxyContin concurrently with comparator opioids.

^d Total reflects total number of patients contributing person-time in any calendar year based on episodes of treatment (ie, prescriptions are not truncated at the end of the calendar year)

Table 9: Most common opioids dispensed concurrently with OxyContin of those analyzed (MarketScan data)

| Rank | 2H2008-1H2009 | 2H2009-1H2010 | 2H2010 | 2011 | 2012 | 2013 | 2014 | 1Q2015-3Q2015 |
|------|---|---|---|---|---|---|---|--|
| 1 | IR Hydrocodone acetaminophen 28,049 (61%) | IR hydrocodone acetaminophen 29,236 (60%) | IR hydrocodone acetaminophen 16,480 (54%) | IR hydrocodone acetaminophen 27,277 (55%) | IR hydrocodone acetaminophen 25,626 (53%) | IR oxycodone SE 21,973 (57%) | IR oxycodone SE 23,651 (61%) | IR oxycodone SE 13,532 (64%) |
| 2 | IR oxycodone SE 19,207 (42%) | IR oxycodone SE 21,449 (44%) | IR oxycodone SE 14,531 (47%) | IR oxycodone SE 24,379 (49%) | IR oxycodone SE 25,345 (52%) | IR hydrocodone acetaminophen 18,167 (47%) | IR hydrocodone acetaminophen 16,414 (42%) | IR hydrocodone acetaminophen 7,786 (37%) |
| 3 | IR hydromorphone 4,485 (10%) | IR hydromorphone 4,488 (9%) | IR hydromorphone 2,625 (9%) | IR hydromorphone 5,044 (10%) | IR hydromorphone 5,104 (11%) | IR hydromorphone 4,179 (11%) | IR hydromorphone 4,131 (11%) | IR hydromorphone 2,163 (10%) |
| 4 | ER morphine 3,398 (7%) | ER morphine 3,489 (7%) | ER morphine 2,117 (7%) | ER morphine 3,597 (7%) | ER morphine 3,240 (7%) | ER morphine 2,544 (7%) | ER morphine 2,547 (7%) | ER morphine 1,526 (7%) |
| 5 | Methadone 1,953 (4%) | Methadone 1,841 (4%) | Methadone 1,016 (3%) | ER oxymorphone 1,655 (3%) | ER oxymorphone 1,651 (3%) | IR morphine 1,049 (3%) | IR morphine 938 (2%) | IR morphine 528 (2%) |

Figure 3: Most common opioids dispensed concurrently with OxyContin of those analyzed (MarketScan data)

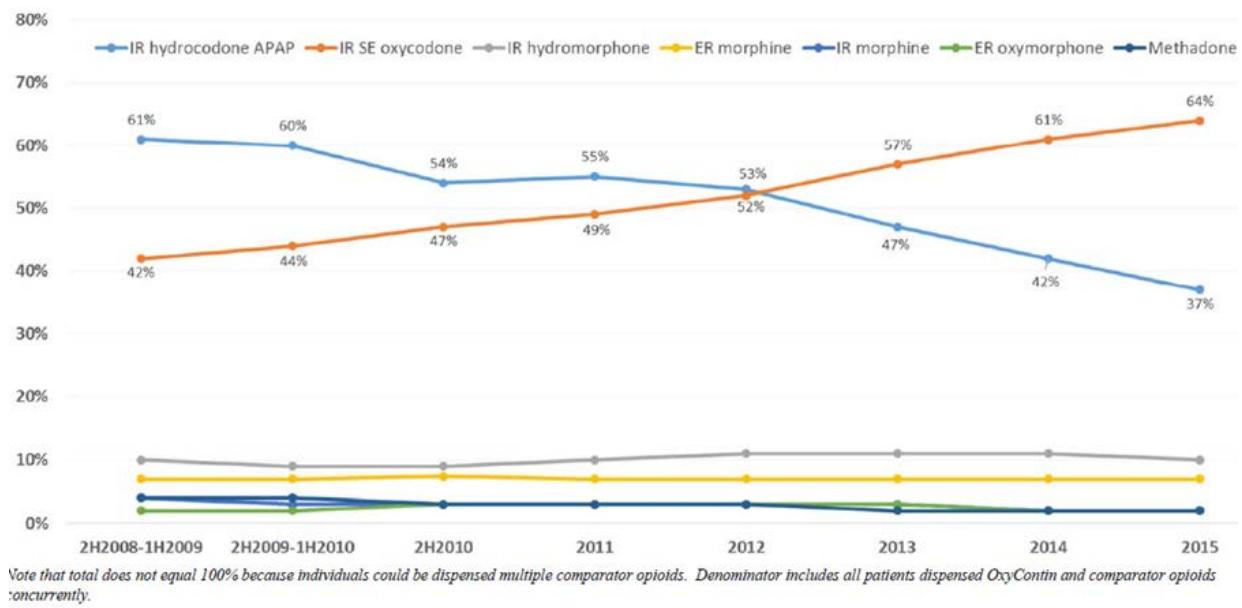


Table 10: Demographics of patients dispensed OxyContin (Medicaid data)

| | 2H2008-1H2009 | 2H2009-1H2010 | 2H2010 | 2011 | 2012 |
|---------------------------------------|---------------|---------------|--------------|--------------|--------------|
| Number of patients | 43,712 | 47,701 | 35,532 | 47,138 | 44,064 |
| Geographic distribution, n (%) | | | | | |
| Northeast | 13,302 (30%) | 16,241 (34%) | 12,663 (36%) | 14,090 (30%) | 12,798 (29%) |
| Midwest | 9,898 (23%) | 11,039 (23%) | 8,493 (24%) | 17,038 (36%) | 14,954 (34%) |
| South | 14,225 (33%) | 14,569 (31%) | 10,467 (29%) | 12,194 (26%) | 12,970 (29%) |
| West | 6,287 (14%) | 5,852 (12%) | 3,909 (11%) | 3,816 (8%) | 3,342 (8%) |
| Age, Years, mean | 47.04 | 46.65 | 47.06 | 47.10 | 47.33 |
| Age, categorized, n (%) | | | | | |
| 0-15 years | 188 (<1%) | 198 (0%) | 117 (<1%) | 223 (<1%) | 221 (1%) |
| 16-34 years | 7,001 (16%) | 8,259 (17%) | 5,804 (16%) | 7,979 (17%) | 7,239 (16%) |
| 35-64 years | 33,980 (78%) | 36,605 (77%) | 27,763 (78%) | 36,563 (78%) | 34,288 (78%) |
| 65-74 years | 1,286 (3%) | 1,402 (3%) | 930 (3%) | 1,330 (3%) | 1,312 (3%) |
| 75+ years | 1,204 (3%) | 1,175 (2%) | 877 (2%) | 999 (2%) | 942 (2%) |
| Unknown | 53 (<1%) | 62 (<1%) | 41 (<1%) | 44 (<1%) | 62 (<1%) |
| Gender, n (%) | | | | | |
| Female | 25,096 (57%) | 26,763 (56%) | 19,912 (56%) | 26,648 (57%) | 25,077 (57%) |
| Male | 18,563 (42%) | 20,876 (44%) | 15,579 (44%) | 20,446 (43%) | 18,925 (43%) |
| Gender Unknown | 53 (<1%) | 62 (<1%) | 41 (<1%) | 44 (<1%) | 62 (<1%) |
| Race, n (%) | | | | | |
| White | 30,028 (69%) | 31,465 (66%) | 23,158 (65%) | 32,469 (69%) | 30,297 (69%) |
| Black | 8,094 (19%) | 9,734 (20%) | 7,416 (21%) | 9,061 (19%) | 8,309 (19%) |
| American Indian | 722 (2%) | 692 (1%) | 518 (1%) | 669 (1%) | 717 (2%) |
| Asian | 213 (<1%) | 242 (1%) | 186 (1%) | 285 (1%) | 251 (1%) |
| Hispanic | 666 (2%) | 710 (1%) | 583 (2%) | 705 (1%) | 751 (2%) |
| Hawaiian | 63 (<1%) | 61 (<1%) | 42 (<1%) | 37 (<1%) | 25 (<1%) |
| Other Race | 2,141 (5%) | 2,937 (6%) | 2,305 (6%) | 2,180 (5%) | 1,936 (4%) |
| Race Unknown | 1,785 (4%) | 1,860 (4%) | 1,324 (4%) | 1,732 (4%) | 1,778 (4%) |

Table 11: Prevalence of relevant diagnoses among patients dispensed OxyContin (Medicaid data)

| | 2H2008-1H2009 (n=43,712) | 2H2009-1H2010 (n=47,701) | 2H2010 (n=35,532) | 2011 (n=47,138) | 2012 (n=44,064) |
|--|-----------------------------|-----------------------------|----------------------|--------------------|--------------------|
| Diagnoses, n (%) | | | | | |
| Pain | 38,831 (89%) | 42,325 (89%) | 29,722 (84%) | 43,505 (92%) | 40,880 (93%) |
| Psychiatric/ Substance Use Disorders | 21,122 (48%) | 22,475 (47%) | 11,717 (33%) | 21,737 (46%) | 21,077 (48%) |

Table 12: Opioid utilization patterns among patients dispensed OxyContin (Medicaid data)

| | 2H2008-1H2009 (n=43,712) | 2H2009-1H2010 (n=47,701) | 2H2010 (n=35,532) | 2011 (n=47,138) | 2012 (n=44,064) |
|---|-------------------------------------|-------------------------------------|------------------------------|----------------------------|----------------------------|
| # Prescriptions dispensed, mean | 6.06 | 6.35 | 4.41 | 5.96 | 6.06 |
| # days dispensed, mean | 136.31 | 143.03 | 94.50 | 135.87 | 138.50 |
| # tablets dispensed, mean | 439.01 | 457.93 | 304.27 | 377.11 | 376.54 |
| # tablets dispensed, median | 258 | 300 | 240 | 208 | 210 |
| # tablets dispensed by tablet strength, Mean | | | | | |
| 10mg | 44.35 | 41.08 | 29.41 | 41.98 | 42.40 |
| 15mg | 3.70 | 5.70 | 4.70 | 7.21 | 9.95 |
| 20mg | 93.41 | 84.20 | 57.03 | 75.95 | 74.97 |
| 30mg | 17.06 | 27.65 | 22.30 | 32.69 | 38.55 |
| 40mg | 117.17 | 112.24 | 70.61 | 83.99 | 79.11 |
| 60mg | 23.39 | 36.18 | 27.20 | 36.97 | 40.81 |
| 80mg | 139.94 | 150.87 | 93.02 | 98.32 | 90.74 |
| Total # Prescriptions Dispensed | 264,900 | 302,898 | 156,839 | 281,167 | 266,888 |
| Total # Tablets Dispensed | 19,189,979 | 21,843,840 | 10,811,152 | 17,776,215 | 16,591,948 |

Table 13: Number of patients dispensed OxyContin, by opioid concomitancy (Medicaid data)

| | 2H2008-1H2009 | 2H2009-1H2010 | 2H2010 | 2011 | 2012 |
|--|----------------------|----------------------|---------------|--------------|--------------|
| Number (%) | | | | | |
| OxyContin alone for the duration of OxyContin prescriptions in that year ^a | 13,345 (31%) | 15,312 (32%) | 12,226 (34%) | 14,263 (30%) | 12,495 (28%) |
| OxyContin dispensed concurrently with comparator opioids in that year ^b | 26,649 (61%) | 29,008 (61%) | 21,525 (61%) | 31,538 (67%) | 30,495 (69%) |
| A mixture of OxyContin alone and OxyContin concurrent with comparator opioids ^c | 21,504 (81%) | 22,919 (79%) | 15,774 (73%) | 24,759 (79%) | 23,574 (77%) |
| OxyContin dispensed concurrently with comparator opioids only | 5,145 (19%) | 6,089 (21%) | 5,751 (27%) | 6,779 (21%) | 6,921 (23%) |
| OxyContin dispensed concurrently with non-comparator opioids in that year | 3,718 (9%) | 3,381 (7%) | 1,781 (5%) | 1,337 (3%) | 1,074 (2%) |
| Total | 43,712 | 47,701 | 35,532 | 47,138 | 44,064 |
| Mean Person Time (Days) | | | | | |
| OxyContin alone for the duration of OxyContin use in that year ^a | 119.1 | 126.2 | 88.2 | 116.8 | 123.7 |
| OxyContin dispensed concurrently with comparator opioids in that year ^b | 144.3 | 150.6 | 98.5 | 144.4 | 145.0 |
| A mixture of OxyContin alone and OxyContin concurrent with comparator opioids ^c | 157.5 | 164.0 | 104.4 | 158.0 | 159.0 |
| OxyContin used alone | 68.9 | 70.3 | 44.1 | 65.4 | 63.0 |
| OxyContin dispensed concurrently with comparator opioids in that year | 88.6 | 93.7 | 60.3 | 92.5 | 96.0 |
| OxyContin dispensed concurrently with comparator opioids only | 89.1 | 100.1 | 82.2 | 94.7 | 97.2 |
| OxyContin dispensed concurrently with non-comparator opioids in that year | 140.7 | 154.0 | 90.0 | 138.1 | 126.3 |
| Total | 136.3 | 143.0 | 94.5 | 135.9 | 138.5 |

^a OxyContin alone indicates OxyContin dispensed without other opioids as defined in Table 2 above (ie, neither comparator nor non-comparator opioid analgesics).

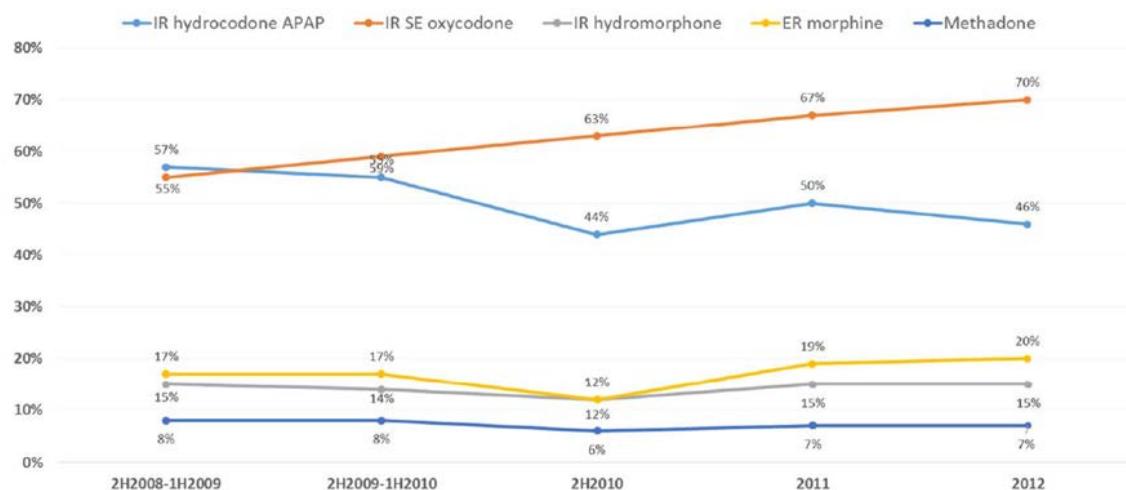
^b OxyContin and comparator opioids concurrently, with or without non-comparator opioids

^c Reflects the number of patients who did not exclusively use OxyContin alone, but had periods of use of OxyContin alone as well as periods of use of OxyContin concurrently with comparator opioids.

Table 14: Most common opioids dispensed concurrently with OxyContin of those analyzed (Medicaid data)

| Rank | 2H2008-1H2009 | 2H2009-1H2010 | 2H2010 | 2011 | 2012 |
|------|---|---|--|---|---|
| 1 | IR hydrocodone-acetaminophen 15,198 (57%) | IR SE oxycodone 17,151 (59%) | IR SE oxycodone 13,649 (63%) | IR SE oxycodone 20,992 (67%) | IR SE oxycodone 21,436 (70%) |
| 2 | IR SE oxycodone 14,788 (55%) | IR hydrocodone-acetaminophen 15,879 (55%) | IR hydrocodone-acetaminophen 9,378 (44%) | IR hydrocodone-acetaminophen 15,619 (50%) | IR hydrocodone-acetaminophen 14,103 (46%) |
| 3 | ER morphine 4,596 (17%) | ER morphine 4,830 (17%) | ER morphine 2,591 (12%) | ER morphine 5,839 (19%) | ER morphine 6,004 (20%) |
| 4 | IR hydromorphone 4,033 (15%) | IR hydromorphone 4,113 (14%) | IR hydromorphone 2,587 (12%) | IR hydromorphone 4,623 (15%) | IR hydromorphone 4,547 (15%) |
| 5 | Methadone 2,194 (8%) | Methadone 2,371 (8%) | Methadone 1,193 (6%) | Methadone 2,278 (7%) | ER oxymorphone 2,395 (8%) |

Figure 4: Most common comparator opioids dispensed concurrently with OxyContin (Medicaid data)



Note that total does not equal 100% because individuals could be dispensed multiple comparator opioids. Denominator includes all patients dispensed OxyContin and comparator opioids concurrently. Though not shown in figure, in 2012, methadone was replaced by ER oxymorphone as the fifth most common comparator opioid dispensed concurrently with OxyContin as shown in Table 12; methadone shown in figure for completeness ($n=2,006$ patients [7%] were prescribed methadone in 2012).

8.2 OUTCOME VALIDATION SUB-STUDY

NOTE: Sponsor description of outcome validation sub-study results (HIRD data only)

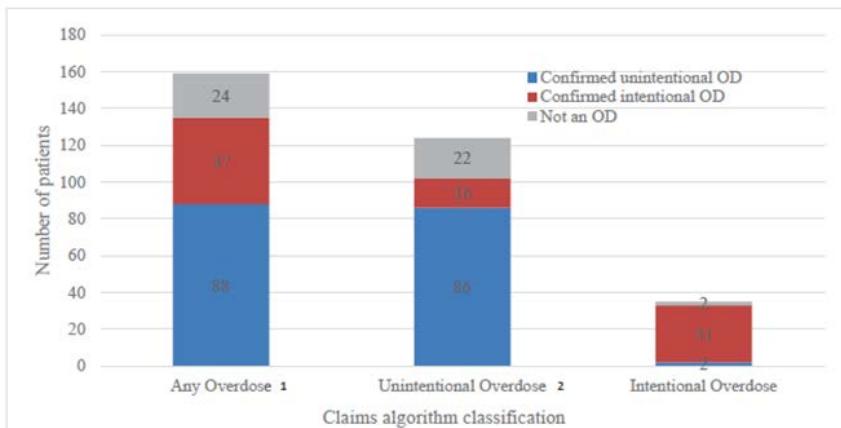
For this sub-study, medical records were requested for 300 randomly selected individuals with claims diagnoses of opioid overdose during the study period of 2008 to 2015 in HIRD, and 159 medical records were reviewed.

Of the 159 cases identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) overdose codes and for which medical records were obtained, 135 (85%; 95% CI = 78-90%) were confirmed overdoses (47 intentional and 88 unintentional; Figure 5 below). The false positive cases consisted of 12 patients (8%) with opioid adverse events or with anesthesia or surgery related events, and 12 (8%) with no relevant event (miscoded or undeterminable). Results were similar by place of setting, and

when excluding the 12 individuals with heroin codes (965.01, E850.0), the PPV among remaining patients was 84% (123/147).

The algorithm to detect unintentional overdose had lower accuracy than the overall overdose algorithm (PPV=69.4%), but a high sensitivity (97.7%) (Figure 5 and Figure 6 below). The lower PPV was due to 16 intentional overdoses being misclassified as unintentional overdoses with the intentionality algorithm (Figure 6).

Figure 5: Chart classifications of events identified as possible opioid-related overdoses using claims-based opioid-related poisoning codes in HIRD

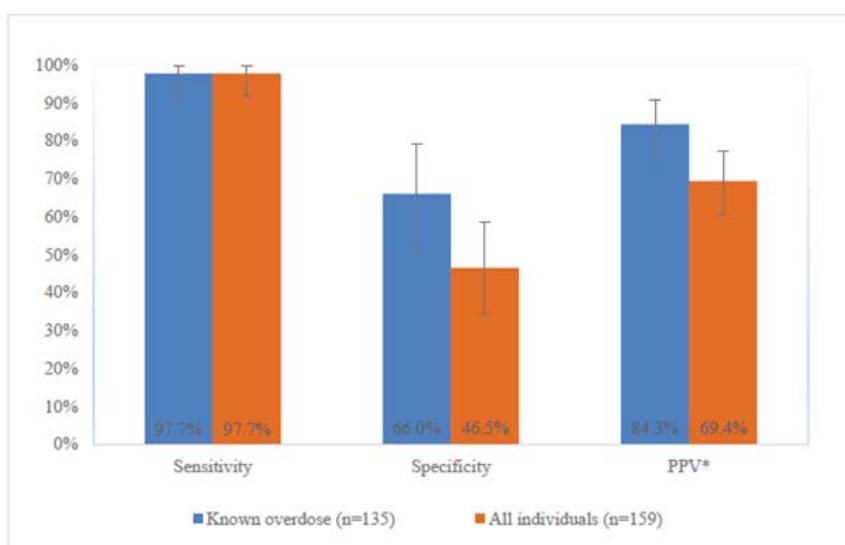


¹Any type of overdose included intentional overdoses, unintentional overdoses, and overdoses of unknown intent. The PPV for any overdose=85%, 95% confidence interval=78%-90% (calculated as a binomial exact confidence interval).

²Among the 159 patients in this validation study, 124 met the claims algorithm for unintentional overdose further defined in Section 6.5.2. Of the 124 classified as unintentional overdose 86 were found on medical record review to have had an unintentional overdose, while 16 had intentional overdose and 22. This represents a PPV of 69.4% (86/124) for unintentional overdose, with a 95%CI of 60.4%-77.3%.

Abbreviations: HIRD=HealthCore Integrated Research Database®; OD=opioid overdose; PPV=positive predictive value.

Figure 6: Performance of unintentional overdose definition among patients with a known overdose and all patients with an overdose code in the validation study in HIRD



Abbreviations: n=number; PPV=positive predictive value.

*Defined as either unintentional or unknown intentionality by medical record.

^bThe PPV for an unintentional overdose among all 159 individuals=86/124 (69.4%).

8.3 MEDICAID DATA USABILITY SUB-ANALYSES

NOTE: Sponsor description of Medicaid MAX data usability sub-study (See Li et al for complete description of study methods)

Background:

The Medicaid MAX data for use in this study has been the subject of extended discussion between Purdue and the US Food and Drug Administration (FDA), primarily focusing on which states and years could be used in a comprehensive review that combines fee-for-service (FFS) and comprehensive managed care (CMC) files. The FDA suggested that Purdue apply recently published screening criteria for Medicaid (Li et al. 2017^{xxxviii}) to select states and years for the 3051-4 common-protocol analyses with Medicaid MAX data.

Specifications of study measures from Li et al. (2017):

Connectivity:

“[T]o test measures of connectivity criteria, we first defined minimum continuous enrollment periods, during which beneficiaries were enrolled exclusively in FFS or CMC plans. We then constructed cohorts in which enrollees met the denominator definitions (i.e., received the first element in the service pair, such as having diabetes diagnosis) for each calendar year. Finally, we identified enrollees with complete service pairs as the numerators (i.e., with the second element, such as having antidiabetic fill) and compared the resulting proportions of enrollees in CMC and FFS plans.”

Continuity:

“[T]o test measures of continuity criteria, we first identified beneficiaries who switched enrollment from FFS to CMC plans with defined minimum lengths of continuous enrollment (4 months before and after enrollment for antidiabetic and antihypertensive refill measures and 4 months before and 3 months after enrollment for the evaluation and management services measures) for each calendar year. We then selected patients meeting the definition of chronic service/treatment use during the FFS period prior to enrollment switch. Lastly, we checked the recurrence of service/ treatment use during the CMC period after enrollment switch and calculated the proportion of continuous use to determine whether a measure was satisfied.”

Evaluation:

“We considered a connectivity measure to be satisfied if a state had at least 50 CMC enrollees in a given study year and the calculated proportion for CMC plans was no more than 10% below the average proportion for FFS plans of the same states from 2006 to 2010.”

^{xxxviii} Li et al. (2017) Internal validation of Medicaid Analytic eXtract (MAX) data capture for comprehensive managed care plan enrollees from 2007 to 2010. *Pharmacoepidemiology and Drug Safety*: 1-10; <https://doi.org/10.1002/pds.4365>

NOTE: The connectivity criteria used for PMR 3051-4 differs slightly, as a more lenient difference of 15% was allowed between the CMC and FFS proportions.

“A continuity measure was considered as satisfied if a state had at least 50 enrollees in a given study year and the calculated proportion was greater than 60%.”

NOTE: The continuity criteria used for PMR 3051-4 also differed as a calculated proportion of 50% or more was considered acceptable.

Table 16: Specifications of study measures noted in Li et al.

| Measures | Enrollment | Numerator | Denominator |
|--|--|--|---|
| Connectivity measures | | | |
| Diabetic patients filling antidiabetic | 3 months after the eligible diagnosis | 1 antidiabetic pharmacy claim record within 3 months after the eligible diagnosis | 1 IP or 2 OT encounter/claims records within 6 months with diagnosis of diabetes [ICD 9 codes 250.x] |
| Hypothyroid patients filling thyroid agents | 3 months after the eligible diagnosis | 1 hypothyroid pharmacy claim record within 3 months after the eligible diagnosis | 1 IP or 2 OT encounter/claims records within 6 months with diagnosis of hypothyroidism [ICD 9 codes 243.x, 244.x] |
| Antibiotic fills following health care visits ^a | 1 month before the prescription fill | 1 IP or OT encounter/claims record within the 1 month preceding the antibiotic fill | 1 pharmacy claim record for oral antibiotics |
| Fracture hospitalizations having follow-up visits | 3 months after the eligible diagnosis | 1 OT encounter/claim record within 3 months after the eligible diagnosis | 1 IP encounter/claim record with fracture [ICD 9 codes 805.xx-829.xx] as primary or secondary diagnosis |
| Continuity measures | | | |
| Antidiabetic refills | 4 months before and 4 months after enrollment switch | Recurrent antidiabetic pharmacy claim record within 4 months after enrollment switch | 2 separate pharmacy claims records for antidiabetics (>30 days apart but within 6 months) and 1 OT or IP claim record with diagnosis of diabetes before enrollment switch |
| Antihypertensive refills | 4 months before and 4 months after enrollment switch | Recurrent antihypertensive pharmacy claim record within 4 months after enrollment switch | 2 separate pharmacy claims records for antihypertensive (>30 days apart but within 6 months) and 1 OT or IP claim with diagnosis of hypertension before enrollment switch |
| E&M services use | 4 months before and 3 months after enrollment switch | Recurrent OT E&S service claim records within 3 months after enrollment switch | 3 OT E&S services claim records (>4 weeks apart but within 2 months) before enrollment switch |

Abbreviations: E&M, evaluation and management; ICD, International Classification of Diseases; IP, inpatient; OT, other therapy.

^aConsidering the large sample size of the antibiotic cohort, our analysis used a 5% random sample of eligible patients for this specific measure.

Final criteria:

“To consider the CMC data as usable in research and policy analyses, states with CMC enrollment of more than 5% (among full-benefit enrollees) had to satisfy at least 3 out of 4 connectivity measures (to accommodate small sample size issues that did not allow stable estimates for some measures in some states) and all 3 continuity measures.”

Sponsor description of results for FFS and CMC usability by state*year*basis of eligibility (BOE) group

Summary of FFS usability:

Not all FFS beneficiaries were retained for the PMR 3051-4 study even if they had a high FFS penetration in the state*year*BOE group. While Li et al. considered FFS as the gold standard to evaluate the completeness of CMC data, during the analysis of the connectivity measures, we came across results that questioned the completeness of FFS in a subset of states. Thus, FFS beneficiaries were only retained among those states, years, and BOE groups in which there were at least 3 connectivity measure percentages that are consistently greater than 40%. For example, within the adult population, FFS beneficiaries in Arkansas had 3 out of 4 connectivity measure percentages greater than 40% in 2010 and 2011. Thus,

the FFS plans in Arkansas for those with BOE adult from 2010 to 2011 were deemed usable. However, the FFS data were excluded for Arkansas*adult in 2008, 2009, and 2012 since those combinations had less than 3 connectivity measures available.

Similarly, within the disabled group, FFS beneficiaries in Arkansas were both retained as usable for all study years (2008-2012), as there were at least 3 connectivity measures at greater than 40%. There were 20 states that had all their years in both the adult and disabled populations included (i.e. 2008-2012).

In some states, only a subset of years was included. For example, in Arkansas, FFS data were retained as usable among the disabled population for all study years (2008-2012); however, only 2010 and 2011 were considered as usable in the adult population. Oregon, on the other hand, had usable FFS plans for study years (2008-2012) in the adult group and only 2008 and 2010 were usable in the disabled group. Some states only had usable FFS plans in one BOE category. For example, Georgia was not usable for any study years (2008-2012) in the adult group and was usable in 2008, 2009, and 2010 for the disabled population. Overall, 6 states didn't have usable FFS plans for the adult population while FFS plans in Delaware and Iowa were not considered as usable within the disabled population.

Summary of CMC usability:

Li et al. used a set of pre-defined cut off values as a standard to make recommendations for the CMC usability. For the PMR 3051-4 study, a connectivity measure was considered to be satisfied if the calculated proportion for CMC plans was no more than 15% below the average proportion for FFS plans of the same states from 2006 to 2010. A continuity measure was considered as satisfied if the calculated proportion was greater than 50% for this study. As mentioned above in the methods, this is a more lenient scenario in comparison to Li et. al, however, other selection criteria were the same.

To evaluate the usability of CMC data, we first checked the FFS proportion in each year*state*BOE group. For example, California*adult had a 24% FFS penetration in 2008 which meant that the CMC data were more than 5% in this combination. Thus, we checked the connectivity and continuity measures for California*adult*2008.

Among the adult population in California*2008, the connectivity measure of diabetic patients with antidiabetic claims in CMC data was 80.40% which was higher than the average proportion of FFS plans, 76.70%. It thus satisfied the selection criteria that CMC plans were no more than 15% below the average proportion of FFS plans of the same state and BOE group. Additionally, California had more than 50 total CMC enrollees (1,020,932) in 2008. Therefore, we considered the connectivity measure of diabetic patients filling antidiabetic claims to be satisfied for the CMC data. Similarly, all other 3 connectivity measures were satisfied for California in 2008.

As for the 3 continuity measures in California*2008, antidiabetic refills, antihypertensive refills, and E&M services use had the proportions of 81%, 77.1%, 52.4%, respectively, for the CMC data. This indicated that all the 3 continuity measures were satisfied as their proportions were greater than 50%. To summarize, we had 4 connectivity measures and 3 continuity measures which were all satisfied for California*adult*2008. Therefore, CMC data were usable in the California*2008*adult category based on the above evaluation

criteria. However, CMC data in California was not considered as usable in 2011 because it had one continuity measure proportion (34.10%) less than 50% even though other inclusion criteria were satisfied.

The continuity measures were not considered if they had less than 50 beneficiaries who switched from FFS to CMC. For example, in Virginia*adult, the 3 continuity measures (71.8%, 85.7%, 62.2%) were all larger than 50% in 2011, however the continuity measure of antidiabetic refills had less than 50 enrollees who switched thus this measure was not evaluated while other measures were.

There were 12 states that had CMC claims deemed usable for all years in both the adult and disabled groups. However, there were 19 states in which the CMC population were deemed unusable for all years in both the adult and disable groups. In the other 19 states (and DC), a subset of year*BOE groups met the criteria for CMC inclusion. For example, in Colorado, CMC data were usable only in 2010 for the adult population.

Comparison with Li et al. results:

Among the 7 of the 29 states (Alabama, Arkansas, Idaho, Iowa, Louisiana, Mississippi, and North Carolina) that Li et al. did not assess, all 7 states did not qualify in our analysis for CMC usability. Among the remaining 22 states assessed in Li et al., for the same years 2007-2010, 6 states differed in the CMC usability conclusion (Kansas, Massachusetts, Missouri, Tennessee, Washington and Wisconsin). Some differed in adult population, some in disabled and some in both.

The results could have differed due to our stratification of BOE categories. Li et al. assumed that selected measures would be expected to reflect essential and consistently covered services regardless of the basis for Medicaid eligibility, however, our data showed a difference between the adult and disabled category in a number of states. For example, we gained Massachusetts in 2010 as compared to Li et al. However, we lost Kansas (2008-2010), Missouri (2008-2010; disabled), Tennessee (2009-2010; adult), Washington (2008-2010, adult) and Wisconsin (2008-2010). For the remaining 22 states that Li et al. did not assess, the additional gain for CMC usability included 5 states from 2008, 7 from 2009 and 2010 for adult population; as well as 3 from 2008, and 4 from 2009 and 2010 for disabled. In 2011-2012, the years that were not available in Li et al. analysis, we have 23 states from 2011 and 22 states from 2012 in the adult population and 22 from 2011 and 25 states in 2012 in the disabled population.

FDA's review of the Medicaid MAX data usability findings

DEPI compared tables in the Medicaid MAX data usability appendix of the PMR 3051-4 study report. Specifically, DEPI compared what the sponsor deemed as usable state*year*BOE groups (Table 11 and 12 in that appendix) to other tables in the Appendix that describe the process for evaluating data usability. Upon review, DEPI found that one state*year*BOE category (Idaho*2010*Disabled) may have been included despite not meeting criteria for FFS claims as detailed above. Other state*year*BOE categories were included despite tables in the PMR 3051-4 study report appendix indicating very low FFS penetration in those specified years (Table 17). A few state*year*BOE groups (Connecticut*2008*Adult, Michigan*2008*Disabled, Nebraska*2009*Adult) may have

been excluded from analysis despite meeting the Li et al. continuity criteria for FFS claims (Table 17).

DEPI also found that many CMC claims were retained, yet there was not enough information to determine whether continuity criteria were met (i.e., <50 beneficiaries in those BOE*state*year categories). This was a significant limitation as 75% of the 12 states that had CMC claims deemed usable for all years in both the adult and disabled groups had one or more BOE*state*year groups where connectivity was unable to be assessed due to the low number of beneficiaries. Additionally, 12 of the 19 states that had subsets of year*BOE groups which met the criteria for CMC inclusion were unable to be assessed for one or more measures of continuity for this same reason (Table 17). As a result, the data from several states may have been included erroneously.

Table 17: FFS data and CMC data usable by state, year and BOE category

| States | Adult-FFS | Disabled-FFS | Adult- CMC | Disabled-CMC |
|--------|----------------------|---------------------|-------------------------------|----------------------------|
| AK | 2008-2012 | 2008-2012 | None | None |
| AL | 2008-2012 | 2011-2012 | None | None |
| AR | 2010-2011 | 2008-2012 | None | None |
| AZ | 2011-2012 | 2011-2012 | 2008-2010*, 2011, 2012* | 2008-2010*, 2011, 2012* |
| CA | 2008-2012 | 2008-2012 | 2008-2010, 2012 | 2008-2012 |
| CO | 2010 | 2008-2010 | 2010* | None |
| CT | 2008†, 2009- 2012 | 2008-2012 | 2010, 2011 | None |
| DC | 2008-2011 | 2009-2012 | 2011* | 2011* |
| DE | Excluded | Excluded | None | None |
| FL | 2008-2012 | 2008-2012 | 2009-2010 | 2009-2012 |
| GA | Excluded | 2008-2009‡, 2010 | 2008-2012* | 2008-2012* |
| HI | 2009-2012 | 2008 | 2012* | 2012* |
| IA | 2009 | Excluded | None | None |
| ID | 2008-2009 | 2008-2009, 2010‡ | None | None |
| IL | 2008-2012 | 2008-2012 | 2009-2012 | 2012 |
| IN | 2011-2012 | 2008-2012 | 2008-2012 | 2008-2012 |
| KS | 2009-2011 | 2008-2009, 2011 | None | None |
| KY | 2008-2009 | 2012 | 2008-2012*, 2009 | 2008-2012* |
| LA | 2008-2011 | 2008-2012 | 2012 | 2012 |
| MA | 2009-2012 | 2008-2012 | 2010-2012* | 2012* |
| MD | 2008-2012 | 2008-2012 | 2008-2009* | 2011-2012* |
| ME | 2011-2012 | 2011-2012 | None | None |
| MI | Excluded | 2008†, 2009,2012 | 2008-2012* | 2008-2012* |

| | | | | |
|----|---|---|--------------------------|---------------------------------|
| MN | 2008-2012 | 2008-2012 | 2008-2009*, 2010-2012 | 2008-2012* |
| MO | 2008-2012 | 2008-2012 | 2008-2012* | None |
| MS | Excluded | 2008¥,2010, 2011-2012¥ | None | 2011-2012* |
| MT | 2008-2012 | 2008-2012 | None | None |
| NC | 2008-2012 | 2008-2012 | None | None |
| ND | 2008-2012 | 2008-2012 | None | None |
| NE | 2008, 2009†, 2010-2012 | 2008-2012 | 2008-2012 | 2008-2012 |
| NH | 2008-2012 | 2008-2012 | None | None |
| NJ | 2008-2010 | 2008-2010, 2012 | 2008-2012* | 2008-2012* |
| NM | 2008-2012 | 2008-2012 | 2008-2012* | 2008-2012* |
| NV | Excluded | 2008-2011 | None | None |
| NY | 2008-2012 | 2008-2012 | 2008-2012 | 2008-2012* |
| OH | 2008-2011 | 2008-2012 | 2011-2012 | 2011-2012 |
| OK | 2008-2012 | 2008-2010, 2012 | None | None |
| OR | 2008-2012 | 2008-2010 | 2009-2012* | 2009-2012* |
| PA | 2008-2012 | 2008-2012 | 2008- 2009,2011 | None |
| RI | 2010 | 2008-2011 | 2008-2011* | 2008-2011* |
| SC | 2008¥ (should have been excluded, discrepant information in percent of FFS enrollment) | 2008-2009, 2010-2012¥ (should have been excluded, discrepant information in percent of FFS enrollment in 2010-2012) | 2012* | 2011-2012* |
| SD | 2008-2012 | 2008-2012 | None | None |
| TN | 2010, 2011- 2012¥ (2011- 2012 should have been excluded, discrepant information in percent of FFS enrollment) | 2008, 2011- 2012¥ (2011- 2012 should have been excluded, discrepant information in percent of FFS enrollment) | 2008,2011- 2012* | 2008-2012* |
| TX | 2008-2012 | 2008-2012 | 2008-2009*, 2010-2012 | 2008-2009*, 2010, 2011-2012* |
| UT | 2010 | 2008,2011- 2012 | 2009-2012* | None |

| | | | | |
|----|-----------|--|-------------------------------------|------------------|
| VA | 2008-2012 | 2008-2012 | 2008-2009*, 2010, 2011*, 2012 | 2008-2012 |
| VT | 2008-2012 | 2008-2012 | None | None |
| WA | Exclude | 2008‡, 2010- 2012 (2008 should have been excluded, discrepant information in percent of FFS enrollment) | None | 2008-2010, 2012* |
| WI | 2008-2012 | 2008-2012 | None | None |
| WV | 2008-2012 | 2008-2012 | None | None |

(FDA generated table using data from the study report)

“Excluded” means that group did not meet FFS connectivity criteria

*Years where continuity was unable to be assessed due to <50 beneficiaries in state*year*BOE category

†Connectivity criteria met but FFS enrollees potentially excluded (based on data provided in tables 11 and 12 of the PMR 3051-4 study report appendices covering Medicaid MAX data usability)

‡Discrepant information in percent of FFS enrollment provided in PMR 3051-4 study report appendix tables

§Connectivity criteria not met but FFS enrollees potentially included (based on data provided in tables 11 and 12 of the PMR 3051-4 study report appendices covering Medicaid MAX data usability)

Overall, CMC treatment episodes were comprised of approximately 60% disabled beneficiaries and 40% adult beneficiaries. There were similar proportions of disabled and adult CMC beneficiaries when comparing treatment episodes involving OxyContin and other opioid analgesics. FFS treatment episodes were comprised of approximately 85% disabled beneficiaries, with OxyContin treatment episodes involving slightly higher percentages of disabled beneficiaries compared to other opioid analgesic episodes. For FFS claims, 23% and 77% of episodes involved any use of OxyContin and primary comparator opioid analgesics, respectively. For CMC claims, 18% and 83% of episodes involved any use of OxyContin and primary comparator opioid analgesics, respectively.

It is important to consider the suitability of the Li et al. criteria for evaluating data for use in PMR 3051-4, as these criteria were not developed specifically to evaluate the usability of Medicaid claims in relation to prescription opioid abuse. At the same time, we do not believe that it is a severe limitation as the continuity and connectivity criteria essentially evaluate the completeness of claims across years and states with changing adoption of CMC insurance coverage.

While there were some minor discrepancies between what data were deemed usable (i.e., Table 11 and 12 in the sponsor’s appendix) and other tables in the sponsor’s Medicaid MAX appendix, the sponsor appropriately implemented the methods for assessing Medicaid data usability proposed by Li et. al, and therefore from the perspective of FDA, the sponsor adequately evaluated the completeness of Medicaid data for use in this study. These minor discrepancies require further clarification by the sponsor, but we do not believe that resolving the noted discrepancies would have meaningfully impacted our interpretation of the primary Medicaid results. The most

notable issues were primarily due to an inability to assess continuity in CMC claims due to the low number of beneficiaries, a limitation also noted by Li et al.

8.4 DESCRIPTIVE TABLES

8.4.1 Medicaid

Table 18: Demographic and clinical characteristics

| | Any use of OxyContin based treatment episodes excluding primary comparators (2.1) | Any use of primary comparator opioids treatment episodes excluding OxyContin (2.1) | OxyContin alone treatment episodes (2.2) | Primary comparator alone opioid treatment episodes (2.2) |
|---|---|--|--|--|
| Total treatment episodes, n (%) | 522,775 20.40% | 2,039,232 79.60% | 196,455 7.67% | 819,930 32.00% |
| Total patients, n (%)* | 94,445 20.43% | 367,814 79.57% | 63,079 13.65% | 256,839 55.56% |
| Mean person-time (months) per treatment episode, mean (sd) | 2.04 2.99 | 2.06 2.90 | 1.43 2.58 | 1.48 2.53 |
| Total person-time (months) per patient, mean (sd) | 7.78 9.97 | 8.10 10.33 | 3.73 6.54 | 4.15 7.19 |
| Demographic characteristics (treatment episode measures) | | | | |
| Age (years) | | | | |
| Mean, SD | 46.67 10.46 | 46.94 10.55 | 47.10 10.51 | 47.28 10.62 |
| Median | 48 | 49 | 49 | 49 |
| Range (min, max) | 16 64 | 16 64 | 16 64 | 16 64 |
| Age category, n (%) | | | | |
| 16-34 | 81,700 15.63% | 316,269 15.51% | 29,427 14.98% | 123,453 15.06% |
| 35-64 | 441,075 84.37% | 1,722,963 84.49% | 167,028 85.02% | 696,477 84.94% |
| Gender, n (%) | | | | |
| Male | 226,900 43.40% | 797,712 39.12% | 87,000 44.28% | 323,947 39.51% |
| Female | 295,875 56.60% | 1,241,520 60.88% | 109,455 55.72% | 495,983 60.49% |
| Geographic region of patient residence (US), n (%) | | | | |
| Midwest | 192,353 36.79% | 598,970 29.37% | 71,750 36.52% | 243,352 29.68% |
| Northeast | 124,364 23.79% | 310,186 15.21% | 46,956 23.90% | 124,721 15.21% |
| South | 90,046 17.22% | 517,380 25.37% | 31,810 16.19% | 200,656 24.47% |
| West | 116,012 22.19% | 612,696 30.05% | 45,939 23.38% | 251,201 30.64% |
| Year of index date, n (%) [#] | | | | |
| 2008 | 84,428 16.15% | 269,802 13.23% | 34,220 17.42% | 113,324 13.82% |
| 2009 | 132,713 25.39% | 472,490 23.17% | 52,139 26.54% | 196,216 23.93% |
| 2010 | 58,097 11.11% | 215,590 10.57% | 22,858 11.64% | 87,893 10.72% |

| | | | | | | | | |
|---|---------|--------|-----------|--------|---------|--------|---------|--------|
| 2011 | 137,222 | 26.25% | 536,537 | 26.31% | 49,093 | 24.99% | 211,594 | 25.81% |
| 2012 | 110,315 | 21.10% | 544,813 | 26.72% | 38,145 | 19.42% | 210,903 | 25.72% |
| Medicaid coverage type, n (%) | | | | | | | | |
| CMC | 227,414 | 43.50% | 1,053,120 | 51.64% | 80,451 | 40.95% | 396,363 | 48.34% |
| FFS | 295,361 | 56.50% | 986,112 | 48.36% | 116,004 | 59.05% | 423,567 | 51.66% |
| Medicaid BOE group, n (%) | | | | | | | | |
| Adult | 131,253 | 25.11% | 550,357 | 26.99% | 45,971 | 23.40% | 208,471 | 25.43% |
| Disabled | 391,522 | 74.89% | 1,488,875 | 73.01% | 150,484 | 76.60% | 611,459 | 74.57% |
| Pain diagnosis, n (%) | | | | | | | | |
| Abdominal pain | 99,797 | 19.09% | 436,472 | 21.40% | 35,412 | 18.03% | 169,465 | 20.67% |
| Amputation | 8,612 | 1.65% | 29,062 | 1.43% | 3,289 | 1.67% | 11,761 | 1.43% |
| Arthritis, arthropathies, osteoarthritis and musculoskeletal pain | 174,234 | 33.33% | 654,673 | 32.10% | 61,811 | 31.46% | 250,189 | 30.51% |
| Back pain | 238,737 | 45.67% | 974,728 | 47.80% | 82,754 | 42.12% | 362,977 | 44.27% |
| Chronic pain | 104,311 | 19.95% | 427,644 | 20.97% | 35,540 | 18.09% | 161,434 | 19.69% |
| Fibromyalgia | 33,511 | 6.41% | 157,272 | 7.71% | 11,001 | 5.60% | 56,721 | 6.92% |
| Headache | 50,025 | 9.57% | 207,486 | 10.17% | 17,193 | 8.75% | 78,435 | 9.57% |
| Malignancy | 76,684 | 14.67% | 298,063 | 14.62% | 29,178 | 14.85% | 122,918 | 14.99% |
| Multiple sclerosis | 5,195 | 0.99% | 24,039 | 1.18% | 1,983 | 1.01% | 10,227 | 1.25% |
| Neuropathic pain | 16,857 | 3.22% | 70,734 | 3.47% | 6,250 | 3.18% | 28,067 | 3.42% |
| Peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers | 20,432 | 3.91% | 85,372 | 4.19% | 7,935 | 4.04% | 34,887 | 4.25% |
| Stroke | 8,288 | 1.59% | 37,164 | 1.82% | 3,099 | 1.58% | 15,446 | 1.88% |
| Liver disease | 36,038 | 6.89% | 154,347 | 7.57% | 13,833 | 7.04% | 63,695 | 7.77% |
| Renal disease | 19,594 | 3.75% | 79,836 | 3.92% | 7,745 | 3.94% | 33,719 | 4.11% |
| COPD | 102,942 | 19.69% | 401,863 | 19.71% | 37,814 | 19.25% | 157,067 | 19.16% |
| Impaired respiratory function | 64,831 | 12.40% | 270,254 | 13.25% | 23,913 | 12.17% | 109,579 | 13.36% |
| Deyo-Charlson comorbidity index | | | | | | | | |
| Mean, SD | 2.03 | 2.80 | 2.02 | 2.83 | 2.10 | 2.83 | 2.08 | 2.86 |
| Median | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| Range (min, max) | 0 | 21.00 | 0 | 30.00 | 0 | 21.00 | 0 | 30.00 |
| Psychiatric comorbidities, n (%) | | | | | | | | |
| Attention deficit hyperactive disorder (ADHD) | 2,353 | 0.45% | 10,398 | 0.51% | 747 | 0.38% | 3,953 | 0.48% |
| Bipolar disorder | 32,554 | 6.23% | 147,251 | 7.22% | 11,849 | 6.03% | 58,424 | 7.13% |
| Borderline personality disorder | 1,766 | 0.34% | 8,560 | 0.42% | 646 | 0.33% | 3,418 | 0.42% |
| Generalized anxiety disorder | 49,405 | 9.45% | 212,176 | 10.40% | 16,895 | 8.60% | 80,971 | 9.88% |
| Major depression disorder | 88,372 | 16.90% | 378,331 | 18.55% | 32,646 | 16.62% | 152,368 | 18.58% |
| Alcoholism | 16,739 | 3.20% | 65,856 | 3.23% | 6,365 | 3.24% | 26,650 | 3.25% |
| History of attempted suicide | 1,399 | 0.27% | 6,084 | 0.30% | 471 | 0.24% | 2,297 | 0.28% |
| Post-traumatic stress disorder | 10,575 | 2.02% | 47,743 | 2.34% | 3,560 | 1.81% | 18,596 | 2.27% |
| Sleep disorder | 36,549 | 6.99% | 146,515 | 7.18% | 12,967 | 6.60% | 56,529 | 6.89% |
| Somatoform disorder | 233 | 0.04% | 1,601 | 0.08% | 85 | 0.04% | 645 | 0.08% |
| Drug dependence | | | | | | | | |

| | | | | | | | | |
|--|---------|--------|-----------|--------|---------|--------|---------|--------|
| Opioid type dependence | 30,472 | 5.83% | 119,537 | 5.86% | 11,655 | 5.93% | 51,155 | 6.24% |
| Non-opioid drug dependence | 32,589 | 6.23% | 119,625 | 5.87% | 11,904 | 6.06% | 47,299 | 5.77% |
| History of overdose/poisoning | 2,657 | 0.51% | 15,485 | 0.76% | 914 | 0.47% | 6,205 | 0.76% |
| Non-opioid medications of abuse potential, n (%) | | | | | | | | |
| Depressants | | | | | | | | |
| Benzodiazepines | 97,110 | 18.58% | 368,051 | 18.05% | 23,623 | 12.02% | 104,049 | 12.69% |
| Barbiturates | 693 | 0.13% | 3,570 | 0.18% | 233 | 0.12% | 1,463 | 0.18% |
| Sleep medications | 53,245 | 10.19% | 193,823 | 9.50% | 15,304 | 7.79% | 58,931 | 7.19% |
| Stimulants | | | | | | | | |
| Amphetamines | 5,551 | 1.06% | 21,590 | 1.06% | 1,349 | 0.69% | 6,858 | 0.84% |
| Methylphenidate | 2,127 | 0.41% | 10,307 | 0.51% | 524 | 0.27% | 3,560 | 0.43% |
| Dextromethorphan | 59 | 0.01% | 248 | 0.01% | 11 | 0.01% | 73 | 0.01% |
| Muscle relaxants | 73,079 | 13.98% | 330,895 | 16.23% | 18,085 | 9.21% | 91,563 | 11.17% |
| Opioid maintenance therapy medication use during treatment episode, n (%) | | | | | | | | |
| Suboxone | 1,094 | 0.21% | 3,618 | 0.18% | 430 | 0.22% | 1,769 | 0.22% |
| Subutex/sublingual buprenorphine tablets | 73 | 0.01% | 374 | 0.02% | 24 | 0.01% | 167 | 0.02% |
| Solution of methadone | 3,127 | 0.60% | 12,954 | 0.64% | 1,369 | 0.70% | 6,590 | 0.80% |
| Duration of treatment episode (months), mean (sd) | 1.40 | 2.80 | 1.46 | 2.78 | 1.20 | 2.56 | 1.30 | 2.61 |
| Healthcare utilization during six months prior to the index date, mean (sd) [^] | | | | | | | | |
| All-cause office visits | 31.82 | 34.16 | 30.52 | 30.80 | 31.94 | 34.95 | 30.60 | 31.50 |
| All-cause ED visits | 2.28 | 4.51 | 2.29 | 4.26 | 2.10 | 4.25 | 2.15 | 4.04 |
| All-cause hospitalizations | 0.74 | 1.54 | 0.73 | 1.48 | 0.72 | 1.53 | 0.72 | 1.47 |
| Exposures | | | | | | | | |
| OxyContin dose, n (%) | | | | | | | | |
| 10 mg | 72,707 | 13.91% | 0 | 0.00% | 28,091 | 14.30% | 0 | 0.00% |
| 15 mg | 10,997 | 2.10% | 0 | 0.00% | 4,004 | 2.04% | 0 | 0.00% |
| 20 mg | 114,431 | 21.89% | 0 | 0.00% | 43,125 | 21.95% | 0 | 0.00% |
| 30 mg | 39,576 | 7.57% | 0 | 0.00% | 13,645 | 6.95% | 0 | 0.00% |
| 40 mg | 114,687 | 21.94% | 0 | 0.00% | 43,009 | 21.89% | 0 | 0.00% |
| 60 mg | 39,059 | 7.47% | 0 | 0.00% | 13,534 | 6.89% | 0 | 0.00% |
| 80 mg | 131,318 | 25.12% | 0 | 0.00% | 51,047 | 25.98% | 0 | 0.00% |
| Usage, n (%) | | | | | | | | |
| Existing (continuing) user | 371,235 | 71.01% | 1,250,822 | 61.34% | 130,803 | 66.58% | 474,891 | 57.92% |
| Incident (new) user | 151,540 | 28.99% | 788,410 | 38.66% | 65,652 | 33.42% | 345,039 | 42.08% |
| Comparator usage, any, n (%) | | | | | | | | |
| ER morphine | 0 | 0.00% | 964,343 | 47.29% | 0 | 0.00% | 360,904 | 44.02% |
| TD Fentanyl | 0 | 0.00% | 564,161 | 27.67% | 0 | 0.00% | 223,515 | 27.26% |
| Methadone tabs/capsules | 0 | 0.00% | 510,728 | 25.05% | 0 | 0.00% | 235,511 | 28.72% |
| IR oxycodone single entity | 133,497 | 25.54% | 290,641 | 14.25% | 0 | 0.00% | 0 | 0.00% |

| | | | | | | | | |
|---|---------|--------|-----------|--------|---------|--------|---------|--------|
| IR hydromorphone | 29,378 | 5.62% | 137,657 | 6.75% | 0 | 0.00% | 0 | 0.00% |
| ER oxymorphone | 4,937 | 0.94% | 14,035 | 0.69% | 0 | 0.00% | 0 | 0.00% |
| Other opioid use (non primary or secondary comparators) | 210,501 | 40.27% | 924,121 | 45.32% | 0 | 0.00% | 0 | 0.00% |
| Transdermal delivery system (fentanyl or buprenorphine), n (%) | 181 | 0.03% | 317,487 | 15.57% | 2 | 0.00% | 91,952 | 11.21% |
| Buprenorphine | 177 | 0.03% | 708 | 0.03% | 0 | 0.00% | 0 | 0.00% |
| Prior use of opioid analgesics, n (%) | | | | | | | | |
| ER opioid analgesic only | 32,438 | 6.20% | 157,941 | 7.75% | 16,489 | 8.39% | 86,306 | 10.53% |
| IR opioid analgesic only | 58,682 | 11.23% | 270,977 | 13.29% | 8,575 | 4.36% | 45,149 | 5.51% |
| Both ER and IR opioid analgesic | 413,007 | 79.00% | 1,519,890 | 74.53% | 158,976 | 80.92% | 626,279 | 76.38% |
| No opioid analgesic | 18,648 | 3.57% | 90,424 | 4.43% | 12,415 | 6.32% | 62,196 | 7.59% |
| Prior use of tramadol | 40,798 | 7.80% | 197,624 | 9.69% | 12,175 | 6.20% | 67,491 | 8.23% |
| Time since the end of the last opioid analgesic (months), mean (SD) | 0.35 | 1.98 | 0.47 | 2.45 | 0.29 | 1.64 | 0.39 | 2.09 |
| Number of different opioid analgesic agents (study drugs) used, mean (SD) | 1.73 | 0.64 | 1.67 | 0.61 | 1.00 | 0 | 1.00 | 0 |
| Number of prescribers of IR or ER opioid analgesics, mean (SD) | 0.95 | 0.86 | 0.93 | 0.86 | 0.75 | 0.65 | 0.74 | 0.66 |
| Number of pharmacies where patient obtained IR or ER opioid analgesics, mean (SD) | 1.00 | 0.91 | 1.00 | 0.86 | 0.77 | 0.63 | 0.82 | 0.63 |

Table 19: Benzodiazepine use for OxyContin and comparators, overall and by period

| | | Prevalence of Benzodiazepine use at baseline | | | | | | | | | | | |
|----------------------|--------------------------------|--|-------|---------|-------|--------------------------------|-------|---------|-------|-------------------------------|-------|---------|-------|
| | | All | | | | Two years before reformulation | | | | Two years after reformulation | | | |
| | | No | | Yes | | No | | Yes | | No | | Yes | |
| | | N | % | N | % | N | % | N | % | N | % | N | % |
| Incident + Prevalent | Any OxyContin | 332,116 | 63.5% | 190,659 | 36.5% | 175,253 | 63.7% | 99,985 | 36.3% | 156,863 | 63.4% | 90,674 | 36.6% |
| | Any ER morphine | 662,223 | 68.7% | 302,120 | 31.3% | 288,859 | 68.3% | 133,785 | 31.7% | 373,364 | 68.9% | 168,335 | 31.1% |
| | Any TD Fentanyl | 347,990 | 61.7% | 216,171 | 38.3% | 176,066 | 61.8% | 108,887 | 38.2% | 171,924 | 61.6% | 107,284 | 38.4% |
| | Any Methadone | 335,376 | 65.7% | 175,352 | 34.3% | 164,870 | 65.9% | 85,415 | 34.1% | 170,506 | 65.5% | 89,937 | 34.5% |
| | Any ER oxymorphone | 49,191 | 75.6% | 15,857 | 24.4% | 13,445 | 72.1% | 5,202 | 27.9% | 35,746 | 77.0% | 10,655 | 23.0% |
| | Any IR oxycodone single-entity | 769,885 | 68.7% | 351,301 | 31.3% | 222,174 | 65.4% | 117,400 | 34.6% | 547,711 | 70.1% | 233,901 | 29.9% |
| | Any IR hydromorphone | 233,124 | 67.9% | 110,136 | 32.1% | 100,689 | 68.1% | 47,205 | 31.9% | 132,435 | 67.8% | 62,931 | 32.2% |
| Prevalent | Any OxyContin | 230,602 | 62.1% | 140,633 | 37.9% | 116,994 | 61.9% | 72,034 | 38.1% | 113,608 | 62.4% | 68,599 | 37.6% |
| | Any ER morphine | 379,188 | 66.3% | 192,473 | 33.7% | 163,875 | 66.4% | 82,767 | 33.6% | 215,313 | 66.2% | 109,706 | 33.8% |
| | Any TD Fentanyl | 210,383 | 60.1% | 139,628 | 39.9% | 106,800 | 60.4% | 70,145 | 39.6% | 103,583 | 59.9% | 69,483 | 40.1% |
| | Any Methadone | 210,767 | 64.0% | 118,383 | 36.0% | 102,577 | 64.3% | 56,831 | 35.7% | 108,190 | 63.7% | 61,552 | 36.3% |
| | Any ER oxymorphone | 28,431 | 74.6% | 9,657 | 25.4% | 6,555 | 68.8% | 2,973 | 31.2% | 21,876 | 76.6% | 6,684 | 23.4% |
| | Any IR oxycodone single-entity | 241,778 | 62.8% | 143,073 | 37.2% | 68,328 | 59.5% | 46,592 | 40.5% | 173,450 | 64.3% | 96,481 | 35.7% |
| | Any IR hydromorphone | 79,687 | 61.0% | 50,921 | 39.0% | 34,934 | 61.8% | 21,556 | 38.2% | 44,753 | 60.4% | 29,365 | 39.6% |
| Incident | Any OxyContin | 101,514 | 67.0% | 50,026 | 33.0% | 58,259 | 67.6% | 27,951 | 32.4% | 43,255 | 66.2% | 22,075 | 33.8% |
| | Any ER morphine | 283,035 | 72.1% | 109,647 | 27.9% | 124,984 | 71.0% | 51,018 | 29.0% | 158,051 | 72.9% | 58,629 | 27.1% |
| | Any TD Fentanyl | 137,607 | 64.3% | 76,543 | 35.7% | 69,266 | 64.1% | 38,742 | 35.9% | 68,341 | 64.4% | 37,801 | 35.6% |
| | Any Methadone | 124,609 | 68.6% | 56,969 | 31.4% | 62,293 | 68.5% | 28,584 | 31.5% | 62,316 | 68.7% | 28,385 | 31.3% |
| | Any ER oxymorphone | 20,760 | 77.0% | 6,200 | 23.0% | 6,890 | 75.6% | 2,229 | 24.4% | 13,870 | 77.7% | 3,971 | 22.3% |
| | Any IR oxycodone single-entity | 528,107 | 71.7% | 208,228 | 28.3% | 153,846 | 68.5% | 70,808 | 31.5% | 374,261 | 73.1% | 137,420 | 26.9% |
| | Any IR hydromorphone | 153,437 | 72.2% | 59,215 | 27.8% | 65,755 | 71.9% | 25,649 | 28.1% | 87,682 | 72.3% | 33,566 | 27.7% |

Abbreviations: ER = extended release; IR = immediate release; N = number; PC = primary comparator; SC = secondary comparator; TD = transdermal; w = with

^All OxyContin categories in this table exclude period w/ concomitant use of any PC or SC, and all comparator categories in this table exclude period w/ concomitant use with Oxy or PC or any other SC

Table 20: Bi-annual rates of opioid overdose, by opioid

| | Any OxyContin, Primary or Secondary Comparator use* | | | | Any OxyContin use* | | | | Any ER morphine tables and capsule use | | | | Any Fentanyl use | | | | |
|--------------------|---|--|---------------|------------------------|------------------------|--|---------------|------------------------|--|--|---------------|------------------------|----------------------|--|---------------|------------------------|--|
| | N Patients | N Cases opioid fatal or non-fatal overdose | Person-months | Rate per 1000 p-months | N Patients | N Cases opioid fatal or non-fatal overdose | Person-months | Rate per 1000 p-months | N Patients | N Cases opioid fatal or non-fatal overdose | Person-months | Rate per 1000 p-months | N Patients | N Cases opioid fatal or non-fatal overdose | Person-months | Rate per 1000 p-months | |
| All users | | | | | | | | | | | | | | | | | |
| July-December 2008 | 152734 | 1074 | 519838.8 | 2.07 | 29037 | 182 | 105320.2 | 1.73 | 43130 | 312 | 143547.2 | 2.17 | 29480 | 228 | 100010.9 | 2.28 | |
| January-June 2009 | 170248 | 1332 | 537358.2 | 2.48 | 27225 | 169 | 96901.7 | 1.74 | 47890 | 360 | 151109.5 | 2.38 | 30015 | 248 | 97274.7 | 2.55 | |
| July-December 2009 | 188803 | 1421 | 615629.0 | 2.31 | 30261 | 196 | 110686.5 | 1.77 | 49448 | 402 | 165857.5 | 2.42 | 28572 | 249 | 95168.4 | 2.62 | |
| January-June 2010 | 184986 | 1379 | 597690.2 | 2.31 | 27800 | 186 | 101885.0 | 1.83 | 47140 | 405 | 157317.7 | 2.57 | 26124 | 218 | 86051.9 | 2.53 | |
| July-December 2010 | 201509 | 1563 | 666493.3 | 2.35 | 29137 | 218 | 107364.3 | 2.03 | 49937 | 434 | 171043.1 | 2.54 | 26495 | 250 | 90398.5 | 2.77 | |
| January-June 2011 | 230162 | 1657 | 686124.1 | 2.42 | 28087 | 181 | 92585.5 | 1.95 | 54984 | 450 | 175090.9 | 2.57 | 28297 | 239 | 88929.0 | 2.69 | |
| July-December 2011 | 252283 | 1701 | 810384.0 | 2.10 | 27230 | 151 | 98033.7 | 1.54 | 59813 | 470 | 203083.0 | 2.31 | 29855 | 226 | 100150.0 | 2.26 | |
| January-June 2012 | 277042 | 1795 | 850313.0 | 2.11 | 25776 | 160 | 90007.9 | 1.78 | 68421 | 483 | 220475.9 | 2.19 | 31280 | 263 | 101304.0 | 2.60 | |
| July-December 2012 | 286114 | 1787 | 899969.0 | 1.99 | 25173 | 150 | 93138.7 | 1.61 | 70287 | 539 | 239618.6 | 2.25 | 30793 | 264 | 103917.8 | 2.54 | |
| All users | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | Any Methadone use | | | | Any ER Oxymorphone use | | | | Any IR SE Oxycodone | | | | Any IR Hydromorphone | | | | |
| | N Patients | N Cases opioid fatal or non-fatal overdose | Person-months | Rate per 1000 p-months | N Patients | N Cases opioid fatal or non-fatal overdose | Person-months | Rate per 1000 p-months | N Patients | N Cases opioid fatal or non-fatal overdose | Person-months | Rate per 1000 p-months | N Patients | N Cases opioid fatal or non-fatal overdose | Person-months | Rate per 1000 p-months | |
| All users | | | | | | | | | | | | | | | | | |
| July-December 2008 | 27025 | 272 | 104559.2 | 2.60 | 2087 | 12 | 5526.9 | 2.17 | 44777 | 211 | 108324.8 | 1.95 | 24125 | 110 | 39510.6 | 2.78 | |
| January-June 2009 | 30707 | 366 | 110716.2 | 3.31 | 3096 | 38 | 8203.4 | 4.63 | 51419 | 287 | 115886.0 | 2.48 | 28448 | 145 | 44191.7 | 3.28 | |
| July-December 2009 | 32412 | 371 | 124046.0 | 2.99 | 3912 | 20 | 11699.1 | 1.71 | 68122 | 361 | 165720.1 | 2.18 | 29077 | 156 | 47272.6 | 3.30 | |
| January-June 2010 | 30439 | 329 | 116455.9 | 2.83 | 4255 | 29 | 13079.2 | 2.22 | 72049 | 428 | 181906.3 | 2.35 | 28004 | 138 | 45951.5 | 3.00 | |
| July-December 2010 | 31058 | 340 | 122451.4 | 2.78 | 5816 | 38 | 18581.9 | 2.04 | 86938 | 487 | 225565.7 | 2.16 | 31662 | 164 | 52012.9 | 3.15 | |
| January-June 2011 | 31852 | 333 | 115756.5 | 2.88 | 8672 | 126 | 27811.8 | 4.53 | 107977 | 592 | 258437.5 | 2.29 | 32814 | 187 | 52179.9 | 3.58 | |
| July-December 2011 | 32931 | 349 | 129168.6 | 2.70 | 11098 | 102 | 41016.0 | 2.49 | 126232 | 617 | 328865.0 | 1.88 | 36191 | 170 | 58694.2 | 2.90 | |
| January-June 2012 | 35005 | 340 | 130206.0 | 2.61 | 10249 | 82 | 35165.3 | 2.33 | 145300 | 731 | 370468.4 | 1.97 | 39205 | 175 | 63681.4 | 2.75 | |
| July-December 2012 | 34329 | 317 | 132215.1 | 2.40 | 6923 | 47 | 23752.6 | 1.98 | 155713 | 780 | 408339.7 | 1.91 | 40516 | 168 | 68591.8 | 2.45 | |

8.4.2 MarketScan

Table 21: Demographic and clinical characteristics

| | Any use of OxyContin based treatment episodes excluding primary comparators (2.1) | Any use of primary comparator opioids treatment episodes excluding OxyContin and other primary comparators (2.1) | OxyContin alone treatment episodes (2.2) | Primary comparator alone opioid treatment episodes (2.2) |
|---|---|--|--|--|
| Total treatment episodes, n (%) | 561,703 | 36.5 | 975,389 | 63.5 |
| Total patients, n (%)* | 122,254 | 40.3 | 181,240 | 59.7 |
| Mean person-time per treatment episode in months, mean (sd) | 1.43 | 2.56 | 1.81 | 2.88 |
| Total person-time per treatment episode in months, mean (sd) | 5.96 | 10.28 | 7.95 | 11.86 |
| Demographic characteristics (treatment episode measures) | | | | |
| Age (years) | | | | |
| Mean, SD | 53.11 | 12.02 | 54.64 | 11.64 |
| Median | 55.00 | | 56.00 | |
| Range (min, max) | 16.00 | 74.00 | 16.00 | 74.00 |
| Age category, n (%) | | | | |
| 16-34 | 51,268 | 9.1% | 66,844 | 7% |
| 35-64 | 426,919 | 76.0% | 726,312 | 75% |
| 65-74 | 83,516 | 14.9% | 182,233 | 19% |
| Gender, n (%) | | | | |
| Male | 276,337 | 49.2% | 415,338 | 43% |
| Female | 285,366 | 50.8% | 560,051 | 57% |
| Geographic region of patient residence (US), n (%) | | | | |
| Midwest | 116,581 | 20.8% | 211,161 | 22% |
| Northeast | 111,153 | 19.8% | 142,647 | 15% |
| South | 209,476 | 37.3% | 383,717 | 39% |
| West | 123,772 | 22.0% | 236,376 | 24% |
| Missing/Unknown | 721 | 0.1% | 1,488 | 0% |
| Health plan type, n (%) | | | | |
| HMO | 66,436 | 11.8% | 158,327 | 16% |
| PPO | 314,282 | 56.0% | 499,367 | 51% |
| CDHP/HDHP | 23,843 | 4.2% | 41,671 | 4% |
| Other | 110,481 | 19.7% | 204,181 | 21% |
| Unknown | 46,661 | 8.3% | 71,843 | 7% |
| Year of index date, n (%) [#] | | | | |

| | | | | | | | | |
|---|---------|-------|---------|-------|--------|-------|---------|-------|
| 2008 | 56,637 | 10.1% | 103,743 | 11% | 22,380 | 10.7% | 43,470 | 11.0% |
| 2009 | 101,591 | 18.1% | 164,693 | 17% | 39,240 | 18.7% | 68,584 | 17.3% |
| 2010 | 51,073 | 9.1% | 83,329 | 9% | 19,656 | 9.4% | 34,498 | 8.7% |
| 2011 | 124,306 | 22.1% | 208,544 | 21% | 45,816 | 21.9% | 84,483 | 21.3% |
| 2012 | 98,785 | 17.6% | 175,547 | 18% | 35,950 | 17.2% | 70,261 | 17.7% |
| 2013 | 71,271 | 12.7% | 133,335 | 14% | 25,995 | 12.4% | 53,476 | 13.5% |
| 2014 | 51,198 | 9.1% | 92,137 | 9% | 18,027 | 8.6% | 35,496 | 9.0% |
| 2015 | 6,842 | 1.2% | 14,061 | 1% | 2,472 | 1.2% | 5,648 | 1.4% |
| Pain diagnosis, n (%) | | | | | | | | |
| Abdominal pain | 80,535 | 14.3% | 179,919 | 18% | 29,483 | 14.1% | 71,735 | 18.1% |
| Amputation | 3,629 | 0.6% | 5,950 | 1% | 1,400 | 0.7% | 2,472 | 0.6% |
| Arthritis, arthropathies, osteoarthritis and musculoskeletal pain | 211,401 | 37.6% | 299,111 | 31% | 74,537 | 35.6% | 114,533 | 28.9% |
| Back pain | 253,930 | 45.2% | 471,567 | 48% | 86,043 | 41.1% | 174,454 | 44.1% |
| Chronic pain | 65,463 | 11.7% | 143,661 | 15% | 21,398 | 10.2% | 52,674 | 13.3% |
| Fibromyalgia | 36,288 | 6.5% | 79,889 | 8% | 12,052 | 5.8% | 29,707 | 7.5% |
| Headache | 40,416 | 7.2% | 82,333 | 8% | 14,018 | 6.7% | 31,696 | 8.0% |
| Malignancy | 125,792 | 22.4% | 255,357 | 26% | 52,040 | 24.8% | 110,659 | 28.0% |
| Multiple sclerosis | 3,973 | 0.7% | 8,746 | 1% | 1,521 | 0.7% | 3,599 | 0.9% |
| Neuropathic pain | 14,164 | 2.5% | 32,678 | 3% | 5,472 | 2.6% | 13,650 | 3.4% |
| Peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers | 19,177 | 3.4% | 38,666 | 4% | 7,354 | 3.5% | 15,720 | 4.0% |
| Stroke | 8,341 | 1.5% | 18,263 | 2% | 3,269 | 1.6% | 7,690 | 1.9% |
| Liver disease | 26,527 | 4.7% | 52,744 | 5% | 10,089 | 4.8% | 21,480 | 5.4% |
| Renal disease | 18,590 | 3.3% | 39,458 | 4% | 7,505 | 3.6% | 16,967 | 4.3% |
| COPD | 64,556 | 11.5% | 129,161 | 13% | 23,929 | 11.4% | 51,942 | 13.1% |
| Impaired respiratory function | 62,946 | 11.2% | 128,888 | 13% | 24,477 | 0.117 | 54,017 | 13.6% |
| Deyo-Charlson comorbidity index | | | | | | | | |
| Mean, SD | 2.03 | 3.06 | 2.42 | 329% | 2.21 | 3.17 | 2.56 | 3.36 |
| Median | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| Range (min, max) | 0.00 | 20.00 | 0.00 | 2400% | 0.00 | 20.00 | 0.00 | 24.00 |
| Psychiatric comorbidities, n (%) | | | | | | | | |
| Attention deficit hyperactive disorder (ADHD) | 2,433 | 0.4% | 3,399 | 0% | 702 | 0.3% | 1,166 | 0.3% |
| Bipolar disorder | 12,755 | 2.3% | 26,646 | 3% | 4,512 | 2.2% | 10,540 | 2.7% |
| Borderline personality disorder | 263 | 0.0% | 756 | 0% | 102 | 0.0% | 299 | 0.1% |
| Generalized anxiety disorder | 37,346 | 6.6% | 69,000 | 7% | 12,391 | 5.9% | 26,053 | 6.6% |
| Major depression disorder | 62,556 | 11.1% | 128,661 | 13% | 22,024 | 10.5% | 50,846 | 12.8% |
| Substance use disorder | 16,038 | 2.9% | 30,911 | 3% | 4,838 | 2.3% | 10,953 | 2.8% |
| Alcoholism | 4,981 | 0.9% | 8,617 | 1% | 1,658 | 0.8% | 3,302 | 0.8% |
| History of attempted suicide | 761 | 0.1% | 1,138 | 0% | 241 | 0.1% | 414 | 0.1% |
| Post-traumatic stress disorder | 3,286 | 0.6% | 7,346 | 1% | 1,106 | 0.5% | 2,891 | 0.7% |
| Sleep disorder | 48,693 | 8.7% | 90,282 | 9% | 17,618 | 8.4% | 36,005 | 9.1% |
| Somatoform disorder | 110 | 0.0% | 475 | 0% | 32 | 0.0% | 193 | 0.0% |

| Drug dependence | | | | | | | | |
|--|---------|-------|---------|-------|---------|-------|---------|-------|
| Opioid type dependence | 9,560 | 1.7% | 18,777 | 2% | 2,952 | 1.4% | 6,916 | 1.7% |
| Non-opioid drug dependence | 7,963 | 1.4% | 15,083 | 2% | 2,374 | 1.1% | 5,184 | 1.3% |
| History of overdose/poisoning | 1,428 | 0.3% | 3,801 | 0% | 423 | 0.2% | 1,355 | 0.3% |
| Non-opioid medications of abuse potential during treatment episode, n (%) | | | | | | | | |
| Depressants | | | | | | | | |
| Benzodiazepines | 86,631 | 15.4% | 154,579 | 16% | 21,350 | 10.2% | 44,308 | 11.2% |
| Barbiturates | 331 | 0.1% | 637 | 0% | 126 | 0.1% | 192 | 0.0% |
| Sleep medications | 51,642 | 9.2% | 94,496 | 10% | 14,691 | 7.0% | 28,497 | 7.2% |
| Stimulants | | | | | | | | |
| Amphetamines | 6,895 | 1.2% | 12,532 | 1% | 1,583 | 0.8% | 3,634 | 0.9% |
| Methylphenidate | 3,336 | 0.6% | 7,331 | 1% | 906 | 0.4% | 2,554 | 0.6% |
| Dextromethorphan | 14 | 0.0% | 14 | 0% | 7 | 0.0% | 1 | 0.0% |
| Muscle relaxants | 68,062 | 12.1% | 130,608 | 13% | 14,877 | 7.1% | 32,326 | 8.2% |
| Opioid maintenance therapy medication use during treatment episode, n (%) | | | | | | | | |
| Suboxone | 1,814 | 0.3% | 1,999 | 0% | 584 | 0.3% | 762 | 0.2% |
| Subutex/sublingual buprenorphine tablets | 346 | 0.1% | 351 | 0% | 96 | 0.0% | 137 | 0.0% |
| Solution of methadone | 50 | 0.0% | 338 | 0% | 17 | 0.0% | 181 | 0.0% |
| Duration of treatment episode (months), mean (sd) | 1.30 | 2.76 | 1.48 | 2.89 | 1.14 | 2.51 | 1.33 | 2.64 |
| Healthcare utilization during six months prior to the index date, mean (sd) ^a | | | | | | | | |
| All-cause office visits | 8.63 | 7.00 | 9.16 | 7.16 | 8.48 | 7.17 | 9.00 | 7.26 |
| All-cause ED visits | 0.67 | 1.62 | 0.79 | 1.82 | 0.62 | 1.48 | 0.76 | 1.75 |
| All-cause hospitalizations | 0.53 | 0.93 | 0.54 | 1.03 | 0.52 | 0.94 | 0.54 | 1.04 |
| Distinct medication classes (defined by the four-digit level of the GPI code) dispensed | 9.25 | 5.03 | 10.13 | 5.10 | 9.27 | 4.98 | 10.07 | 5.08 |
| Exposures | | | | | | | | |
| OxyContin dose, n (%) | | | | | | | | |
| 10 mg | 184,071 | 32.8% | | | 71,193 | 34.0% | | |
| 15 mg | 18,435 | 3.3% | | | 6,504 | 3.1% | | |
| 20 mg | 192,733 | 34.3% | | | 71,276 | 34.0% | | |
| 30 mg | 49,120 | 8.7% | | | 15,887 | 7.6% | | |
| 40 mg | 107,831 | 19.2% | | | 38,289 | 18.3% | | |
| 60 mg | 34,789 | 6.2% | | | 10,956 | 5.2% | | |
| 80 mg | 59,351 | 10.6% | | | 21,100 | 10.1% | | |
| Usage, n (%) | | | | | | | | |
| Existing (continuing) user | 395,420 | 70.4% | 676,600 | 69.4% | 142,230 | 67.9% | 269,650 | 68.1% |
| Incident (new) user | 166,283 | 29.6% | 298,789 | 30.6% | 67,306 | 32.1% | 126,266 | 31.9% |
| Comparator usage, any, n (%) | | | | | | | | |
| ER morphine | | | 383,442 | 39.3% | | | 147,513 | 37.3% |

| | | | | | | | | |
|---|---------|-------|---------|-------|---------|-------|---------|-------|
| TD Fentanyl | | | 441,383 | 45.3% | | | 178,085 | 45.0% |
| Methadone tabs/capsules | | | 150,564 | 15.4% | | | 70,318 | 17.8% |
| IR oxycodone single entity | 148,267 | 26.4% | 122,702 | 12.6% | | | | |
| IR hydromorphone | 24,217 | 4.3% | 67,264 | 6.9% | | | | |
| ER oxymorphone | 5,769 | 1.0% | 10,630 | 1.1% | | | | |
| Other opioid use (non primary or secondary comparators) | 229,127 | 40.8% | 451,161 | 46.3% | | | | |
| Transdermal delivery system (fentanyl or buprenorphine), n (%) | 551 | 0.1% | 441,995 | 45.3% | | | 178,085 | 45.0% |
| Buprenorphine | 551 | 0.1% | 1,074 | 0.1% | | | | |
| Prior use of opioid analgesics, n (%) | | | | | | | | |
| ER opioid analgesic only | 35,112 | 6.3% | 89,298 | 9.2% | 17,346 | 8.3% | 48,188 | 12.2% |
| IR opioid analgesic only | 73,231 | 13.0% | 114,103 | 11.7% | 8,739 | 4.2% | 18,465 | 4.7% |
| Both ER and IR opioid analgesic | 420,080 | 74.8% | 734,587 | 75.3% | 172,133 | 82.1% | 307,137 | 77.6% |
| No opioid analgesic | 33,280 | 5.9% | 37,401 | 3.8% | 11,318 | 5.4% | 22,126 | 5.6% |
| Prior use of tramadol | 41,886 | 7.5% | 79,506 | 8.2% | 11,844 | 5.7% | 26,765 | 6.8% |
| Time since the end of the last opioid analgesic (months), mean (sd) | 0.49 | 2.79 | 0.49 | 2.78 | 0.33 | 2.00 | 0.39 | 2.29 |
| Number of different opioid analgesic agents (study drugs) used, mean (sd) | 1.73 | 0.64 | 1.67 | 0.62 | 1.00 | 0.00 | 1.00 | 0.00 |

Table 22: NDI-linkable versus non-linkable populations

| | Any use of OxyContin based treatment episodes excluding primary comparators (2.1) | | | | Any use of primary comparator opioids treatment episodes excluding OxyContin (2.1) | | | |
|--|---|-------|------------------|-------|--|-------|------------------|-------|
| | NDI linkable | | Non-NDI linkable | | NDI linkable | | Non-NDI linkable | |
| Total treatment episodes, n (%) | 561,703 | 12.01 | 1,179,442 | 25.22 | 975,389 | 20.86 | 1,959,309 | 41.90 |
| Total patients, n (%)* | 122,254 | 13.70 | 255,600 | 28.64 | 181,240 | 20.31 | 333,487 | 37.36 |
| Mean person-time per treatment episode in months, mean (sd) | 1.43 | 2.56 | 1.47 | 2.69 | 1.81 | 2.88 | 2.10 | 3.20 |
| Total person-time per treatment episode in months, mean (sd) | 5.96 | 10.28 | 6.47 | 12.38 | 7.95 | 11.86 | 9.96 | 15.18 |
| Demographic characteristics (treatment episode measures) | | | | | | | | |
| Age (years) | | | | | | | | |
| Mean, SD | 53.11 | 12.02 | 51.21 | 11.45 | 54.64 | 11.64 | 52.22 | 11.17 |
| Median | 55.00 | | 53.00 | | 56.00 | | 53.00 | |
| Range (min, max) | 16.00 | 74.00 | 16.00 | 74.00 | 16.00 | 74.00 | 16.00 | 74.00 |
| Age category, n (%) | | | | | | | | |
| 16-34 | 51,268 | 9.1% | 111,136 | 9.4% | 66,844 | 6.9% | 146,589 | 7.5% |
| 35-64 | 426,919 | 76.0% | 959,809 | 81.4% | 726,312 | 74.5% | 1,586,780 | 81.0% |
| 65-74 | 83,516 | 14.9% | 108,497 | 9.2% | 182,233 | 18.7% | 225,940 | 11.5% |
| Gender, n (%) | | | | | | | | |
| Male | 276,337 | 49.2% | 556,721 | 47.2% | 415,338 | 42.6% | 785,172 | 40.1% |
| Female | 285,366 | 50.8% | 622,721 | 52.8% | 560,051 | 57.4% | 1,174,137 | 59.9% |

| | | | | | | | | |
|---|---------|-------|---------|-------|---------|-------|-----------|-------|
| Geographic region of patient residence (US), n (%) | | | | | | | | |
| Midwest | 116,581 | 20.8% | 288,945 | 24.5% | 211,161 | 21.6% | 518,873 | 26.5% |
| Northeast | 111,153 | 19.8% | 239,872 | 20.3% | 142,647 | 14.6% | 280,367 | 14.3% |
| South | 209,476 | 37.3% | 359,278 | 30.5% | 383,717 | 39.3% | 660,855 | 33.7% |
| West | 123,772 | 22.0% | 258,844 | 21.9% | 236,376 | 24.2% | 452,109 | 23.1% |
| Missing/Unknown | 721 | 0.1% | 32,503 | 2.8% | 1,488 | 0.2% | 47,105 | 2.4% |
| Health plan type, n (%) | | | | | | | | |
| HMO | 66,436 | 11.8% | 148,502 | 12.6% | 158,327 | 16.2% | 294,914 | 15.1% |
| PPO | 314,282 | 56.0% | 719,186 | 61.0% | 499,367 | 51.2% | 1,141,147 | 58.2% |
| CDHP/HDHP | 23,843 | 4.2% | 82,238 | 7.0% | 41,671 | 4.3% | 125,754 | 6.4% |
| Other | 110,481 | 19.7% | 178,340 | 15.1% | 204,181 | 20.9% | 317,879 | 16.2% |
| Unknown | 46,661 | 8.3% | 51,176 | 4.3% | 71,843 | 7.4% | 79,615 | 4.1% |
| Year of index date, n (%) | | | | | | | | |
| 2008 | 56,637 | 10.1% | 102,581 | 8.7% | 103,743 | 10.6% | 182,941 | 9.3% |
| 2009 | 101,591 | 18.1% | 189,328 | 16.1% | 164,693 | 16.9% | 296,037 | 15.1% |
| 2010 | 51,073 | 9.1% | 79,550 | 6.7% | 83,329 | 8.5% | 127,728 | 6.5% |
| 2011 | 124,306 | 22.1% | 208,294 | 17.7% | 208,544 | 21.4% | 343,127 | 17.5% |
| 2012 | 98,785 | 17.6% | 181,359 | 15.4% | 175,547 | 18.0% | 302,417 | 15.4% |
| 2013 | 71,271 | 12.7% | 147,257 | 12.5% | 133,335 | 13.7% | 247,531 | 12.6% |
| 2014 | 51,198 | 9.1% | 176,393 | 15.0% | 92,137 | 9.4% | 290,502 | 14.8% |
| 2015 | 6,842 | 1.2% | 94,680 | 8.0% | 14,061 | 1.4% | 169,026 | 8.6% |
| Pain diagnosis, n (%) | | | | | | | | |
| Abdominal pain | 80,535 | 14.3% | 144,629 | 12.3% | 179,919 | 18.4% | 307,386 | 15.7% |
| Amputation | 3,629 | 0.6% | 7,230 | 0.6% | 5,950 | 0.6% | 10,675 | 0.5% |
| Arthritis, arthropathies, osteoarthritis and musculoskeletal pain | 211,401 | 37.6% | 484,765 | 41.1% | 299,111 | 30.7% | 657,231 | 33.5% |
| Back pain | 253,930 | 45.2% | 571,531 | 48.5% | 471,567 | 48.3% | 1,054,457 | 53.8% |
| Chronic pain | 65,463 | 11.7% | 170,470 | 14.5% | 143,661 | 14.7% | 358,647 | 18.3% |
| Fibromyalgia | 36,288 | 6.5% | 97,189 | 8.2% | 79,889 | 8.2% | 213,211 | 10.9% |
| Headache | 40,416 | 7.2% | 97,054 | 8.2% | 82,333 | 8.4% | 195,368 | 10.0% |
| Malignancy | 125,792 | 22.4% | 154,732 | 13.1% | 255,357 | 26.2% | 290,491 | 14.8% |
| Multiple sclerosis | 3,973 | 0.7% | 10,171 | 0.9% | 8,746 | 0.9% | 22,059 | 1.1% |
| Neuropathic pain | 14,164 | 2.5% | 30,312 | 2.6% | 32,678 | 3.4% | 65,949 | 3.4% |
| Peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers | 19,177 | 3.4% | 34,858 | 3.0% | 38,666 | 4.0% | 64,975 | 3.3% |
| Stroke | 8,341 | 1.5% | 14,758 | 1.3% | 18,263 | 1.9% | 30,242 | 1.5% |
| Liver disease | 26,527 | 4.7% | 44,631 | 3.8% | 52,744 | 5.4% | 81,378 | 4.2% |
| Renal disease | 18,590 | 3.3% | 29,937 | 2.5% | 39,458 | 4.0% | 59,347 | 3.0% |
| COPD | 64,556 | 11.5% | 122,430 | 10.4% | 129,161 | 13.2% | 227,343 | 11.6% |
| Impaired respiratory function | 62,946 | 11.2% | 95,607 | 8.1% | 128,888 | 13.2% | 173,483 | 8.9% |
| Deyo-Charlson comorbidity index | | | | | | | | |
| Mean, SD | 2.03 | 3.06 | 1.32 | 2.36 | 2.42 | 3.29 | 1.56 | 2.58 |
| Median | 1.00 | | 0.00 | | 1.00 | | 0.00 | |
| Range (min, max) | 0.00 | 20.00 | 0.00 | 22.00 | 0.00 | 24.00 | 0.00 | 25.00 |

| Psychiatric comorbidities, n (%) | | | | | | | | |
|---|---------|-------|---------|-------|---------|-------|---------|-------|
| Attention deficit hyperactive disorder (ADHD) | 2,433 | 0.4% | 6,314 | 0.5% | 3,399 | 0.3% | 10,086 | 0.5% |
| Bipolar disorder | 12,755 | 2.3% | 27,766 | 2.4% | 26,646 | 2.7% | 58,649 | 3.0% |
| Borderline personality disorder | 263 | 0.0% | 615 | 0.1% | 756 | 0.1% | 1,663 | 0.1% |
| Generalized anxiety disorder | 37,346 | 6.6% | 96,071 | 8.1% | 69,000 | 7.1% | 172,621 | 8.8% |
| Major depression disorder | 62,556 | 11.1% | 149,437 | 12.7% | 128,661 | 13.2% | 294,988 | 15.1% |
| Substance use disorder | 16,038 | 2.9% | 43,811 | 3.7% | 30,911 | 3.2% | 86,518 | 4.4% |
| Alcoholism | 4,981 | 0.9% | 11,748 | 1.0% | 8,617 | 0.9% | 18,397 | 0.9% |
| History of attempted suicide | 761 | 0.1% | 1,943 | 0.2% | 1,138 | 0.1% | 3,307 | 0.2% |
| Post-traumatic stress disorder | 3,286 | 0.6% | 9,340 | 0.8% | 7,346 | 0.8% | 18,806 | 1.0% |
| Sleep disorder | 48,693 | 8.7% | 117,529 | 10.0% | 90,282 | 9.3% | 207,849 | 10.6% |
| Somatoform disorder | 110 | 0.0% | 488 | 0.0% | 475 | 0.0% | 1,144 | 0.1% |
| Drug dependence | | | | | | | | |
| Opioid type dependence | 9,560 | 1.7% | 28,241 | 2.4% | 18,777 | 1.9% | 56,188 | 2.9% |
| Non-opioid drug dependence | 7,963 | 1.4% | 19,815 | 1.7% | 15,083 | 1.5% | 38,927 | 2.0% |
| History of overdose/poisoning | 1,428 | 0.3% | 2,802 | 0.2% | 3,801 | 0.4% | 7,406 | 0.4% |
| Non-opioid medications of abuse potential during treatment episode, n (%) | | | | | | | | |
| Depressants | | | | | | | | |
| Benzodiazepines | 86,631 | 15.4% | 180,770 | 15.3% | 154,579 | 15.8% | 321,250 | 16.4% |
| Barbiturates | 331 | 0.1% | 576 | 0.0% | 637 | 0.1% | 1,305 | 0.1% |
| Sleep medications | 51,642 | 9.2% | 110,466 | 9.4% | 94,496 | 9.7% | 207,110 | 10.6% |
| Stimulants | | | | | | | | |
| Amphetamines | 6,895 | 1.2% | 18,330 | 1.6% | 12,532 | 1.3% | 34,653 | 1.8% |
| Methylphenidate | 3,336 | 0.6% | 7,343 | 0.6% | 7,331 | 0.8% | 16,677 | 0.9% |
| Dextromethorphan | 14 | 0.0% | 3 | 0.0% | 14 | 0.0% | 50 | 0.0% |
| Muscle relaxants | 68,062 | 12.1% | 161,487 | 13.7% | 130,608 | 13.4% | 321,082 | 16.4% |
| Opioid maintenance therapy medication use during treatment episode, n (%) | | | | | | | | |
| Suboxone | 1,814 | 0.3% | 4,201 | 0.4% | 1,999 | 0.2% | 4,694 | 0.2% |
| Subutex/sublingual buprenorphine tablets | 346 | 0.1% | 711 | 0.1% | 351 | 0.0% | 940 | 0.0% |
| Solution of methadone | 50 | 0.0% | 141 | 0.0% | 338 | 0.0% | 670 | 0.0% |
| Duration of treatment episode (months), mean (sd) | 1.30 | 2.76 | 1.40 | 3.08 | 1.48 | 2.89 | 1.69 | 3.33 |
| Healthcare utilization during six months prior to index date, mean (sd) [^] | | | | | | | | |
| All-cause office visits | 8.63 | 7.00 | 7.77 | 6.19 | 9.16 | 7.16 | 8.26 | 6.57 |
| All-cause ED visits | 0.67 | 1.62 | 0.60 | 1.67 | 0.79 | 1.82 | 0.69 | 1.82 |
| All-cause hospitalizations | 0.53 | 0.93 | 0.46 | 0.89 | 0.54 | 1.03 | 0.42 | 0.95 |
| Distinct medication classes (defined by the four-digit level of the GPI code) dispensed | 9.25 | 5.03 | 8.83 | 4.96 | 10.13 | 5.10 | 9.65 | 5.02 |
| Exposures | | | | | | | | |
| OxyContin dose, n (%) | | | | | | | | |
| 10 mg | 184,071 | 32.8% | 390,155 | 33.1% | | | | |
| 15 mg | 18,435 | 3.3% | 41,595 | 3.5% | | | | |

| | | | | | | | | |
|---|---------|-------|---------|-------|---------|-------|-----------|-------|
| 20 mg | 192,733 | 34.3% | 381,380 | 32.3% | | | | |
| 30 mg | 49,120 | 8.7% | 109,031 | 9.2% | | | | |
| 40 mg | 107,831 | 19.2% | 218,931 | 18.6% | | | | |
| 60 mg | 34,789 | 6.2% | 76,512 | 6.5% | | | | |
| 80 mg | 59,351 | 10.6% | 126,183 | 10.7% | | | | |
| Usage, n (%) | | | | | | | | |
| Existing (continuing) user | 395,420 | 70.4% | 829,329 | 70.3% | 676,600 | 69.4% | 1,418,769 | 72.4% |
| Incident (new) user | 166,283 | 29.6% | 350,113 | 29.7% | 298,789 | 30.6% | 540,540 | 27.6% |
| Comparator usage, any, n (%) | | | | | | | | |
| ER morphine | | | | | 383,442 | 39.3% | 787,319 | 40.2% |
| TD Fentanyl | | | | | 441,383 | 45.3% | 837,133 | 42.7% |
| Methadone tabs/capsules | | | | | 150,564 | 15.4% | 334,857 | 17.1% |
| IR oxycodone single entity | 148,267 | 26.4% | 308,329 | 26.1% | 122,702 | 12.6% | 257,806 | 13.2% |
| IR hydromorphone | 24,217 | 4.3% | 51,493 | 4.4% | 67,264 | 6.9% | 130,023 | 6.6% |
| ER oxymorphone | 5,769 | 1.0% | 12,570 | 1.1% | 10,630 | 1.1% | 22,980 | 1.2% |
| Other opioid use (non primary or secondary comparators) | 229,127 | 40.8% | 498,083 | 42.2% | 451,161 | 46.3% | 924,896 | 47.2% |
| Transdermal delivery system (fentanyl or buprenorphine), n (%) | 551 | 0.1% | 1,561 | 0.1% | 441,995 | 45.3% | 838,758 | 42.8% |
| Buprenorphine | 551 | 0.1% | 1,561 | 0.1% | 1,074 | 0.1% | 2,937 | 0.1% |
| Prior use of opioid analgesics, n (%) | | | | | | | | |
| ER opioid analgesic only | 35,112 | 6.3% | 71,483 | 6.1% | 89,298 | 9.2% | 189,497 | 9.7% |
| IR opioid analgesic only | 73,231 | 13.0% | 146,639 | 12.4% | 114,103 | 11.7% | 195,337 | 10.0% |
| Both ER and IR opioid analgesic | 420,080 | 74.8% | 882,167 | 74.8% | 734,587 | 75.3% | 1,503,113 | 76.7% |
| No opioid analgesic | 33,280 | 5.9% | 79,153 | 6.7% | 37,401 | 3.8% | 71,362 | 3.6% |
| Prior use of tramadol | 41,886 | 7.5% | 90,810 | 7.7% | 79,506 | 8.2% | 162,228 | 8.3% |
| Time since the end of the last opioid analgesic (months), mean (sd) | 0.49 | 2.79 | 0.56 | 3.29 | 0.49 | 2.78 | 0.52 | 3.11 |
| Number of different opioid analgesic agents (study drugs) used, mean (sd) | 1.73 | 0.64 | 1.74 | 0.64 | 1.67 | 0.62 | 1.69 | 0.63 |

Table 23: Bi-annual rates of opioid overdose, by opioid

| | Any OxyContin, Primary or Secondary Comparator use | | | | Any OxyContin use | | | | Any ER morphine tables and capsule use | | | | Any Fentanyl use | | | |
|--------------------------|--|-------------------------------|-------------------------------|-------|--|-------------------------------|-------------------------------|-------|--|-------------------------------|-------------------------------|------|--|-------------------------------|-------------------------------|--|
| | N Cases opioid fatal or non-fatal overdose | | Rate per Person- months | | N Cases opioid fatal or non-fatal overdose | | Rate per Person- months | | N Cases opioid fatal or non-fatal overdose | | Rate per Person- months | | N Cases opioid fatal or non-fatal overdose | | Rate per Person- months | |
| | N Patients | | | | N Patients | | | | N Patients | | | | N Patients | | | |
| All users | | | | | | | | | | | | | | | | |
| July-December 2008 | 82,981 | 319 | 246,033 | 1.297 | 21,507 | 85 | 69,942 | 1.215 | 15,555 | 85 | 51,939 | 1.64 | 18,007 | 76 | 62,268 | 1.22 |
| January-June 2009 | 80,317 | 325 | 223,330 | 1.455 | 21,233 | 80 | 61,096 | 1.309 | 15,255 | 90 | 48,161 | 1.87 | 17,411 | 84 | 56,375 | 1.49 |
| July-December 2009 | 92,691 | 292 | 266,091 | 1.097 | 25,523 | 83 | 80,889 | 1.026 | 15,945 | 78 | 53,249 | 1.46 | 17,575 | 82 | 60,120 | 1.36 |
| January-June 2010 | 97,044 | 266 | 257,581 | 1.033 | 24,364 | 91 | 73,638 | 1.236 | 16,085 | 45 | 50,315 | 0.89 | 17,462 | 77 | 56,037 | 1.37 |
| July-December 2010 | 112,044 | 325 | 317,682 | 1.023 | 27,335 | 90 | 87,575 | 1.028 | 17,936 | 69 | 60,784 | 1.14 | 19,145 | 94 | 66,441 | 1.41 |
| January-June 2011 | 116,361 | 416 | 308,775 | 1.347 | 27,029 | 105 | 81,216 | 1.293 | 18,981 | 81 | 59,863 | 1.35 | 19,233 | 98 | 62,735 | 1.56 |
| July-December 2011 | 120,215 | 433 | 326,863 | 1.325 | 25,735 | 106 | 80,934 | 1.310 | 18,984 | 91 | 63,178 | 1.44 | 19,406 | 110 | 65,658 | 1.68 |
| January-June 2012 | 115,691 | 455 | 300,019 | 1.517 | 23,681 | 94 | 71,139 | 1.321 | 18,522 | 111 | 58,842 | 1.89 | 18,310 | 98 | 59,852 | 1.64 |
| July-December 2012 | 116,703 | 400 | 308,017 | 1.299 | 23,030 | 92 | 72,086 | 1.276 | 18,137 | 86 | 60,340 | 1.43 | 17,656 | 86 | 60,758 | 1.42 |
| January-June 2013 | 92,418 | 328 | 232,174 | 1.413 | 17,640 | 53 | 52,445 | 1.011 | 14,643 | 57 | 46,915 | 1.21 | 14,071 | 78 | 45,259 | 1.72 |
| July-December 2013 | 92,291 | 264 | 231,567 | 1.140 | 17,056 | 39 | 51,849 | 0.752 | 14,186 | 45 | 46,232 | 0.97 | 13,462 | 69 | 44,474 | 1.55 |
| January-June 2014 | 69,355 | 271 | 156,713 | 1.729 | 12,430 | 43 | 34,888 | 1.233 | 9,809 | 75 | 29,006 | 2.59 | 9,700 | 52 | 29,177 | 1.78 |
| July-December 2014 | 64,219 | 219 | 142,824 | 1.533 | 10,814 | 52 | 31,040 | 1.675 | 8,702 | 37 | 26,105 | 1.42 | 8,547 | 51 | 26,138 | 1.95 |
| January-June 2015 | 21,328 | 94 | 40,938 | 2.296 | 3,640 | 16 | 8,397 | 1.905 | 3,444 | 14 | 7,944 | 1.76 | 3,445 | 27 | 7,784 | 3.47 |
| July-October 2015 | 3,969 | 18 | 3,951 | 4.556 | 652 | ≤10 | 713 | 1.403 | 717 | ≤10 | 798 | 5.01 | 765 | ≤10 | 794 | 3.78 |
| Any Methadone use | | | | | | | | | | | | | | | | |
| | Any ER Oxymorphone use | | | | Any IR SE Oxycodeine | | | | Any IR Hydromorphone | | | | | | | |
| | N Cases opioid fatal or non-fatal overdose | Rate per Person- months | N Patients | | N Cases opioid fatal or non-fatal overdose | Rate per Person- months | N Patients | | N Cases opioid fatal or non-fatal overdose | Rate per Person- months | N Patients | | N Cases opioid fatal or non-fatal overdose | Rate per Person- months | N Patients | Rate per 1000 p- months ^a |
| | N Patients | | | | N Patients | | | | N Patients | | | | N Patients | | | |
| All users | | | | | | | | | | | | | | | | |
| July-December 2008 | 7,266 | 47 | 29,103 | 1.61 | 2,303 | ≤10 | 6,674 | 0.60 | 26,705 | 63 | 50,304 | 1.25 | 13,495 | 22 | 14,349 | 1.53 |
| January-June 2009 | 7,066 | 46 | 26,516 | 1.73 | 2,520 | ≤10 | 6,946 | 1.01 | 23,496 | 47 | 43,668 | 1.08 | 14,939 | 31 | 15,321 | 2.02 |
| July-December 2009 | 7,434 | 24 | 29,505 | 0.81 | 2,946 | ≤10 | 9,096 | 0.33 | 32,473 | 57 | 61,482 | 0.93 | 15,791 | 25 | 16,764 | 1.49 |
| January-June 2010 | 7,535 | 33 | 27,932 | 1.18 | 3,333 | ≤10 | 9,699 | 1.03 | 37,911 | 68 | 68,862 | 0.99 | 16,259 | 25 | 16,842 | 1.48 |
| July-December 2010 | 8,421 | 32 | 34,614 | 0.92 | 4,255 | 12 | 13,439 | 0.89 | 46,803 | 113 | 91,598 | 1.23 | 18,760 | 22 | 20,455 | 1.08 |
| January-June 2011 | 8,285 | 54 | 31,787 | 1.70 | 4,652 | 25 | 14,483 | 1.73 | 50,787 | 136 | 95,440 | 1.42 | 19,651 | 37 | 21,152 | 1.75 |
| July-December 2011 | 8,024 | 44 | 32,297 | 1.36 | 4,990 | 29 | 16,964 | 1.71 | 55,210 | 154 | 106,886 | 1.44 | 20,984 | 33 | 23,639 | 1.40 |
| January-June 2012 | 7,585 | 58 | 29,312 | 1.98 | 4,381 | 21 | 14,091 | 1.49 | 55,504 | 160 | 103,544 | 1.55 | 20,322 | 35 | 22,704 | 1.54 |
| July-December 2012 | 7,222 | 49 | 29,293 | 1.67 | 3,695 | 23 | 12,290 | 1.87 | 58,404 | 154 | 110,970 | 1.39 | 20,205 | 33 | 23,475 | 1.41 |
| January-June 2013 | 5,662 | 41 | 21,726 | 1.89 | 2,808 | 21 | 9,055 | 2.32 | 46,199 | 133 | 83,915 | 1.58 | 16,253 | 40 | 18,990 | 2.11 |
| July-December 2013 | 5,271 | 32 | 21,002 | 1.52 | 2,567 | 15 | 9,160 | 1.64 | 48,124 | 100 | 86,019 | 1.16 | 16,180 | 33 | 19,632 | 1.68 |
| January-June 2014 | 3,503 | 24 | 12,703 | 1.89 | 2,036 | 12 | 6,715 | 1.79 | 39,387 | 106 | 64,860 | 1.63 | 11,078 | 30 | 12,575 | 2.39 |
| July-December 2014 | 2,917 | 25 | 10,621 | 2.35 | 1,770 | ≤10 | 6,240 | 0.80 | 38,265 | 115 | 61,921 | 1.86 | 10,200 | 34 | 11,397 | 2.98 |
| January-June 2015 | 1,057 | ≤10 | 2,788 | 2.15 | 524 | ≤10 | 1,536 | 2.60 | 12,183 | 46 | 18,192 | 2.53 | 3,505 | ≤10 | 3,647 | 2.19 |
| July-October 2015 | 234 | ≤10 | 274 | 10.94 | 117 | 0 | 144 | 0.00 | 2,051 | ≤10 | 1,766 | 5.66 | 519 | ≤10 | 351 | 2.85 |

Table 24: Rate ratios and ratio of rate ratios (RORR) for OxyContin and secondary comparators

| Opioid analgesic | Exposure period category | MarketScan ⁱ | | | |
|------------------|---|-----------------------------|-----------------------------|--|--|
| | | Unadjusted rate ratio (CI) | Adjusted rate ratio (CI) | Unadjusted ratio of rate ratio (CI) ⁱⁱⁱ | Adjusted ratio of rate ratio (CI) ⁱⁱⁱ |
| OxyContin | Any use ⁱⁱ (with or without concomitant opioid analgesic use periods) | 0.75 (0.59-0.95)* | 0.69 (0.55-0.86)* | ref | |
| ER Oxymorphone | | 1.99 (1.06-3.76)* | 1.74 (0.94-3.24) | 2.65 (1.35-5.22)* | 2.54 (1.31-4.92)* |
| SE IR Oxycodone | | 1.28 (1.00-1.65)* | 1.20 (0.94-1.54) | 1.71 (1.21-2.41)* | 1.75 (1.26-2.44)* |
| IR Hydromorphone | | 1.08 (0.74-1.58) | 1.03 (0.72-1.47) | 1.44 (0.92-2.25) | 1.50 (0.99-2.29) |
| OxyContin | Use alone (without concomitant opioid analgesic use periods) | 0.69 (0.47-1.02) | 0.64 (0.44-0.94)* | ref | |
| ER Oxymorphone | | 3.28 (0.99-10.90) | 2.76 (0.84-9.08) | 4.74 (1.34-16.74)* | 4.30 (1.23-15.04)* |
| SE IR Oxycodone | | 1.36 (1.01-1.84)* | 1.29 (0.96-1.73) | 1.97 (1.21-3.21)* | 2.01 (1.24-3.25)* |
| IR Hydromorphone | | 0.83 (0.53-1.28) | 0.83 (0.54-1.25) | 1.20 (0.67-2.15) | 1.29 (0.73-2.26) |

(FDA generated table using data from the PMR 3051-4 study report)

Key: *=statistically significant ($p<0.05$), ⁱ=unintentional overdose outcome only, ⁱⁱ=excluding periods with concomitant comparator use; ⁱⁱⁱ=null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group)

8.4.3 HIRD

Table 25: Demographic and clinical characteristics

| | Any use of OxyContin based treatment episodes excluding primary comparators (2.1) | | Any use of primary comparator opioids treatment episodes excluding OxyContin and other primary comparators (2.1) | | OxyContin alone treatment episodes (2.2) | | Primary comparator alone opioid treatment episodes (2.2) | |
|--|---|------|--|------|--|------|--|------|
| Total treatment episodes, n (%) | 378,441 | 36.6 | 654,462 | 63.4 | 142,928 | 13.8 | 269,348 | 26.1 |
| Total patients, n (%)* | 81,137 | 42.3 | 110,619 | 57.7 | 54,683 | 28.5 | 80,556 | 42.0 |
| Mean person-time per treatment episode in months, mean (SD) | 1.4 | 2.3 | 2.1 | 2.8 | 0.9 | 1.8 | 1.4 | 2.3 |
| Total person-time per patient in months, mean (SD) | 6.1 | 11.4 | 9.5 | 13.9 | 2.8 | 7.0 | 4.7 | 9.3 |
| Demographic characteristics (treatment episode measures) | | | | | | | | |
| Age (years) | | | | | | | | |
| Mean, SD | 51.4 | 12.2 | 53.4 | 11.9 | 52.2 | 12.2 | 54.1 | 11.9 |
| Median | 53 | | 54 | | 54 | | 55 | |
| Range (min, max) | 16 | 74 | 16 | 74 | 16 | 74 | 16 | 74 |
| Age category, n (%) | | | | | | | | |
| 16-34 | 41,247 | 10.9 | 51,821 | 7.9 | 14,366 | 10.1 | 19,437 | 7.2 |
| 35-64 | 288,850 | 76.3 | 481,294 | 73.5 | 108,024 | 75.6 | 194,676 | 72.3 |
| 65-74 | 48,344 | 12.8 | 121,347 | 18.5 | 20,538 | 14.4 | 55,235 | 20.5 |
| Gender, n (%) | | | | | | | | |
| Male | 188,455 | 49.8 | 271,693 | 41.5 | 71,160 | 49.8 | 111,083 | 41.2 |
| Female | 189,986 | 50.2 | 382,769 | 58.5 | 71,768 | 50.2 | 158,265 | 58.8 |
| Geographic region of patient residence (US), n (%) | | | | | | | | |
| Midwest | 68,298 | 18.0 | 84,987 | 13.0 | 26,572 | 18.6 | 35,936 | 13.3 |
| Northeast | 95,739 | 25.3 | 185,681 | 28.4 | 37,751 | 26.4 | 79,320 | 29.4 |
| South | 92,286 | 24.4 | 178,771 | 27.3 | 33,121 | 23.2 | 71,862 | 26.7 |
| West | 122,101 | 32.3 | 204,923 | 31.3 | 45,475 | 31.8 | 82,188 | 30.5 |
| Missing/Unknown | 17 | 0.0 | 100 | 0.0 | ≤10 | 0.0 | 42 | 0.0 |
| Health plan type, n (%) | | | | | | | | |
| HMO | 74,828 | 19.8 | 121,282 | 18.5 | 28,316 | 19.8 | 49,573 | 18.4 |
| PPO | 267,971 | 70.8 | 489,324 | 74.8 | 101,247 | 70.8 | 201,635 | 74.9 |
| CDHP/HDHP | 35,638 | 9.4 | 43,805 | 6.7 | 13,364 | 9.4 | 18,118 | 6.7 |

| | | | | | | | | |
|---|---------|------|---------|------|--------|------|---------|------|
| Other | ≤10 | 0.0 | 50 | 0.0 | 0 | 0.0 | 21 | 0.0 |
| Unknown | ≤10 | 0.0 | ≤10 | 0.0 | ≤10 | 0.0 | ≤10 | 0.0 |
| Year of index date, n (%) [#] | | | | | | | | |
| 2008 | 40,872 | 10.8 | 72,177 | 11.0 | 16,170 | 11.3 | 30,611 | 11.4 |
| 2009 | 74,696 | 19.7 | 119,965 | 18.3 | 29,299 | 20.5 | 50,364 | 18.7 |
| 2010 | 31,045 | 8.2 | 49,044 | 7.5 | 12,123 | 8.5 | 20,644 | 7.7 |
| 2011 | 70,866 | 18.7 | 117,319 | 17.9 | 26,455 | 18.5 | 48,026 | 17.8 |
| 2012 | 53,134 | 14.0 | 96,288 | 14.7 | 19,802 | 13.9 | 39,159 | 14.5 |
| 2013 | 44,874 | 11.9 | 77,422 | 11.8 | 16,378 | 11.5 | 31,267 | 11.6 |
| 2014 | 42,342 | 11.2 | 79,704 | 12.2 | 14,876 | 10.4 | 31,335 | 11.6 |
| 2015 | 20,612 | 5.4 | 42,543 | 6.5 | 7,825 | 5.5 | 17,942 | 6.7 |
| Pain diagnosis, n (%) | | | | | | | | |
| Abdominal pain | 55,554 | 14.7 | 120,612 | 18.4 | 20,708 | 14.5 | 48,921 | 18.2 |
| Amputation | 2,857 | 0.8 | 5,109 | 0.8 | 1,125 | 0.8 | 2,181 | 0.8 |
| Arthritis, arthropathies, osteoarthritis and musculoskeletal pain | 164,603 | 43.5 | 243,429 | 37.2 | 59,366 | 41.5 | 95,544 | 35.5 |
| Back pain | 193,211 | 51.1 | 374,626 | 57.2 | 67,568 | 47.3 | 143,060 | 53.1 |
| Chronic pain | 63,456 | 16.8 | 138,170 | 21.1 | 21,503 | 15.0 | 51,716 | 19.2 |
| Fibromyalgia | 39,200 | 10.4 | 92,439 | 14.1 | 13,156 | 9.2 | 34,993 | 13.0 |
| Headache | 37,038 | 9.8 | 76,413 | 11.7 | 13,041 | 9.1 | 29,987 | 11.1 |
| Malignancy | 66,937 | 17.7 | 129,599 | 19.8 | 28,182 | 19.7 | 58,040 | 21.5 |
| Multiple sclerosis | 3,294 | 0.9 | 8,255 | 1.3 | 1,317 | 0.9 | 3,674 | 1.4 |
| Neuropathic pain | 10,627 | 2.8 | 26,043 | 4.0 | 4,232 | 3.0 | 10,897 | 4.0 |
| Peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers | 15,248 | 4.0 | 32,313 | 4.9 | 5,982 | 4.2 | 13,621 | 5.1 |
| Stroke | 5,713 | 1.5 | 12,687 | 1.9 | 2,271 | 1.6 | 5,518 | 2.0 |
| Liver disease | 19,365 | 5.1 | 37,360 | 5.7 | 7,559 | 5.3 | 15,486 | 5.7 |
| Renal disease | 12,484 | 3.3 | 28,541 | 4.4 | 5,105 | 3.6 | 12,478 | 4.6 |
| COPD | 49,926 | 13.2 | 104,775 | 16.0 | 18,698 | 13.1 | 42,641 | 15.8 |
| Impaired respiratory function | 42,264 | 11.2 | 80,588 | 12.3 | 16,614 | 11.6 | 34,180 | 12.7 |
| Deyo-Charlson comorbidity index | | | | | | | | |
| Mean, SD | 1.7 | 2.8 | 2.0 | 3.0 | 1.9 | 3.0 | 2.2 | 3.1 |
| Median | 0 | | 1 | | 0 | | 1 | |
| Range (min, max) | 0 | 18 | 0 | 21 | 0 | 18 | 0 | 21 |
| Psychiatric comorbidities, n (%) | | | | | | | | |
| Attention deficit hyperactive disorder (ADHD) | 3,000 | 0.8 | 3,770 | 0.6 | 1,055 | 0.7 | 1,434 | 0.5 |
| Bipolar disorder | 9,957 | 2.6 | 22,387 | 3.4 | 3,595 | 2.5 | 8,939 | 3.3 |
| Borderline personality disorder | 466 | 0.1 | 805 | 0.1 | 174 | 0.1 | 317 | 0.1 |
| Generalized anxiety disorder | 41,413 | 10.9 | 76,718 | 11.7 | 14,214 | 9.9 | 29,501 | 11.0 |
| Major depression disorder | 58,692 | 15.5 | 119,470 | 18.3 | 21,508 | 15.0 | 48,066 | 17.8 |

| | | | | | | | | |
|--|--------|------|---------|------|--------|------|--------|------|
| Alcoholism | 5,882 | 1.6 | 9,130 | 1.4 | 2,080 | 1.5 | 3,633 | 1.3 |
| History of attempted suicide | 1,071 | 0.3 | 1,898 | 0.3 | 374 | 0.3 | 761 | 0.3 |
| Post-traumatic stress disorder | 2,917 | 0.8 | 6,553 | 1.0 | 995 | 0.7 | 2,545 | 0.9 |
| Sleep disorder | 43,448 | 11.5 | 80,297 | 12.3 | 16,137 | 11.3 | 32,463 | 12.1 |
| Somatoform disorder | 157 | 0.0 | 567 | 0.1 | 60 | 0.0 | 211 | 0.1 |
| Drug dependence | | | | | | | | |
| Opioid type dependence | 11,343 | 3.0 | 23,706 | 3.6 | 3,601 | 2.5 | 8,886 | 3.3 |
| Non-opioid drug dependence | 8,840 | 2.3 | 19,215 | 2.9 | 2,786 | 1.9 | 7,087 | 2.6 |
| History of overdose/poisoning | 1,110 | 0.3 | 3,160 | 0.5 | 342 | 0.2 | 1,109 | 0.4 |
| Non-opioid medications of abuse potential during treatment episode, n (%) | | | | | | | | |
| Depressants | | | | | | | | |
| Benzodiazepines | 60,818 | 16.1 | 109,074 | 16.7 | 14,984 | 10.5 | 32,087 | 11.9 |
| Barbiturates | 220 | 0.1 | 517 | 0.1 | 66 | 0.0 | 192 | 0.1 |
| Sleep medications | 37,809 | 10.0 | 71,087 | 10.9 | 10,672 | 7.5 | 22,033 | 8.2 |
| Stimulants | | | | | | | | |
| Amphetamines | 6,627 | 1.8 | 12,392 | 1.9 | 1,689 | 1.2 | 3,823 | 1.4 |
| Methylphenidate | 3,032 | 0.8 | 6,085 | 0.9 | 900 | 0.6 | 2,025 | 0.8 |
| Dextromethorphan | 22 | 0.0 | 19 | 0.0 | ≤10 | 0.0 | ≤10 | 0.0 |
| Muscle relaxants | 46,593 | 12.3 | 99,258 | 15.2 | 10,816 | 7.6 | 26,734 | 9.9 |
| Opioid maintenance therapy medication use during treatment episode, n (%) | | | | | | | | |
| Suboxone | 655 | 0.2 | 802 | 0.1 | 222 | 0.2 | 334 | 0.1 |
| Subutex/sublingual buprenorphine tablets | 201 | 0.1 | 253 | 0.0 | 66 | 0.0 | 102 | 0.0 |
| Solution of methadone | 16 | 0.0 | 148 | 0.0 | 5 | 0.0 | 81 | 0.0 |
| Duration of treatment episode (months), mean (SD) | 1.3 | 2.8 | 1.6 | 3.0 | 1.1 | 2.4 | 1.4 | 2.7 |
| Healthcare utilization during six months prior to the index date, mean (SD) [^] | | | | | | | | |
| All-cause office visits | 8.4 | 6.9 | 9.0 | 7.2 | 8.2 | 7.0 | 8.8 | 7.3 |
| All-cause ED visits | 0.4 | 1.0 | 0.4 | 1.2 | 0.4 | 1.0 | 0.4 | 1.1 |
| All-cause hospitalizations | 0.5 | 1.0 | 0.5 | 1.1 | 0.5 | 1.0 | 0.5 | 1.1 |
| Distinct medication classes (defined by the four-digit level of the GPI code) dispensed | 10.6 | 6.2 | 11.9 | 6.4 | 10.6 | 6.1 | 11.7 | 6.4 |
| Exposures | | | | | | | | |
| OxyContin dose, n (%) | | | | | | | | |
| 10 mg | 58,648 | 15.5 | | | 13,769 | 9.6 | | |
| 15 mg | 5,600 | 1.5 | | | 1,399 | 1.0 | | |
| 20 mg | 58,147 | 15.4 | | | 14,067 | 9.8 | | |
| 30 mg | 16,329 | 4.3 | | | 3,488 | 2.4 | | |
| 40 mg | 35,003 | 9.2 | | | 8,418 | 5.9 | | |

| | | | | | | | | |
|---|---------|------|---------|------|---------|------|---------|------|
| 60 mg | 12,806 | 3.4 | | | 2,385 | 1.7 | | |
| 80 mg | 26,529 | 7.0 | | | 6,035 | 4.2 | | |
| Usage, n (%) | | | | | | | | |
| Existing (continuing) user | 225,196 | 59.5 | 362,879 | 55.5 | 78,601 | 55.0 | 139,094 | 51.6 |
| Incident (new) user | 153,245 | 40.5 | 291,583 | 44.6 | 64,327 | 45.0 | 130,254 | 48.4 |
| Comparator usage, any, n (%) | | | | | | | | |
| ER morphine | | | 252,960 | 38.7 | | | 96,702 | 35.9 |
| TD Fentanyl | | | 272,898 | 41.7 | | | 110,786 | 41.1 |
| Methadone tabs/capsules | | | 128,604 | 19.7 | | | 61,860 | 23.0 |
| IR oxycodone single entity | 96,452 | 25.5 | 89,639 | 13.7 | | | | |
| IR hydromorphone | 17,397 | 4.6 | 46,086 | 7.0 | | | | |
| ER oxymorphone | 3,602 | 1.0 | 6,200 | 0.9 | | | | |
| Other opioid use (non primary or secondary comparators) | 153,387 | 40.5 | 290,985 | 44.5 | | | | |
| Transdermal delivery system (fentanyl or buprenorphine), n (%) | 399 | 0.1 | 273,269 | 41.8 | 31 | 0.0 | 110,829 | 41.1 |
| Buprenorphine | 399 | 0.1 | 654 | 0.1 | 31 | 0.0 | 63 | 0.0 |
| Prior use of opioid analgesics, n (%) | | | | | | | | |
| ER opioid analgesic only | 24,936 | 6.6 | 66,015 | 10.1 | 15,127 | 10.6 | 41,899 | 15.6 |
| IR opioid analgesic only | 41,159 | 10.9 | 59,691 | 9.1 | 4,982 | 3.5 | 9,827 | 3.6 |
| Both ER and IR opioid analgesic | 290,450 | 76.7 | 508,673 | 77.7 | 116,988 | 81.9 | 205,558 | 76.3 |
| No opioid analgesic | 21,896 | 5.8 | 20,083 | 3.1 | 5,831 | 4.1 | 12,064 | 4.5 |
| Prior use of tramadol | 25,255 | 6.7 | 48,768 | 7.5 | 8,086 | 5.7 | 18,366 | 6.8 |
| Time since the end of the last opioid analgesic (months), mean (SD) | 0.5 | 2.9 | 0.4 | 2.6 | 0.3 | 1.9 | 0.3 | 2.1 |
| Number of different opioid analgesic agents (study drugs + other opioids) used, mean (SD) | 1.7 | 0.6 | 1.7 | 0.6 | 1.0 | 0.0 | 1.0 | 0.0 |
| Prescribing physician specialty (on index date), n (%) | | | | | | | | |
| General, internal medicine or family practice physician | 842 | 0.2 | 1,551 | 0.2 | 342 | 0.2 | 584 | 0.2 |
| Pain specialist | 24,899 | 6.6 | 72,806 | 11.1 | 4,590 | 3.2 | 18,439 | 6.8 |
| Other specialist | 154,297 | 40.8 | 254,207 | 38.8 | 34,962 | 24.5 | 77,976 | 28.9 |
| Non-physician | 31,297 | 8.3 | 48,267 | 7.4 | 4,942 | 3.5 | 11,773 | 4.4 |
| Unknown | 20,869 | 5.5 | 34,097 | 5.2 | 4,725 | 3.3 | 10,065 | 3.7 |
| Missing | 146,237 | 38.6 | 243,534 | 37.2 | 93,367 | 65.3 | 150,511 | 55.9 |
| Number of prescribers of IR or ER opioid analgesics, mean (SD) | 1.2 | 0.5 | 1.2 | 0.6 | 1.1 | 0.5 | 1.2 | 0.5 |
| Number of pharmacies where patient obtained IR or ER opioid analgesics, mean (SD) | 1.2 | 0.6 | 1.2 | 0.5 | 1.1 | 0.5 | 1.1 | 0.5 |

Table 26: Benzodiazepine use among those dispensed OxyContin and comparator opioids, overall and by period

| | | Prevalence of Benzodiazepine use at baseline (within 3 months) | | | | | | | | | | | |
|---|-----------------------------------|--|-------|---------|-------|------------------------|-------|--------|-------|-------------------------|-------|--------|-------|
| | | All | | | | Pre-period (2008-2010) | | | | Post-period (2011-2015) | | | |
| | | No | | Yes | | No | | Yes | | No | | Yes | |
| | | N | % | N | % | N | % | N | % | N | % | N | % |
| Combined (incident and prevalent) | Any OxyContin | 255,133 | 67.4% | 123,308 | 32.6% | 97,455 | 66.5% | 49,158 | 33.5% | 157,678 | 68.0% | 74,150 | 32.0% |
| | Any ER morphine | 177,116 | 70.0% | 75,844 | 30.0% | 57,927 | 68.1% | 27,161 | 31.9% | 119,189 | 71.0% | 48,683 | 29.0% |
| | Any TD Fentanyl | 177,364 | 65.0% | 95,534 | 35.0% | 67,315 | 63.8% | 38,167 | 36.2% | 110,049 | 65.7% | 57,367 | 34.3% |
| | Any Methadone | 90,912 | 70.7% | 37,692 | 29.3% | 35,421 | 70.0% | 15,195 | 30.0% | 55,491 | 71.2% | 22,497 | 28.8% |
| | Any ER oxymorphone | 17,198 | 66.1% | 8,811 | 33.9% | 6,459 | 67.2% | 3,148 | 32.8% | 10,739 | 65.5% | 5,663 | 34.5% |
| | Any IR oxycodone single-entity | 350,222 | 74.5% | 120,099 | 25.5% | 70,681 | 71.4% | 28,244 | 28.6% | 279,541 | 75.3% | 91,855 | 24.7% |
| | Any IR hydromorphone | 137,302 | 72.6% | 51,920 | 27.4% | 41,671 | 71.4% | 16,658 | 28.6% | 95,631 | 73.1% | 35,262 | 26.9% |
| Prevalent | Any OxyContin | 145,482 | 64.6% | 79,714 | 35.4% | 44,406 | 62.8% | 26,315 | 37.2% | 101,076 | 65.4% | 53,399 | 34.6% |
| | Any ER morphine | 95,229 | 67.9% | 45,016 | 32.1% | 23,400 | 64.3% | 13,002 | 35.7% | 71,829 | 69.2% | 32,014 | 30.8% |
| | Any TD Fentanyl | 92,018 | 63.2% | 53,590 | 36.8% | 25,743 | 60.4% | 16,875 | 39.6% | 66,275 | 64.4% | 36,715 | 35.6% |
| | Any Methadone | 53,543 | 69.5% | 23,483 | 30.5% | 15,636 | 68.0% | 7,352 | 32.0% | 37,907 | 70.1% | 16,131 | 29.9% |
| | Any ER oxymorphone | 9,500 | 63.8% | 5,388 | 36.2% | 2,912 | 64.2% | 1,621 | 35.8% | 6,588 | 63.6% | 3,767 | 36.4% |
| | Any IR oxycodone single-entity | 88,518 | 65.1% | 47,470 | 34.9% | 17,551 | 62.7% | 10,440 | 37.3% | 70,967 | 65.7% | 37,030 | 34.3% |
| | Any IR hydromorphone | 31,661 | 61.9% | 19,510 | 38.1% | 8,246 | 58.4% | 5,882 | 41.6% | 23,415 | 63.2% | 13,628 | 36.8% |
| Incident | Any OxyContin | 109,651 | 71.6% | 43,594 | 28.4% | 53,049 | 69.9% | 22,843 | 30.1% | 56,602 | 73.2% | 20,751 | 26.8% |
| | Any ER morphine | 81,887 | 72.6% | 30,828 | 27.4% | 34,527 | 70.9% | 14,159 | 29.1% | 47,360 | 74.0% | 16,669 | 26.0% |
| | Any TD Fentanyl | 85,346 | 67.0% | 41,944 | 33.0% | 41,572 | 66.1% | 21,292 | 33.9% | 43,774 | 67.9% | 20,652 | 32.1% |
| | Any Methadone | 37,369 | 72.5% | 14,209 | 27.5% | 19,785 | 71.6% | 7,843 | 28.4% | 17,584 | 73.4% | 6,366 | 26.6% |
| | Any ER oxymorphone | 7,698 | 69.2% | 3,423 | 30.8% | 3,547 | 69.9% | 1,527 | 30.1% | 4,151 | 68.6% | 1,896 | 31.4% |
| | Any IR oxycodone single-entity | 261,704 | 78.3% | 72,629 | 21.7% | 53,130 | 74.9% | 17,804 | 25.1% | 208,574 | 79.2% | 54,825 | 20.8% |
| | Any IR hydromorphone | 105,641 | 76.5% | 32,410 | 23.5% | 33,425 | 75.6% | 10,776 | 24.4% | 72,216 | 76.9% | 21,634 | 23.1% |

Table 27: NDI-linkable versus non-linkable populations

| | Any use of OxyContin based treatment episodes excluding primary comparators (2.1) | | | | Any use of primary comparator opioids treatment episodes excluding OxyContin (2.1) | | | |
|---|---|------|------------------|------|--|------|------------------|------|
| | NDI linkable | | Non-NDI linkable | | NDI linkable | | Non-NDI linkable | |
| Total treatment episodes, n (%) | 378,441 | 36.6 | 240,802 | 40.4 | 654,462 | 63.4 | 354,728 | 59.6 |
| Total patients, n (%)* | 81,137 | 42.3 | 53,411 | 45.9 | 110,619 | 57.7 | 62,865 | 54.1 |
| Mean person-time per treatment episode in months, mean (SD) | 1.4 | 2.3 | 1.4 | 2.4 | 2.1 | 2.8 | 2.1 | 2.8 |
| Total person-time per treatment episode in months, mean (SD) | 6.1 | 11.4 | 6.1 | 11.0 | 9.5 | 13.9 | 9.4 | 13.1 |
| Demographic characteristics (treatment episode measures) | | | | | | | | |
| Age (years) | | | | | | | | |
| Mean, SD | 51.4 | 12.2 | 50.9 | 11.5 | 53.4 | 11.9 | 51.1 | 11.1 |
| Median | 53 | | 53 | | 54 | | 52 | |
| Range (min, max) | 16 | 74 | 16 | 74 | 16 | 74 | 16 | 74 |
| Age category, n (%) | | | | | | | | |
| 16-34 | 41,247 | 10.9 | 24,195 | 10.0 | 51,821 | 7.9 | 30,375 | 8.6 |
| 35-64 | 288,850 | 76.3 | 195,002 | 81.0 | 481,294 | 73.5 | 291,980 | 82.3 |
| 65-74 | 48,344 | 12.8 | 21,605 | 9.0 | 121,347 | 18.5 | 32,373 | 9.1 |
| Gender, n (%) | | | | | | | | |
| Male | 188,455 | 49.8 | 117,178 | 48.7 | 271,693 | 41.5 | 148,072 | 41.7 |
| Female | 189,986 | 50.2 | 123,624 | 51.3 | 382,769 | 58.5 | 206,656 | 58.3 |
| Geographic region of patient residence (US), n (%) | | | | | | | | |
| Midwest | 68,298 | 18.0 | 52,577 | 21.8 | 84,987 | 13.0 | 51,791 | 14.6 |
| Northeast | 95,739 | 25.3 | 56,775 | 23.6 | 185,681 | 28.4 | 90,791 | 25.6 |
| South | 92,286 | 24.4 | 78,240 | 32.5 | 178,771 | 27.3 | 131,834 | 37.2 |
| West | 122,101 | 32.3 | 53,112 | 22.1 | 204,923 | 31.3 | 80,133 | 22.6 |
| Missing/Unknown | 17 | 0.0 | 98 | 0.0 | 100 | 0.0 | 179 | 0.1 |
| Health plan type, n (%) | | | | | | | | |
| HMO | 74,828 | 19.8 | 55,891 | 23.2 | 121,282 | 18.5 | 82,208 | 23.2 |
| PPO | 267,971 | 70.8 | 159,175 | 66.1 | 489,324 | 74.8 | 232,229 | 65.5 |

| | | | | | | | | |
|---|---------|------|---------|------|---------|------|---------|------|
| CDHP/HDHP | 35,638 | 9.4 | 25,736 | 10.7 | 43,805 | 6.7 | 40,291 | 11.4 |
| Other | ≤10 | 0.0 | 0 | 0.0 | 50 | 0.0 | 0 | 0.0 |
| Unknown | ≤10 | 0.0 | 0 | 0.0 | ≤10 | 0.0 | 0 | 0.0 |
| Year of index date, n (%) | | | | | | | | |
| 2008 | 40,872 | 10.8 | 19,338 | 8.0 | 72,177 | 11.0 | 32,022 | 9.0 |
| 2009 | 74,696 | 19.7 | 35,506 | 14.7 | 119,965 | 18.3 | 53,790 | 15.2 |
| 2010 | 31,045 | 8.2 | 13,992 | 5.8 | 49,044 | 7.5 | 21,041 | 5.9 |
| 2011 | 70,866 | 18.7 | 31,793 | 13.2 | 117,319 | 17.9 | 43,989 | 12.4 |
| 2012 | 53,134 | 14.0 | 24,484 | 10.2 | 96,288 | 14.7 | 34,184 | 9.6 |
| 2013 | 44,874 | 11.9 | 38,847 | 16.1 | 77,422 | 11.8 | 55,950 | 15.8 |
| 2014 | 42,342 | 11.2 | 49,010 | 20.4 | 79,704 | 12.2 | 71,355 | 20.1 |
| 2015 | 20,612 | 5.4 | 27,832 | 11.6 | 42,543 | 6.5 | 42,397 | 12.0 |
| Pain diagnosis, n (%) | | | | | | | | |
| Abdominal pain | 55,554 | 14.7 | 34,331 | 14.3 | 120,612 | 18.4 | 65,282 | 18.4 |
| Amputation | 2,857 | 0.8 | 1,864 | 0.8 | 5,109 | 0.8 | 2,227 | 0.6 |
| Arthritis, arthropathies, osteoarthritis and musculoskeletal pain | 164,603 | 43.5 | 107,910 | 44.8 | 243,429 | 37.2 | 130,538 | 36.8 |
| Back pain | 193,211 | 51.1 | 124,755 | 51.8 | 374,626 | 57.2 | 205,432 | 57.9 |
| Chronic pain | 63,456 | 16.8 | 43,187 | 17.9 | 138,170 | 21.1 | 79,932 | 22.5 |
| Fibromyalgia | 39,200 | 10.4 | 26,127 | 10.8 | 92,439 | 14.1 | 51,729 | 14.6 |
| Headache | 37,038 | 9.8 | 24,582 | 10.2 | 76,413 | 11.7 | 43,109 | 12.2 |
| Malignancy | 66,937 | 17.7 | 39,203 | 16.3 | 129,599 | 19.8 | 64,122 | 18.1 |
| Multiple sclerosis | 3,294 | 0.9 | 2,142 | 0.9 | 8,255 | 1.3 | 4,074 | 1.1 |
| Neuropathic pain | 10,627 | 2.8 | 7,510 | 3.1 | 26,043 | 4.0 | 13,100 | 3.7 |
| Peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers | 15,248 | 4.0 | 8,595 | 3.6 | 32,313 | 4.9 | 13,812 | 3.9 |
| Stroke | 5,713 | 1.5 | 3,004 | 1.2 | 12,687 | 1.9 | 5,731 | 1.6 |
| Liver disease | 19,365 | 5.1 | 12,363 | 5.1 | 37,360 | 5.7 | 20,163 | 5.7 |
| Renal disease | 12,484 | 3.3 | 8,260 | 3.4 | 28,541 | 4.4 | 12,901 | 3.6 |
| COPD | 49,926 | 13.2 | 32,998 | 13.7 | 104,775 | 16.0 | 51,582 | 14.5 |
| Impaired respiratory function | 42,264 | 11.2 | 23,908 | 9.9 | 80,588 | 12.3 | 39,028 | 11.0 |
| Deyo-Charlson comorbidity index | | | | | | | | |
| Mean, SD | 1.7 | 2.8 | 1.6 | 2.7 | 2.0 | 3.0 | 1.8 | 2.9 |
| Median | 0 | | 0 | | 1 | | 1 | |
| Range (min, max) | 0 | 18 | 0 | 19 | 0 | 21 | 0 | 18 |
| Psychiatric comorbidities, n (%) | | | | | | | | |
| Attention deficit hyperactive disorder (ADHD) | 3,000 | 0.8 | 1,721 | 0.7 | 3,770 | 0.6 | 2,441 | 0.7 |
| Bipolar disorder | 9,957 | 2.6 | 5,763 | 2.4 | 22,387 | 3.4 | 11,968 | 3.4 |

| | | | | | | | | |
|---|--------|------|--------|------|---------|------|--------|------|
| Borderline personality disorder | 466 | 0.1 | 140 | 0.1 | 805 | 0.1 | 425 | 0.1 |
| Generalized anxiety disorder | 41,413 | 10.9 | 27,092 | 11.3 | 76,718 | 11.7 | 43,234 | 12.2 |
| Major depression disorder | 58,692 | 15.5 | 38,675 | 16.1 | 119,470 | 18.3 | 65,007 | 18.3 |
| Alcoholism | 5,882 | 1.6 | 3,160 | 1.3 | 9,130 | 1.4 | 4,488 | 1.3 |
| History of attempted suicide | 1,071 | 0.3 | 692 | 0.3 | 1,898 | 0.3 | 1,165 | 0.3 |
| Post-traumatic stress disorder | 2,917 | 0.8 | 2,626 | 1.1 | 6,553 | 1.0 | 4,184 | 1.2 |
| Sleep disorder | 43,448 | 11.5 | 31,251 | 13.0 | 80,297 | 12.3 | 47,224 | 13.3 |
| Somatoform disorder | 157 | 0.0 | 104 | 0.0 | 567 | 0.1 | 222 | 0.1 |
| Drug dependence | | | | | | | | |
| Opioid type dependence | 11,343 | 3.0 | 6,876 | 2.9 | 23,706 | 3.6 | 13,049 | 3.7 |
| Non-opioid drug dependence | 8,840 | 2.3 | 5,416 | 2.2 | 19,215 | 2.9 | 9,716 | 2.7 |
| History of overdose/poisoning | 1,110 | 0.3 | 722 | 0.3 | 3,160 | 0.5 | 1,591 | 0.4 |
| Non-opioid medications of abuse potential during treatment episode, n (%) | | | | | | | | |
| Depressants | | | | | | | | |
| Benzodiazepines | 60,818 | 16.1 | 37,226 | 15.5 | 109,074 | 16.7 | 58,784 | 16.6 |
| Barbiturates | 220 | 0.1 | 131 | 0.1 | 517 | 0.1 | 197 | 0.1 |
| Sleep medications | 37,809 | 10.0 | 21,900 | 9.1 | 71,087 | 10.9 | 37,190 | 10.5 |
| Stimulants | | | | | | | | |
| Amphetamines | 6,627 | 1.8 | 3,584 | 1.5 | 12,392 | 1.9 | 6,302 | 1.8 |
| Methylphenidate | 3,032 | 0.8 | 1,654 | 0.7 | 6,085 | 0.9 | 3,449 | 1.0 |
| Dextromethorphan | 22 | 0.0 | | | 19 | 0.0 | 22 | 0.0 |
| Muscle relaxants | 46,593 | 12.3 | 30,847 | 12.8 | 99,258 | 15.2 | 57,749 | 16.3 |
| Opioid maintenance therapy medication use during treatment episode, n (%) | | | | | | | | |
| Suboxone | 655 | 0.2 | 352 | 0.1 | 802 | 0.1 | 475 | 0.1 |
| Subutex/sublingual buprenorphine tablets | 201 | 0.1 | 102 | 0.0 | 253 | 0.0 | 160 | 0.0 |
| Solution of methadone | 16 | 0.0 | 11 | 0.0 | 148 | 0.0 | 77 | 0.0 |
| Duration of treatment episode (months), mean (sd) | 1.3 | 2.8 | 1.3 | 2.8 | 1.6 | 3.0 | 1.7 | 3.1 |
| Healthcare utilization during six months prior to index date, mean (SD) ^a | | | | | | | | |
| All-cause office visits | 8.4 | 6.9 | 8.2 | 6.5 | 9.0 | 7.2 | 8.7 | 7.0 |
| All-cause ED visits | 0.4 | 1.0 | 0.4 | 1.1 | 0.4 | 1.2 | 0.5 | 1.2 |
| All-cause hospitalizations | 0.5 | 1.0 | 0.5 | 0.9 | 0.5 | 1.1 | 0.5 | 1.0 |
| Distinct medication classes (defined by the four-digit level of the GPI code) dispensed | 10.6 | 6.2 | 10.6 | 6.1 | 11.9 | 6.4 | 11.9 | 6.4 |
| Exposures | | | | | | | | |

| | | | | | | | | |
|---|---------|------|---------|------|---------|------|---------|------|
| OxyContin dose, n (%) | | | | | | | | |
| 10 mg | 58,648 | 15.5 | 39,775 | 16.5 | | | | |
| 15 mg | 5,600 | 1.5 | 4,247 | 1.8 | | | | |
| 20 mg | 58,147 | 15.4 | 37,392 | 15.5 | | | | |
| 30 mg | 16,329 | 4.3 | 11,902 | 4.9 | | | | |
| 40 mg | 35,003 | 9.2 | 21,056 | 8.7 | | | | |
| 60 mg | 12,806 | 3.4 | 8,202 | 3.4 | | | | |
| 80 mg | 26,529 | 7.0 | 13,952 | 5.8 | | | | |
| Usage, n (%) | | | | | | | | |
| Existing (continuing) user | 225,196 | 59.5 | 140,428 | 58.3 | 362,879 | 55.5 | 186,278 | 52.5 |
| Incident (new) user | 153,245 | 40.5 | 100,374 | 41.7 | 291,583 | 44.6 | 168,450 | 47.5 |
| Comparator usage, any, n (%) | | | | | | | | |
| ER morphine | | | | | 252,960 | 38.7 | 137,901 | 38.9 |
| TD Fentanyl | | | | | 272,898 | 41.7 | 152,937 | 43.1 |
| Methadone tabs/capsules | | | | | 128,604 | 19.7 | 63,890 | 18.0 |
| IR oxycodone single entity | 96,452 | 25.5 | 64,439 | 26.8 | 89,639 | 13.7 | 48,429 | 13.7 |
| IR hydromorphone | 17,397 | 4.6 | 11,048 | 4.6 | 46,086 | 7.0 | 23,784 | 6.7 |
| ER oxymorphone | 3,602 | 1.0 | 2,325 | 1.0 | 6,200 | 0.9 | 3,916 | 1.1 |
| Other opioid use (non primary or secondary comparators) | 153,387 | 40.5 | 96,563 | 40.1 | 290,985 | 44.5 | 158,929 | 44.8 |
| Transdermal delivery system (fentanyl or buprenorphine), n (%) | 399 | 0.1 | 377 | 0.2 | 273,269 | 41.8 | 153,228 | 43.2 |
| Buprenorphine | 399 | 0.1 | 377 | 0.2 | 654 | 0.1 | 528 | 0.1 |
| Prior use of opioid analgesics, n (%) | | | | | | | | |
| ER opioid analgesic only | 24,936 | 6.6 | 14,737 | 6.1 | 66,015 | 10.1 | 35,806 | 10.1 |
| IR opioid analgesic only | 41,159 | 10.9 | 26,959 | 11.2 | 59,691 | 9.1 | 33,044 | 9.3 |
| Both ER and IR opioid analgesic | 290,450 | 76.7 | 183,677 | 76.3 | 508,673 | 77.7 | 273,860 | 77.2 |
| No opioid analgesic | 21,896 | 5.8 | 15,429 | 6.4 | 20,083 | 3.1 | 12,018 | 3.4 |
| Prior use of tramadol | 25,255 | 6.7 | 18,747 | 7.8 | 48,768 | 7.5 | 28,889 | 8.1 |
| Time since the end of the last opioid analgesic (months), mean (SD) | 0.5 | 2.9 | 0.5 | 3.0 | 0.4 | 2.6 | 0.4 | 2.5 |
| Number of different opioid analgesic agents (study drugs + other opioids) used, mean (SD) | 1.7 | 0.6 | 1.7 | 0.6 | 1.7 | 0.6 | 1.7 | 0.6 |
| Prescribing physician specialty (on index date), n (%) | | | | | | | | |
| General, internal medicine or family practice physician | 842 | 0.2 | 247 | 0.1 | 1,551 | 0.2 | 506 | 0.1 |
| Pain specialist | 24,899 | 6.6 | 10,890 | 4.5 | 72,806 | 11.1 | 26,812 | 7.6 |

| | | | | | | | | |
|---|---------|------|--------|------|---------|------|---------|------|
| Other specialist | 154,297 | 40.8 | 72,973 | 30.3 | 254,207 | 38.8 | 101,495 | 28.6 |
| Non-physician | 31,297 | 8.3 | 16,918 | 7.0 | 48,267 | 7.4 | 20,830 | 5.9 |
| Unknown | 20,869 | 5.5 | 47,966 | 19.9 | 34,097 | 5.2 | 74,213 | 20.9 |
| Missing | 146,237 | 38.6 | 91,808 | 38.1 | 243,534 | 37.2 | 130,872 | 36.9 |
| Number of prescribers of IR or ER opioid analgesics, mean (SD) | 1.2 | 0.5 | 1.2 | 0.6 | 1.2 | 0.6 | 1.2 | 0.6 |
| Number of pharmacies where patient obtained IR or ER opioid analgesics, mean (SD) | 1.2 | 0.6 | 1.2 | 0.6 | 1.2 | 0.5 | 1.2 | 0.6 |

Table 28: Bi-annual rates of opioid overdose, by opioid analgesic

| | Any OxyContin, Primary or Secondary Comparator use | | | | Any OxyContin use | | | | Any ER morphine tables and capsule use | | | | Any Fentanyl use | | | |
|---------------------|--|--|-------------------|-------------------------------|------------------------|--|-------------------|-------------------------------|--|--|-------------------|-------------------------------|----------------------|--|-------------------|-------------------------------|
| | N Patients | N Cases opioid fatal or non-fatal overdose | Person- months | Rate per 1000 p- months | N Patients | N Cases opioid fatal or non-fatal overdose | Person- months | Rate per 1000 p- months | N Patients | N Cases opioid fatal or non-fatal overdose | Person- months | Rate per 1000 p- months | N Patients | N Cases opioid fatal or non-fatal overdose | Person- months | Rate per 1000 p- months |
| | | | | | | | | | | | | | | | | |
| All users | | | | | | | | | | | | | | | | |
| July-December 2008 | 58,134 | 212 | 168,937.4 | 1.25 | 15,622 | 66 | 48,017.4 | 1.37 | 9,763 | 49 | 33,543.9 | 1.46 | 11,164 | 40 | 39,110.7 | 1.02 |
| January-June 2009 | 56,150 | 171 | 159,207.4 | 1.07 | 15,404 | 39 | 44,377.6 | 0.88 | 9,788 | 36 | 32,540.4 | 1.11 | 10,877 | 52 | 36,279.0 | 1.43 |
| July-December 2009 | 59,003 | 175 | 169,294.9 | 1.03 | 16,476 | 57 | 50,334.7 | 1.13 | 9,481 | 37 | 33,228.0 | 1.11 | 10,274 | 49 | 35,903.0 | 1.36 |
| January-June 2010 | 58,937 | 177 | 161,584.2 | 1.10 | 15,274 | 43 | 45,489.2 | 0.95 | 9,126 | 39 | 30,766.2 | 1.27 | 9,966 | 52 | 33,787.9 | 1.54 |
| July-December 2010 | 61,448 | 199 | 173,548.0 | 1.15 | 15,795 | 52 | 46,859.3 | 1.11 | 9,163 | 33 | 32,809.9 | 1.01 | 10,010 | 48 | 35,663.1 | 1.35 |
| January-June 2011 | 64,423 | 190 | 176,808.4 | 1.07 | 15,463 | 36 | 44,388.9 | 0.81 | 9,990 | 39 | 34,056.9 | 1.15 | 10,126 | 38 | 35,294.5 | 1.08 |
| July-December 2011 | 67,293 | 214 | 191,088.7 | 1.12 | 14,855 | 34 | 44,305.3 | 0.77 | 10,299 | 52 | 37,704.1 | 1.38 | 10,275 | 46 | 37,475.6 | 1.23 |
| January-June 2012 | 64,525 | 183 | 176,794.7 | 1.04 | 13,337 | 39 | 40,104.2 | 0.97 | 10,160 | 45 | 35,231.7 | 1.28 | 9,548 | 38 | 33,306.1 | 1.14 |
| July-December 2012 | 65,262 | 197 | 183,191.0 | 1.08 | 12,542 | 32 | 39,484.5 | 0.81 | 10,217 | 46 | 37,449.8 | 1.23 | 9,123 | 42 | 32,754.3 | 1.28 |
| January-June 2013 | 59,447 | 162 | 158,583.3 | 1.02 | 11,382 | 40 | 34,526.6 | 1.16 | 8,956 | 25 | 31,515.0 | 0.79 | 7,715 | 35 | 27,215.0 | 1.29 |
| July-December 2013 | 60,018 | 190 | 159,153.4 | 1.19 | 10,918 | 38 | 34,090.3 | 1.11 | 8,607 | 52 | 31,594.9 | 1.65 | 7,391 | 35 | 26,894.6 | 1.30 |
| January-June 2014 | 58,931 | 134 | 142,741.5 | 0.94 | 9,963 | 20 | 29,400.6 | 0.68 | 8,386 | 28 | 28,108.9 | 1.00 | 6,839 | 20 | 23,428.7 | 0.85 |
| July-December 2014 | 62,600 | 177 | 157,616.7 | 1.12 | 9,426 | 38 | 30,110.9 | 1.26 | 8,976 | 43 | 31,888.6 | 1.35 | 6,660 | 31 | 24,639.2 | 1.26 |
| January-June 2015 | 57,690 | 165 | 137,704.8 | 1.20 | 8,060 | 29 | 25,001.9 | 1.16 | 8,257 | 29 | 27,906.0 | 1.04 | 5,619 | 43 | 20,166.2 | 2.13 |
| July-September 2015 | 40,537 | 73 | 61,912.9 | 1.18 | 5,407 | 13 | 10,409.6 | 1.25 | 6,254 | 14 | 12,458.7 | 1.12 | 4,120 | ≤10 | 8,512.0 | 1.17 |
| | Any Methadone use | | | | Any ER Oxymorphone use | | | | Any IR SE Oxycodone | | | | Any IR Hydromorphone | | | |
| All users | | | | | | | | | | | | | | | | |
| July-December 2008 | 6,476 | 39 | 25,320.6 | 1.54 | 1,438 | ≤10 | 4,097.6 | 2.44 | 19,211 | 55 | 37,026.3 | 1.49 | 10,977 | 15 | 12,176.8 | 1.23 |
| January-June 2009 | 6,221 | 39 | 23,852.8 | 1.64 | 1,538 | ≤10 | 4,516.1 | 0.66 | 16,385 | 28 | 33,002.0 | 0.85 | 11,697 | 16 | 12,751.8 | 1.25 |
| July-December 2009 | 5,954 | 23 | 23,694.0 | 0.97 | 1,632 | ≤10 | 5,238.3 | 0.95 | 20,102 | 40 | 39,381.3 | 1.02 | 11,296 | 21 | 12,591.4 | 1.67 |
| January-June 2010 | 5,879 | 22 | 22,863.0 | 0.96 | 1,787 | ≤10 | 5,515.7 | 1.09 | 21,864 | 47 | 41,893.9 | 1.12 | 11,998 | 18 | 12,198.9 | 1.48 |
| July-December 2010 | 5,761 | 40 | 23,395.1 | 1.71 | 2,069 | ≤10 | 6,372.6 | 0.94 | 24,308 | 56 | 49,185.1 | 1.14 | 11,935 | 17 | 13,681.0 | 1.24 |
| January-June 2011 | 5,865 | 38 | 22,882.6 | 1.66 | 2,229 | 13 | 7,221.2 | 1.80 | 26,509 | 62 | 54,258.6 | 1.14 | 12,331 | 17 | 14,267.5 | 1.19 |
| July-December 2011 | 5,901 | 41 | 24,488.5 | 1.67 | 2,252 | 14 | 7,803.1 | 1.79 | 29,137 | 83 | 61,770.1 | 1.34 | 12,878 | 21 | 15,719.0 | 1.34 |
| January-June 2012 | 5,503 | 25 | 21,715.5 | 1.15 | 1,990 | ≤10 | 6,320.8 | 1.42 | 29,798 | 73 | 61,860.5 | 1.18 | 12,035 | 20 | 14,702.8 | 1.36 |
| July-December 2012 | 5,329 | 32 | 22,546.5 | 1.42 | 1,597 | ≤10 | 5,445.4 | 0.73 | 31,670 | 92 | 68,014.5 | 1.35 | 12,178 | 18 | 15,453.0 | 1.16 |
| January-June 2013 | 4,589 | 16 | 18,785.4 | 0.85 | 1,490 | ≤10 | 5,046.0 | 0.79 | 29,999 | 76 | 61,400.8 | 1.24 | 10,917 | 17 | 13,446.1 | 1.26 |
| July-December 2013 | 4,258 | 28 | 18,307.8 | 1.53 | 1,336 | ≤10 | 4,976.0 | 1.21 | 31,637 | 69 | 63,139.6 | 1.09 | 10,921 | 21 | 13,415.4 | 1.57 |
| January-June 2014 | 4,083 | 20 | 15,821.9 | 1.26 | 1,203 | ≤10 | 4,231.1 | 1.65 | 32,757 | 56 | 59,763.8 | 0.94 | 9,912 | 18 | 11,645.8 | 1.55 |
| July-December 2014 | 4,073 | 21 | 17,147.0 | 1.22 | 1,130 | ≤10 | 4,437.1 | 1.80 | 36,277 | 90 | 68,800.2 | 1.31 | 10,463 | 21 | 12,965.7 | 1.62 |
| January-June 2015 | 3,590 | 22 | 14,506.9 | 1.52 | 1,032 | ≤10 | 3,960.9 | 1.01 | 34,704 | 70 | 63,201.4 | 1.11 | 9,390 | 20 | 11,321.6 | 1.77 |
| July-September 2015 | 2,955 | ≤10 | 6,366.2 | 1.41 | 827 | ≤10 | 1,724.1 | 2.32 | 23,132 | 30 | 29,124.9 | 1.03 | 5,767 | 16 | 5,122.6 | 3.12 |

8.5 EXPOSURE TIME DATA

Table 29: The number of overdoses (cases) and exposure time for analyses involving OxyContin and primary comparators (incident user cohort only)

| Opioid analgesic ⁱ | Exposure period category | Medicaid | | | | MarketScan | | | | HIRD | | | |
|-------------------------------|--|------------|---------|-------------|---------|------------|--------|-------------|---------|------------|--------|-------------|---------|
| | | Pre-period | | Post-period | | Pre-period | | Post-period | | Pre-period | | Post-period | |
| | | Cases | PMs | Cases | PMs | Cases | PMs | Cases | PMs | Cases | PMs | Cases | PMs |
| OxyContin | Any use ⁱ | 198 | 113,884 | 153 | 87,758 | 57 | 75,220 | 52 | 88,378 | 85 | 95,483 | 61 | 86,036 |
| ER morphine | (with or without concomitant opioid analgesic use periods) | 601 | 218,595 | 741 | 307,429 | 64 | 48,237 | 128 | 102,988 | 75 | 73,733 | 141 | 106,453 |
| fentanyl | | 259 | 111,684 | 332 | 130,052 | 64 | 53,784 | 124 | 100,993 | 94 | 82,531 | 94 | 88,465 |
| methadone | | 528 | 143,107 | 482 | 163,693 | 19 | 16,071 | 56 | 27,322 | 58 | 53,118 | 75 | 53,799 |
| OxyContin | Use alone | 69 | 51,166 | 42 | 29,192 | 18 | 31,262 | ≤10 | 30,769 | 37 | 41,461 | 17 | 29,741 |
| ER morphine | (without concomitant opioid analgesic use periods) | 193 | 72,789 | 201 | 91,287 | 15 | 16,861 | 29 | 33,344 | 25 | 27,562 | 43 | 33,208 |
| fentanyl | | 83 | 40,571 | 116 | 46,323 | 25 | 21,630 | 33 | 38,709 | 28 | 31,957 | 26 | 33,634 |
| methadone | | 284 | 82,396 | 262 | 96,821 | ≤10 | 9,159 | 23 | 15,355 | 40 | 32,324 | 46 | 31,320 |

(FDA generated table from PMR 2051-4 study report)

Key: ⁱ=excludes periods dispensed OxyContin or primary comparator concomitantly; person-months (PMs)

Table 30: The number of overdoses (cases) and exposure time for analyses involving OxyContin and secondary comparators (combined cohort)

| Opioid analgesic | Exposure period category | Medicaid | | | | MarketScan ⁱ | | | | HIRD | | | |
|------------------|--|------------|---------|-------------|---------|-------------------------|---------|-------------|---------|------------|---------|-------------|---------|
| | | Pre-period | | Post-period | | Pre-period | | Post-period | | Pre-period | | Post-period | |
| | | Cases | PMs | Cases | PMs | Cases | PMs | Cases | PMs | Cases | PMs | Cases | PMs |
| OxyContin | Any use ⁱ | 504 | 295,514 | 356 | 226,471 | 156 | 207,722 | 176 | 311,936 | 118 | 135,011 | 121 | 209,374 |
| ER Oxymorphone | (with or without concomitant opioid analgesic use periods) | 82 | 29,452 | 228 | 83,908 | 13 | 24,073 | 65 | 60,419 | 17 | 14,125 | 39 | 32,598 |
| SE IR Oxycodone | | 769 | 342,913 | 1861 | 930,372 | 82 | 119,024 | 388 | 439,392 | 63 | 77,018 | 332 | 361,878 |
| IR Hydromorphone | | 294 | 92,782 | 380 | 133,165 | 41 | 36,826 | 110 | 91,193 | 35 | 27,087 | 87 | 73,280 |
| OxyContin | Use alone | 236 | 143,156 | 131 | 92,079 | 56 | 97,454 | 56 | 140,826 | 58 | 63,959 | 43 | 90,142 |
| ER Oxymorphone | (without concomitant opioid analgesic use periods) | 29 | 9,680 | 97 | 31,470 | ≤10 | 7,465 | 24 | 18,206 | ≤10 | 4,634 | 11 | 9,022 |
| SE IR Oxycodone | | 555 | 262,717 | 1421 | 749,396 | 53 | 89,960 | 278 | 346,222 | 44 | 59,672 | 245 | 292,462 |
| IR Hydromorphone | | 178 | 62,344 | 255 | 90,916 | 32 | 25,739 | 65 | 63,181 | 25 | 19,499 | 65 | 53,705 |

(FDA generated table from PMR 2051-4 study report)

Key: ⁱⁱ=excludes periods dispensed OxyContin or primary comparator concomitantly; numbers are based on the combined (incident and prevalent) cohort; person-months (PMs)

8.6 UNINTENTIONAL OVERDOSE OUTCOME ANALYSES

Table 31: Rate ratios of unintentional fatal or non-fatal overdose (OD) among patients with any OxyContin use and any primary comparator use in the two years before and two years after the reformulation, Medicaid

| | Ratio of Rates during Post- vs. Pre-Reformulation Periods | | | Ratio of Ratios for Comparator Opioids vs. OxyContin | | |
|--|---|---------|---------|--|---------|---------|
| | Adjusted Rate Ratio | 95% LCL | 95% UCL | Adjusted Ratio of Rate Ratios | 95% LCL | 95% UCL |
| Any non-overlapping use[^] | | | | | | |
| OxyContin | 0.96 | 0.85 | 1.09 | Ref | - | - |
| ER morphine | 0.94 | 0.87 | 1.01 | 0.97 | 0.85 | 1.12 |
| TD fentanyl | 1.01 | 0.91 | 1.12 | 1.05 | 0.90 | 1.23 |
| Methadone | 0.86 | 0.79 | 0.95 | 0.90 | 0.77 | 1.04 |

Abbreviations: LCL=lower confidence limit; UCL=upper confidence limit; ER=extended release; TD=transdermal; Ref=referent; vs=versus.

[^]Treatment episodes that had overlapping use of more than one of the primary comparators or OxyContin at the same time were excluded.

Table 32: Rate ratios of unintentional fatal or non-fatal overdose (OD) among patients with OxyContin only use and primary comparator opioid analgesic only use in the two years before and two years after the reformulation, Medicaid

| | Ratio of Rates during Post- vs. Pre-Reformulation Periods | | | Ratio of Ratios for Comparator Opioids vs. OxyContin | | |
|---|---|---------|---------|--|---------|---------|
| | Adjusted Rate Ratio | 95% LCL | 95% UCL | Adjusted Ratio of Rate Ratios | 95% LCL | 95% UCL |
| Use without concomitant opioids ("Only use") | | | | | | |
| OxyContin | 0.81 | 0.64 | 1.02 | Ref | - | - |
| ER morphine | 1.00 | 0.86 | 1.16 | 1.24 | 0.93 | 1.63 |
| TD fentanyl | 1.05 | 0.86 | 1.28 | 1.30 | 0.95 | 1.77 |
| Methadone | 0.86 | 0.75 | 0.98 | 1.06 | 0.81 | 1.40 |

Abbreviations: ER=extended release; LCL=lower confidence limit; UCL=upper confidence limit; TD=transdermal; Ref=referent; vs=versus.

Table 33: Rate ratios of unintentional fatal or non-fatal overdose among patients with any OxyContin use and any primary comparator opioid analgesics use in the two years before and five years after the reformulation, MarketScan

| | Ratio of Rates during Post- vs. Pre-Reformulation Periods | | | Ratio of Ratios for Comparator Opioids vs. OxyContin | | |
|--|---|---------|---------|--|---------|---------|
| | Adjusted Rate Ratio | 95% LCL | 95% UCL | Adjusted Ratio of Rate Ratios | 95% LCL | 95% UCL |
| Any non-overlapping use[^] | | | | | | |
| OxyContin | 0.88 | 0.73 | 1.06 | Ref | - | - |
| ER morphine | 1.01 | 0.82 | 1.23 | 1.14 | 0.87 | 1.50 |
| TD fentanyl | 1.06 | 0.88 | 1.27 | 1.20 | 0.93 | 1.55 |
| Methadone | 1.10 | 0.86 | 1.42 | 1.25 | 0.92 | 1.71 |

Abbreviations: LCL=lower confidence interval; UCL=upper confidence limit; ER=extended release; TD=transdermal; Ref=referent; vs=versus.

[^]Treatment episodes that had overlapping use of more than one of the primary comparators or OxyContin at the same time were excluded.

Table 34: Rate ratios of unintentional fatal or non-fatal overdose among patients with OxyContin only use and primary comparator opioid analgesics only use in the two years before and five years after the reformulation, MarketScan

| | Ratio of Rates during Post- vs. Pre-Reformulation Periods | | | Ratio of Ratios for Comparator Opioids vs. OxyContin | | |
|---|---|---------|---------|--|---------|---------|
| | Adjusted Rate Ratio | 95% LCL | 95% UCL | Adjusted Ratio of Rate Ratios | 95% LCL | 95% UCL |
| Use without concomitant opioids ("Only use") | | | | | | |
| OxyContin | 0.67 | 0.46 | 0.99 | Ref | - | - |
| ER morphine | 1.16 | 0.80 | 1.70 | 1.72 | 1.01 | 2.94 |
| TD fentanyl | 1.19 | 0.84 | 1.69 | 1.77 | 1.06 | 2.97 |
| Methadone | 1.22 | 0.83 | 1.79 | 1.81 | 1.05 | 3.11 |

Abbreviations: LCL=lower confidence interval; UCL=upper confidence limit; ER=extended release; TD=transdermal; Ref=referent; vs=versus.

Table 35: Rate ratios of unintentional fatal or non-fatal overdose among any OxyContin use and any primary comparator opioid analgesic use in the two years before and five years after the reformulation, HIRD

| | Ratio of Rates during Post- vs. Pre-Reformulation Periods | | | Ratio of Ratios for Comparator Opioids vs. OxyContin | | |
|--|---|---------|---------|--|---------|---------|
| | Adjusted Rate Ratio | 95% LCL | 95% UCL | Adjusted Ratio of Rate Ratios | 95% LCL | 95% UCL |
| Any non-overlapping use^a | | | | | | |
| OxyContin | 0.84 | 0.64 | 1.10 | Ref | - | - |
| ER morphine | 0.87 | 0.69 | 1.09 | 1.04 | 0.73 | 1.47 |
| TD fentanyl | 0.88 | 0.68 | 1.12 | 1.04 | 0.72 | 1.51 |
| Methadone | 0.99 | 0.75 | 1.31 | 1.18 | 0.81 | 1.73 |

Abbreviations: HIRD=HealthCore Integrated Research Database®; LCL=lower confidence interval; UCL=upper confidence limit; ER=extended release; TD=transdermal; Ref=referent; vs=versus.

^aTreatment episodes that had overlapping use of more than one of the primary comparators or OxyContin at the same time were excluded.

Table 36: Rate ratios of unintentional fatal or non-fatal overdose among patients with OxyContin only use and primary comparator opioid analgesic only use in the two years before and five years after the reformulation, HIRD

| | Ratio of Rates during Post- vs. Pre-Reformulation Periods | | | Ratio of Ratios for Comparator Opioids vs. OxyContin | | |
|---|---|---------|---------|--|---------|---------|
| | Adjusted Rate Ratio | 95% LCL | 95% UCL | Adjusted Ratio of Rate Ratios | 95% LCL | 95% UCL |
| Use without concomitant opioids (“Only use”) | | | | | | |
| OxyContin | 0.50 | 0.31 | 0.81 | Ref | - | - |
| ER morphine | 1.02 | 0.66 | 1.56 | 2.04 | 1.08 | 3.84 |
| TD fentanyl | 0.72 | 0.47 | 1.12 | 1.45 | 0.75 | 2.82 |
| Methadone | 0.90 | 0.62 | 1.31 | 1.81 | 1.00 | 3.28 |

Abbreviations: HIRD=HealthCore Integrated Research Database®; ER=extended release; LCL=lower confidence limit; UCL=upper confidence limit; TD=transdermal; Ref=referent; vs=versus.

8.7 RESULTS OF ANALYSES WITH BENZODIAZEPINE AS A CONFOUNDER VERSUS EFFECT MODIFIER

Table 36: Rate ratios, and ratio of rate ratios, of opioid overdose (intentional and unintentional; fatal and non-fatal) among those dispensed any OxyContin (with or without other opioid analgesics concomitantly) versus any primary comparator opioid analgesic in the two years before and five years after the reformulation, HIRD database

NOTE: The adjusted rate ratios shown below are additionally adjusted for baseline benzodiazepine use (dispensing within 3 months of treatment episode initiation). The p-values for the opioid analgesic group x baseline benzodiazepine interaction (p for interaction in table) using an unadjusted model are also shown.

| | Two years before [REF] vs. Five years after reformulation | | | OxyContin vs. Comparator Opioids | | | Two years before [REF] vs. Five years after reformulation | | | OxyContin vs. Comparator Opioids | | | P-interaction (by baseline benzo use) |
|----------------------------------|---|---------|---------|-------------------------------------|---------|---------|---|---------|---------|--|---------|---------|--|
| | Rate Ratio (2 year vs. 5 year) ⁰ | 95% LCL | 95% UCL | Ratio of Rate Ratio ⁰ | 95% LCL | 95% UCL | Adjusted* Rate Ratio ⁰ | 95% LCL | 95% UCL | Adjusted* Ratio of Rate Ratio ⁰ | 95% LCL | 95% UCL | |
| Incident and Prevalent | | | | | | | | | | | | | |
| Total overdose(Fatal + Nonfatal) | | | | | | | | | | | | | |
| Any OxyContin [*] | 0.91 | 0.69 | 1.21 | Ref | | | 0.85 | 0.65 | 1.11 | Ref | | | |
| Any ER morphine | 1.02 | 0.80 | 1.29 | 1.11 | 0.77 | 1.60 | 0.93 | 0.75 | 1.17 | 1.10 | 0.78 | 1.54 | 0.77 |
| Any TD Fentanyl | 0.97 | 0.75 | 1.25 | 1.06 | 0.72 | 1.55 | 0.89 | 0.70 | 1.13 | 1.04 | 0.73 | 1.49 | 0.85 |
| Any Methadone | 1.15 | 0.86 | 1.53 | 1.25 | 0.84 | 1.87 | 1.03 | 0.79 | 1.35 | 1.21 | 0.84 | 1.76 | 0.70 |

*Models adjusted for demographics and clinical characteristics. For all adjusted regression models in the HIRD we made the following modifications to the covariates with low sample size categories to allow for convergence:

a) classified patients with unknown geographic region to west; b) classified other and unknown health plan type to CDHP/HDHP; c) combined the 'ER' and 'ER + IR' categories in the prior use of opioid analgesics category to an 'Any ER' category; intentional overdose models adjusted only for age and sex (due to convergence limitations).

⁰ Calculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

^{*}All OxyContin categories in this table exclude period w/ concomitant use of any PC, and all comparator categories in this table exclude period w/ concomitant use with Oxy or any other PC

Key: LCL = lower confidence limit; UCL = upper confidence limit

Table 37: Rate ratios, and ratio of rate ratios, of opioid overdose (intentional and unintentional; fatal and non-fatal) among those dispensed only OxyContin (without other opioid analgesics concomitantly) versus only primary comparator opioid analgesics in the two years before and five years after the reformulation, HIRD database

NOTE: The adjusted rate ratios shown below are additionally adjusted for baseline benzodiazepine use (dispensing within 3 months of treatment episode initiation). The p-values for the opioid analgesic group \times baseline benzodiazepine interaction (p for interaction in table) using an unadjusted model are also shown.

| | Two years before [REF] vs. Five years after reformulation | | | OxyContin vs. Comparator Opioids | | | Two years before [REF] vs. Five years after reformulation | | | OxyContin vs. Comparator Opioids | | | P-interaction (by baseline benzo use) | |
|--|---|---------|---------|----------------------------------|---------|---------|---|---------|---------|--|---------|---------|--|--|
| | Rate Ratio (2 year vs. 5 year) ⁰ | 95% LCL | 95% UCL | Ratio of Rate Ratio ⁰ | 95% LCL | 95% UCL | Adjusted* Rate Ratio ⁰ | 95% LCL | 95% UCL | Adjusted* Ratio of Rate Ratio ⁰ | 95% LCL | 95% UCL | | |
| | | | | | | | | | | | | | | |
| Incident and Prevalent | | | | | | | | | | | | | | |
| Total overdose(Fatal + Nonfatal) | | | | | | | | | | | | | | |
| Use of only OxyContin (without the use of other opioids) | 0.53 | 0.32 | 0.87 | Ref | | | 0.52 | 0.32 | 0.85 | Ref | | | | |
| Use of only ER morphine | 1.21 | 0.78 | 1.87 | 2.29 | 1.18 | 4.45 | 1.14 | 0.75 | 1.75 | 2.18 | 1.17 | 4.07 | 0.4913 | |
| Use of only TD Fentanyl | 0.76 | 0.49 | 1.20 | 1.45 | 0.73 | 2.89 | 0.73 | 0.47 | 1.13 | 1.40 | 0.73 | 2.69 | 0.8130 | |
| Use of only Methadone | 1.03 | 0.70 | 1.52 | 1.96 | 1.04 | 3.71 | 0.91 | 0.63 | 1.31 | 1.74 | 0.97 | 3.13 | 0.7305 | |

*Models adjusted for demographics and clinical characteristics. For all adjusted regression models in the HIRD we made the following modifications to the covariates with low sample size categories to allow for convergence:

a) classified patients with unknown geographic region to west; b) classified other and unknown health plan type to CDHP/HDHP; c) combined the 'ER' and 'ER + IR' categories in the prior use of opioid analgesics category to an 'Any ER' category; intentional overdose models adjusted only for age and sex (due to convergence limitations).

⁰ Calculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

[^]All OxyContin categories in this table exclude period w/ concomitant use of any PC, and all comparator categories in this table exclude period w/ concomitant use with Oxy or any other PC

Key: LCL = lower confidence limit; UCL = upper confidence limit

Table 38: Rate ratios, and ratio of rate ratios, of opioid overdose (intentional and unintentional; fatal and non-fatal) among those dispensed any OxyContin (with or without other opioids analgesics concomitantly) versus any primary comparator opioid analgesics in the two years before and two years after the reformulation, Medicaid database

NOTE: The adjusted rate ratios shown below are additionally adjusted for baseline benzodiazepine use (dispensing within 3 months of treatment episode initiation). The p-values for the opioid analgesic group x baseline benzodiazepine interaction (p for interaction in table) using an unadjusted model are also shown.

| | Two years before [REF] vs. Two years after reformulation | | | OxyContin vs. Comparator Opioids | | | Two years before [REF] vs. Two years after reformulation | | | OxyContin vs. Comparator Opioids | | | P-interaction (by baseline benzo use) [^] |
|-----------------------------------|---|------------|------------|--------------------------------------|---------|------------|---|------------|------------|--|---------|------------|--|
| | Rate Ratio ^o | 95% LCL | 95% UCL | Ratio of Rate Ratios ^o | 95% LCL | 95% UCL | Adjusted* Rate Ratio ^o | 95% LCL | 95% UCL | Adjusted* Ratio of Rate Ratios ^o | 95% LCL | 95% UCL | |
| Incident and Prevalent | | | | | | | | | | | | | |
| Total overdose (Fatal + Nonfatal) | | | | | | | | | | | | | |
| Any OxyContin | 1.03 | 0.92 | 1.16 | | | | 1.00 | 0.89 | 1.13 | | | | |
| Any ER morphine | 0.93 | 0.86 | 1.01 | 0.90 | 0.79 | 1.04 | 0.91 | 0.84 | 0.98 | 0.91 | 0.79 | 1.04 | 0.638 |
| Any TD Fentanyl | 1.08 | 0.97 | 1.19 | 1.04 | 0.89 | 1.22 | 1.07 | 0.96 | 1.19 | 1.07 | 0.91 | 1.25 | 0.440 |
| Any Methadone | 0.87 | 0.80 | 0.96 | 0.85 | 0.73 | 0.98 | 0.86 | 0.79 | 0.94 | 0.86 | 0.74 | 1.00 | 0.542 |

*Models adjusted for demographics and clinical characteristics. For all adjusted regression models in the HIRD we made the following modifications to the covariates with low sample size categories to allow for convergence:

a) classified patients with unknown geographic region to west; b) classified other and unknown health plan type to CDHP/HDHP; c) combined the 'ER' and 'ER + IR' categories in the prior use of opioid analgesics category to an 'Any ER' category; intentional overdose models adjusted only for age and sex (due to convergence limitations).

^o Calculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

[^]All OxyContin categories in this table exclude period w/ concomitant use of any PC, and all comparator categories in this table exclude period w/ concomitant use with Oxy or any other PC

Key: LCL = lower confidence limit; UCL = upper confidence limit

Table 39: Stratified - Among only those **with** baseline benzodiazepine dispensing: Rate ratios, and ratio of rate ratios, of opioid overdose among those dispensed any OxyContin versus any primary comparator opioid analgesics, Medicaid database

| | Two years before [REF] vs. Two years after reformulation | | | OxyContin vs. Comparator Opioids | | |
|--|---|------------|------------|--------------------------------------|---------|------------|
| | Rate Ratio ^o | 95% LCL | 95% UCL | Ratio of Rate Ratios ^o | 95% LCL | 95% UCL |
| Incident and Prevalent | | | | | | |
| Total overdose (Fatal + Nonfatal) | | | | | | |
| Any OxyContin | 1.00 | 0.85 | 1.18 | | | |
| Any ER morphine | 0.97 | 0.87 | 1.09 | 0.97 | 0.79 | 1.18 |
| Any TD Fentanyl | 1.00 | 0.87 | 1.15 | 1.00 | 0.81 | 1.24 |
| Any Methadone | 0.83 | 0.73 | 0.96 | 0.83 | 0.67 | 1.03 |

^oCalculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

Key: LCL = lower confidence limit; UCL = upper confidence limit

Table 40: Stratified - Among only those **without** baseline benzodiazepine dispensing: Rate ratios, and ratio of rate ratios, of opioid overdose among those dispensed any OxyContin versus any primary comparator opioid analgesics, Medicaid database

| | Two years before [REF] vs. Two years after reformulation | | | OxyContin vs. Comparator Opioids | | |
|--|---|------------|------------|--------------------------------------|---------|------------|
| | Rate Ratio ^o | 95% LCL | 95% UCL | Ratio of Rate Ratios ^o | 95% LCL | 95% UCL |
| Incident and Prevalent | | | | | | |
| Total overdose (Fatal + Nonfatal) | | | | | | |
| Any OxyContin | 1.04 | 0.88 | 1.22 | | | |
| Any ER morphine | 0.91 | 0.82 | 1.00 | 0.88 | 0.72 | 1.06 |
| Any TD Fentanyl | 1.15 | 0.99 | 1.33 | 1.11 | 0.89 | 1.38 |
| Any Methadone | 0.91 | 0.80 | 1.03 | 0.88 | 0.71 | 1.08 |

^oCalculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

Key: LCL = lower confidence limit; UCL = upper confidence limit

Table 41: Rate ratios, and ratio of rate ratios, of opioid overdose (intentional and unintentional; fatal and non-fatal) among those dispensed only OxyContin (without other opioid analgesics concomitantly) versus only primary comparator opioid analgesics in the two years before and two years after the reformulation, Medicaid database

NOTE: The adjusted rate ratios shown below are additionally adjusted for baseline benzodiazepine use (dispensing within 3 months of treatment episode initiation). The p-values for the opioid analgesic group \times baseline benzodiazepine interaction (p for interaction in table) using an unadjusted model are also shown.

| | Two years before [REF] vs. Two years after reformulation | | | OxyContin vs. Comparator Opioids | | | Two years before [REF] vs. Two years after reformulation | | | OxyContin vs. Comparator Opioids | | | P-interaction (by baseline benzo use) [^] | |
|--|---|------------------------|------------|---|---------|---------|---|------------|------------|---|------------|------------|--|--|
| | Rate Ratio ^o | 95% LCL | 95% UCL | Ratio of Rate Ratios ^o | 95% LCL | 95% UCL | Adjusted* Rate Ratio ^o | 95% LCL | 95% UCL | Ratio of Rate Ratios ^o | 95% LCL | 95% UCL | | |
| | | Incident and Prevalent | | | | | | | | | | | | |
| Total overdose (Fatal + Nonfatal) | | | | | | | | | | | | | | |
| Use of only OxyContin (without the use of other opioids) | 0.86 | 0.69 | 1.08 | | | | 0.85 | 0.68 | 1.07 | | | | | |
| Use of only ER morphine | 1.01 | 0.87 | 1.16 | 1.17 | 0.89 | 1.53 | 1.00 | 0.87 | 1.15 | 1.18 | 0.90 | 1.54 | 0.735 | |
| Use of only TD Fentanyl | 1.09 | 0.90 | 1.32 | 1.26 | 0.94 | 1.70 | 1.08 | 0.89 | 1.31 | 1.27 | 0.94 | 1.72 | 0.903 | |
| Use of only Methadone | 0.88 | 0.77 | 1.00 | 1.01 | 0.78 | 1.32 | 0.87 | 0.77 | 0.99 | 1.03 | 0.79 | 1.34 | 0.980 | |

*Models adjusted for demographics and clinical characteristics. For all adjusted regression models in the HIRD we made the following modifications to the covariates with low sample size categories to allow for convergence:

a) classified patients with unknown geographic region to west; b) classified other and unknown health plan type to CDHP/HDHP; c) combined the 'ER' and 'ER + IR' categories in the prior use of opioid analgesics category to an 'Any ER' category; intentional overdose models adjusted only for age and sex (due to convergence limitations).

^o Calculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

[^]All OxyContin categories in this table exclude period w/ concomitant use of any PC, and all comparator categories in this table exclude period w/ concomitant use with Oxy or any other PC

Key: LCL = lower confidence limit; UCL = upper confidence limit

Table 42: Stratified - Among only those **with** baseline benzodiazepine dispensing: Rate ratios, and ratio of rate ratios, of opioid overdose among those dispensed only OxyContin versus only primary comparator opioid analgesics, Medicaid database

| | Two years before [REF] vs. Two years after reformulation | | | OxyContin vs. Comparator Opioids | | |
|--|---|------|------|--------------------------------------|---------|---------|
| | Rate Ratio ^o | 95% | 95% | Ratio of Rate Ratios ^o | 95% LCL | 95% UCL |
| | | LCL | UCL | | | |
| Incident and Prevalent | | | | | | |
| Total overdose (Fatal + Nonfatal) | | | | | | |
| Use of only OxyContin (without the use of other opioids) | 0.82 | 0.58 | 1.15 | | | |
| Use of only ER morphine | 1.06 | 0.84 | 1.33 | 1.30 | 0.86 | 1.95 |
| Use of only TD Fentanyl | 1.06 | 0.80 | 1.40 | 1.29 | 0.83 | 2.00 |
| Use of only Methadone | 0.87 | 0.70 | 1.07 | 1.06 | 0.71 | 1.58 |

^oCalculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

Key: LCL = lower confidence limit; UCL = upper confidence limit

Table 43: Stratified - Among only those **without** baseline benzodiazepine dispensing: Rate ratios, and ratio of rate ratios, of opioid overdose among those dispensed only OxyContin versus only primary comparator opioid analgesics, Medicaid database

| | Two years before [REF] vs. Two years after reformulation | | | OxyContin vs. Comparator Opioids | | |
|--|---|------|------|--------------------------------------|---------|---------|
| | Rate Ratio ^o | 95% | 95% | Ratio of Rate Ratios ^o | 95% LCL | 95% UCL |
| | | LCL | UCL | | | |
| Incident and Prevalent | | | | | | |
| Total overdose (Fatal + Nonfatal) | | | | | | |
| Use of only OxyContin (without the use of other opioids) | 0.86 | 0.64 | 1.16 | | | |
| Use of only ER morphine | 0.98 | 0.82 | 1.18 | 1.14 | 0.80 | 1.62 |
| Use of only TD Fentanyl | 1.10 | 0.85 | 1.42 | 1.28 | 0.86 | 1.90 |
| Use of only Methadone | 0.87 | 0.74 | 1.03 | 1.02 | 0.72 | 1.43 |

^oCalculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

Key: LCL = lower confidence limit; UCL = upper confidence limit