JOINT MEETING OF THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE AND THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE

OXYCONTIN® (OXYCODONE HYDROCHLORIDE) EXTENDED-RELEASE TABLETS

NDA 022272

POSTMARKETING REQUIREMENT BRIEFING DOCUMENT

Advisory Committee Meeting

September 10-11, 2020

PURDUE PHARMA L.P.

One Stamford Forum
201 Tresser Boulevard
Stamford, CT 06901-3431

ADVISORY COMMITTEE BRIEFING MATERIALS

AVAILABLE FOR PUBLIC RELEASE

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LIST OF ABBREVIATIONS AND ACRONYMS

ADP	abuse-deterrent properties
ADF	abuse-deterrent formulation
APAP	paracetamol (or acetaminophen)
ARDR	abuse report dispensing ratio
aRRs	adjusted declines in the incidence rates
ASI-MV	Addiction Severity Index-Multimedia Version
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMC	comprehensive managed care
COPD	chronic obstructive pulmonary disease
cP	centipoise
DCI	Deyo-Charlson Index
DEA	Drug Enforcement Agency
DUI	driving under the influence
DWI	driving while intoxicated
ED	Emergency department
E_{max}	maximum effect
ER	extended release
FAERS	FDA Adverse Event Reporting System
FDA	United States Food and Drug Administration
FFS	fee-for-service
GEE	generalized estimating equations
HCl	hydrochloride
HIRD	HealthCore Integrated Research Database
ICD-9-CM	Clinical Modification of the 9th Revision of the International Classification of Diseases
ICD-10	10th Revision of the International Classification of Diseases
IQR	interquartile range
IR	immediate release
IRs	incidence rates
IRR	Incidence rate ratio
ITS	interrupted time series
IV	intravenous
LAAM	levacetylmethadol
MME	milligram morphine equivalent
NA	not applicable
NAVIPPRO	National Addictions Vigilance Intervention and Prevention Program
NDA	New Drug Application
NDI	National Death Index
NOMAD	National Opioid Medication Abuse Deterrence

NPDS	National Poison Data System
NSDUH	National Survey on Drug Use and Health
NVS	National Vital Statistics
OD	overdose
OTP	Opioid Treatment Program
PC	poison center
PEO	polyethylene oxide
PMR	postmarketing requirement
PO	Taken by mouth
PPV	Positive predictive value
Q	yearly quarter of 3 months
RADARS	Researched Abuse, Diversion and Addiction-Related Surveillance
RAPID	Researchers and Participants Interacting Directly
RoR	ratio of ratios
RoRR	ratio of rate ratios
RxPATROL	Rx Pattern Analysis Tracking Robberies and Other Losses
SD	standard deviation
SKIP	Survey of Key Informants' Patients Program
TANF	temporary assistance for needy families
TD	transdermal
TMA	thrombotic microangiopathy
TTP	thrombotic thrombocytopenic purpura
US	United States

1   EXECUTIVE OVERVIEW

Purdue has been asked by FDA to participate in a Joint Advisory Committee meeting to discuss findings related to the OxyContin postmarketing requirement (PMR) epidemiology studies that evaluated the effect of the reformulation of OxyContin on abuse of OxyContin and its consequences, including overdose.

Purdue and its external advisors, including experts in epidemiology, conclude that the reformulation of OxyContin reduced abuse of OxyContin by non-oral routes and resulted in decreased overdose relative to the original formulation. These postmarketing studies demonstrate that the abuse-deterrent properties of OxyContin have had the predicted effects on abuse and provide an incremental improvement over the original formulation that did not have these properties. Nonetheless, Purdue is not seeking new claims or other changes to the OxyContin labeling based on these results and has no plans to proactively engage FDA in labeling discussions related to the PMR studies.

* * *

Prescription opioid medication abuse is a meaningful component of the public health crisis involving all opioids. Abuse-deterrent formulations (ADFs) of prescription opioid medications are but one part of a multi-faceted approach to mitigate this crisis, and FDA continues to encourage the development of such formulations (FDA 2018).

OxyContin is an extended-release (ER) tablet formulation of oxycodone hydrochloride (HCl) approved for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. When taken as intended (tablet swallowed intact as directed), OxyContin is designed to provide delivery of oxycodone HCl over 12 hours.

Original OxyContin became a target of abuse when it was realized that breaking, crushing, or chewing could rapidly release oxycodone from the extended-release matrix of the tablet. Despite labeling warning against it, some people began purposefully crushing the tablet into powder for oral, intranasal insufflation ("snorting"), and/or intravenous (IV) injection abuse.

With this understanding, Purdue refocused its efforts on developing a formulation of OxyContin designed to make the tablet more difficult to manipulate to deter unintentional misuse and intentional misuse and abuse. By incorporating an inactive polymer, polyethylene oxide (PEO), Purdue pursued an approach that made the tablet harder, more crush resistant, and more difficult (due to gelling properties) to prepare for injection. See Appendices 2 and 3 for more details on the reformulation history and PEO.

The goals for reformulating the original OxyContin tablet were:

1. Addition of abuse-deterrent properties (ADP, i.e., hardness and gelling); while,

2. Ensuring bioequivalence to the original formulation to provide comparable therapeutic efficacy for pain patients to whom the product is prescribed and taken as indicated.

Prior to approval of the reformulated product, it was hypothesized that the greatest impact of the reformulation would be on individuals who manipulate the tablet before administration (i.e., non-oral routes of crushing and snorting and/or crushing, dissolving and injecting). The reformulation was not expected to deter oral abuse of intact tablets such as taking more medication than prescribed or more often than prescribed or recommended. Nor was the reformulation expected to eliminate abuse of OxyContin and its consequences (CDER 2009).

Purdue worked closely with FDA and experts in drug chemistry, opioid abuse, and epidemiology to develop a four-part testing framework that evaluates abuse-deterrence to test these hypotheses. Although not available at the time of reformulation, a similar framework is presented in FDA's 2015 Guidance on Abuse-Deterrent Opioids – Evaluation and Labeling (as well as its 2013 predecessor). This includes laboratory, clinical, and epidemiology studies as follows:

- *In vitro laboratory manipulation and extraction studies* designed to evaluate physical and chemical properties of reformulated OxyContin under common and extreme "real-world" conditions

- *Clinical pharmacokinetic testing* to determine bioavailability of tablets administered intact or when manipulated

- *Clinical abuse potential studies* identify subject/participant-reported drug attributes (e.g., "drug-liking" and "take drug again") and preferences in recreational drug abusers

- *Postmarketing epidemiological studies*, the subject of this document, evaluate and measure the effectiveness of the reformulation in the real world on reducing abuse of OxyContin and its consequences, compared to the original formulation

The laboratory and clinical body of work, completed in 2010, tested the reformulation to failure whenever possible, thus establishing the strengths and weaknesses of reformulated OxyContin across numerous testing protocols.

As noted in the FDA-approved full prescribing information for OxyContin, Section 9.2 Abuse Deterrence Studies (approved in April 2013), the laboratory and clinical results are summarized as follows:

1) Abuse via injection is expected to be difficult; and

2) A reduction in abuse via the intranasal route is expected.

These informed expectations were the focus of, and have been confirmed by, the postmarketing epidemiological studies. OxyContin is the only product to complete all four parts of this testing framework and therefore it is the only product that has confirmed premarket expectations of abuse deterrence with real-world postmarketing data.

1.1 Overview of Postmarketing Studies

1.1.1 Background of Postmarketing Requirements

Prior to approval of the reformulation and to avoid conveying a false sense of security about the safety of the reformulation, Purdue agreed with FDA not to add language in the full prescribing information about the reformulation's abuse-deterrent properties (ADP) at that time. As a result, reformulated OxyContin was introduced with no change to the tradename or reference to abuse deterrence in the label. In April 2010, the reformulation of OxyContin was approved. In early August 2010, Purdue ceased shipping original OxyContin and a few days later started shipping the FDA-approved reformulation with ADP. This quick transition provided a rare opportunity to compare the "before and after" reformulation trends of a product that was replaced with a bioequivalent reformulation with abuse-deterrent properties.

As a condition of approval in April 2010, Purdue began to conduct a variety of postmarketing epidemiology studies to monitor and quantify the impact of the reformulation on abuse of OxyContin and its consequences. As evaluating the effects of abuse-deterrent formulations was a new and unprecedented area of investigation, numerous studies were conducted across a range of populations, data sources, outcomes and time horizons. Data from these studies were regularly submitted to FDA. With time, FDA determined that three of the original data sources could be further modified into formal studies. In addition, FDA required a fourth study to assess overdose. Formal postmarketing requirements were issued in 2016 and are the primary focus of this briefing document (see Appendix 1 for more details on the regulatory history).

1.1.2 Summary of Postmarketing Requirements and Study Design

The formal studies measured OxyContin abuse and overdose after reformulation compared to OxyContin abuse and overdose before reformulation. Each study measured the same outcomes for comparator opioid drugs (both licit and illicit, depending on data availability for comparators) during the same time frame. Comparisons to other opioids serve to determine whether changes in outcomes following the introduction of reformulated OxyContin were specific to the reformulation of OxyContin and not the result of secular or other trends affecting all opioids.

The data source, goal, study period, population, sample size, and key outcomes of each study are summarized in Table 1.

Table 1.   Formal Postmarketing Requirement Studies

Study and Data Source	NAVIPPRO Treatment Centers (PMR 3051-1)	RADARS Treatment Centers (PMR 3051-3)	RADARS Poison Centers (PMR 3051-2)	Insured Populations/ Medicaid & Commercial (PMR 3051-4)
Goal	Assess changes in frequency of self-reported past 30-day non-oral abuse	Assess changes in frequency of self-reported past month abuse	Assess changes in calls concerning OxyContin intentional abuse exposures	Assess changes in unintentional overdose rates among insured patients prescribed OxyContin or comparators
Study Period Before/After OxyContin Reformulation	Two years/four years	Two years/five years	Two years/five years	Two years/up to five years
Population	Individuals assessed for substance abuse treatment	Individuals at substance abuse treatment centers	Individuals with intentional exposures reported	Insured individuals with an opioid prescription
Final sample size	66,897 assessments from 34 centers in 10 states	63,528 assessments from 373 centers in 49 states	308,465 human exposures involving opioid analgesics 56 centers in 49 states	Across three data sources, patients dispensed OxyContin =297,836 Patients dispensed at least one of the primary comparator opioids = 659,673
Key Outcomes	Abuse (non-oral, by route, overall)	Abuse (overall)	Abuse (overall, by route)	Fatal and non-fatal unintentional overdose

NAVIPPRO, National Addictions Vigilance Intervention and Prevention Program; PMR, postmarketing requirement; RADARS, Researched Abuse, Diversion and Addiction-related Surveillance.
Overall abuse includes all routes of abuse either because route was not specified or all routes are reported together.
Two years/Four years or Two years/Five years = 2-year period before (3Q2008-2Q2010) vs 4-year period (1Q2011-4Q2014) or 5-year period (1Q2011-4Q2015) after reformulation.

1.1.3 Key Findings of Formal Postmarketing Requirements

See Section 5 of this document for detailed study results.

NAVIPPRO Treatment Centers Study

- Reports of non-oral OxyContin abuse showed an abrupt step-down following OxyContin reformulation (-52% or -32%, depending on statistical model) from the last quarter of the pre-reformulation period (2Q2010) to the first quarter of the post-reformulation period (1Q2011), and continued to decline throughout the post-reformulation period.

- The comparator opioids did not show an abrupt drop in abuse followed by an ongoing decline after the OxyContin reformulation.

- Abuse by swallowing intact OxyContin tablets did not change after the reformulation.

RADARS Treatment Centers Study

- There was a step-down in reports of overall OxyContin abuse (all routes) following the reformulation (-27% or -15%, depending on statistical model) from 2Q2010 to 1Q2011, with a continued decline through the remainder of the post-period.

- Reports of abuse of ER morphine and immediate release (IR) hydrocodone products did not show a step-down following the OxyContin reformulation. A similar step-down and continued decline were observed for the comparator group of Other Schedule II opioids.

RADARS Poison Centers Study

- There was a step-down (-28% or -14%, depending on statistical model) in reports of intentional OxyContin abuse immediately after reformulation (2Q2010 to 1Q2011). The decline persisted through the five years following reformulation.

- While all comparators showed declines that extended over the post-reformulation period, none showed an immediate step-down following reformulation similar to that seen for OxyContin.

Insured Populations Study

- During periods following dispensings of each, there was no significant change in the rates of unintentional opioid overdose following the OxyContin reformulation in OxyContin recipients overall, as compared to recipients of comparator opioids overall.

- Among the subgroup of patients who received OxyContin alone with no other concomitant opioid treatment, the overdose rate declined following the introduction of reformulated OxyContin. The decline in overdose events was greater for recipients of OxyContin alone than for any of the comparator opioids alone.

1.1.4 Totality of Evidence

The formal postmarketing studies required by FDA involve numerous analyses, large volumes of data, and comprise a range of different data collection instruments, methods, populations, and statistical approaches. Each study has its limitations, largely because they are all observational studies in which the data were originally collected for different purposes. As is typical of these studies, when considered together, the design limitations of a single study may be mitigated when its findings are supported by the design strengths and findings of other studies (Roland 2017). More reliable answers to research questions are obtained by integrating results from several different approaches, each with different and unrelated key sources of potential bias.

Purdue has also identified published literature to inform the question of the impact of reformulated OxyContin on abuse and related outcomes. This includes additional data sources, methods, populations, and outcomes (e.g., ex-US experience, spontaneous adverse events, drug diversion data, online monitoring, regional cohort studies, street price, and dispensing data). These studies are not described in detail in this document but may be found in the Literature Review outlined in Appendix 4.

The extensive research conducted by Purdue, including the formal PMR studies, coupled with research reported in published literature, collectively provide a methodical approach to understanding the totality of evidence to gain considerable insight into the impact of the reformulation of OxyContin on abuse and the consequences of abuse.

1.2 Conclusions

The OxyContin PMR studies assessing the impact of the reformulation represent the culmination of a multi-year scientific exchange with FDA and experts in the fields of epidemiology and drug abuse behavior. The four PMR studies reflect the output of a new and evolving area of scientific research and represent a rare opportunity to evaluate the impact of the reformulation of OxyContin on abuse and overdose.

The totality of evidence using diverse studies, endpoints, study populations, and methods provides a comprehensive understanding of the impact of the reformulation on abuse of OxyContin. The PMR data demonstrate a reduction in abuse of reformulated OxyContin compared to the original formulation and show a reduction in rates of overdose in those prescribed OxyContin alone. These studies demonstrate that the abuse-deterrent properties of OxyContin have had the predicted effects on OxyContin abuse and provide an incremental improvement over the formulation without these properties. The framework used to reformulate, evaluate, and confirm the ADP of OxyContin can continue to be considered for other products to make prescription opioids less attractive to individuals intent on abusing via manipulation.

Drug abuse in the US is complex, evolving, and a composite of multiple distinctive "subepidemics" of different drugs (e.g., prescription opioids, heroin, methadone, synthetic opioids, cocaine, and methamphetamine), each with its own demographic and geographic characteristics (Jalal 2018, Zoorob 2019). Reformulation of OxyContin was hypothesized to reduce the abuse of this specific product via routes requiring manipulation; however, and importantly, it was not expected that the reformulation of a single product would reduce abuse of other products or reduce overall abuse of opioids or non-opioid drugs.

Prescription opioids remain an important component in the management of serious pain for appropriate patients (Chou 2009, American Geriatrics Society Panel 2009, US Department of Veterans Affairs 2017, National Pain Center 2017, Dowell 2016), but their use must be balanced against the known and potentially serious risk of both accidental misuse and deliberate abuse.

Abuse-deterrent formulations continue to be one part of a comprehensive multi-stakeholder approach to help address the complex public health issue of prescription opioid abuse, and their availability helps to ensure access by legitimate patients in need of prescription opioids. However, care should be taken to avoid a false sense of security regarding opioids with ADP. It is clear that all opioids, including those with FDA-recognized ADP, carry risks of addiction, misuse, and abuse, which can lead to overdose and death.

2 INTRODUCTION

Abuse of prescription opioid medications represents a meaningful component of the public health crisis involving all opioids. Abuse-deterrent formulations are intended to create barriers to abuse by physical and/or chemical manipulations. In 2013, based on laboratory, clinical, and postmarketing data, FDA approved labeling stating that OxyContin has ADP that are expected to make it more difficult to abuse via injection and inhalation. FDA continues to encourage the development of abuse-deterrent formulations (FDA 2018) as an important part of a multi-faceted approach to help mitigate the opioid abuse crisis. However, abuse of ADFs by injection, insufflation, and oral routes is still possible. All prescription opioids, including those with FDA-recognized ADP, carry risks of addiction, abuse, and misuse, which can lead to opioid overdose (OD) and opioid involved death.

The OxyContin PMR studies to assess the impact of the reformulation represent the culmination of a multi-year scientific exchange with FDA and with experts in the fields of epidemiology and drug abuse behavior. The four PMR studies reflect the output of a new and evolving area of scientific research and represent a rare opportunity to evaluate the impact on abuse, OD, and death when a marketed opioid product is replaced with a bioequivalent formulation that incorporates ADP.

The remainder of this document is divided into several sections:

- Section 3 summarizes the background to and rationale for the OxyContin reformulation.

- Section 4 discusses common design and methodology features of the four PMR studies.

- Section 5, the primary focus of this document, presents the study results and key findings of the four PMR studies.

Appendices accompanying this document include:

- Regulatory history of OxyContin leading up to its approval, relabeling, and ongoing interactions with FDA (Appendix 1).

- Descriptions of the laboratory and clinical studies to assess abuse deterrence and the reformulation history (Appendix 2).

- Additional details of PEO used in OxyContin (Appendix 3).

- A descriptive review of the relevant peer-reviewed literature since introduction of the OxyContin reformulation (Appendix 4).

3 BACKGROUND

3.1 Rationale for Reformulating OxyContin

OxyContin is a single entity, ER tablet formulation of oxycodone hydrochloride (HCl). OxyContin is approved for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. When taken as intended (tablet swallowed intact), OxyContin is designed to provide delivery of oxycodone over 12 hours.

Original OxyContin became a target of abuse after it was recognized that breaking, crushing, or chewing could rapidly release oxycodone from the extended-release matrix of the tablet. Abusers began crushing the formulation for oral use, crushing and then inhaling the powder for intranasal use, and crushing and dissolving the powder for IV injection. Epidemiologic evidence indicated that abuse of the original OxyContin formulation was commonly via these non-oral routes (Hays 2004, Sees 2005). Correspondingly, in the NAVIPPRO Treatment Centers PMR study (Section 5.1), results indicate that in the two years prior to introduction of reformulated OxyContin in 2010, individuals entering substance abuse treatment centers who reported OxyContin abuse frequently reported insufflation (55.9%) and injection (34.8%, Data on file, PMR 3051-1). There was also a concern that some pain patients would chew, or their caregivers would crush, the tablets for easier swallowing or administration through gastrointestinal tubes, causing unintentional exposure and associated unintended consequences.

As reports of abuse involving manipulation of OxyContin emerged, Purdue refocused its efforts on developing a formulation of OxyContin designed to deter abuse by routes that required manipulation. In 2005 Purdue pursued an approach that used a physical/chemical barrier to manipulation by incorporating the inactive polymer PEO, which resulted in the development of the current reformulation approved in 2010 (see Appendix 1 for the regulatory history of the reformulated OxyContin, Appendix 2 for a description of the formulation and development history, and Appendix 3 for additional details on PEO).

Neither the 2015 FDA Guidance for Industry on Abuse-Deterrent Opioids – Evaluation and Labeling (FDA 2015), nor the predecessor 2013 draft guidance, existed during the development and FDA approval of the OxyContin reformulation. Yet, the approach used to reformulate or change the physical and chemical properties of the OxyContin tablet was consistent with the later published recommendations in the Guidance. The Guidance notes that development of an abuse-deterrent opioid product should be directed by the need to reduce abuse known or expected to occur with similar products.

Therefore, the two primary goals for reformulating the original OxyContin tablet were:

1. Adding ADP (i.e., hardness and gelling) to make the tablet more difficult to break, crush, and dissolve as well as to impede preparation for intravenous injection. The tablet was designed to hinder the release of more oxycodone in a shorter period of time than intended and to create a viscous gel when prepared for injection.

2. Achieving bioequivalence to the original formulation to provide comparable therapeutic efficacy and not disrupt appropriate dosing and use of the product as indicated.

According to the general framework subsequently set forth in the FDA 2015 Guidance (FDA 2015), the reformulation of OxyContin is categorized as:

> *"Physical/chemical barriers* – Physical barriers can prevent chewing, crushing, cutting, grating, or grinding of the dosage form. Chemical barriers, such as gelling agents, can resist extraction of the opioid using common solvents like water, simulated biological media, alcohol, or other organic solvents. Physical and chemical barriers can limit drug release following mechanical manipulation, or change the physical form of a drug, rendering it less amenable to abuse."

The FDA Guidance defines ADP as those properties shown to meaningfully deter abuse, even though they do not fully prevent abuse. Abuse is defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect. Although these properties may be equated, or confused, with, "tamper-resistant," FDA used the term abuse-deterrent rather than tamper-resistant because the latter term is used to describe product packaging required for certain classes of drugs, devices, and cosmetics (FDA 2015).

The extensive laboratory and clinical testing that led to the characterization and incorporation of ADP in reformulated OxyContin are described in Appendix 2.

Incorporating ADP into a tablet does not produce a product that is abuse-proof, nor do these properties necessarily prevent addiction, OD, and death by any route of administration. Importantly, as reformulated OxyContin is bioequivalent to original OxyContin in order to provide comparable therapeutic benefit to patients, reformulated OxyContin was not, and is not, expected to have a direct impact on abuse or misuse by swallowing more intact tablets than prescribed or without legitimate purpose.

3.2 Anticipated Impact of the Reformulation

It was not possible at the time of approval in 2010 to predict how the patterns of abuse would shift and it was not expected that the reformulation of a single product would reduce abuse of other products or reduce overall abuse of opioids or non-opioid drugs.

However, experts in fields of drug abuse and addiction anticipated that the reformulation of OxyContin would have the greatest impact on individuals who manipulate the tablet before administration via non-oral routes. It was expected that the reformulation would have limited direct impact on intact oral abuse (swallowed whole), would result in some switching to other opioids without ADP (including illicit opioids), and would still be able to be abused by all routes.

Purdue's goal was to incrementally improve deterrence of the most commonly employed methods of manipulation of OxyContin by reformulating the product with ADP.

3.3 Market Introduction of Reformulated OxyContin

Prior to approval of the reformulation, and to avoid conveying a false sense of security about the safety of the reformulation, Purdue agreed with FDA not to add language in the labeling about the reformulation's ADP at that time. As a result, reformulated OxyContin was introduced with no change to the tradename or reference to abuse deterrence in the label. Purdue ceased shipping original OxyContin to wholesalers in August 2010 and commenced shipment of reformulated OxyContin a few days later. By December 2010, 91% of OxyContin prescriptions were filled with reformulated OxyContin (Figure 1).

Figure 1.   Transition of OxyContin Weekly Prescriptions Dispensed at Pharmacies
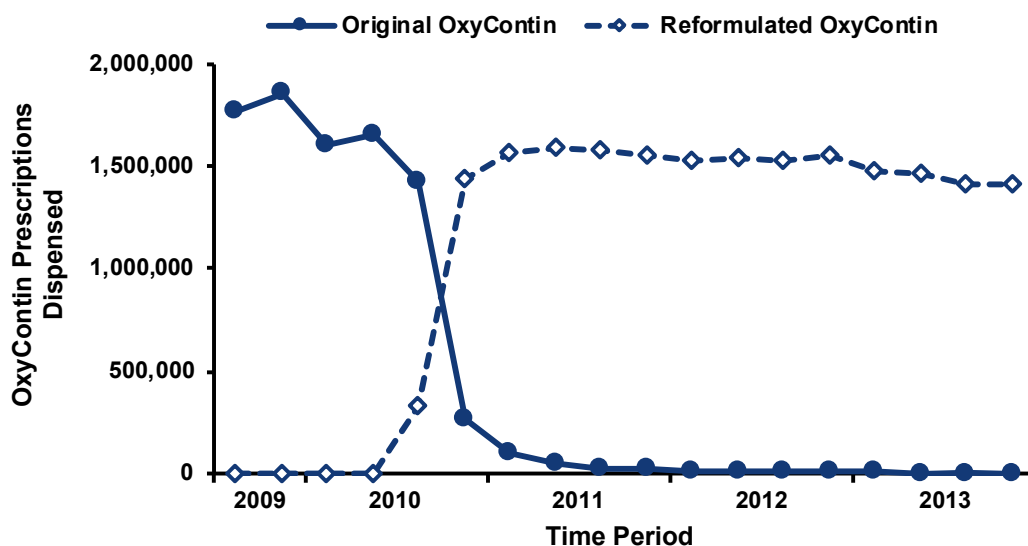
4 POSTMARKETING EPIDEMIOLOGY STUDIES OF ABUSE DETERRENCE OVERVIEW

The formal PMR studies were designed in consultation with FDA to evaluate abuse, OD, and OD death associated with OxyContin using multiple data sources and populations. Each study compared outcomes in the OxyContin post-reformulation period (up to five years) to outcomes in a two-year pre-reformulation period. The abrupt and complete change in product formulation enabled a pre/post comparison to evaluate the effects of the formulation change. The PMR studies excluded a 6-month market transition period beginning in 2010 when both the original and reformulated versions of OxyContin were available in pharmacies. The data source, goal, population, and key outcomes of each formal PMR study are summarized in Table 2. PMR Studies 3051-1, -2, and -3 are all surveillance studies that give insight into preferred drugs and sometimes routes among persons with self-affirmed recent histories of opioid abuse. PMR Study 3051-4 is entirely different in that the target population is patients under ordinary medical care and the outcome is not which drugs are chosen for abuse, but whether or not the patient experiences an OD.

Table 2.   Formal Postmarketing Requirement Studies

Study and Data Source	NAVIPPRO Treatment Centers (PMR 3051-1)	RADARS Treatment Centers (PMR 3051-3)	RADARS Poison Centers (PMR 3051-2)	Insured Populations/ Medicaid & Commercial (PMR 3051-4)
Goal	Assess changes in frequency of reported non-oral abuse	Assess changes in frequency of reported abuse	Assess changes in calls concerning OxyContin intentional abuse exposures	Assess changes in unintentional overdose rates among insured patients prescribed OxyContin or comparators
Population	Individuals assessed for substance abuse treatment	Individuals at substance abuse treatment centers	Individuals with intentional exposures reported	Insured individuals with an opioid prescription
Key Outcomes	Abuse (non-oral, by route, overall)	Abuse (overall)	Abuse (overall, by route)	Fatal and non-fatal unintentional overdose

NAVIPPRO, National Addictions Vigilance Intervention and Prevention Program; PMR, postmarketing requirement; RADARS, Researched Abuse, Diversion and Addiction-related Surveillance. Overall abuse includes all routes of abuse either because route was not specified or abuse by all routes are reported together.

The studies involve numerous analyses of data and comprise a range of different data collection instruments and methods, populations, and statistical approaches. The varied data sources, populations and analytic techniques provide complementary perspectives for the understanding of the overall impact of the reformulation of OxyContin.

Purdue has also identified published literature to inform the question of the impact of reformulated OxyContin on abuse and related outcomes. This includes additional data sources, methods, populations, and outcomes (e.g., ex-US experience, spontaneous adverse events, drug diversion data, online monitoring, regional cohort studies, street price, and dispensing data). These studies are not described in detail in this document but may be found in the Literature Review outlined in Appendix 4.

4.1 Estimating Relative Changes in OxyContin Abuse

Basic counts of abuse cases (numerators) cannot be appropriately understood unless considered in the context of a denominator (Secora 2014). Most etiologic epidemiological study designs rely on risks or rates to compare groups (e.g., trends over time or abuse of one product compared to another).

The numerator for either a risk or a rate ($risk = \frac{cases}{population\ at\ risk}, rate = \frac{cases}{population\ time\ at\ risk}$) is the number of events observed in the studied population over the timeframe of the study.

The denominator for risk is the number of individuals in the studied population at risk of becoming a case during the time period of the study. For a rate, the denominator is the amount of time each person in the population spends at risk. The numerator of a risk or rate is a count of a subset (the cases) of those people or days who form the denominator. As such, the numerator in a risk or rate comes from the denominator. This relationship is able to distinguish risks and rates from other relationship measures, such as ratios. Ratios that are not based on risks or rates (because the numerator does not come from the denominator) are not informative about relative differences in risks or rates.

In the three PMR studies focused on drugs of choice for abuse, there is no information on the size of the population at risk, i.e., opioid abusers in a region or all abusers in the US. Hence, none of these three studies can actually compute a risk or rate because there is no appropriate denominator to reflect the population at risk or the population time at risk. In contrast is the overdose PMR study (Insured Populations Study, PMR 3051-4). This study was conducted in populations with enumerated denominators, therefore the population of persons and person-days at risk was directly observed. Thus, the OD study provides direct estimates of the rate and relative differences in rates.

Because there is not a direct measure of the true at-risk or exposed population of persons who are abusers or who are at risk for becoming abusers in the three PMR surveillance studies (PMR 3051-1, -2, and -3), suitable proxy measures are needed (Secora 2014). The general uncertainty about which denominator to which to refer these data is acknowledged by FDA (Secora 2014), with subsequent guidance recommending two estimates of population risk (FDA 2015). As set forth in the guidance, two denominators were prespecified in the three PMR studies of abuse:

- Population denominator, Model 1, which produces an estimate of abuse risk as a proportion.

- Drug utilization denominator (volume of dispensed units stemming from a prescription), Model 2a, where each tablet dispensed may be considered an exposure opportunity (Secora 2014); which produces an abuse report dispensing ratio (ARDR).

A denominator of drug utilization (Model 2a) leads to a ratio, which may be of interest, but does not lead to an epidemiologically defined risk or rate.

In both treatment centers studies (NAVIPPRO, RADARS Treatment Centers), Model 1 yields a proportion using the total number of abuse assessments (or survey respondents in RADARS) across centers as the population denominator. In the RADARS Poison Center Study, the abuse calls per 100,000 population used the 2010 US Census data in the coverage area as the population denominator, considering in effect that each person in the population was "at risk" for being the subject of a poison center call. Model 2a employs the total dispensing volume for each product to define a measure that is the ratio of calls or abuse reports to volume of presumed drug utilization.

The choice of denominator is highly consequential. The use of drug dispensing volume (Model 2a) as a denominator raises concerns. Because use by pain patients represents most of the use of drug dispensed, the measure is best viewed as a ratio of the number of abusers to dispensing to non-abusers (this is the "abuse report dispensing ratio", ARDR). As noted earlier, this ratio has serious limitations and is not a measure of risk.

The ARDR may produce misleading relative comparisons between products if the relation between volume dispensed and numbers of abusers varies between products. Consider the impact on ARDR if there is a reduction in total prescriptions to patients while the size of the abuse population for that product remains constant and there is no change in abuse cases. The reduction in sales will misleadingly inflate the ARDR even when the abuse risk has not changed. For example, if prescribing of OxyContin declined with a corresponding shift in prescribing to another product, such as ER morphine, without any real change in abuse of either product, the relative abuse using the ARDR will appear much greater for OxyContin than for ER morphine. The degree of misdirection corresponds to the size of the shift in prescribing.

Regarding Model 1, using the number of assessments as a denominator to compute a prevalence of abuse is most useful only when the patients under assessment (at the treatment center) represent abusing persons generally. The representativeness of the persons receiving treatment for abuse can only be surmised.

In summary, for the purposes of the briefing document, findings for the three PMR studies of abuse (NAVIPPRO, RADARS Treatment Centers, RADARS Poison Centers) will be presented using both a population proportion as an estimate of abuse risk (Model 1) and the abuse report dispensing ratio (ARDR, Model 2a). While the proportion of abuse (Model 1) is based upon the number of assessments, it is also not a direct estimate of abuse risk in the general population. The abuse proportions calculated under Model 1 are measures of preference for particular opioids *among abusing persons,* as estimated from individuals entering substance abuse treatment centers (NAVIPPRO and some RADARS), opioid abuse treatment centers (most RADARS), or individuals whose problems related to abuse give rise to poison center calls. The ARDR values produced by Model 2 have uncertain interpretations because the denominator is unrelated to the numerator.

4.2 Common Study Design Elements

4.2.1   Study Periods

Study data were compared before and after introduction of the reformulation of OxyContin in August 2010 (Figure 2). The baseline two-year pre-reformulation period for all studies is from July 1, 2008 through June 30, 2010 when OxyContin was the only ER oxycodone product on the market. The analyses excluded a six-month market transition period from July 2010 through December 2010, for most of which both the original and reformulated versions of OxyContin were available in pharmacies. The post-reformulation period began in January 2011 and the length varied by study from two to five years after the transition period. The length of post-period was specified according to the timeframe of data availability when the PMR studies were issued in 2016. The NAVIPPRO Treatment Centers Study ended in December 2014 due to screen changes used in the collection of oxycodone and OxyContin data in 2014. In the Insured Populations Study data collection in the private insurance databases ended in September 2015 due to the switchover from ICD-9 diagnostic codes to ICD-10 diagnostic codes. The Medicaid insurance analyses ended in December 2012 due to data availability.

Figure 2.   Study Time Period
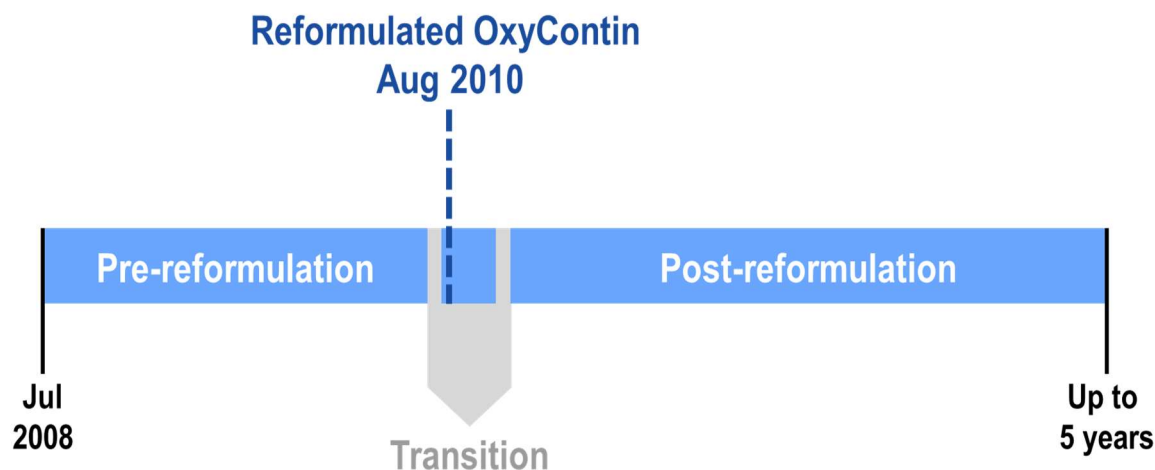
4.2.2   Comparators

Comparator opioids were used in all studies to assess whether changes in outcomes following the introduction of reformulated OxyContin were specific to OxyContin. The comparator opioids were evaluated in the same manner as for OxyContin. The results for the comparator opioids were used as a frame of reference to understand the declines in abuse of opioids that may be due to competing population-based opioid interventions, such as prescription drug monitoring programs, or other secular trends. The results for OxyContin abuse are then evaluated in relation to the comparator opioids to determine whether the changes observed for OxyContin are likely due to the reformulation or other secular trends.

As set forth by FDA, the primary comparators used for comparison to OxyContin in the two treatment centers studies and RADARS Poison Centers study were:

- **Extended-release (ER) morphine**, an extended-release formulation, had a relatively large market share and provides a single-entity ER opioid comparator that is subject to the same regulatory actions as OxyContin, therefore serving as a useful comparator.

- **Immediate-release (IR) hydrocodone combination products** also have a relatively large market share. IR hydrocodone combination products provide a comparison to an IR opioid that has a very different profile of abuse than OxyContin, as it is very rarely abused via the injection route (presumably due to the acetaminophen), and so does not reflect secular trends in abuse via injecting and is only occasionally abused intranasally.

- "**Other Schedule II Opioids**" is a comprehensive group of Schedule II opioid analgesics other than OxyContin and methadone, includes IR oxycodone, ER and IR hydrocodone

combination products, ER and IR oxymorphone, ER and IR hydromorphone, and ER and IR morphine. This group covers most opioids dispensed in the United States (US), approximately 92% of units dispensed during the study period (Figure 3). This composite group would be expected to have been less influenced by specific individual opioid market forces, such as an individual opioid losing patent exclusivity, or a formulary coverage decision that increases/constrains market access to an individual opioid product. The outcomes observed in the group of Other Schedule II opioids may reflect interventions intended to curb abuse of opioid analgesics generally (e.g., prescription drug monitoring programs, pill mill legislation, opioid-class Risk Evaluation and Mitigation Strategies), providing a measure of the overall level of opioid abuse in the US. However, this group may represent the products that have a larger market share with more weight.

The secondary comparators were (depending on data availability per study) ER oxymorphone, IR oxycodone, IR oxycodone-acetaminophen, methadone and heroin.

In the Insured Populations Study, comparator opioids were chosen based on comparability to OxyContin in indications and expected dispensing patterns. The primary comparators were ER morphine, TD fentanyl, and methadone tablets/capsules and were selected because they have the same labeled indications as OxyContin and had a long marketing history with a large, stable market share throughout the study period. The secondary comparator opioids were ER oxymorphone, IR oxycodone tablets, and IR hydromorphone tablets (all single-entity).

4.3 Statistical Analysis

Abuse and OD were analyzed in all studies in comparison to available denominators. For the NAVIPPRO and RADARS Treatment Centers studies, reports of abuse of specific opioids (and routes of abuse in NAVIPPRO) were summed by calendar quarter. The primary denominators were the number of assessments or survey respondents in each system in each calendar quarter. The RADARS Poison Centers data were handled analogously, except that the US census population in the area covered by poison centers in the RADARS System was taken as the quarterly denominators. Reports per 100 assessments per quarter in treatment centers (or per 100,000 population in Poison Centers) were the outcome, and calendar time categorized was taken as the predictor. Analyses using a quarterly proportion (or rate per population) as the dependent variable and a single time predictor are referred to throughout this report as "Model 1" analyses, following a convention settled on by FDA and Purdue jointly. For each Model 1 analysis, there was a series of representations of calendar time, the same in each study, using coarser and coarser categories: (1) individual quarters kept separate, supporting visual inspection; (2) ordinal (1, 2, 3, …) representations in the pre- and post-reformulation periods taken separately, to permit interrupted time series (ITS) analyses; (3) and finally, all pre-reformulation quarters grouped together and all post-reformulation quarters grouped together. In

the ITS analyses and the pre-post analysis, Model 1 yielded coefficients that characterized pre-post change for OxyContin and each of the comparator opioids, as well as coefficients corresponding to interaction terms between Study Drug (taken pairwise, OxyContin and each of the comparators) and pre-post estimates. Taking the basic pre-post estimate as a ratio measure, the interaction terms were ratios of ratios (RoRs).

Model 1 analyses describe temporal patterns of abuse. In the absence of direct measures of illicit drug availability, and following FDA guidance, an elaborated set of models (including Model 2a) was undertaken, in which the denominator (incorporated statistically as an offset term) was switched to the quarterly volume of unit dispensing of each product for the region of the cases using three-digit ZIP codes. The numbers of assessments or survey respondents (or intentional pharmaceutical exposure calls) were retained in the models as covariate predictors to account for the volume of activity in settings from where the cases arose. The predicted quantity was reports per tablets dispensed, adjusted for center activity level, or ARDR. Time functions were as in Model 1.

4.4 Caveats in Interpretation of Findings

As discussed in Section 4.1, Model 1 essentially describes what was seen in abusing populations while the interpretation of Model 2a depends on the relationship between product obtained from illicit channels and retail dispensing volume:

1. Declines in prescription pharmacy unit dispensing volume will tend to increase measures based on Model 2a relative to Model 1. Conversely, increases in dispensing volume will depress such measures.

2. If a prescription opioid were to become increasingly more available through illicit channels due to expanded supply and falling prices, the extent of abuse by either measure (Model 1 or Model 2a) would increase, without any change in the product itself. If the increase in availability from illicit channels is proportional to regional retail pharmacy unit dispensing volume, then the use of dispensing volume as a denominator in Model 2a estimates of ARDR will offset the effect of illicit market price and availability.

3. If illicit availability is unchanged, but retail pharmacy dispensing volume increases, then Model 1 will correctly reflect the unchanging abuse, but Model 2a will show a *decline* in the abuse reports per units (tablets/capsules) dispensed, incorrectly suggesting an evolution toward lower abuse.

Figure 3 below shows that dispensing volume for OxyContin declined substantially over the PMR study periods, while dispensing volume for ER morphine increased, leading inevitably (that is, mathematically) to discrepancies between Model 1 and Model 2a results for these

products. Figure 3 shows temporal evolution of dispensing that follows similar arcs for IR
hydrocodone and for Other Schedule II opioids, not so dramatic as for OxyContin or ER
morphine in relative change over time, but with more than an order of magnitude greater
dispensing volume.

Figure 3. **National Retail Pharmacy Unit Dispensing From 3Q2008 to 4Q2015 for
OxyContin, ER Morphine, IR Hydrocodone, and Other Schedule II Opioids**
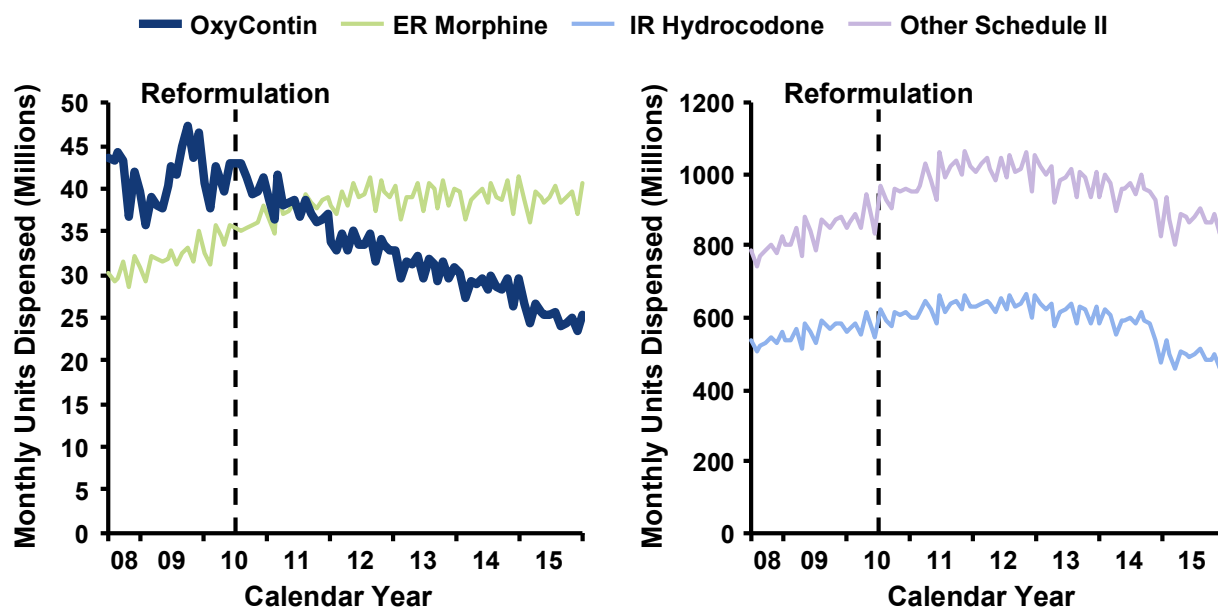
ER, extended release; IR, immediate release
Dashed line indicates introduction of reformulated OxyContin.

For the RADARS Poison Centers Study, the number of intentional pharmaceutical exposures
was used as a covariate for Model 2a. The denominator of Model 2a, as in the two treatment
centers studies remained pharmacy dispensing volume, which entailed the same concerns as
outline above for the use of dispensing volume as a denominator in the treatment centers studies.

The Insured Populations Study is fundamentally different from the three PMR abuse surveillance
studies in that it incorporates well-characterized denominators and in that it captures all the
events (OD and opioid-involved death) within the denominator. The person-time denominator
counts days under observation and at risk during times of presumed use of OxyContin and
comparators, days to which an OD event, fatal or nonfatal, might in principle be observed. Rates,
ratios of rates from before to after the OxyContin reformulation, and RoRs between study drugs
all arise naturally from the data assembly and study design.

5 POSTMARKETING STUDY RESULTS

5.1 The NAVIPPRO Treatment Centers Study (PMR 3051-1)

Study Findings

- Among individuals being evaluated for treatment of substance abuse, reported past-30-day non-oral abuse (insufflation and injection) of OxyContin dropped abruptly (-52% or -32%, depending on statistical model) from 2Q2010 to 1Q2011 following OxyContin reformulation and continued to decline throughout the post-reformulation period.

- The comparator opioids did not show an abrupt drop in abuse followed by an ongoing decline after the OxyContin reformulation.

- Abuse by swallowing intact OxyContin tablets did not change after the reformulation.

5.1.1 Objective

The objective of the NAVIPPRO Treatment Centers Study was to assess whether the introduction of reformulated OxyContin in August 2010 was followed by changes in abuse of OxyContin that differed from contemporaneous changes in abuse of comparators.

5.1.2 Design

The study design was a retrospective analysis of ongoing standardized clinical assessments collected at participating substance abuse treatment sites.

The study comparison involved two periods:

- 2-year baseline pre-reformulation period (July 1, 2008 through June 30, 2010).

- 4-year post-reformulation period (January 1, 2011 through December 31, 2014).

A six-month transition period is displayed in time series trendlines but was excluded from formal analyses.

Individual assessments conducted at admissions to the treatment centers were the unit of analysis.

The first comparison was between OxyContin and a set of comparator drugs for the proportion of individuals reporting abuse in the preceding 30 days by each route. A second analysis considered

the reports in relation to the number of tablets dispensed of each drug at retail pharmacies in the 3-digit ZIP code of the respondent and calendar quarter of the evaluation.

5.1.3 Data Sources

The NAVIPPRO System collects self-reported data on use and abuse of individual drugs (legal and illegal) in the preceding 30 days among adults assessed at entry into substance abuse treatment centers across the US. The treatment centers submit the HIPAA-compliant, de-identified individual level data to the NAVIPPRO Program (Butler 2008).

The Addiction Severity Index - Multimedia Version (ASI-MV) is a standardized, computer-administered clinical assessment of substance abuse and related social, health, and economic problems. In addition to product-specific information, the ASI-MV collects data on route of administration and frequency of abuse for each drug abused in the past 30 days. For prescription medications, questions are supported by on-screen photos.

As changes in the prescription drug market occur, the ASI-MV questions and photos used to assist in product identification are modified.

Sites have continually entered and left the NAVIPPRO System since the initiation of the ASI-MV surveillance program. The principal analyses, reported here, pertained to sites with at least one assessment in each quarter of the study period (July 2008 through the end of 2014).

The analysis omitted assessments occurring within 30 days following a previous assessment.

5.1.4 Outcome: Abuse of OxyContin or Comparators

Abuse was counted when there was a report of abuse in the past month of either OxyContin or a comparator (see below). For the principal analysis, non-oral (insufflation or IV injection) abuse was assessed. Other routes of abuse were also assessed including insufflation (snorting) alone, injection alone, swallowing intact or other oral (swallowing otherwise by chewing or dissolving and drinking).

Non-oral abuse was chosen as the primary outcome because OxyContin's reformulation made the product more difficult to manipulate for insufflation or IV injection. The study outcomes were quarterly abuse reports for OxyContin and each of the comparator opioids. The comparators were included to differentiate the impact of non-product-specific opioid abuse interventions and secular trends in opioid use from the effect of the OxyContin reformulation during the study period.

The primary comparators were: ER morphine; IR hydrocodone; and Other Schedule II opioids, an inclusive group of opioid products that omitted ER oxycodone, methadone, and TD fentanyl patches.

Secondary comparators were: ER oxymorphone, IR oxycodone, methadone, and heroin.

For the principal analysis, "OxyContin" as an abuse outcome was defined when an individual reported that one of the products abused was original OxyContin in the pre-period or either original or reformulated OxyContin in the post-period.

5.1.5   Covariates

Quarterly retail pharmacy unit dispensing volume by three-digit ZIP Code were used as a denominator for some ratio analyses (Model 2a, see below). Prescription volume data were based on dispensing estimates compiled by the medical data firm IQVIA. The quarterly number of ASI-MV assessments served as denominator (Model 1, see below) or as a covariate (Model 2a) to adjust for quarterly assessment volume.

5.1.6   Strengths

Population: NAVIPPRO captures information on an otherwise hard-to-reach group of abusers entering substance abuse treatment. The centers enrolled in the system are distributed throughout the US.

Data granularity: NAVIPPRO includes route-specific abuse information for each product.

Clinically meaningful measures of abuse: The outcome used in the ASI-MV surveillance program (report of having abused a product) is consistent with FDA's definition of abuse as "the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect (FDA 2017a)." Data from the ASI-MV is integrated into clinical care.

5.1.7   Limitations

Misclassification: Data are self-reported without a proctor. Recall bias may overestimate the use of products with well-known names and characteristics and underestimate the prevalence of the use of other products.

Convenience sample: Centers were included on the basis of a local decision to join NAVIPPRO and to use the ASI-MV as part of standard clinical workflow. Persons entering or being assessed for treatment for substance abuse are unlikely to be typical of all substance abusers in the community. Factors such as limited treatment program capacity, law enforcement and judicial practices, and other political, social, geographic, and economic factors may have influenced the number of individuals being assessed for treatment. Since substance abuse patterns vary geographically, the convenience sample of NAVIPPRO sites may not reflect national trends.

Measure of drug available to abusers: Retail pharmacy unit dispensing volume by ZIP code (Model 2a below) was used as a proxy for drug available to abusers, but the correlation of dispensing volume with availability to abusers is unknown.

The correlation may be low because many abusers obtain opioid product from illicit channels and the products may have their origin as dispensed drug from a different supplier region.

5.1.8 Statistical Analyses

The principal analyses were conducted using statistical regression modeling. Regression models presented here followed FDA guidance (Secora 2014, FDA 2015). The designation of the models as Model 1 and Model 2a follows that of the original report and the discussions with FDA.

- *Proportion reporting abuse (Model 1).* The number of persons reporting abuse in the preceding 30 days of each substance ("abuse cases") in each calendar quarter was the dependent variable in a Poisson regression model with the quarterly number of ASI-MV assessments as offset (denominator), scaled per 100 assessments. Fitted results are therefore number of abuse cases per 100 assessments.

- *Quarterly Abuse Report Dispensing Ratio (ARDR) (Model 2a)*. Quarterly numbers of abuse cases formed the dependent variable with quarterly retail pharmacy unit dispensing volume as an offset (denominator) scaled per 10,000 units. The number of ASI-MV assessments entered the regression as a covariate. Fitted results should be read as the quarterly number of abuse cases per 10,000 units dispensed, adjusted for the quarterly numbers of assessments.

Additional analyses and sensitivity analyses were conducted and submitted to FDA, including multiple variations of attributes in the primary analyses, as outlined in the protocol or requested by FDA. Variations in attributes included OxyContin definitions, site selection criteria, study periods, secondary comparator opioids and additional models. Many of the additional analyses and sensitivity analyses were conducted as a matrix with multiple combinations of attributes applied. While there were minor differences in the results for each of the other analyses and sensitivity analyses compared to the principal analyses, none affected the interpretations of the principle analyses.

Calendar time, before and after the OxyContin reformulation, was the main predictor of outcomes. Each Poisson regression model was implemented with three different representations of calendar time.

- *Quarterly Values* – Calendar quarters from July 2008 through December 2014 formed a single multivalued predictor. Quarter-by-quarter estimates from the fitted model were plotted for visual inspection.

- *Interrupted Time Series Analysis* – Log-linear regression was conducted for the pre- and post-reformulation periods separately (July 2008 through June 2010 and January 2011 through December 2014) with calendar time represented as an ordinal variable with unit increase for each calendar quarter. The pre- and post-reformulation slopes were compared, and the immediate shift was evaluated (percent change between the model-fitted last quarter of the pre-period to the first quarter of the post-period).

- *Changes Comparing Post- to Pre-period* – Quarters were classed as in a dichotomous variable coming either from the pre- or post-periods. The differences were expressed as percent change from the pre-reformulation to the post-reformulation period for OxyContin and each of the comparators. A ratio of ratios (RoR) comprises: (1) the numerator, the ratio comparing abuse reports in the pre-period to those in the post-period for a comparator opioid, and (2) the denominator, the pre-to-post ratio for OxyContin. An RoR with a value greater than one indicates that relative to the declines in abuse estimated for OxyContin, the comparator had an increase, no change, or smaller decline. An RoR less than one corresponds to a more pronounced decline for the comparator.

5.1.9   Results

5.1.9.1 Population Characteristics

Sites with at least one assessment per quarter during the entirety of the pre- and post-reformulation periods resulted in a final sample size of 66,897 ASI-MV assessments from 34 sites located in 10 states (CA, CO, FL, MD, MI, NC, NE, NM, OK, WY). These sites emerged from a total NAVIPPRO ASI-MV system activity of 398,490 assessments from 998 sites in 43 states.

Figure 4 displays retail pharmacy unit dispensing volume data for OxyContin and primary comparators, used in Model 2a showing patterns that reflected the national sales data presented above, in Figure 3. After introduction of the reformulation, the number of tablets of OxyContin dispensed decreased over the study time frame. The number of tablets of ER morphine dispensed increased through 2012 and then remained steady. The numbers of units dispensed of IR hydrocodone and Other Schedule II opioids (range ~150-400 million units/quarter) were at least 10 times greater than OxyContin (range ~8-14 million units/quarter). For both IR hydrocodone and Other Schedule II opioids, the numbers of units dispensed gradually increased through 2012 and then declined by about the same amount through 2014. The retail dispensing volume associated with the ZIP codes of the NAVIPPRO treatment centers closely tracked the national sales figures already provided in Figure 3.

Figure 4.   Retail Pharmacy Unit Dispensing Volume From 3Q2008 to 4Q2014
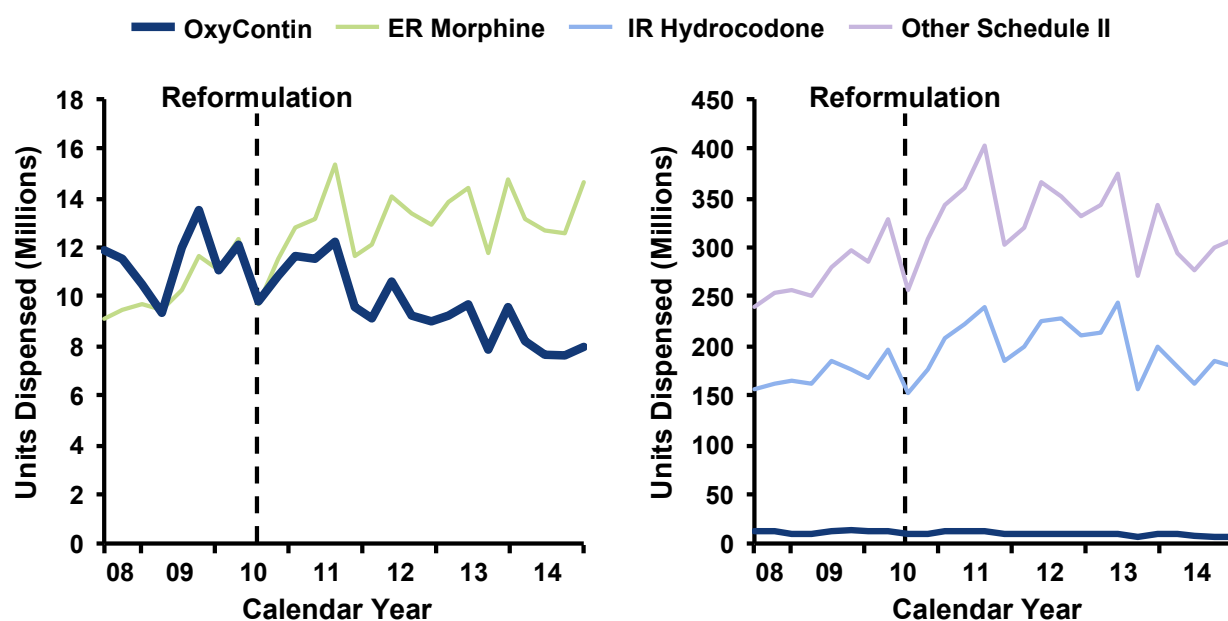
ER, extended release; IR, immediate release.
Dashed line indicates introduction of reformulated OxyContin.

Population characteristics, including demographics, treatment modality and variables associated with drug use patterns, are provided for assessments by drug group in Table 3.

In the opioid abusing study population, approximately 55% reporting abuse of OxyContin or a primary comparator were male. Few were older than 55 years, with most reports from those aged 21 to 54 years. The majority were white. A narrow majority was evaluated in in-patient facilities and most others were evaluated in outpatient/non-methadone treatment settings. About half reported pain. Individuals reporting an injection of at least one opioid in the preceding 30 days varied by drug group (54% OxyContin, 76% ER morphine, 31% IR hydrocodone). The median number of opioid products used in the preceding 30 days ranged from four to six.

As evident in Table 3, persons reporting abuse of OxyContin or one of the comparator opioids were similar to one another but differed from the overall NAVIPPRO Treatment Centers populations. These differences led to a stratified analysis by treatment modality. There was within-stratum homogeneity on the remaining items in Table 3. The stratified results were similar to those for the main analyses, presented below.

Table 3. **Population Characteristics for ASI-MV Assessments Included in the NAVIPPRO Treatment Centers Study**

Response	Category	Any OxyContin	ER Morphine	IR Hydrocodone	Other Schedule II	All Assessments
Age, %	Younger than 21	16.7	16.0	20.4	16.7	11.1
	21 to 34	62.6	65.8	52.8	57.6	42.0
	35 to 54	19.5	18.0	24.6	23.8	40.6
	55 and older	1.2	0.2	2.2	1.8	6.3
Gender, %	Male	56.6	52.1	51.6	54.2	69.3
	Female	43.4	47.9	48.4	45.8	30.7
Race, %	White	78.6	89.9	78.3	76.9	61.4
	Black	8.8	2.5	8.8	10.4	19.5
	Hispanic	9.0	4.5	8.2	9.2	11.0
	Other	3.5	3.1	4.7	3.5	8.1
Pain, %	No	51.2	46.1	45.1	46.8	70.2
	Yes	48.7	53.7	54.7	53.0	29.6
	Unknown/missing	0.1	0.2	0.2	0.3	0.2
Modality, %	Residential/inpatient	55.4	54.6	43.2	49.0	21.4
	Outpatient/non-methadone	27.9	37.7	37.2	31.4	31.8
	Methadone/LAAM	5.4	2.2	3.7	5.2	2.1
	Drug court	1.2	0.9	1.8	1.3	5.2
	Probation/parole	4.2	1.4	4.7	4.6	7.3
	DUI/DWI	1.2	0.9	2.4	2.4	21.5
	Other corrections	0.8	0.5	1.9	1.3	4.1
	TANF (welfare)	0.3	0	0	0	0.2
	Other	3.6	1.8	5.2	4.8	6.6
	Unknown/missing	0	0	0	0	0
Injection History, %	At least 1 prescription opioid injected	54.1	75.9	31.3	42.4	5.6
Number opioids past 30 days	Mean	6.6	7.5	5.6	5.2	0.4
	Median	6.0	6.0	5.0	4.0	0

All OxyContin, original and reformulated OxyContin; DUI, driving under the influence; DWI, driving while intoxicated; ER, extended-release; IR Hydrocodone, immediate-release hydrocodone combination products; LAAM, levacetylmethadol; TANF, temporary assistance for needy families. Percentages are based on total number of assessments from 2-year pre-reformulation to 4-year post-reformulation period. Only sites with quarterly assessment data are included in analysis. There are total 66,897 assessments.

5.1.9.2 Quarterly Values for Non-Oral Abuse

The quarter-by-quarter fitted extent of self-reported non-oral abuse of OxyContin and the primary comparators from July 2008 through December 2014 are displayed in Figure 5, Model 1 (proportion) and Figure 6, Model 2a (ARDR).

Figure 5. Quarterly Fitted Reports, Non-Oral Abuse, Model 1 and 2a, NAVIPPRO Treatment Centers Study
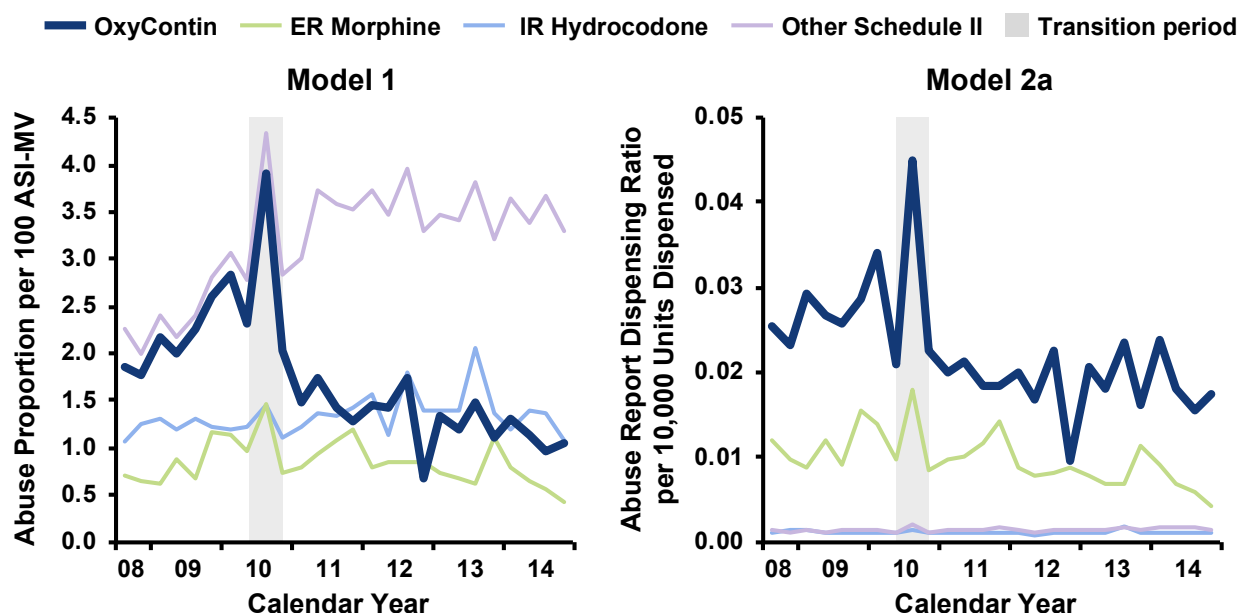
ASI-MV, Addiction Severity Index-Multimedia Version; ER, extended release; IR, immediate release; Model 1, abuse proportion per ASI-MV; Model 2a, abuse report dispensing ratio per 10,000 retail pharmacy unit dispensing volume adjusted for total number of ASI-MV assessments.

Figure 5, Model 1 indicates an abrupt drop in proportion of ASI-MV assessments that reported non-oral abuse for OxyContin after the reformulation. There is, in addition, a reversal of trend from an increase over the pre-period to a decline over the post-reformulation period. In contrast, the proportion of reports among all ASI-MV of 30-day non-oral abuse of Other Schedule II opioids and IR hydrocodone increased. ER morphine showed a slight long-term downward trend. The quarterly ARDR for 30-day non-oral abuse, adjusted for the number of ASI-MV assessments, is displayed in Figure 5, Model 2a. There was an abrupt drop in the ARDR in the post-reformulation period with a downward trend afterwards. While there was a long-term downward trend in ARDR for ER morphine, there was no abrupt drop in the ER morphine ARDR after the OxyContin reformulation.

The relations between the different study drugs as measured by the absolute levels of abuse reports as a proportion of all ASI-MV (Model 1) are very different from the relations between ARDR values for the same products (Model 2a). Pharmacy dispensings of OxyContin and ER morphine were 20 to 50 times lower than sales of IR hydrocodone and Other Schedule II opioids (see Figure 3). The effect of the enormous difference in sales (and therefore in the denominators of the ARDRs for the different products) was to elevate the ARDR for OxyContin and ER morphine relative to the others, with the result that OxyContin and ER morphine loom large in Model 2a presentations like Figure 6, while IR hydrocodone and Other Schedule II products almost disappear. The difference between the left and right graphs in Figure 6 emphasizes that while Model 2a provides statistical control for temporal factors that are closely linked to retail dispensing volume, the absolute values of the ARDR do not correspond to any recognized epidemiologic measure.

5.1.9.3   Interrupted Time Series Analyses of Non-Oral Abuse

To formalize the impression provided by the figures of quarterly reports presented above, ITS analyses were conducted. The fitted trendlines are displayed in Figure 6, Model 1 (proportion) and Figure 6, Model 2a (ARDR).

Figure 6.   Interrupted Times Series Analyses, Non-Oral Abuse, Model 1 and 2a, NAVIPPRO Treatment Centers Study
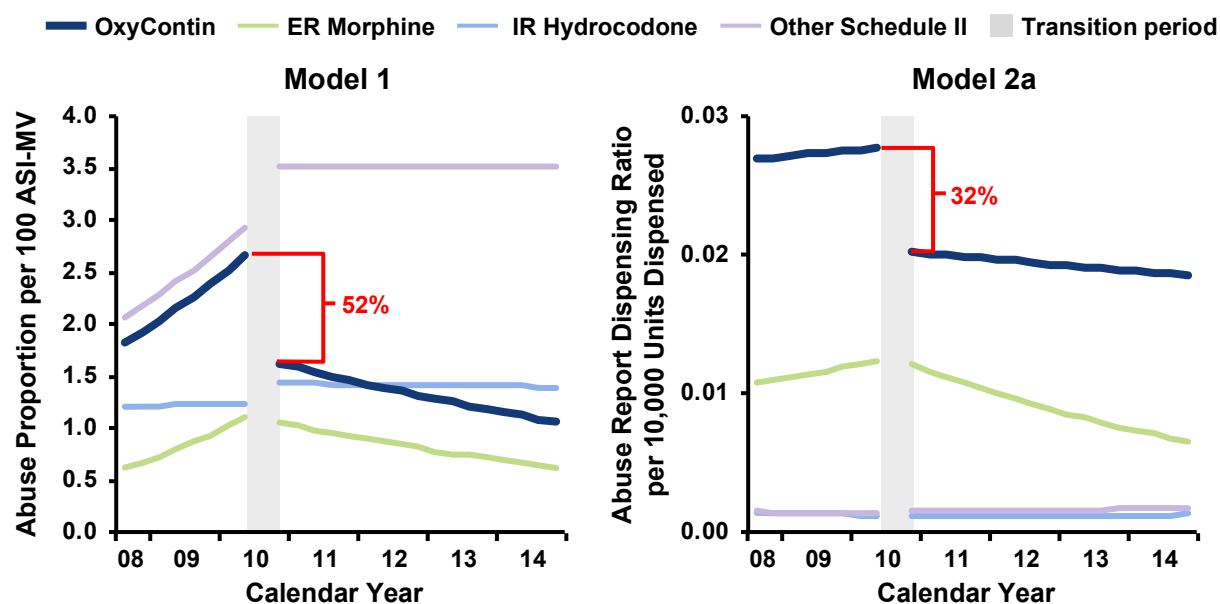
ASI-MV, Addiction Severity Index-Multimedia Version; ER, extended release; IR, immediate release; Model 1, abuse proportion per ASI-MV; Model 2a, abuse report dispensing ratio per 10,000 retail pharmacy unit dispensing volume adjusted for total number of ASI-MV assessments. Non-oral abuse assumed to be 0 if number of any abuse case is missing or 00

Figure 6, Model 1 provides results of the ITS analyses evaluating the proportion of reported 30-day non-oral abuse among persons responding to the ASI-MV. The quarterly values of Figure 6, Model 1 have been assembled into separate linear trendline estimates, before and after reformulation, for OxyContin and each of the primary comparators. The proportion of reports of non-oral abuse of OxyContin rose before the reformulation (slope +5.6%/quarter [2008Q3 to 2010Q2]), dropped immediately (-52.1% [2010Q2 to 2011Q1]) and continued to fall afterwards (slope -2.6%/quarter [2011Q1 to 2014Q4]). The immediate shift in non-oral abuse was much smaller for ER morphine or increased for IR hydrocodone and Other Schedule II opioids (-7.9%, +13.9% and +18.1%, respectively). The declining slopes following reformulation were more pronounced for ER morphine (-3.3%/quarter) and much less pronounced for IR hydrocodone and Other Schedule II opioids (-0.1%/quarter, and 0.0%/quarter, respectively).

Figure 6, Model 2a provides results of the ITS analyses evaluating the ratio of reported non-oral abuse in the preceding 30 days adjusted for retail pharmacy dispensing volume and adjusted for the number of ASI-MV assessments as a covariate. The ARDR of non-oral abuse of OxyContin was flat before the reformulation (slope +0.4%/quarter [2008Q3 to 2010Q2]), dropped immediately (-32.2%/quarter [2010Q2 to 2011Q1]), and fell slowly afterwards (slope -0.5%/quarter [2011Q1 to 2014Q4]). The immediate shift in non-oral abuse was less negative for ER morphine and increased for IR hydrocodone and Other Schedule II opioids (-6.5%, +8.8% and +9.9% respectively). Declines in slopes following reformulation were more pronounced for ER morphine (-3.8%/quarter) than for OxyContin and similarly pronounced for IR hydrocodone and Other Schedule II opioids (+0.8%/quarter and +0.9%/quarter, respectively).

5.1.9.4 Changes in Non-Oral Abuse of OxyContin Relative to Comparators, Post- vs. Pre-Reformulation

A summary of changes from before to after OxyContin reformulation as a percentage change for OxyContin and each of the comparator drugs is provided in Figure 7 as proportion (Model 1) and an ARDR (Model 2a). Point estimates and error bars for the comparison of each of the comparators against OxyContin are also provided in Figure 7. For these RoR assessments, a value greater than one means that either the comparator did not decline or did not decline as much as did OxyContin.

Figure 7.   **Percent Change and RoR, Non-Oral Abuse, Model 1 and 2a, NAVIPPRO Treatment Centers Study**
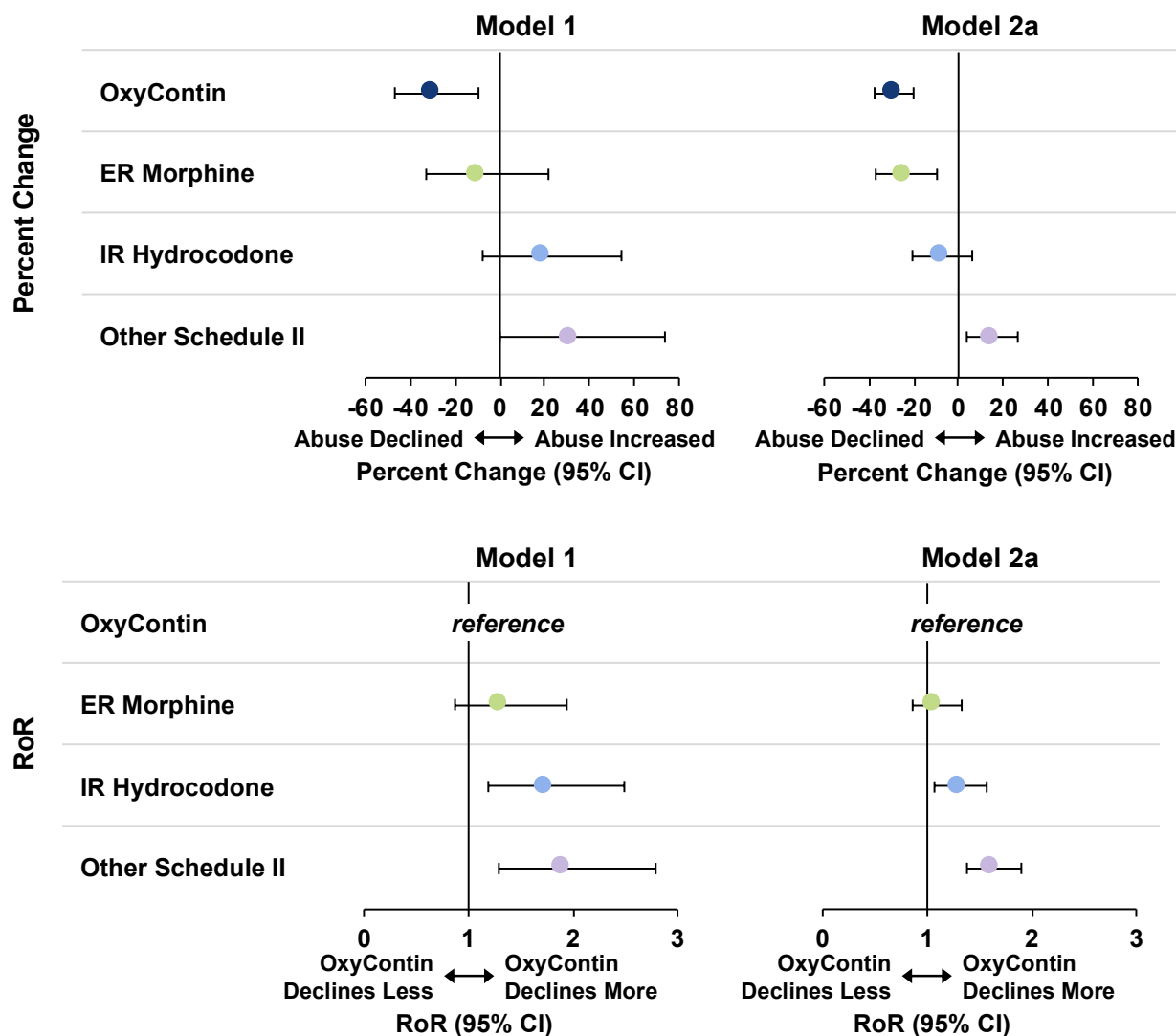
CI, confidence interval; ER, extended release; IR, immediate release; RoR, ratio of ratios. ASI-MV, Addiction Severity Index-Multimedia Version; Model 1, abuse proportion per ASI-MV; Model 2a, abuse report dispensing ratio per 10,000 retail pharmacy unit dispensing volume adjusted for total number of ASI-MV assessments.

The decline in percent change (upper panel) in proportion of reports of non-oral abuse in the preceding 30 days (Figure 7, Model 1) was more pronounced for OxyContin (-30.7%, 95%CI: -46.9, -9.5) compared with ER morphine (-9.6%, 95%CI: -32.9, +21.7), IR hydrocodone (+19.3%, 95%CI: -7.7, +54.3), and Other Schedule II opioids (+31.6%, 95%CI: -0.3, +73.7). The RoR analyses (Figure 7, Model 1) (lower panel), evaluating pre- to post- changes for comparator relative to changes for OxyContin, indicate a similar change in proportion of

reported non-oral abuse in the preceding 30 days for OxyContin compared with ER morphine (+1.30%, 95%CI: 0.87, 1.94) and a markedly more pronounced decline for non-oral abuse of OxyContin compared with IR hydrocodone (1.72, 95%CI: 1.19, 2.49) and Other Schedule II opioids (1.90, 95%CI: 1.29, 2.79).

Figure 7, Model 2a provides corresponding results for the occurrence of non-oral abuse in the preceding 30 days accounting for retail pharmacy unit dispensing volume (ARDR), using ASI-MV assessments as a covariate. The decline in percent change in the ARDR of reports of non-oral abuse in the preceding 30 days was more pronounced for OxyContin (-29.3%, 95%CI: -37.5, -20.1) compared with ER morphine (-24.5%, 95%CI: -37.0, -9.6), IR hydrocodone (-8.2%, 95%CI: -20.6, +6.1), and Other Schedule II opioids (+14.5%, 95%CI: +3.7, +26.4). The pre- to post- changes for opioid comparators relative to changes for OxyContin, indicate a similar non-oral abuse in the preceding 30 days ratio change for ER morphine that was similar to that for OxyContin (RoR 1.07, 95%CI: 0.86, 1.33) and had a markedly more pronounced decline for non-oral abuse for IR hydrocodone (RoR 1.30, 95%CI: 1.07, 1.57) and Other Schedule II opioids (RoR 1.62, 95%CI: 1.38, 1.90).

5.1.9.5   Abuse by Swallowing Intact Tablets

Oral abuse of OxyContin by swallowing intact tablets is a possible alternative comparator to non-oral OxyContin abuse, as the reformulation would not be expected to have a direct effect on swallowing intact tablets. The quarter-by-quarter fitted extent of self-reported abuse in the preceding 30 days by swallowing intact tablets of OxyContin, ER morphine, IR hydrocodone, and Other Schedule II opioids during 3Q2008–4Q2014 are displayed in Figure 8, Model 1 (proportion) and Figure 8, Model 2a (ARDR).

Figure 8. **Quarterly Fitted Reports, Oral Swallow Intact Abuse, Model 1 and 2a, NAVIPPRO Treatment Centers Study**
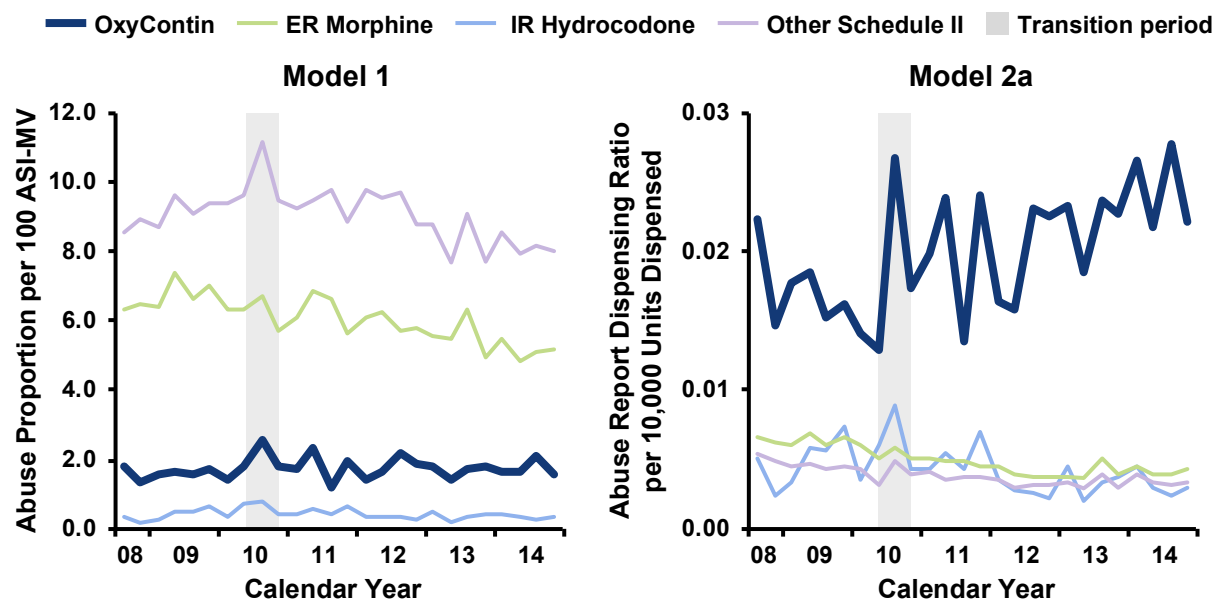
ASI-MV, Addiction Severity Index-Multimedia Version; ER, extended release; IR, immediate release; Model 1, abuse proportion per ASI-MV; Model 2a, abuse report dispensing ratio per 10,000 retail pharmacy unit dispensing volume adjusted for total number of ASI-MV assessments.

For Model 1, no observable change in abuse of OxyContin by swallowing intact tablets is apparent during the study period, similar to the comparator opioids. Abuse of comparator opioids by swallowing intact tablets remained relatively flat. There is a clear distinction between the declining non-oral abuse of OxyContin in Model 1 (Figure 5) and abuse by swallowing intact tablets, suggesting that the forces that led to the abrupt decline in non-oral abuse (presumably the reformulation) did not diminish abuse by swallowing intact tablets.

For Model 2a, OxyContin ARDR by swallowing intact tablets increased over the post-reformulation period (Figure 8). Because retail pharmacy unit dispensing volume for OxyContin was increasing in the pre-period and decreasing in the post-period (Figure 5), the inverse pattern – a fall in ARDR before reformulation and a rise following reformulation – can be seen to have arisen in the face of an unchanged abuse proportion (Model 1) as a result of pharmacy dispensing volume.

5.2 RADARS Treatment Centers Study—Change in Abuse Among Adults Entering Treatment (PMR 3051-3)

Study Findings

- Reports of overall OxyContin abuse (all routes) in the RADARS treatment centers dropped abruptly (-27% or -15%, depending on statistical model) from 2Q2010 to after the OxyContin reformulation, 1Q2011, and continued to decline thereafter.

- Reports of abuse of ER morphine and IR hydrocodone products did not show an abrupt drop after the reformulation.

- The group of Other Schedule II opioids showed a temporal pattern of abuse reports similar to that of OxyContin.

5.2.1 Objectives

The objective of the RADARS Treatment Centers Study was to assess whether the introduction of reformulated OxyContin in August 2010 was followed by changes in self-reported overall abuse (all routes) for OxyContin that differed from those of comparators among adults under care at substance abuse treatment centers in the RADARS System Treatment Centers Program Combined.

5.2.2 Background

The RADARS Treatment Centers Study and the RADARS Poison Centers Study (Section 5.3) are further analyses of previously published data from the RADARS System Treatment Centers Programs Combined (Severtson 2016). The authors of the earlier publication summarized the patterns in their review of the data as follows: "Overall, OxyContin demonstrated the greatest relative decrease in rates of abuse and diversion of all opioid groups throughout the study period. As importantly, the time course of change in the various opioid groups was different. OxyContin prescriptions, diversion, and abuse all decreased abruptly, within months or one year after its reformulation depending on the program. The initial steep decrease was followed by a more gradual decrease. During the initial decrease, it is likely that there were no major confounders acting to reduce diversion and abuse of OxyContin."

The PMR for analysis of the data from the two RADARS programs called for evaluations based on an analytic design parallel to the ones used in the NAVIPPRO Treatment Centers Study (Section 5.1).

5.2.3 Design

The study design was a retrospective analysis of past month reports of opioid abuse collected from participating substance abuse treatment centers.

The study consisted of two periods:

- 2-year baseline pre-reformulation period (July 1, 2008 through June 30, 2010)

- 5-year post-reformulation period (January 1, 2011 through December 31, 2015)

Individual respondent reports were the unit of analysis.

As in the NAVIPPRO analysis, the first comparison was between OxyContin and a set of comparator drugs for the proportion of individuals reporting past month abuse. A second analysis considered the abuse reports in relation to the number of units dispensed of each drug at retail pharmacies in the 3-digit ZIP code of the respondent and calendar quarter of the evaluation.

5.2.4 Data Sources

The RADARS System Treatment Centers Programs Combined consists of adults treated in substance abuse treatment centers. The data from these groups are reported through the Opioid Treatment Program (OTP) and the Survey of Key Informants' Patients Program (SKIP).

The RADARS OTP and SKIP record the specific prescription opioid products reported by persons entering or enrolled in substance abuse treatment. OTP collects information primarily from public facilities that use medication-assisted treatment, whereas the SKIP includes primarily private facilities that do not use medication-assisted treatment. The centers enrolled in the system are distributed throughout the US and within the study period include 35 states for OTP and 50 states for SKIP. Each patient was offered the opportunity to complete an anonymous, standardized, self-administered questionnaire that solicited information on specific prescription drugs "used to get high" in the past month (Dart 2015). Respondents could select specific brand, generic, other or unknown products from a set of opioid groupings including buprenorphine, fentanyl, heroin, hydrocodone, hydromorphone hydrochloride, methadone hydrochloride, morphine sulfate, oxycodone, oxymorphone hydrochloride, tapentadol hydrochloride, and tramadol hydrochloride. Information on the formulation (IR or ER) and the product name was sought. Additionally, the programs gathered gender, age, and race/ethnicity socio-demographic information from survey respondents. Although the entire survey instruments are not identical for the programs, they are identical for the first set of questions addressing past month abuse. Each OTP and SKIP principal investigator is allowed to ask additional questions only after the core set has been presented.

As changes in the prescription drug market occurred, the survey questions for product identification were modified. An important physical change was introduced in the second quarter of 2011, when the original one-page form was recast, with drug-identification options displayed on the back of the new two-sided document for OTP. The same changes were introduced on the multi-page form for SKIP.

Data were aggregated across the two groups of individuals entering treatment for opioid use disorder. OTP and SKIP have important differences:

- OTP centers are federally approved opioid treatment centers that use medication-assisted treatments (methadone and buprenorphine), while the majority of SKIP centers do not offer medication assisted therapy;

- Individuals entering OTP centers were asked to voluntarily complete a standardized, self-administered survey before entering the treatment program. For SKIP, key informants invite patients to voluntarily complete the standardized, self-administered survey. The patients are persons enrolled in substance abuse treatment who have reported an opioid as a primary drug of abuse.

5.2.5 Selection Criteria

For the present analysis, respondents were excluded if they did not provide a valid three-digit ZIP code, if the survey was returned after the close of data collection for a given quarter, or if the response pattern was indicative of careless response. Careless responses, defined as an endorsement of nine or more consecutive items in a column or endorsed abuse of more than 23 opioid products in the past month, were excluded on the basis of having implausible response patterns (Severtson 2018). Surveys prior to 2009 were not evaluated for careless responses.

5.2.6 Outcome: Abuse of OxyContin or Comparators

Abuse was counted when there was a report of past month abuse of OxyContin or a comparator opioid. Routes of abuse were not available.

The primary comparators for the study were: ER morphine; IR hydrocodone; and Other Schedule II opioids, excluding ER oxycodone and methadone.

The secondary comparators were IR oxycodone, methadone, and heroin.

5.2.7 Covariates

Quarterly retail pharmacy unit dispensing volume by three-digit ZIP Code was used as a denominator for a statistical model, Model 2a (see below). Prescription volume data were based on sales estimates compiled by the medical data firm IQVIA.

The quarterly number of respondents in the study centers served as a denominator (Model 1, see below) or as a covariate (Model 2a) to adjust for quarterly respondent volume.

5.2.8 Strengths

Population: The RADARS System Treatment Centers Programs Combined captures information on an otherwise hard-to-reach group of abusers. Centers are distributed throughout the US (35 states from OTP and 50 states from SKIP within the study period). The RADARS Treatment Centers Programs Combined had a combined 85% response rate to survey invitations.

Clinically meaningful measures of abuse: The abuse outcome used in the RADARS System Treatment Centers Programs Combined surveillance program represents respondent-reported use for abuse and is consistent with the FDA definition of abuse as "the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect" (FDA 2017a).

5.2.9 Limitations

Misclassification: Data are self-reported without a proctor. Respondents may not have been able to reliably distinguish between products. The data do not distinguish between routes of abuse.

Convenience sample: Centers are included on the basis of their decision to join RADARS System Treatment Centers Programs Combined, and individuals were included if they agree to complete the survey. Factors such as limited treatment center capacity, law enforcement and judicial practices, and other political, social, geographic, and economic factors may influence the number of individuals enrolled in a treatment center.

Measure of drug available to abusers: Retail pharmacy unit dispensing volume by ZIP code (Model 2a below) was used as a proxy for drug available to abusers, but the correlation of dispensing volume with availability to abusers is unknown. The correlation may be low because many abusers obtain opioid product from illicit channels and the products may have their origin as dispensed drug from a different supplier region.

5.2.10 Statistical Analyses

The principle analyses were conducted using statistical regression modeling. Regression models presented here followed FDA guidance (Secora 2014, FDA 2015) and resembled those used in the NAVIPPRO Treatment Centers Study. The designation of presented models as Model 1 and Model 2a follows that of the original report and the discussions with FDA.

- *Proportion reporting overall abuse (Model 1).* The number of persons identifying each substance for getting high in the preceding month ("abuse cases") in each calendar quarter is the dependent variable in a Poisson regression model with the quarterly number of

respondents as offset (denominator), scaled per 100 respondents. Fitted results are therefore number of abuse cases per 100 respondents.

- *Quarterly Abuse Report Dispensing Rate (ARDR) (Model 2a)*. Quarterly numbers of abuse cases are the dependent variable with quarterly retail pharmacy unit dispensing volume as an offset (denominator) scaled per 100,000 units. The quarterly number of respondents in the OTP and SKIP programs enters the regression as a covariate. Fitted results should be read as the quarterly number of abuse cases per 100,000 units dispensed, adjusted for the quarterly numbers of respondents.

Additional analyses and sensitivity analyses were conducted and submitted to FDA, including multiple variations of attributes in the primary analyses, as outlined in the protocol or requested by FDA. Variations in attributes included OxyContin definitions, site selection criteria, region, study periods, secondary comparator opioids and additional models. Many of the additional analyses and variations in attributes were conducted as a matrix with multiple combinations of attributes applied. While there were minor differences in the results for each of the other analyses and sensitivity analyses compared to the principle analyses, none affected the interpretations of the principle analyses.

Calendar time, before and after the OxyContin reformulation, was the main predictor of outcomes. Each Poisson regression model was implemented with three different representations of calendar time.

- *Quarterly Values* – Calendar quarters from July 2008 through December 2015 formed a single multivalued predictor. Quarter-by-quarter observed estimates were plotted for visual inspection.

- *Interrupted Time Series Analysis* – Log-linear regression was conducted for the pre- and post-reformulation periods separately (July 2008 through June 2010 and January 2011 through December 2015) with calendar time represented as an ordinal variable with unit increase for each calendar quarter. The pre- and post-reformulation slopes were compared, and the immediate shift was evaluated (percent change between the model-fitted last quarter of the pre-period to the first quarter of the post-period).

- *Changes Comparing Post- to Pre-period* – Quarters were classed as in a dichotomous variable coming either from the pre- and post-periods. The differences were expressed as percent change from the pre-reformulation to the post-reformulation period for OxyContin and each of the comparators. The RoR comprises: (1) the numerator, the ratio comparing abuse reports in the pre-period to those in the post-period for a comparator opioid, and (2) the denominator, the pre-to-post ratio for OxyContin. An RoR with a value greater than one indicates that relative to the declines in abuse estimated for OxyContin, the comparator had

an increase, no change, or smaller decline. An RoR less than one corresponds to a more pronounced decline for the comparator.

5.2.11 Results

5.2.11.1 Population Characteristics

During the study period from July 2008 to December 2015, OTP gathered data from up to 64 sites per year in the two-year pre-reformulation period and from up to 76 sites per year in the five-year post-reformulation period from 35 states, yielding approximately 6,400 survey respondents annually. During the same time period, SKIP had a key informant network of up to 58 sites each year in the two-year pre-reformulation period and up to 154 sites each year in the five-year post-reformulation period from 50 states, yielding approximately 2,100 survey respondents annually. In total, the final sample size was 63,528 assessments from 373 centers in 49 states.

Table 4 presents demographic characteristics of persons reporting abuse of OxyContin and the primary comparator opioids. The results are reported separately for pre-reformulation and post-reformulation periods. The demographic characteristics are largely similar between products and between the pre- and post-reformulation periods. There are generally more male (range: 49% to 54%) than female abusers for OxyContin and all primary comparator opioids. Most of the population is white (range: 84% to 91%). Of note is the large number of distinct opioid products that respondents identified themselves as having used in the preceding month.

Table 4. **Demographics Summary of OxyContin and Primary Comparator Opioids – 2y/5y, RADARS Treatment Centers Study**

Value	OxyContin		ER Morphine		IR Hydrocodone		Other Schedule II Opioids	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Gender[1], %								
Male	2,567 (53.75)	3,621 (53.39)	679 (54.23)	1,475 (53.93)	1,791 (49.46)	5,044 (50.83)	3,174 (50.06)	8,835 (50.88)
Female	1,899 (39.76)	3,073 (45.31)	481 (38.42)	1,222 (44.68)	1,561 (43.11)	4,785 (48.22)	2,735 (43.13)	8,349 (48.08)
Age, years								
Mean (SD)	31.14 (9.59)	32.56 (9.65)	32.68 (10.35)	33.5 (9.69)	33.2 (10.35)	33.52 (9.88)	33.05 (10.38)	33.04 (9.81)
Median (IQR)	28 (24, 36)	30 (25, 38)	30 (25, 38)	31 (26, 39)	30 (25, 40)	31 (26, 39)	30 (25, 39)	31 (26, 38)
N	4,645	6,735	1,208	2,715	3,519	9,874	6,156	17,266
Race[2], %								
White	4,224 (88.44)	5,909 (87.13)	1,128 (90.10)	2,480 (90.68)	3,049 (84.20)	8,470 (85.35)	5,422 (85.51)	15,076 (86.81)
Latino	196 (4.10)	270 (3.98)	45 (3.59)	81 (2.96)	210 (5.80)	435 (4.38)	340 (5.36)	690 (3.97)
African-American	154 (3.22)	326 (4.81)	34 (2.72)	86 (3.14)	196 (5.41)	578 (5.82)	293 (4.62)	924 (5.32)
Native American	106 (2.22)	205 (3.02)	29 (2.32)	76 (2.78)	99 (2.73)	335 (3.38)	161 (2.54)	509 (2.93)
Asian or Pacific Islander	26 (0.54)	46 (0.68)	9 (0.72)	16 (0.59)	15 (0.41)	65 (0.65)	32 (0.50)	106 (0.61)
Other	75 (1.57)	93 (1.37)	12 (0.96)	29 (1.06)	57 (1.57)	146 (1.47)	97 (1.53)	254 (1.46)
Number of items endorsed								
Mean (SD)	8.80 (5.02)	8.30 (5.25)	11.37 (5.62)	10.20 (5.57)	9.04 (5.23)	7.70 (5.00)	8.28 (4.87)	6.71 (4.62)
Median (IQR)	8 (5, 12)	7 (4, 11)	11 (7, 15)	9 (6, 14)	8 (5, 12)	6 (4, 10)	7 (5, 11)	5 (3, 9)
N	4,776	6,782	1,252	2,735	3,621	9,924	6,341	17,366

ER, extended release; IQR, interquartile range; IR, immediate release; SD, standard deviation.
[1]Respondents with unknown values for gender were not included in this table, therefore percentages for gender do not add to 100%.
[2]Respondents could mark more than 1 race, therefore frequencies may add to more than 100%.

5.2.11.2 Quarterly Values

The observed quarter-by-quarter self-reported past month abuse of OxyContin and the primary comparators from July 2008 to December 2015 are displayed in Figure 9, Model 1 (proportion) and Figure 9, Model 2a (ARDR).

Figure 9. **Quarterly Observed Reports, Overall Abuse, Model 1 and 2a, RADARS Treatment Centers Study**
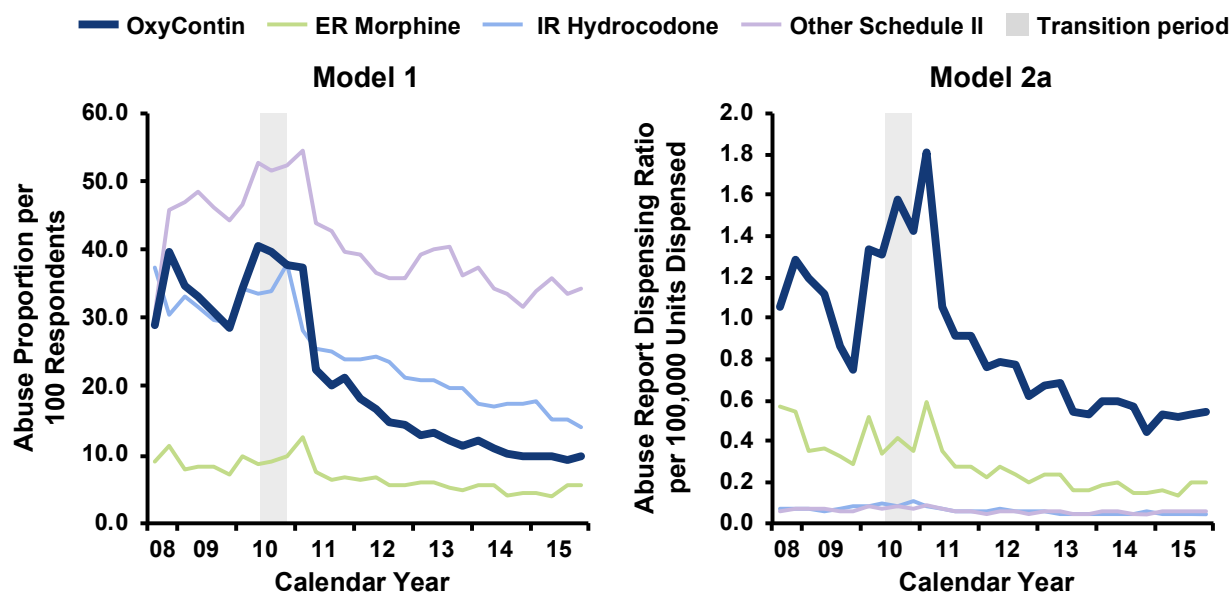
ER, extended release; IR, immediate release; Model 1, abuse proportion per 100 respondents; Model 2a, abuse report dispensing ratio per 100,000 retail pharmacy unit dispensing volume adjusted for total number of respondents.

Figure 9, Model 1 indicates an abrupt drop followed by a clear downward trend in the abuse proportions in the remainder of the post-reformulation period for OxyContin and each of the primary comparators. The corresponding proportions before reformulation were variable but trending upward. The decline in observed abuse proportion appears to be more pronounced for OxyContin than primary comparators, with ER morphine appearing to be relatively flat compared to other opioids considered.

Figure 9, Model 2a indicates a trend toward lower quarterly ARDRs in the post-reformulation period compared to the pre-reformulation period for OxyContin and ER morphine. The decline represents a change from the pre-reformulation trend for OxyContin, but not for ER morphine, as the variable trend in OxyContin abuse in the pre-period resulted in an abrupt drop after the reformulation. The declining trend in the pre-period for ER morphine continued in the post-period without the pronounced drop observed for OxyContin abuse. Further, the decreasing volume of retail pharmacy unit dispensings (the denominator) for OxyContin and increasing

volume for ER morphine affect the abuse trends in opposite directions. Conclusions for Model 2a throughout are therefore affected by temporal changes in retail pharmacy unit dispensing volume.

Both measures of abuse cases (abuse cases as a proportion of all respondents and adjusted abuse reports per 100,000 units dispensed ratio) show a series of nearly synchronous local peaks for all study drugs in the second half of 2010 (the transition period) and the first quarter of 2011. The similarity across products is consistent with the possibility that the reformulation of OxyContin could have initiated a period of instability in patterns of drug abuse. The quarter-to-quarter variation suggests that individual quarterly values need to be interpreted with caution.

5.2.11.3   Interrupted Time Series Analyses Results

To formalize the comparison of trends provided by the figures of quarterly observed reports presented above, ITS analyses were conducted and the fitted trendlines are displayed in Figure 10, Model 1 (proportion) and Figure 10, Model 2a (ARDR).

Figure 10.   **Interrupted Times Series Analyses, Overall Abuse, Model 1 and 2a, RADARS Treatment Centers Study**
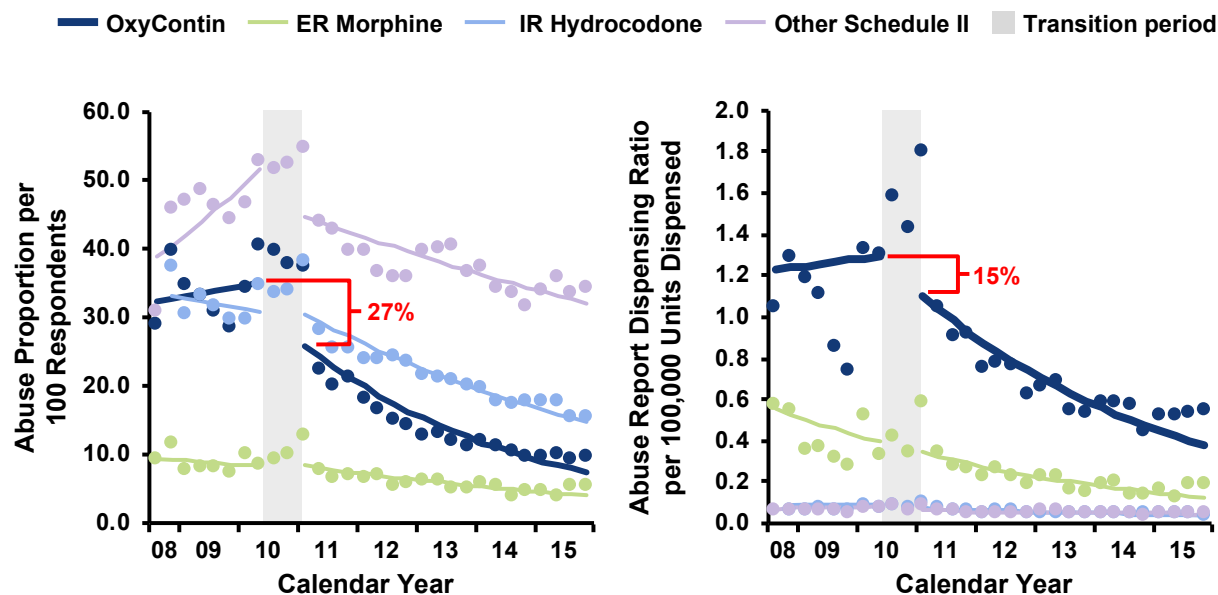
ER, extended release; IR, immediate release; Model 1, abuse proportion per 100 respondents; Model 2a, abuse report dispensing ratio per 100,000 retail pharmacy unit dispensing volume adjusted for total number of respondents.

Figure 10, Model 1 provides results of the ITS analyses evaluating the proportion of overall abuse reports for OxyContin and each of the primary comparator opioids. The proportion of reports of abuse exposures of OxyContin had a slight incline before the reformulation (slope

+1.2%/quarter [3Q2008 to 2Q2010]), dropped immediately (-26.7% [2Q2010 to 1Q2011]) and then declined further thereafter (slope -6.4%/quarter [1Q2011 to 4Q2015]). Immediate shifts in overall abuse were absent for ER morphine and IR hydrocodone (+0.2%, -1.3% respectively). There was an immediate shift of –13.4% for Other Schedule II opioids. Secular declines after the OxyContin reformulation, indicated by the slopes following reformulation were similar to those for OxyContin (slopes -3.7%/quarter, -3.7%/quarter, and –1.7%/quarter, respectively for the three comparators).

Figure 10, Model 2a provides results of the ITS analyses evaluating the ARDR per 100,000 units dispensed. The ARDR of overall abuse for OxyContin was relatively flat before the reformulation (slope +0.8%/quarter [3Q2008 to 2Q2010]), dropped immediately (-15.3% [2Q2010 to 1Q2011]) and had a continued decline thereafter (slope -5.4%/quarter [1Q2011 to 4Q2015]). Immediate shifts in overall abuse were similar for ER morphine (-14.1%) and IR hydrocodone (-16.0%) and more pronounced for Other Schedule II opioids (-28.0%). Declines in slopes following reformulation were similar to OxyContin for ER morphine and IR hydrocodone (-5.2%/quarter and -3.4%/quarter, respectively) but had less decline for Other Schedule II opioids (-1.7%/quarter).

Overall, Figure 10 confirms the initial impression of an immediate drop and ongoing decline in the reports of OxyContin abuse following reformulation. There is a comparable drop and decline for Other Schedule II opioids. Taken in relation to retail pharmacy unit dispensing volume (ARDR), reports of OxyContin abuse again drop immediately after the reformulation and continue to fall, as do reports for Other Schedule II opioids.

5.2.11.4 Changes in Overall Abuse of OxyContin Relative to Comparators, Post- vs. Pre-Reformulation

A summary of changes from before to after OxyContin reformulation as percentage figure for OxyContin and each of the comparator drugs is provided in the upper panel of Figure 11; the lower panel shows point estimates and error bars for the comparison of each of the comparator opioids against OxyContin as a reference. For these RoR assessments, a value greater than one means that either the comparator did not decline or did not decline as much as did OxyContin. Model 1 assesses abuse cases as a proportion of all respondents, and Model 2a shows the ARDR per 100,000 retail pharmacy units dispensed.

Figure 11.   Percent Change and RoR, Overall Abuse, Model 1 and 2a, RADARS Treatment Centers Study
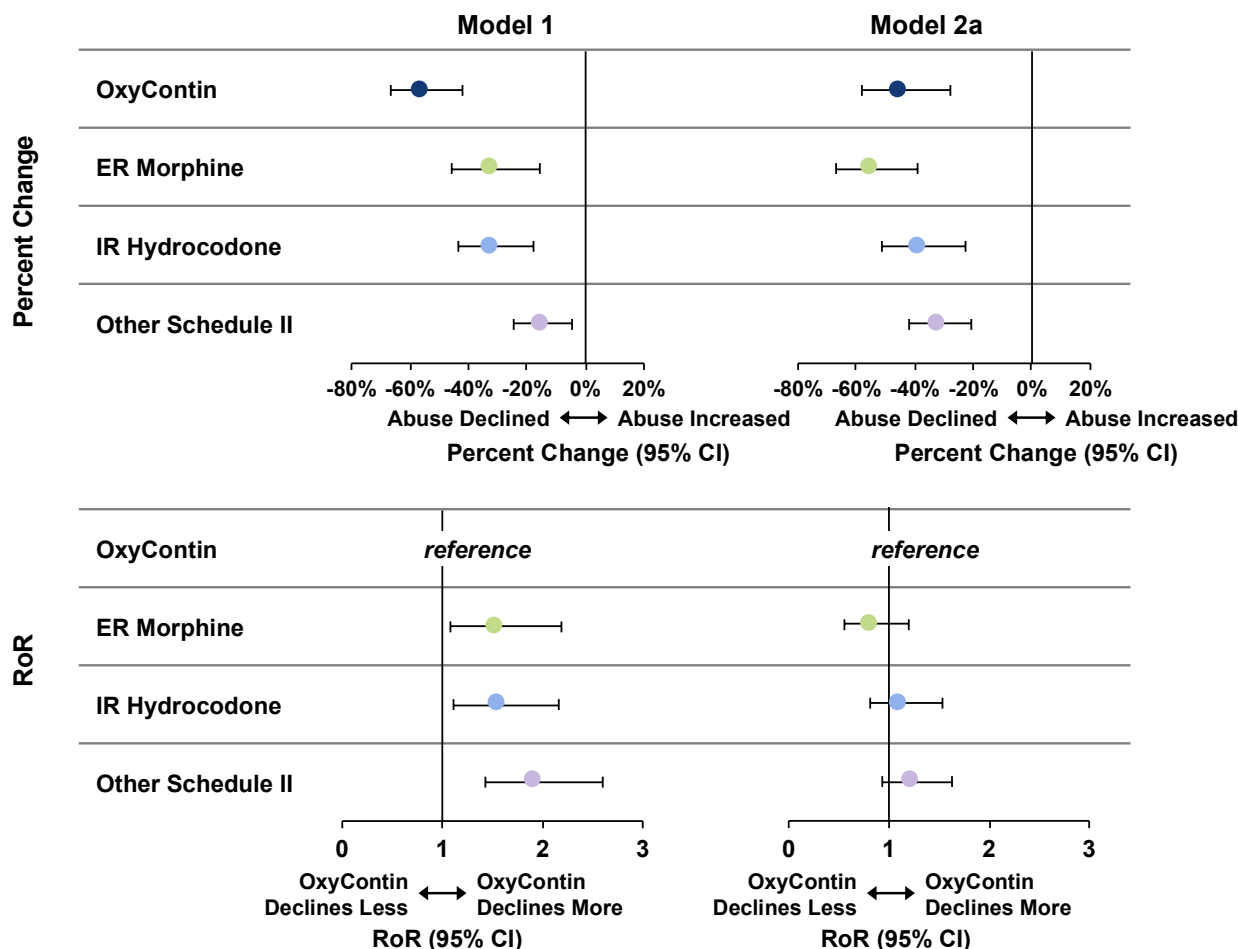
ER, extended release; IR, immediate release; Model 1, abuse proportion per 100 cases; Model 2a, abuse report dispensing ratio per 100,000 retail pharmacy unit dispensing volume adjusted for total number of respondents.

In Figure 11, Model 1, the percent change in proportion (upper panel) of past month reports of overall abuse is more pronounced for OxyContin (-56.0%, 95%CI: -66.6% to -42.1%) compared to ER morphine (-32.3%, CI: -45.7% to -15.6%), IR hydrocodone (-31.8%, 95%CI: -43.5% to -17.8%), and Other Schedule II opioids (-15.2%, 95%CI: -24.6% to -4.6%). The RoR analyses (lower panel) evaluating pre- to post- changes for comparator relative to changes for OxyContin, indicate a markedly more pronounced decline for overall abuse of OxyContin compared to ER morphine (1.54, 95%CI: 1.08 to 2.19), IR hydrocodone (1.55, 95%CI: 1.11 to 2.16), and Other Schedule II opioids (1.93, 95%CI: 1.43 to 2.60).

Figure 11, Model 2a provides corresponding results of the occurrence of past month ARDR for overall abuse and adjusting for number of respondents as a covariate. The percent decline in ARDR of past month overall abuse was less pronounced for OxyContin (-45.1%, 95%CI: -58.12 to -27.91%) compared to ER morphine (-55.2%, 95%CI: -67.0% to -39.1%) and more pronounced compared to IR hydrocodone (-38.7%, 95%CI: -51.3% to -22.7%) and Other Schedule II opioids (-32.2%, 95%CI: -42.0% to -20.8%). The evaluation of post- to pre- changes for opioid comparators relative to changes for OxyContin, indicate a less pronounced past month overall ARDR decline for OxyContin compared to ER morphine (RoR 0.82, 95%CI: 0.56 to 1.20) and a more pronounced decline for overall abuse of OxyContin compared to IR hydrocodone (RoR 1.12, 95%CI: 0.81 to 1.54) and Other Schedule II opioids (RoR 1.23, 95%CI: 0.93 to 1.63).

5.3 RADARS Poison Centers Study — Changes in Reports of Intentional Abuse to Poison Centers (PMR 3051-2)

Study Findings

- Among calls to participating poison centers, there was a step-down (-28% or -14%, depending on statistical model) in intentional OxyContin abuse exposures from 2Q2010 to immediately after reformulation, 1Q2011. A decline continued through the five years following reformulation.

- While all comparators showed declines in intentional abuse that extended over the post-reformulation period, none showed an immediate step-down following reformulation compared to that seen for OxyContin.

5.3.1 Objectives

The objective of the RADARS Poison Centers Study was to assess whether the introduction of reformulated OxyContin in August 2010 was followed by changes for OxyContin that differed from those of comparators in the frequency of calls to US poison centers in which Intentional Abuse was reported.

5.3.2 Background

The RADARS Poison Centers Study and the RADARS Treatment Centers Study (Section 5.2) are further analyses of previously published data from the RADARS System Treatment Centers Programs Combined (Severtson 2016). The authors of the earlier publication summarized the patterns in their review of the data as follows: "Overall, OxyContin demonstrated the greatest relative decrease in rates of abuse and diversion of all opioid groups throughout the study period. As importantly, the time course of change in the various opioid groups was different. OxyContin prescriptions, diversion, and abuse all decreased abruptly, within months or one year after its reformulation depending on the program. The initial steep decrease was followed by a more gradual decrease. During the initial decrease, it is likely that there were no major confounders acting to reduce diversion and abuse of OxyContin."

The PMR analysis of the data from the two RADARS programs called for evaluations based on an analytic design parallel to the ones used in the NAVIPPRO Treatment Centers Study (Section 5.1).

5.3.3   Design

The RADARS Poison Centers Study was a retrospective observational surveillance study of time trends in cases managed by US poison centers. Before and after the introduction of reformulated OxyContin and by calendar quarter, the trends in calls concerning Intentional Abuse exposures of OxyContin and comparators were examined in relation to regional population size and retail pharmacy unit dispensing volume.

The study involved two periods:

- 2-year baseline pre-reformulation period (July 1, 2008 through June 30, 2010)

- 5-year post-reformulation period (January 1, 2011 through December 31, 2015)

5.3.4   Data Source

The RADARS System Poison Center Program (RADARS PC) dataset is a resource for studying opioid exposures (Cicero 2007, Davis 2014, Hughes 2007). RADARS PC obtains data from participating poison centers. During the study period, RADARS System PC data coverage ranged from 46 to 50 poison centers throughout the US serving 82.5% to 94.3% of the US population. Medical professionals (nurses, pharmacists, physician assistants, and physicians) trained in medical and clinical toxicology manage calls to the poison centers from individuals and healthcare providers not trained in toxicology seeking advice for the care of exposed individuals (Mowry 2016).

Each poison center collected data using a common electronic format. Poison centers receive calls concerning (among other potential toxins) drug exposures, including prescription opioids. RADARS PC data include demographics, specific opioids abused, reasons for exposure, and limited information on routes of abuse.

Poison center calls are thought to reflect more of the experience of "novel opioid experimenters" (By 2018, Davis 2014), as opposed to experienced opioid abusers, and thereby offer a different perspective on substance abuse. Poison center calls are known to under-report the most severe exposure incidents, such as OD and death (National Academies of Sciences Engineering and Medicine 2017, Secora 2014). However, the national standards for methods of data collection have remained the same throughout the study period.

Reports of non-exposures and non-human exposures were excluded, as were reports in which the exposed person was less than or equal to five years of age.

5.3.5   Outcomes: Abuse of OxyContin or Comparators

Each poison center case is categorized during the call by an experienced specialist in poison information. "Intentional Abuse" is a defined subcategory under the category of "Reason for

Exposure," defined as "An exposure resulting from the intentional improper or incorrect use where the case was likely attempting to gain a high, euphoric effect, or some other psychotropic effect, including recreational use of a substance for any effect" (Mowry 2016). The definition is very similar to that used by FDA. Abuse of OxyContin or a comparator opioid is defined in this analysis as a call of Intentional Abuse exposure by any route for that substance. OxyContin exposure included reports mentioning original OxyContin in the pre-reformulation period and original or reformulated OxyContin in the post-reformulation period, as well as any call that did not specify whether the product form was original or reformulated.

The primary comparators were ER morphine, IR hydrocodone, and Other Schedule II opioids excluding OxyContin and methadone.

The secondary comparator opioids were ER oxymorphone, IR oxycodone, methadone, and heroin.

Routes of abuse were collected for each call without specific attribution to a given drug if multiple drugs were involved in the report. Cases that involved multiple substances and multiple routes were considered missing and excluded from route-specific calculations.

5.3.6 Covariates

The primary covariate was calendar time, classified in three ways, as explained in Statistical Analysis.

For Model 1 (see below), the rate of abuse exposure calls per calendar quarter was calculated in relation to population size. The sum of the calls of exposed cases was divided by the sum of the population size across all covered 3-digit ZIP Codes of the participating poison centers. The population sizes used for this calculation were based on 2010 US Census, without adjustment for population growth.

Quarterly retail pharmacy unit dispensing volume within the service area, defined by 3-digit ZIP codes of the participating poison centers, were used as a denominator for Model 2a (see below). Prescription volume data were based on sales estimates compiled by IQVIA. The quarterly number of poison center calls concerning intentional prescription medicine exposures was used as a covariate in Model 2a to account for the extent of use of poison centers.

5.3.7 Strengths

Population: During the study period, the service areas of the RADARS PC included 82.5% to 94.3% of the US population. Callers to poison centers include persons who might not ordinarily use other health services.

Quality and stability of data: Poison center specialists probe for the specific product name in every exposure. RADARS PC utilizes consistent reporting guidance and training, including standardized fields used to capture cases. RADARS personnel review case narratives to check the quality of coded data.

5.3.8 Limitations

Misclassification: Data from the RADARS PC rely on self-reports from exposed individuals or other reporters, such as caregivers. Voluntary oral reports are subject to misidentification of specific products and missing information.

Selection bias: Factors associated with misuse and abuse of prescription drugs may also affect the probability of seeking assistance from a poison center. Poison center data do not reliably capture the most severe exposure-related outcomes such as fatal OD.

Missing formulation data: The proportion of missing formulation (IR versus ER) was different by opioid and increased over the study period, ranging from 44% to 78% for morphine and from 11% to 41% for oxycodone. Because the proportion of missing data increases over time, the magnitude of estimated declines over time were overestimated differentially for each opioid.

Measure of drug available to abusers: Retail pharmacy unit dispensing volume by ZIP code (Model 2a below) was used as a proxy for drug available to abusers, but the correlation of dispensing volume with availability to abusers is unknown and may be low. The correlation may be low because many abusers obtain opioid product from illicit channels and the products may have their origin as dispensed drug from a different supplier region.

5.3.9 Statistical Analyses

The principle analyses were conducted using statistical regression modeling. Regression models presented here follow FDA guidance (Secora 2014, FDA 2015). The designation as Model 1 and Model 2a follows that of the original report and the discussions with FDA. The poison center data have a different structure from the data emerging from the two treatment centers studies, so that the models described are similar in intent and structure but differ in some details.

- *Rate of abuse per population (Model 1).* Poisson regression model that fits the quarterly number of abuse exposure calls as the dependent variable, accounting for the 2010 census population in 3-digit ZIP codes in the coverage area of the poison centers as an offset (denominator). The result is a fitted quarterly rate of abuse-related calls in the study population. The population is scaled to give a "quarterly rate per 100,000 population."

- *Quarterly Abuse Report Dispensing Rate (ARDR) (Model 2a)*. Poisson regression model that fits the quarterly number of abuse exposure calls as the dependent variable while accounting for the quarterly retail pharmacy unit dispensing volume in a 3-digit ZIP code in the coverage

area as an offset (denominator). The model includes covariate adjustment for the total number of intentional pharmaceutical exposures in each quarter, intended to serve as a stand-in for the population tendency to utilize the services of poison control centers, which may have varied over time. The dispensing volume is scaled per 100,000 units.

Additional analyses and sensitivity analyses were conducted and submitted to FDA, including multiple variations of attributes in the principle analyses, as outlined in the protocol or requested by FDA. Variations in attributes included OxyContin definitions, route of abuse definitions, study periods, secondary comparator opioids and exploratory models. Many of the additional analyses and variations in attributes were conducted as a matrix with multiple combinations of attributes applied. While there were minor differences in the results for each of the other analyses and sensitivity analyses compared to the principle analyses, none affected the interpretations of the principle analyses.

Each Poisson regression was implemented using three different formulations for calendar time.

- *Quarterly Values* – Calendar quarters from July 2008 through December 2015 formed a single multivalued predictor. Quarter-by-quarter observed estimates were plotted for visual inspection.

- *Interrupted Time Series Analysis* – Log-linear regression was conducted for the pre- and post-reformulation periods separately (July 2008 through June 2010 and January 2011 through December 2015) with calendar time represented as an ordinal variable with unit increase for each calendar quarter. The pre- and post-reformulation slopes were compared, and the immediate shift was evaluated (percent change between the model-fitted last quarter of the pre-period to the first quarter of the post-period).

- *Changes Comparing Post- to Pre-period* – Quarters were classed as in a dichotomous variable coming either from the pre- and post-periods. The differences were expressed as percent change from the pre-reformulation to the post-reformulation period for OxyContin and each of the comparators. The RoR is comprised of: (1) the numerator, the ratio comparing abuse reports in the pre-period to those in the post-period for a comparator opioid, and (2) the denominator, the pre-to-post ratio for OxyContin. An RoR with a value greater than one indicates that relative to the declines in abuse estimated for OxyContin, the comparator had an increase, no change, or smaller decline. An RoR less than one corresponds to a more pronounced decline for the comparator.

5.3.10 Results

5.3.10.1 Population Characteristics

During the study period, 3Q2008 to 4Q2015, there were 308,465 human exposures involving opioid analgesics from a total of 56 centers in 49 states.

Characteristics associated with the abuse exposure calls are shown in Table 5. Just over two-thirds of OxyContin Intentional Abuse exposure reports occurred in males; the male predominance was somewhat smaller for the primary comparator opioids. The mean number of substances for Intentional Abuse across OxyContin and primary comparator opioids ranged from 1.8 to 2.2. The mean age for OxyContin Intentional Abuse exposure calls and for all primary comparators was around 30 years.

Several characteristics were different between the pre- and post-reformulation periods. The post-period calls were associated with slightly older ages than the pre-period for each product. The rate of calls reporting moderate or major effect rose from pre- to post-reformulation for all products.

Table 5.   Demographics Summary of OxyContin and Primary Comparator Opioids – 2y/5y, RADARS Poison Centers Study

Variable	Value	OxyContin Pre	OxyContin Post	ER Morphine Pre	ER Morphine Post	IR Hydrocodone Pre	IR Hydrocodone Post	Other Schedule II Opioids Pre	Other Schedule II Opioids Post
n		1,084	1,309	258	494	3,523	6,895	5,564	12,084
Gender	Female	324 (29.9%)	429 (32.8%)	86 (33.3%)	180 (36.4%)	1,461 (41.5%)	2,865 (41.6%)	2,212 (39.8%)	4,852 (40.2%)
	Male	758 (69.9%)	880 (67.2%)	172 (66.7%)	314 (63.6%)	2,060 (58.5%)	4,028 (58.4%)	3,347 (60.2%)	7,225 (59.8%)
	Unknown	2 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (<0.1%)	5 (0.1%)	7 (0.1%)
Age, years	Mean (SD)	27.9 (11.43)	30.5 (13.37)	29.9 (13.35)	35.3 (15.54)	30.6 (13.55)	32.9 (14.57)	30.3 (13.50)	32.5 (14.09)
Number of substances	Mean (SD)	2.1 (1.31)	2.1 (1.27)	1.8 (1.30)	2.0 (1.27)	2.2 (1.34)	2.2 (1.29)	2.1 (1.29)	2.1 (1.24)
Medical outcome	No effect	84 (7.7%)	104 (7.9%)	16 (6.2%)	31 (6.3%)	494 (14.0%)	921 (13.4%)	714 (12.8%)	1,433 (11.9%)
	Minor effect	289 (26.7%)	349 (26.7%)	47 (18.2%)	135 (27.3%)	991 (28.1%)	1,950 (28.3%)	1,474 (26.5%)	3,371 (27.9%)
	Moderate effect	291 (26.8%)	419 (32.0%)	76 (29.5%)	156 (31.6%)	741 (21.0%)	1,774 (25.7%)	1,204 (21.6%)	3,388 (28.0%)
	Major effect	86 (7.9%)	128 (9.8%)	17 (6.6%)	40 (8.1%)	169 (4.8%)	383 (5.6%)	309 (5.6%)	789 (6.5%)
	Death	5 (0.5%)	7 (0.5%)	1 (0.4%)	2 (0.4%)	19 (0.5%)	23 (0.3%)	20 (0.4%)	46 (0.4%)
	Not followed	88 (8.1%)	74 (5.7%)	31 (12.0%)	34 (6.9%)	355 (10.1%)	565 (8.2%)	587 (10.5%)	898 (7.4%)
	Unable to follow-potentially toxic	219 (20.2%)	205 (15.7%)	67 (26.0%)	82 (16.6%)	686 (19.5%)	1,071 (15.5%)	1,139 (20.5%)	1,807 (15.0%)
	Confirmed non-exposure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Unrelated effect	21 (1.9%)	18 (1.4%)	3 (1.2%)	14 (2.8%)	59 (1.7%)	160 (2.3%)	103 (1.9%)	272 (2.3%)
	Death, indirect report	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	1 (0.1%)	5 (0.4%)	0 (0.0%)	0 (0.0%)	9 (0.3%)	48 (0.7%)	14 (0.3%)	80 (0.7%)

ER, extended release; IR hydrocodone, immediate release hydrocodone combination products; Pre, 3Q2008 through 2Q2010; Post, 1Q2011 through 4Q2015.
SD, standard deviation.
Frequency (percent) presented unless otherwise specified.

5.3.10.2 Quarterly Values for Calls for Intentional Abuse

Reported Intentional Abuse of OxyContin and the primary comparators during 3Q2008–4Q2015 are displayed in Figure 12, Model 1 (abuse rate per 100,000 population) and Figure 12, Model 2a (ARDR).

Figure 12.   Quarterly Observed Reports, Intentional Abuse, Model 1 and 2a, RADARS Poison Centers Study
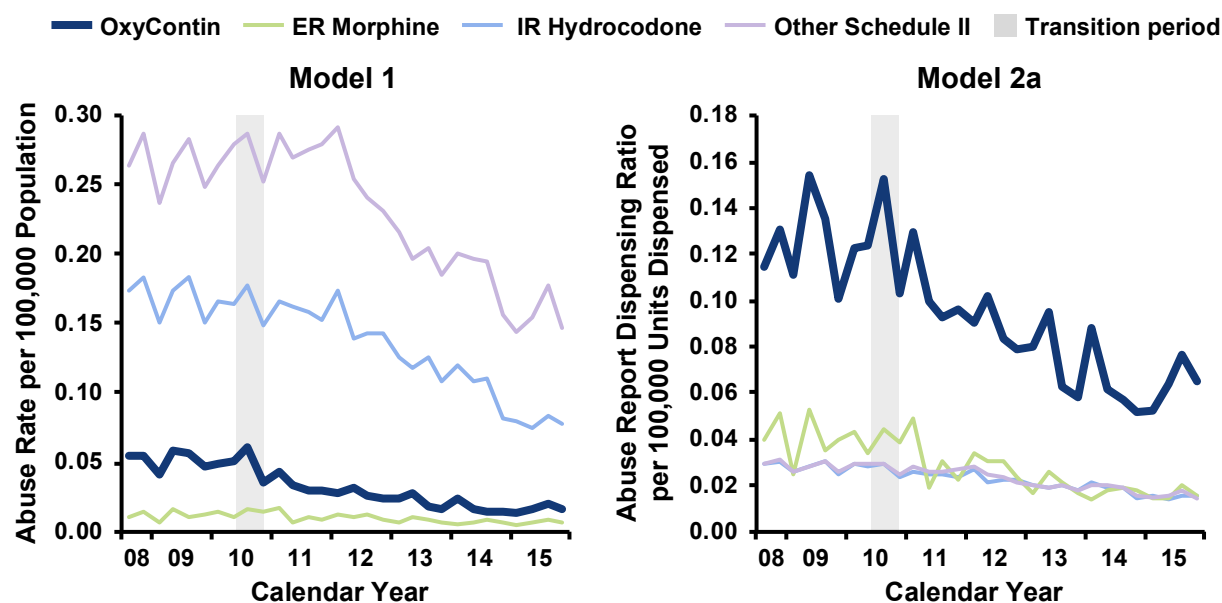
ER, extended release; IR, immediate release; Model 1, abuse rate per 100,000 population; Model 2a, abuse report dispensing ratio per 100,000 retail pharmacy unit dispensing volume adjusted for intentional pharmaceutical exposure calls.

For OxyContin and each of the comparators, Figure 12, Model 1 and Model 2a suggest a steeper decline in both measures in the period after OxyContin reformulation than before. A modest drop after 3Q2010 was observed for OxyContin in both measures. Changes in abuse in the more formal ITS analyses are presented below.

5.3.10.3 Interrupted Time Series for Calls for Intentional Abuse

Interrupted time series analyses were conducted to compare trends in the figures of the quarterly observed calls reported above, and the fitted trendlines are displayed in Figure 13, Model 1 and Model 2a. The trendlines are superimposed on the quarterly observed values, presented as dots.

Figure 13.   Interrupted Time Series Analyses, Intentional Abuse, Model 1 and 2a, RADARS Poison Centers Study
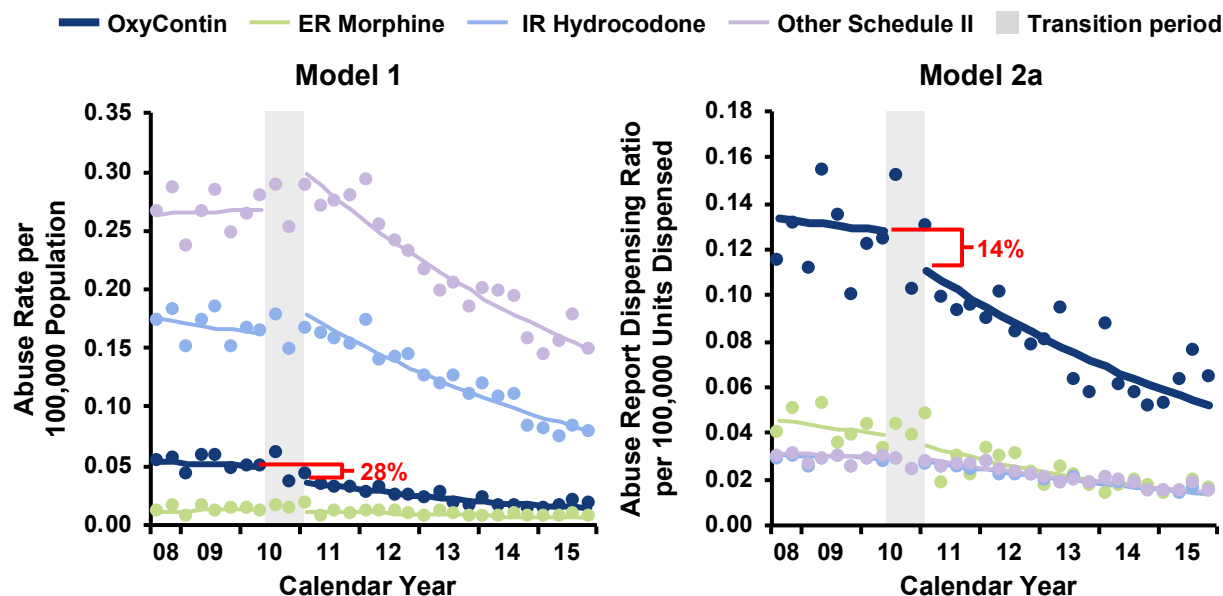
ER, extended release; IR, immediate release; Model 1, abuse rate per 100,000 population; Model 2a, abuse report dispensing ratio per 100,000 retail pharmacy unit dispensing volume adjusted for intentional pharmaceutical exposure calls.

Figure 13, Model 1 shows that the quarterly rate of calls per 100,000 population for Intentional Abuse of OxyContin was nearly flat before the reformulation (3Q2008 to 2Q2010: slope -1.0%/ quarter), dropped immediately (2Q2010 to 1Q2011: -27.5%) and continued to fall afterwards (1Q2011 to 4Q2015: slope -4.9%/quarter). The fitted immediate shifts in rates corresponded to either smaller declines or increases for ER morphine, IR hydrocodone and Other Schedule II opioids (-3.7%; +10.0%; and +11.4%, respectively). The downward slopes for the fitted quarterly rate per 100,000 population following reformulation were similar to those for OxyContin slopes (-3.5%/quarter; -4.2%/quarter; and -3.6%/quarter, respectively).

Figure 13, Model 2a provides results of the ITS analyses and quarterly fitted values evaluating the ARDR per quarter per 100,000 units dispensed, with statistical adjustment for the numbers of calls with reports of intentional prescription drug exposures. The adjusted fitted ARDR of mentions of OxyContin was flat before the reformulation (3Q2008 to 2Q2010: slope -0.6%/ quarter) then dropped immediately (2Q2010 to 1Q2011: -13.6%) and fell gradually afterwards (1Q2011 to 4Q2015 slope -3.9%/quarter). The immediate shift in the adjusted rate per 100,000 units dispensed was similar for ER morphine (-13.2%), lower for IR hydrocodone (-5.4%) and lower for Other Schedule II opioids (–3.5%). The downward slopes following reformulation

were similar to OxyContin for ER morphine, IR hydrocodone and Other Schedule II opioids
(-4.9%/quarter; -3.5%/quarter; and -3.6%/quarter, respectively).

5.3.10.4 Changes in Calls for Intentional Abuse of OxyContin Relative to Comparators, Post- vs. Pre-Reformulation

A summary of changes from before to after OxyContin reformulation as percentage figure for
OxyContin and each of the comparator drugs is provided in the upper panel of Figure 14; the
lower panel shows point estimates and error bars for the comparison of each of the comparators
against OxyContin. For these RoR assessments, a value greater than one means that either the
comparator did not decline or did not decline as much as did OxyContin. Model 1 assesses rate
of quarterly calls reporting abuse per 100,000 population, Model 2a indicates the ARDR per
100,000 retail pharmacy units dispensed.

Figure 14.   **Percent Change and RoR, Intentional Abuse Calls, Model 1 and 2a, RADARS Poison Centers Study**
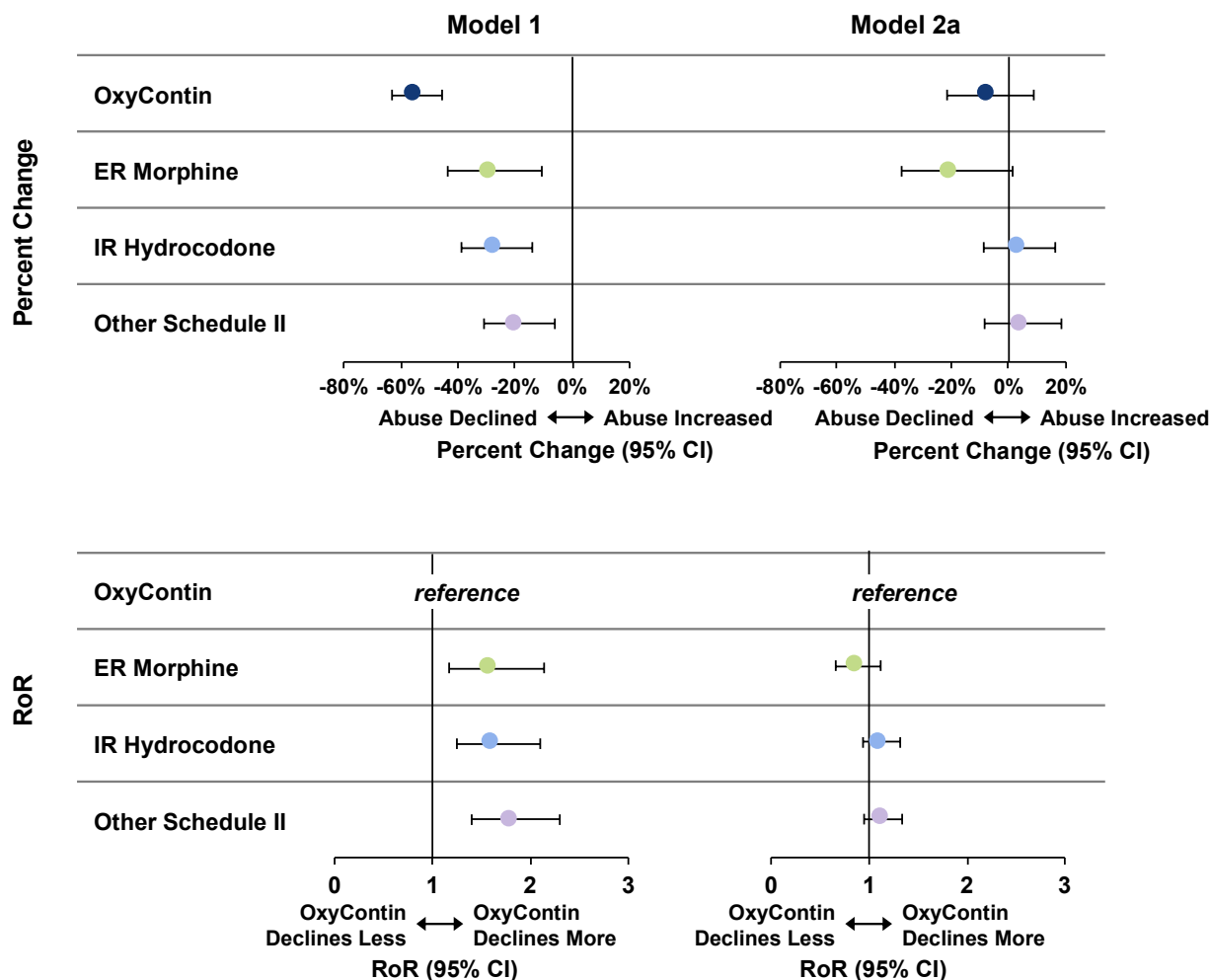
RoR, ratio of ratios; CI, confidence interval; ER, extended release; IR, immediate release; Model 1, abuse rate per 100,000 population; Model 2a, abuse report dispensing ratio per 100,000 retail pharmacy unit dispensing volume adjusted for intentional pharmaceutical exposure calls.

The percent change in quarterly rate of calls with mentions of abuse (Figure 14, Model 1) was more pronounced for OxyContin (-55.2%, 95%CI: -63.1% to -45.6%) than for ER morphine (-29.0%, 95%CI: -43.6% to -10.7%), IR hydrocodone (-27.5%, 95%CI: -38.8% to -14.0%) or Other Schedule II opioids (-19.5%, CI: -30.9% to -6.2%). The elevated RoRs for Figure 14, Model 1 reflect the markedly less pronounced declines in quarterly rate of calls with mentions of ER morphine (1.59, 95%CI: 1.17 to 2.14), IR hydrocodone (1.62, 95%CI:1.25 to 2.10), and Other Schedule II opioids (1.80, 95%CI: 1.40 to 2.30) than for OxyContin.

Figure 14, Model 2a provides corresponding results of the ARDR, adjusting for total mentions of intentional pharmaceutical exposures as a covariate. The percent change decline in ratio of Intentional Abuse reports are less pronounced for OxyContin (-7.7%, 95%CI: -21.6% to +8.7%) than for ER morphine (-20.4%, 95%CI: -37.5% to +1.3%). The percent change increased for IR hydrocodone (+3.0%, 95%CI: -8.8% to +16.2%), and Other Schedule II opioids (+4.05% 95%CI: -8.5% to +18.4%). The evaluation of pre- to post- changes for comparator relative to changes for OxyContin, indicate similar adjusted rates in comparison to OxyContin for ER morphine (0.86, 95%CI: 0.66 to 1.12), IR hydrocodone (1.12, 95%CI: 0.94 to 1.32), and Other Schedule II opioids (1.13, 95%CI: 0.95 to 1.34).

5.3.10.5 Analyses by Route of Abuse

The oral and non-oral quarterly rates of calls reporting Intentional Abuse of OxyContin and the primary comparators during 3Q2008–4Q2015 per 100,000 population are displayed in Figure 15, Model 1. The oral and non-oral quarterly ARDR of Intentional Abuse per 100,000 retail pharmacy units dispensed are shown in Figure 15, Model 2a.

Figure 15.   Intentional Abuse Calls by Non-Oral and Oral Routes, RADARS Poison Centers Study
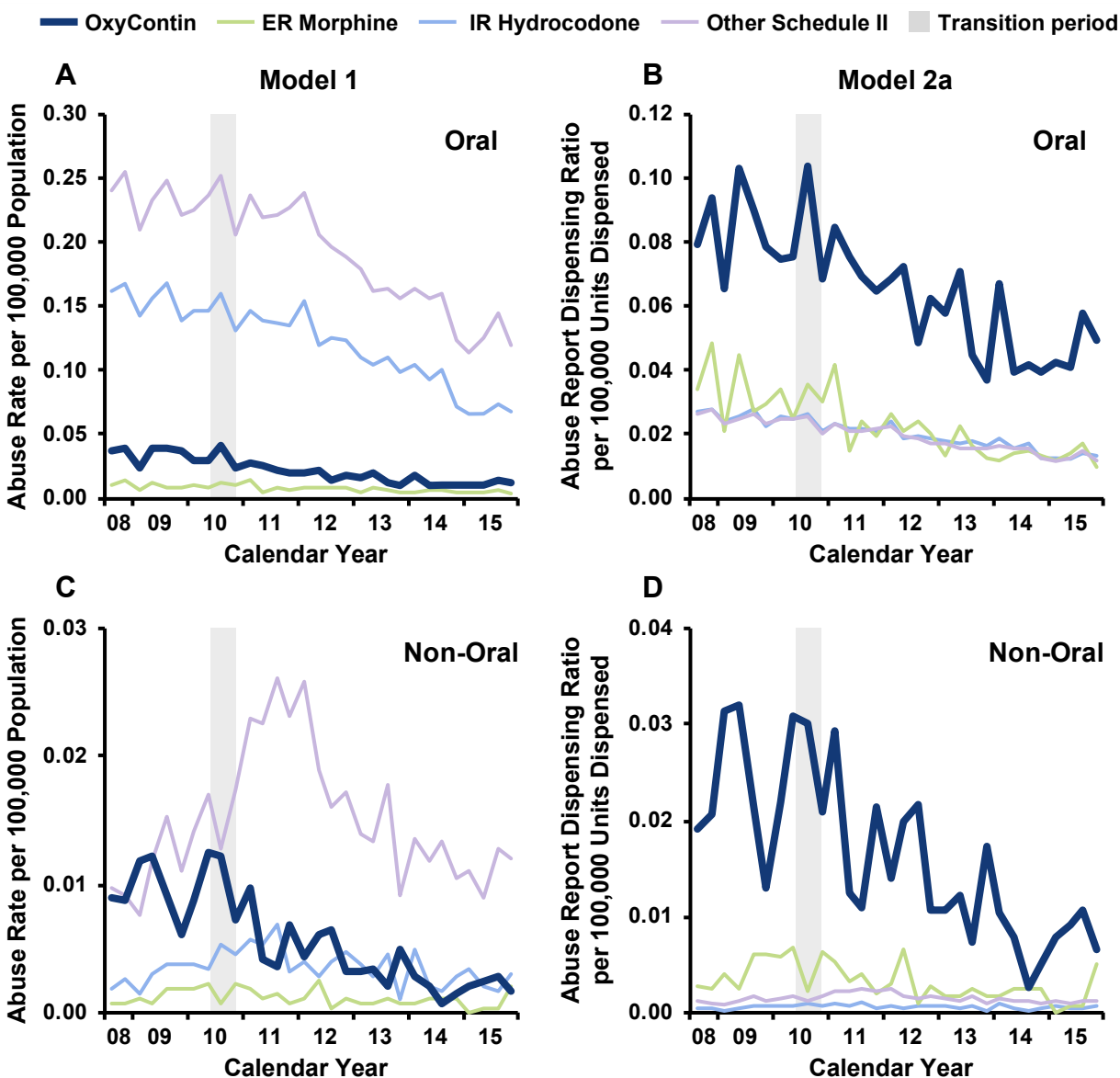
ER, extended release; IR, immediate release; Model 1, abuse rate per 100,000 population; Model 2a, abuse report dispensing ratio per 100,000 retail pharmacy unit dispensing volume adjusted for intentional pharmaceutical exposure calls.

As indicated above, the route of abuse was attributed to a specific route (oral or non-oral [injection or inhalation]) for cases where only one specific substance was mentioned or one route of abuse for multiple substances was indicated. When the data were analyzed by route of

administration rather than any route (i.e., Intentional Abuse), the attribution of *non-oral* abuse results indicated a more pronounced decline for OxyContin relative to IR hydrocodone and Other Schedule II opioids (Figure 15C and 15D).

An additional analysis was conducted using a broader route of abuse definition by which information on exposures that involved multiple drugs and/or multiple routes was included. If there were multiple drugs and multiple routes, each drug would be assigned the route with the highest risk for an adverse outcome. For *non-oral* abuse, results for OxyContin and ER morphine did not materially change; however, results for IR hydrocodone and Other Schedule II opioids were attenuated to various extents when the by-route definition was changed.

The *oral* route of abuse results indicated similar declines in Intentional Abuse exposure calls between OxyContin and primary comparator opioids (Figure 15A and 15B). An additional analysis was conducted using route of abuse information on exposures that involved multiple drugs and/or multiple routes. For *oral* abuse, results were not materially different when the route of abuse definition was changed.

Oral abuse of OxyContin has been suggested as an alternative comparator to non-oral OxyContin abuse, as the reformulation would not be expected to have a direct effect on a route (swallowing intact tablets) of abuse that did not require manipulation.

Trendlines for oral Intentional Abuse exposure calls of OxyContin are shown in Figure 15A (abuse rate per 100,000 population) and Figure 15B (ARDR per 100,000 retail pharmacy units dispensed). For OxyContin, trendlines indicate a similar decline for non-oral and oral routes of OxyContin abuse following reformulation.

5.4 The Insured Populations Study (PMR 3051-4)

Study Findings

- In insured patients under regular medical care following the OxyContin reformulation, there was no significant overall change from before the reformulation in the rates of unintentional opioid OD in all OxyContin recipients or in recipients of comparator opioids.

- For patients who received OxyContin with no other concomitant opioid treatment, the OD rate declined following the introduction of reformulated OxyContin. The decline was greater for recipients of OxyContin than for any of the opioid comparators.

- In each of the time periods and in each of the data sources, the rate of OD was higher for those receiving the comparators than for those receiving OxyContin.

5.4.1 Objective

The Insured Populations Study sought to estimate the change in the rates of unintentional OD and opioid-involved death among persons recently dispensed OxyContin or comparator opioids, comparing the two years before reformulation to up to five years after.

5.4.2 Background

Larochelle (2015) found a decline in the OD rate ascribed to prescription opioids after reformulated OxyContin entered the market in US health insurance data, but the investigators did not attempt to associate OD with particular products. Studies outside of the US have indicated a post-reformulation decline in OD associated with OxyContin, though not in opioid OD overall (Degenhardt 2015, Jauncey 2018, Larance 2018). Despite the extensive literature to date, there have not been large studies that have directly evaluated the impact of OxyContin's reformulation on OD in individuals dispensed OxyContin vs. other opioids in the US.

5.4.3 Methods

5.4.3.1 Study Population

The Insured Populations Study drew on the national Medicaid database (analyzed by the STATinMED corporation) and two commercial insurance claims databases for identifying OD. These were the IBM MarketScan Commercial and Medicare Supplemental Claims and Encounters database (MarketScan, analyzed by IBM) and the HealthCore Integrated Research

Database (HIRD, analyzed by HealthCore). Observation in the Medicaid population was restricted to treatment episodes that were from fee-for-service (FFS) or comprehensive managed care (CMC) plans, in which groups defined on the combination of state, year, and basis of eligibility group met the research usability criteria of Li (2017). MarketScan collects data from employers and health plans. The HIRD includes commercial and Medicare Advantage health plan members insured through Anthem (Blue Cross Blue Shield), a national health insurance provider. The data from each source were restricted to populations linkable to the National Death Index (NDI), a central computerized index of death record information maintained by the National Center for Health Statistics and derived from state vital statistics records (Williams 1992, Skopp 2017). For inclusion in this study, individuals were required to be aged 16–74 years (16–64 years in Medicaid) and to have had at least three months of continuous health plan enrollment prior to eligible opioid dispensings.

5.4.3.2 Study Design

The study design was a retrospective dynamic cohort comparing rates of unintentional OD before and after the OxyContin reformulation. For the commercial insurance data, the study period ran from July 1, 2008 through June 30, 2010 as the pre-reformulation period, when only the original formulation of OxyContin was available and from January 1, 2011 to September 30, 2015 for the post-reformulation period. The primary temporal comparison was between the five-year post-reformulation period and the two-year pre-reformulation period in the commercial health insurance databases. The comparison in the Medicaid data used the same pre-reformulation period as those in the commercial data sources, but a two-year post-reformulation period, due to the unavailability of more recent data. Analyses included all qualifying users. A secondary analysis entailed a restriction to new users, that is persons who had not received a dispensing of a study opioid in the three months preceding first noted use. Further sensitivity analyses included an alternative post-period of three years in the commercial databases.

5.4.3.3 Exposures – OxyContin and Comparators

The primary exposures were evaluated as "treatment episodes" (see below) for OxyContin or a comparator opioid. The comparisons were intended to capture the secular trends in OD resulting from changes in medical practice, drug regulations, and the nonprescription availability of legal and illicit products.

Primary comparator opioids were ER morphine, TD fentanyl, and methadone tablets/capsules.

Secondary comparator opioids consisted of ER oxymorphone, IR oxycodone tablets, and IR hydromorphone tablets (all single-entity).

5.4.3.4 Treatment Episodes

The time available for observation in each patient was divided into treatment episodes.

Treatment episodes were derived for individuals with any dispensing of OxyContin or a comparator opioid between July 1, 2008 and September 30, 2015, with at least three months of continuous health plan eligibility prior to the included opioid dispensing.

A treatment episode was intended to represent continuous and unchanging use of one or a combination of the study drugs. In the simplest case, a treatment episode would correspond to a single dispensing of a study drug, in which case the episode would start on the day of dispensing and end when 1.5 times the days-supply for that dispensing had elapsed. An episode could be extended to include sequential dispensings of the same product, so long as the gap between two successive dispensings was less than 1.5 times the number of days of product supplied at the earlier dispensing. Dispensing of a different product terminated an episode and began a new episode. In the new episode exposure was attributed to both products so long as there was potential use for each, as determined by being within the interval of 1.5 times days' supply. A treatment episode with use of multiple products was terminated if an individual discontinued any of the opioids that defined the episode. A new episode began immediately thereafter, with exposure labeled to match the products still in use. In this way, the opioids attached to any day of observation were those for which there were remaining days' supply from earlier dispensings of the same product.

A treatment episode stopped if a recipient died, terminated health insurance coverage, or reached the end of the pre- or post-reformulation time periods.

An OD event (see below) terminated a treatment episode, with a new episode starting on the following day for non-fatal cases.

Treatment episodes that involved concomitant use of two or more study drugs (OxyContin plus comparator opioids) were excluded from further consideration of comparative analyses. Treatment episodes that included use of a non-study Schedule II opioid were retained, but exposure for each treatment episode was classified in subcategories including:

- "Any use" of the study drug (i.e., with or without concomitant use of non-study Schedule II opioid use) and

- "Only use" of the drug (i.e., without any concomitant use of a Schedule II opioid).

"Only use" treatment episodes represented approximately one-third of the "any use" person-time.

5.4.3.5   Outcomes – Overdose Events

The primary outcome was unintentional OD, i.e., OD events not classified as reflecting intentional self-harm. Events were restricted to those that occurred during a treatment episode.

Intentionality for OD was defined with a previously validated algorithm for health insurance claims using the Clinical Modification of the 9th Revision of the International Classification of Diseases (ICD-9-CM, Green 2019) or from codes for intentional self-harm under the ICD-10 system, which is used to encode death certificates.

Partial validation, that is assessment of predictive value alone, of the ICD-9-CM opioid OD algorithm in insurance claims was conducted in a separate study through medical record review for 159 cases in the HIRD. Standardized data collection techniques were used to abstract information from the medical records in individuals whose claims data included the ICD-9-CM codes that flagged opioid OD and intentionality. Abstraction included presenting signs, symptoms, treatments and treatment responses and patient medical history. Results from this validation study were similar to those from previous work: among the 159 cases identified by ICD-9-CM codes, 135 were confirmed as opioid OD, giving a positive predictive value (PPV) of 85% (95% CI 78–90%; Beachler 2018).

Opioid-involved death in the linked NDI files employed the NDI's standard probabilistic matching between NDI records and identifying data from insurers. Cause of death in the NDI is coded using the 10th Revision of the ICD (ICD-10). ICD-10 codes allow deaths to be classified as resulting from an opioid exposure and allow for the recording of intentional self-harm.

FDA has requested an analysis including both OD designated as intentional and OD not so designated. These have not been completed at all the study sites at the time of preparation of this document. The proportion of all OD events not classified as resulting from intentional self-harm ranged from 89% to 94% in the three data sources. The results for OD events not designated as intentional presented below therefore represent almost all of the data. Where analyses of both all OD and OD-not-designated-as-intentional have been completed, the quantitative results are similar and the interpretation is the same.

5.4.3.6 Covariates

To allow for covariate status that might change over the course of the study, all characteristics were reevaluated at the beginning of each opioid treatment episode. Demographic characteristics were those present at the beginning of each treatment episode. Clinical characteristics and comorbidities were assessed in the health insurance claims using a 3- or 6-month lookback period prior to the beginning of each treatment episode. Time-dependent covariates were evaluated at the beginning of each treatment episode.

5.4.3.7 Statistical Analyses

This study compared pre-post changes in OD rates between recipients of OxyContin and comparator opioids. Individuals could contribute person-time to both the pre- and post-periods, and to treatment with any of the study drugs. Analyses were conducted using unadjusted, covariate-adjusted, and propensity-score weighted Poisson regression models with repeated-measures Generalized Estimating Equations (GEE). The estimates incorporated robust ("sandwich") variance estimators and independent covariance matrices for repeated observations.

Incidence rates (IRs) and all comparison measures were derived from fitted values in the regressions, as carried out separately at each of the data sources. IRs arose from saturated models in which each combination of drug and comparison period was individually represented in a single model. Comparisons between periods within drug and between drugs were obtained by serially removing interaction terms, leaving effects for trends within drug, and differences in trends between drugs. The selection of a Poisson regression followed a preliminary check on the distribution of the events in relation to their fitted values. The variance of the distribution of events was almost exactly that predicted under a Poisson model.

Approximately 10% of patients with an OD had subsequent OD events. The occurrence of a prior event was flagged in regressions using time-varying covariate "prior OD event".

The main estimates of effect in this study were the terms corresponding to the ratio of pre-post ratios (RoRs) comparing the post-period over pre-period ratio for each of the comparators against the corresponding ratio for OxyContin. As with all aspects of the modeling, the adjusted RoRs (aRoRs) were adjusted for baseline demographic and clinical covariates.

Further adjusted relative risks (aRRs) and adjusted ratio of ratio measures (aRoRs) were also determined among new users of the study drugs, using propensity score weighting to account for the difference in covariate distribution between the pre-period and the post-period. The results were very similar to those of the all-user models given in this summary. Other sensitivity analyses included the main results stratified by incident versus prevalent opioid use, fatal versus non-fatal OD status, OD status designated as intentional versus unintentional, restriction of the post-period to three years in the commercial databases, and stratification of the results by CMC versus FFS status in the Medicaid database. None of the sensitivity analysis results differed substantially from those presented in this summary. Results of these analyses have been submitted to FDA.

Results from the two commercial databases (HIRD and MarketScan) were pooled using a DerSimonian and Laird random-effects meta-analysis (DerSimonian 1986, DerSimonian 2015). Because all the results were highly concordant, the meta-analysis was in effect an inverse-variance weighted summary of the two data sources. The Medicaid population was not included

in the pooled analyses given anticipated differences in this population compared with beneficiaries of commercial health insurers (See Table 6 below and the accompanying discussion in Section 5.4.7.1).

5.4.4   Strengths

Data sources reflect general medical populations: The Insured Populations Study relied on data in persons with no selection criteria based on health in three large national health insurance claims databases. Individuals could be tracked longitudinally with a high degree of certainty. Linkage to the NDI provided information on deaths that might not have appeared in insurance claims.

Diversity of populations: Commercial and Medicaid populations have substantially different socio-economic status.

Robust design and statistical methods: The retrospective cohort is a standard epidemiologic study design. The study utilized contemporaneous opioid comparators, regression adjustment, propensity score weighting, and numerous sensitivity analyses to assess confounding and other biases. The design tailored outcome and exposure measures to the administratively complete data sources.

5.4.5   Limitations

Narrow study setting: By definition of the data source and the exposure, the Insured Populations Study addresses patients under regular medical care. It does not address use, abuse, misuse or risks of opioid products outside of regular medical care.

No attribution of OD: Insurance claims data with ICD-9-CM codes and the ICD-10 codes used for death certificates do not permit identification of specific drugs involved in an OD or opioid-involved death. The rates observed in these patients may therefore be due to a combination of OD involving the known recently prescribed opioids, illicitly obtained products, or other medications.

Chronic-use assumption for exposure classification: The definition of exposure periods incorporated the days of drug supplied at each dispensing and is most accurate when products are used chronically and as intended. The exposure algorithms do not account for the possibility that some of the agents were intended as breakthrough pain medication, to be used only as needed. These as-needed products may have been available for use over periods substantially longer than the days-supply.

5.4.6   Diverse Factors Affecting Overdose

Many pathways could lead to changes in rates of OD among users of prescribed OxyContin or comparators following the OxyContin reformulation. Reductions in OD rates in OxyContin recipients could be due to:

1. Inability of patients or caregivers to readily manipulate reformulated OxyContin for easier administration, e.g., in powder or solution, with attendant risks of dosage error. This would be a direct physical consequence of the reformulation in OxyContin recipients.

2. A patient's search for alternatives: Persons who abused OxyContin by IV administration or insufflation before the reformulation may have asked prescribers to switch them to other opioid products. The resulting decline in OD rates among OxyContin recipients and rise among users of other products would be an indirect consequence of the reformulation, mediated by behavior change.

An increase in OD rates in OxyContin users following reformulation might also result from:

3. Providers prescribing OxyContin to new patients at higher risk of abuse and OD, given a perceived reduced risk of abuse with reformulated OxyContin compared with other opioid alternatives. These prescribing tendencies could be a delayed effect, because of the fact that the reformulation occurred and was not widely known initially. The resulting rise in OD rates among recipients of OxyContin and possible decline among users of other products would be an indirect consequence of the reformulation, mediated by prescriber behavior change.

This study does not attempt to separate any of the modes of effect listed above.

5.4.7   Results

5.4.7.1 Study Population

The population consisted of 297,836 patients dispensed OxyContin and 659,673 patients dispensed at least one of the primary comparators (ER morphine, TD fentanyl, or methadone; Table 6). Patient characteristics were largely similar between OxyContin treatment episodes and primary comparator opioid treatment episodes. The average time of observation during exposure to OxyContin was shorter than for the comparator drugs in each data source. The average age at the start of a treatment episode ranged from 47–55 years (Table 6). There was a modest predominance of females throughout, slightly more pronounced for comparators than for OxyContin. The distribution of pain diagnoses was similar between OxyContin recipients and comparators. For OxyContin, Medicaid patients differed from those in the commercial health insurance data sources in having higher

prevalence of each pain category, as well as more chronic obstructive pulmonary disease
(COPD) and depression. Medicaid patients had much higher prevalence of both opioid and
non-opioid drug dependence than did the commercial health insurance beneficiaries. Across
users of each of the study drugs within each data base, about one in six treatment episodes
was marked by recent benzodiazepine use (Table 6).

Table 6. **Demographic and Clinical Characteristics Summary of OxyContin and Primary Comparator Opioid Use in the Medicaid, MarketScan, and HIRD Databases**

Variable	Value	Any OxyContin Use*			Any Primary Comparator Opioid Use^		
		Medicaid	MarketScan	HIRD	Medicaid	MarketScan	HIRD
Treatment episodes	n	522,775	561,703	378,441	2,039,232	975,389	654,462
Total person-time per patient, 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)
Patients, n		94,445	122,254	81,137	367,814	181,240	110,619
Gender, n (%)	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, n (%)	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)
	Arthritis, arthropathies, osteoarthritis and musculoskeletal pain	174,234 (33.3)	211,401 (37.6)	164,603 (43.5)	654,673 (32.1)	299,111 (30.7)	243,429 (37.2)

| Variable | Value | Any OxyContin Use* | | | Any Primary Comparator Opioid Use^ | | |
		Medicaid	MarketScan	HIRD	Medicaid	MarketScan	HIRD
	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)

COPD, Chronic Obstructive Pulmonary Disease; DCI, Deyo-Charlson Index; ER, extended release; HIRD, HealthCore Integrated Research Database; SD, standard deviation; TD, transdermal.
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.

5.4.7.2 Incidence of Overdose During Any OxyContin Use

The incidence rates of OD during any-OxyContin and any-primary-comparator-opioid periods of use are presented in Table 7. As noted above, "any" use of a study drug was defined for OxyContin as use possibly in conjunction with another Schedule II opioid, but not with any of the primary comparators. For the primary comparators, "any" use is use possibly in conjunction with another Schedule II opioid, but not in conjunction with OxyContin or any of the other primary comparators.

The IRs for OD during any-OxyContin treatment episodes varied by data source from 0.8 (MarketScan) to 1.6 (Medicaid) OD events per 1,000 person-months. The OxyContin IRs were uniformly lower in the same periods than the IRs during any-primary-comparator-opioid use, which varied between 0.9 and 2.9 OD events per 1,000 person-months (Table 7). The relative differences are displayed as values greater than one in the right-hand column of Table 7, which shows the incidence rate ratios (IRRs) in any-comparator to any-OxyContin in each data source and each time period. In all data sources, the IRs for OD during any-OxyContin person-time were modestly lower after reformulation than before. The aRRs for the post-period versus the pre-period were: Medicaid: aRR 0.93, 95% CI 0.83–1.04; MarketScan/HIRD: aRR 0.86, 95% CI 0.75–1.00.

Table 7. **Incidence Rates of Unintentional Fatal or Non-Fatal Overdose Among Any OxyContin and Any Primary Comparator Opioid (Non-Overlapping)^ Use 2 Years Before and 5 Years After the Reformulation in the Medicaid, MarketScan and HIRD Databases**

Unintentional Fatal or Non-Fatal Overdose	Period	Patients	Overdoses	Person-Months	IR per 1,000 Person-Months	IRR (Comp / OxyContin)
Medicaid*						
OxyContin	Pre	54,855	630	384,417	1.64	-
ER morphine	Pre	98,795	1,352	581,045	2.33	1.42
TD fentanyl	Pre	59,597	780	337,179	2.31	1.41
Methadone	Pre	55,930	1,201	421,755	2.85	1.74
OxyContin	Post*	53,161	569	349,899	1.63	-
ER morphine	Post*	132,902	1,794	803,822	2.23	1.37
TD fentanyl	Post*	62,377	860	359,083	2.4	1.47
Methadone	Post*	60,932	1,205	477,538	2.52	1.55
MarketScan						
OxyContin	Pre	51,027	212	268,476	0.79	--
ER morphine	Pre	34,180	185	190,891	0.97	1.23
TD fentanyl	Pre	37,991	194	216,440	0.90	1.14
Methadone	Pre	13,262	100	102,965	0.97	1.23
OxyContin	Post	82,797	344	459,907	0.75	--
ER morphine	Post	60,206	407	378,948	1.07	1.44
TD fentanyl	Post	57,861	404	373,612	1.08	1.45
Methadone	Post	18,396	209	177,857	1.18	1.57
HIRD						
OxyContin	Pre	34,740	156	176,145	0.89	--
ER morphine	Pre	19,523	128	121,089	1.06	1.19
TD fentanyl	Pre	21,992	151	132,254	1.14	1.29
Methadone	Pre	10,859	95	86,429	1.10	1.24
OxyContin	Post	53,217	256	314,899	0.81	--
ER morphine	Post	37,153	302	293,756	1.03	1.26
TD fentanyl	Post	31,662	277	250,060	1.11	1.36
Methadone	Post	14,943	209	169,022	1.24	1.52

ER, extended release; HIRD, HealthCore Integrated Research Database; IR, incidence rate; IRR, incidence rate ratio; TD, transdermal.

*A post period of 2 years was used for the Medicaid database instead of a 5 year post period.

^Treatment episodes that had overlapping use of more than one of the primary comparators or OxyContin at the same time were excluded.

Table 8 presents the results of the aRoR calculations, which compare the relative decline in OD rates in "any" users (persons with permitted use of non-study Schedule II opioids) during OxyContin use vs. comparator use from before to after the reformulation of OxyContin. In these

measures, a value greater than one indicates that the comparator was associated with a slower rate of decline in the OD rate (that is a less negative trend) than was OxyContin. Although there was an indication for superiority (faster decline in OD rates over time) for OxyContin against each comparator in each data source, the confidence limits were wide with respect to the measured gains. By the same token, in none of the data sources was there significant evidence that the reformulation had disadvantaged OxyContin recipients with respect to the risk of OD, and the lower bounds, all close to an aRoR of 1, put high confidence on at least a near-equivalence if not a superiority for OxyContin recipients.

Table 8.   Relative Changes in Unintentional Overdose Rates Before and After OxyContin Reformulation of August 2010. "Any" Use, Including with Concomitant Non-Study Schedule II Opioids. Changes in Primary Comparators Relative to Changes in OxyContin in the Medicaid, MarketScan, and HIRD databases

| | Data Source | | | | | | | | |
| | Medicaid | | | MarketScan | | | HIRD | | |
	aRoR	95% LCL	95% UCL	aRoR	95% LCL	95% UCL	aRoR	95% LCL	95% UCL
Any OxyContin	Ref			Ref			Ref		
Any ER morphine	0.97	0.85	1.12	1.14	0.87	1.50	1.04	0.73	1.47
Any TD fentanyl	1.05	0.90	1.23	1.20	0.93	1.55	1.04	0.72	1.51
Any methadone	0.90	0.77	1.04	1.25	0.92	1.71	1.18	0.81	1.73

HIRD, HealthCore Integrated Research Database; aRoR, adjusted ratio of ratios, comparing Post-/Pre- rate ratios of overdose between each comparator opioid versus OxyContin as the reference group; LCL and UCL, lower and upper confidence limit; Ref, reference group; ER, extended release; TD, transdermal.

5.4.7.3 Incidence of Overdose During Only OxyContin Use

Incidence rates of OD among persons who were receiving OxyContin exclusively ("only-OxyContin") and single primary comparator opioids exclusively ("only-primary-comparator-opioids") are presented in Table 9. The IRs for OD during only-OxyContin treatment episodes ranged from 0.4 (MarketScan) to 1.5 (Medicaid) OD events per 1,000 person-months. Incidence rates during only-primary-comparator-opioid ranged from 0.6 to 2.7 OD events per 1,000 person-months. The IRRs comparing each comparator in each period to OxyContin are displayed as values greater than one in the right-hand column of Table 9, which shows the ratio of rates in

only-comparator to only-OxyContin in each data source and each time period. With one exception (ER morphine in HIRD in the pre-reformulation period), the rate of OD was higher in comparators than in OxyContin.

In all data sources, the IR for OD during only-use OxyContin exposure time was lower after reformulation than before the reformulation. After covariate adjustment the declines in the IRs (the aRRs) for only-OxyContin were: Medicaid, aRR 0.80, 95% CI 0.63–1.01; MarketScan/HIRD combined, aRR 0.57, 95%CI 0.42–0.77.

Table 9. **Incidence Rates of Unintentional Fatal or Non-Fatal Overdose Among Only OxyContin and Only Primary Comparator Opioid (Non-Overlapping)^ Use 2 Years Before and 5 Years After the Reformulation by Database in the Medicaid, MarketScan, and HIRD databases**

Unintentional Fatal or Nonfatal Opioid Overdose	Period	Patients	Overdoses	Person-Months	IR per 1,000 Person-Months	IRR (Comp / OxyContin)
Medicaid*						
Only OxyContin	Pre	37,609	213	143,156	1.49	-
Only ER morphine	Pre	62,532	364	180,388	2.02	1.36
Only TD fentanyl	Pre	39,929	221	111,001	1.99	1.34
Only Methadone	Pre	41,245	590	220,697	2.67	1.80
Only OxyContin	Post*	32,464	111	92,079	1.21	-
Only ER morphine	Post*	79,474	426	211,101	2.02	1.67
Only TD fentanyl	Post*	40,646	221	105,633	2.09	1.74
Only Methadone	Post*	44,367	541	235,976	2.29	1.90
MarketScan						
Only OxyContin	Pre	34,457	56	97,454	0.57	-
Only ER morphine	Pre	21,707	39	64,175	0.61	1.06
Only TD fentanyl	Pre	26,676	48	77,764	0.62	1.07
Only Methadone	Pre	9,749	40	53,956	0.74	1.29
Only OxyContin	Post	52,617	56	140,826	0.40	-
Only ER morphine	Post	37,468	88	115,790	0.76	1.91
Only TD fentanyl	Post	40,873	102	124,640	0.82	2.06
Only Methadone	Post	13,225	88	88,928	0.99	2.49
HIRD						
Only OxyContin	Pre	23,635	57	63,959	0.89	-
Only ER morphine	Pre	12,543	32	40,538	0.79	0.89
Only TD fentanyl	Pre	15,845	46	45,981	1.00	1.12
Only Methadone	Pre	8,131	54	46,873	1.15	1.29
Only OxyContin	Post	34,728	41	90,142	0.45	-
Only ER morphine	Post	23,020	71	82,527	0.86	1.89
Only TD fentanyl	Post	23,041	61	79,376	0.77	1.69
Only Methadone	Post	10,964	100	83,859	1.19	2.62

ER, extended-release; HIRD, HealthCore Integrated Research Database®; IR, incidence rate; IRR, incidence rate ratio; TD, transdermal.
*A post period of two years was used for the Medicaid database instead of a five-year post–period.
^Treatment episodes that had overlapping use of more than one of the primary comparators or OxyContin at the same time were excluded.

The aRoRs comparing only-comparator use against only-OxyContin use were more favorable to OxyContin than were the corresponding values from the any-use comparison, as seen in Table 10. Many of the individual lower bounds came close to or excluded unity.

Table 10. **Relative Changes in Unintentional Overdose Rates Before and After OxyContin Reformulation of August 2010. "Only" Use – No Concomitant Schedule II Opioids. Changes in Primary Comparators Relative to Changes in OxyContin in the Medicaid, MarketScan, and HIRD databases**

	Data Source								
	Medicaid			MarketScan			HIRD		
	aRoR	95% LCL	95% UCL	aRoR	95% LCL	95% UCL	aRoR	95% LCL	95% UCL
Only OxyContinˆ	Ref			Ref			Ref		
Only ER morphine	1.24	0.93	1.63	1.72	1.01	2.94	2.04	1.08	3.84
Only TD fentanyl	1.30	0.95	1.77	1.77	1.06	2.97	1.45	0.75	2.82
Only methadone	1.06	0.81	1.40	1.81	1.05	3.11	1.81	1.00	3.28

HIRD, HealthCore Integrated Research Database; aRoR, adjusted ratio of ratios, comparing Post-/Pre- rate ratios of overdose between each comparator opioid versus OxyContin as the reference group; LCL and UCL, lower and upper confidence limit; Ref, reference group; ER, extended release; TD, transdermal

5.4.7.4 OxyContin Versus Comparators, Summarized

Figure 16 summarizes the comparison of pre-post comparisons for OxyContin and the primary comparators for both only-use and any-use. The ratios are constructed with OxyContin as the common reference for each of the primary comparators, which are considered separately. An RoR greater than the null indicates that the post-period OxyContin OD rates fell by more than the post-period rates for comparators, taking the pre-period as a baseline in all cases.

Figure 16.   Adjusted Ratio of Rate Ratios Comparing the Rate Ratio of Unintentional Overdose in the Post- Versus Pre- Reformulation Period for Primary Comparators to the Rate Ratio of Unintentional Overdose in the Post- Versus Pre-Reformulation Period for OxyContin in the Medicaid and Pooled MarketScan/HIRD Databases
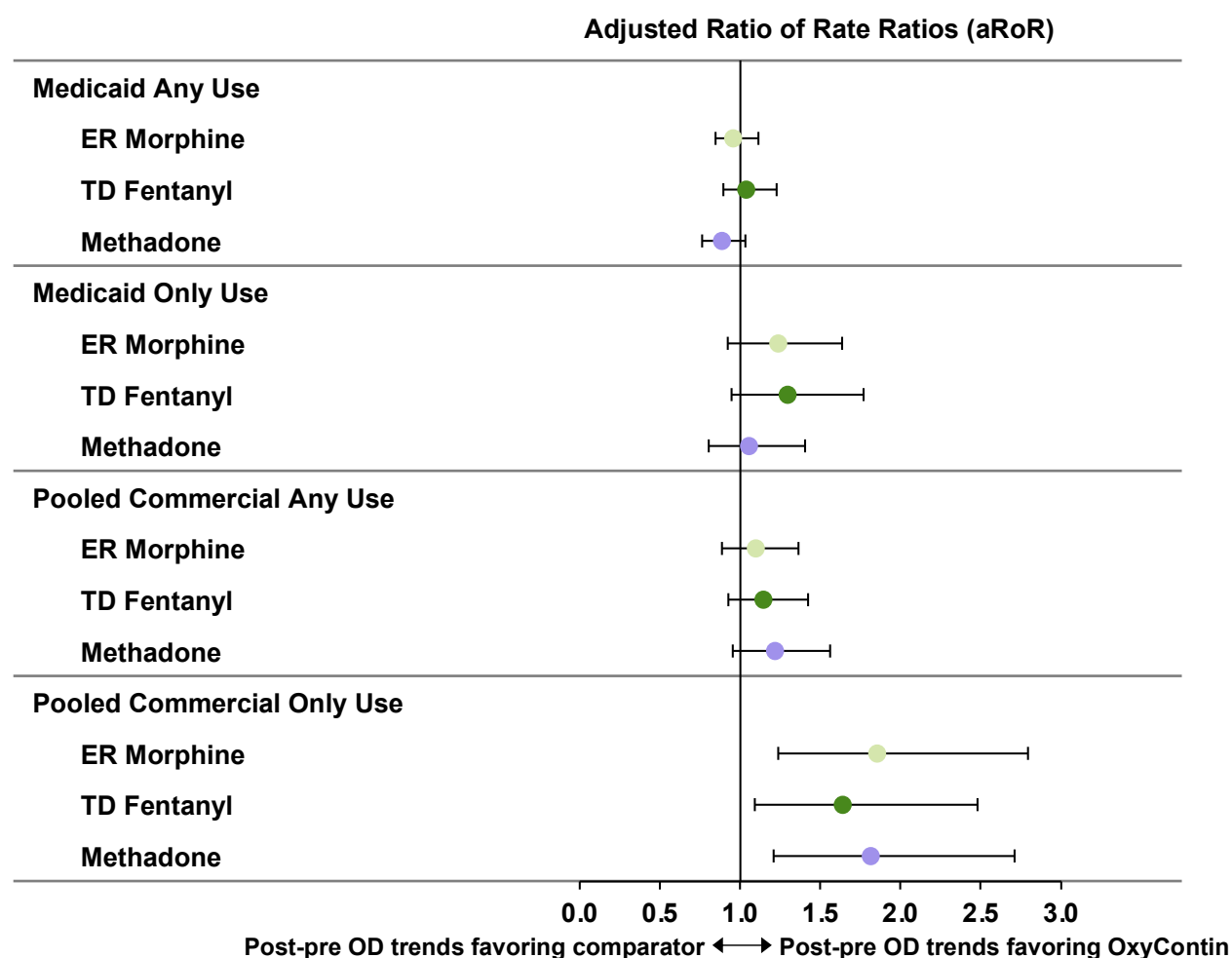
aRoRs, adjusted ratio of rate ratios; ER, extended-release; OD, overdose; TD, transdermal.
Any Use=Concurrent use of opioids other than the study drugs was permitted.
Only Use=No concurrent use of any opioid.

In the "only-use" comparisons, which were restricted to person-time exposed only to OxyContin or only to a single primary comparator and not to any Other Schedule II opioids, there was lower OD incidence in the post-reformulation period than in the pre-reformulation period for OxyContin, but not for most comparator opioids. The pre-to-post comparison was more favorable for OxyContin than for the primary comparators. Medicaid aRoRs comparing primary

comparators to OxyContin ranged from 1.06 to 1.30; for each comparison the lower bound of the 95%CI included 1.0. The effect was substantially larger in the commercial data sources; the MarketScan/HIRD combined aRoRs ranged from 1.64 to 1.85 comparing the primary comparators to OxyContin, in every case with the lower bound of the 95%CI that excluded the no-effect level of 1. The aRoRs greater than 1 indicated that the adjusted IR in the comparator either had not fallen or had not fallen as fast over time as had the adjusted IR in OxyContin recipients.

For "any-use" exposures, the post- versus pre-reformulation rate ratios (RRs) of OD were similar for OxyContin and each of the primary comparators. The similarity is reflected in the fact that aRoRs comparing rates during use of comparator opioids to rates during use of OxyContin were near 1 and their 95%CIs included 1 in every case, indicating that the pre- to post-reformulation changes in OD rates were similar across products. In Medicaid patients, the aRoRs ranged from 0.90 to 1.05. In the pooled MarketScan/HIRD results, the aRoR ranged from 1.10 to 1.22.

Interpretation of the "only-" and "any-" use figures should be informed by the fact that the definitions are based on dates and quantities of pharmacy dispensings. A period of "only-use" exposure could include some additional use of drug dispensed earlier but not previously consumed. This could be the case, for example, for an immediate release product prescribed to cover breakthrough pain in persons primarily following a regimen with extended release drugs. Similarly, persons with concurrent dispensings for different products may be using one of them only on an as-needed basis.

5.4.7.5 Sensitivity Analyses

Additional sensitivity analyses were conducted and submitted to FDA, as outlined in the protocol or requested by FDA, and as described in Section 5.4.3.7. Results using secondary comparators were largely similar to those based on the primary comparators. The adjusted figures presented in Figure 17 were nearly identical to the corresponding crude figures, indicating essentially no net measurable confounding.

Results were similar when the population was stratified by prevalent versus incident (new) use, by the presence of absence of benzodiazepine use in the 90 days preceding the beginning of a treatment episode (HIRD), and with restriction of the post-period in the commercial health insurance databases to three years to match the available post-period in Medicaid. Results were also similar with outcomes restricted to either fatal or non-fatal OD and to the presence or absence of a designation as intentional OD.

5.4.8 Conclusion

In insured patients under regular medical care, the rate of OD during OxyContin use was lower after the introduction of reformulated OxyContin than before. There were similar declines in the

rate of OD for persons who were dispensed the comparator opioids. However, there was little evidence for a greater drop in the OD rate in persons dispensed any OxyContin relative to persons dispensed any of the comparator opioids. In contrast, there appears to have been a preferential decline in the OD in OxyContin recipients who did not receive any other opioid relative to persons receiving any of the comparators as single-product therapy. The effect was strongest in the commercial health insurance data, and only suggestive in Medicaid.

In each of the time periods, and in each of the data sources, the rate of OD was higher for persons receiving each of the comparators than for persons receiving OxyContin.

The setting in which patients received the study drugs may affect the interpretation of the results. Two of the data sources are commercial health insurance databases, whose participants were for the most part currently employed or the dependents of employed persons. In all the data sources, observation time started with the dispensing of a study drug and stopped when a short period had elapsed following the last run-out of the days' supply. Since each opioid dispensing in the US requires a new prescription, "exposure" was restricted to observation time during which individuals had recently visited a prescriber.

5.5 Key Findings from the Formal Postmarketing Studies

In individuals entering treatment for substance abuse in the NAVIPPRO Treatment Centers Study, reports of non-oral abuse of OxyContin in the preceding 30 days dropped abruptly (-52% or -32%, depending on statistical model) from the last quarter (2Q2010) of the model-fitted pre-period to the first quarter (1Q2011) of the model-fitted post-period following OxyContin reformulation and continued to decline throughout the post-reformulation period. The comparator opioids did not show an abrupt drop in abuse followed by an ongoing decline after the OxyContin reformulation. Abuse by swallowing intact OxyContin tablets did not change from before to after reformulation.

In the RADARS Treatment Centers Study, past month reports of overall OxyContin abuse (all routes) showed a step-down (-27% or -15%, depending on statistical model) after the OxyContin reformulation and continued to decline thereafter. Reports of abuse of ER morphine and IR hydrocodone products did not show an abrupt drop after the reformulation, while the group of Other Schedule II opioids showed a temporal pattern of abuse reports similar to that of OxyContin.

In the RADARS Poison Centers Study, among calls to poison centers, there was an immediate step-down (-28% or -14%, depending on statistical model) in intentional OxyContin abuse calls after reformulation. A further decline continued through the five years following reformulation. While all comparators showed declines that extended over the post-reformulation period, none showed an immediate step-down following reformulation comparable to those seen for OxyContin.

In the Insured Populations Study, there was no significant overall change in the rates of unintentional opioid OD following the OxyContin reformulation in OxyContin recipients or in recipients of comparator opioids. However, among the subgroup of patients who received OxyContin alone, the OD rate declined following the introduction of reformulated OxyContin. The decline in OD events was greater for recipients of OxyContin alone than for any of the comparator opioids alone. In each of the time periods, and in each of the data sources, the rate of OD was uniformly higher for those receiving the comparators than for those receiving OxyContin.

In summary, the four PMR studies provide evidence for a reduction in abuse or OD following the reformulation of OxyContin.

6   CONCLUSIONS

The OxyContin PMR studies to assess the impact of the reformulation represent the culmination of a multi-year scientific exchange with FDA and experts in the fields of epidemiology and drug abuse behavior. The four PMR studies reflect the output of a new and evolving area of scientific research and represent a rare opportunity to evaluate the impact of the reformulation of OxyContin on abuse and overdose.

The totality of evidence using diverse studies, endpoints, study populations, and methods provides a comprehensive understanding of the impact of the reformulation on abuse of OxyContin. The PMR data demonstrate a reduction in abuse of reformulated OxyContin compared to the original formulation and show a reduction in rates of overdose in those prescribed OxyContin alone. These studies demonstrate that the abuse-deterrent properties of OxyContin have had the predicted effects on OxyContin abuse and provide an incremental improvement over the formulation without these properties. The framework used to reformulate, evaluate, and confirm the ADP of OxyContin can continue to be considered for other products to make prescription opioids less attractive to individuals intent on abusing via manipulation.

Drug abuse in the US is complex, evolving, and a composite of multiple distinctive "subepidemics" of different drugs (e.g., prescription opioids, heroin, methadone, synthetic opioids, cocaine, and methamphetamine), each with its own demographic and geographic characteristics (Jalal 2018, Zoorob 2019). Reformulation of OxyContin was hypothesized to reduce the abuse of this specific product via routes requiring manipulation; however, and importantly, it was not expected that the reformulation of a single product would reduce abuse of other products or reduce overall abuse of opioids or non-opioid drugs.

Prescription opioids remain an important component in the management of serious pain for appropriate patients (Chou 2009, American Geriatrics Society Panel 2009, US Department of Veterans Affairs 2017, National Pain Center 2017, Dowell 2016), but their use must be balanced against the known and potentially serious risk of both accidental misuse and deliberate abuse.

Abuse-deterrent formulations continue to be one part of a comprehensive multi-stakeholder approach to help address the complex public health issue of prescription opioid abuse, and their availability helps to ensure access by legitimate patients in need of prescription opioids. However, care should be taken to avoid a false sense of security regarding opioids with ADP. It is clear that all opioids, including those with FDA-recognized ADP, carry risks of addiction, misuse, and abuse, which can lead to overdose and death.

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8   APPENDIX 1: REGULATORY HISTORY OF REFORMULATED OXYCONTIN

8.1 History and Regulatory Actions to Approval, Launch, and Abuse-Deterrence Labeling

When taken as intended (tablet swallowed intact), OxyContin's ER mechanism slowly releases oxycodone over a period of 12 hours. After the initial product launch in 1996, original OxyContin became a target of abuse after it was recognized that breaking, crushing, or chewing could rapidly release oxycodone from the extended-release matrix of the tablet. Abusers began crushing the formulation to enhance the effect of oral use, crushing then inhaling the powder for intranasal use, and crushing and dissolving the powder for IV injection. Epidemiologic evidence indicated that the original OxyContin formulation was commonly abused via these non-oral routes (Hays 2004, Sees 2005). For example, in the two years prior to introduction of reformulated OxyContin in 2010, individuals entering substance abuse treatment centers frequently reported having abused original OxyContin via inhalation (55.9%) and injection (34.8%, Data on file, PMR 3051-1). There was also a concern that some pain patients would chew, or their caregivers would crush, the tablets for easier swallowing or administration through gastrointestinal tubes, causing unintentional exposure and associated unintended consequences.

As reports of abuse involving manipulation of OxyContin began to emerge, Purdue refocused its effort on developing a formulation of OxyContin designed to deter abuse by routes that required manipulation. In 2005 Purdue pursued an approach that used a physical/chemical barrier to manipulation by incorporating the polymer PEO, which resulted in the development of the current reformulation, which was approved in 2010.

Bioequivalence studies began in 2006, and an NDA was filed for 10-40 mg dosage strengths of OxyContin in November 2007. Following Advisory Committee recommendations in May 2008, FDA sought, and Purdue provided, additional laboratory data to further characterize the abuse-deterrent properties of the drug. Additional studies were completed, and in March 2009, a comprehensive laboratory-based in vitro manipulation assessment of abuse deterrence, along with all supplemental information on all tablet strengths (10–80 mg), were submitted to FDA with the NDA. A second Advisory Committee meeting was held in September 2009 to review the laboratory data, the Committees voted favorably for approval and FDA approved the reformulation in April 2010. On August 5, 2010, Purdue ceased shipping original OxyContin and on August 9, 2010 commenced shipping the FDA-approved reformulation with ADP.

In April 2013, FDA revised OxyContin's label to include in part the following statement about the ADP of the drug:

> "…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..."

In April 2013, FDA also published notice of its determination that original OxyContin had been withdrawn from sale for safety reasons concluding that "[o]riginal OxyContin… poses an increased potential for abuse by certain routes of administration, when compared with reformulated OxyContin. Based on the totality of the data and information available to the Agency at this time, FDA concludes that the benefits of original OxyContin no longer outweigh its risks."

A timeline summary is presented in Figure 17.

Figure 17.   History and Regulatory Actions to Approval, Launch, and Abuse Deterrence Labeling
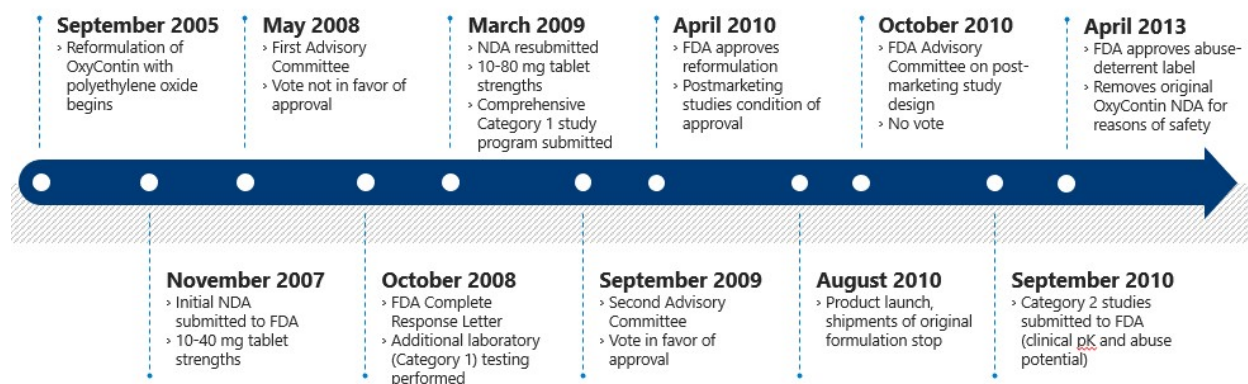
8.2 History and Regulatory Actions Related to Postmarketing Requirements Studies

In April 2010, as a condition of approval of reformulated OxyContin, FDA requested a proposal for postmarketing epidemiology studies to address whether the new OxyContin formulation resulted in a decrease in misuse and abuse and their consequences: addiction, OD, and death (FDA Approval Letter 2010). Because the new formulation of OxyContin was the first abuse-deterrent opioid subject to postmarketing requirements of this type, relevant study methodologies

had not yet been developed. After receiving input during another Advisory Committee meeting in October 2010, Purdue worked closely with the Agency to develop an appropriate epidemiology program. Throughout the approximately 4-year period from October 2010 to October 2014, there were extensive communications between FDA and Purdue on study design and data were regularly submitted to FDA.

In May 2013, FDA acknowledged that Purdue should rely on three data sources for its "formal" epidemiological studies (NAVIPPRO, National Poison Data System [NPDS], and RADARS PC) and requested submission of revised final protocols for those studies. Purdue conducted those three formal studies and multiple supplemental studies designed to determine impacts of reformulated OxyContin. In October 2014, Purdue submitted a supplemental NDA that included the findings to date of the epidemiology studies and proposed revised labeling that described those findings.

In January 2015, FDA informed Purdue that it was planning to convene an Advisory Committee meeting in July 2015 to review the pending NDA supplement. Prior to the meeting, Purdue received FDA's first detailed reviews of the data and analyses generated in the three formal studies. FDA was not aligned with Purdue's conclusions and suggested multiple methodological improvements to enhance the utility of the studies in determining the impact of reformulated OxyContin. Purdue further engaged with the Agency to pursue these modifications. Accordingly, Purdue withdrew the supplemental NDA and the planned July 2015 Advisory Committee meeting was cancelled.

Following withdrawal of the supplemental NDA, FDA formally modified the PMRs in a March 2016 letter. The letter stated that the data submitted in support of Purdue's supplemental NDA had helped the Agency to better understand which studies and analyses would contribute substantively to assessing the 'real world' impact of reformulated OxyContin. The Agency also concluded that the three formal studies it had directed Purdue to conduct in fulfillment of the original PMR requirements would not be able to provide the information needed to fulfill the new postmarketing requirements.

Based on its determinations, FDA revised the required PMRs to include four studies. Three were modifications to the previous studies, requiring different analyses of these datasets. The fourth required study would measure the change in the incidence of nonfatal and fatal OD associated with OxyContin. Final study reports were submitted between July 2018 and August 2019. Purdue continues to supply FDA with additional information and analyses for all four studies in the form of responses to FDA's Information Requests.

A timeline summary related to PMRs is presented in Figure 18.

Figure 18.   History and Regulatory Actions Related to Postmarketing Requirements
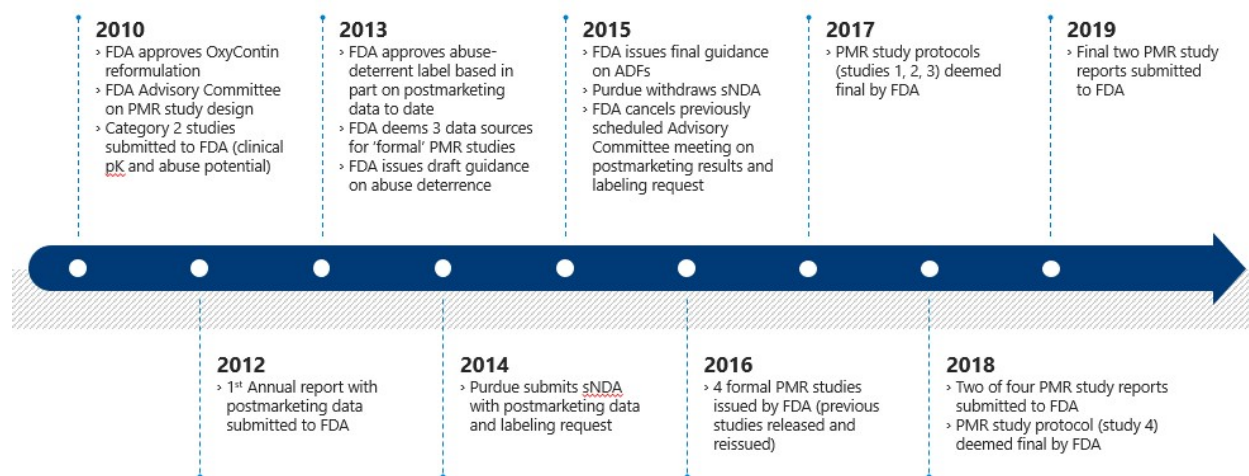
9   APPENDIX 2: REFORMULATION HISTORY AND CHARACTERIZATION OF ABUSE DETERRENCE

9.1 Reformulation History

Multiple technologies were pursued to reformulate OxyContin as well as to develop analgesics with reduced abuse potential. Reformulation efforts included the addition of sequestered orally bioavailable opioid antagonists that were intended to be released with manipulation and antagonists with low oral bioavailability formulated without sequestration. In parallel, with evaluation of antagonist-based products, studies of physical/chemical approaches exploring various excipient combinations and manufacturing processes, such as melt-extruded multi-particulates, were conducted. In all, these attempts were unsuccessful in meeting the combined goals of bioequivalence and ADP.

Input from experts on the chemistry of drugs of abuse and methods of abuse informed the ultimate approach to reformulation. Hardness and gelling properties are common complaints that frustrate many who want to quickly render a tablet into powder for subsequent use via nasal insufflation or IV injection. Many abusers do not want to spend more than a few minutes manipulating a tablet before they can use it (Cone 2006). Therefore, increasing the amount of time and effort needed to manipulate the formulation was thought to make the formulation less attractive for purposeful abuse.

In 2005, efforts intensified on a development program targeting an ER, single-entity formulation bioequivalent to original OxyContin but containing a different inactive excipient, PEO, and manufactured using a different process. The focus was on making the product incrementally more difficult to abuse by crushing or reducing the particle size of the tablets in order to increase the rate of drug release, and on making it more difficult to prepare for abuse by injection.

Consequently, those efforts resulted in a reformulation of OxyContin where the tablets resist crushing and form a viscous gel when exposed to aqueous liquids making preparation for injection difficult.

9.2 Reformulation Composition and Manufacturing

All strengths (10, 15, 20, 30, 40, 60, and 80 mg) of reformulated OxyContin have the same qualitative composition, excluding the cosmetic tablet coat. PEO is the largest component and serves several functions. PEO is well-tolerated and has been used as an inactive ingredient in multiple widely used prescription and over the counter medications. When OxyContin tablets are taken as directed (i.e., swallowed whole), PEO is a release-rate controlling excipient ensuring that the tablets have the required pharmacokinetic profile to be bioequivalent to original OxyContin and deliver medication over 12 hours. In addition, PEO is critical to achieving the

resistance to particle size reduction and high viscosity on hydration that form the basis of the ADP. In order to make the tablets harder and resist crushing, the compressed tablet cores are heated above the melting point of the PEO and allowed to cool. On cooling, the tablet cores are significantly harder than prior to heating; this is the result of the network of fused connections formed within the compressed tablet when the PEO solidifies. Hardness and resistance to crushing of the reformulation as compared to the original formulation is shown in Figure 19. More information about PEO used in OxyContin is found in Appendix 3.

Figure 19.   Crushing of Original OxyContin and Reformulated OxyContin

Original oxycontin (left) and reformulated OxyContin (right) following attempts to crush with 2 spoons (top) and a mortar and pestle (bottom).

The viscous solution obtained upon extraction of the tablet contents into small volumes of aqueous liquid (such as in preparation for abuse via injection) is the result of hydration of the PEO. This gelling property of the reformulation is shown in Figure 20.

Figure 20.   Preparation for Injection of Original and Reformulated OxyContin

Original OxyContin (left) is readily aspirated into a needle; reformulated OxyContin forms a viscous hydrogel when preparing for abuse by injection and is difficult to draw into a syringe (the syringe is empty).

9.3   Laboratory and Clinical Characterization of the Reformulation to Assess Abuse-Deterrent Properties

During the development process and throughout early experience with the reformulation, testing models designed to assess ADP were needed. In the late 2000s, this type of product characterization was new, evolving, and undefined by regulatory agencies. Working closely with FDA as well as with experts in the chemistry of drugs of abuse, methods of opioid abuse, and epidemiology, four categories of evaluation were identified with the goal of developing a testing framework in which each category is meaningful and directionally informs the next.

The categories of abuse deterrence evaluation studies that were conducted are as follows.

1. *In vitro laboratory manipulation and extraction studies* designed to evaluate physical and chemical properties of reformulated OxyContin under common and extreme "real-world" conditions

2. *Clinical Pharmacokinetic testing* to determine bioavailability of tablets administered intact or when manipulated

3. *Clinical abuse potential studies* identifying subject/participant-reported drug attributes (e.g., "drug-liking" and "take drug again") and corresponding preferences in recreational drug abusers

4. *Postmarketing epidemiological studies*, the subject of this discussion, evaluating and measuring the effectiveness of the reformulation in the real world on reducing abuse of OxyContin and its consequences compared to the original formulation.

The *in vitro* laboratory and clinical body of work (referenced as 1, 2, and 3 above), completed in 2010, tested the reformulation to failure whenever possible, thus establishing the strengths and weaknesses of reformulated OxyContin across numerous testing protocols. The findings from these assessments are summarized in the FDA-approved full prescribing information for OxyContin, Section 9.2 Abuse Deterrence Studies (approved in April 2013, excerpted below). The summary in this excerpt notes that the data demonstrated that abuse via injection is expected to be difficult and that reduced abuse via the intranasal route is expected. These informed expectations have been confirmed in the postmarketing epidemiological studies, the last category of testing (indicated as 4 above).

The following is excerpted from the OxyContin full prescribing information, Section 9.2 Abuse.

Abuse Deterrence Studies

OXYCONTIN is formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse. For the purposes of describing the results of studies of the abuse-deterrent characteristics of OXYCONTIN resulting from a change in formulation, in this section, the original formulation of OXYCONTIN, which is no longer marketed, will be referred to as "original OxyContin" and the reformulated, currently marketed product will be referred to as "OXYCONTIN".

In Vitro Testing
In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that, relative to original OxyContin, there is an increase in the ability of OXYCONTIN to resist crushing, breaking, and dissolution using a variety of tools and solvents. The results of these studies also support this finding for OXYCONTIN relative to an immediate-release oxycodone. When subjected to an aqueous environment, OXYCONTIN gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.

Clinical Studies
In a randomized, double-blind, placebo-controlled 5-period crossover pharmacodynamic study, 30 recreational opioid users with a history of intranasal drug abuse received intranasally administered active and placebo drug treatments. The five treatment arms were finely crushed OXYCONTIN 30 mg tablets, coarsely crushed OXYCONTIN 30 mg tablets, finely crushed original OxyContin 30 mg tablets, powdered oxycodone HCl 30 mg, and placebo. Data for finely crushed OXYCONTIN, finely crushed original OxyContin, and powdered oxycodone HCl are described below.

Drug liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar scale of 0 to 100 where 50 represents a neutral response, 0 represents the strongest negative response ("definitely would not take drug again") and 100 represents the strongest positive response ("definitely would take drug again").

Twenty-seven of the subjects completed the study. Incomplete dosing due to granules falling from the subjects' nostrils occurred in 34% (n = 10) of subjects with finely crushed OXYCONTIN, compared with 7% (n = 2) of subjects with finely crushed original OxyContin and no subjects with powdered oxycodone HCl.

The intranasal administration of finely crushed OXYCONTIN was associated with a numerically lower mean and median drug liking score and a lower mean and median score for take drug again, compared to finely crushed original OxyContin or powdered oxycodone HCl as summarized in Table 5 [as numbered within the Full Prescribing Information].

Table 5: Summary of Maximum Drug Liking (Emax) Data Following Intranasal Administration

* Bipolar scales (0 = maximum negative response, 50 = neutral response, 100 = maximum positive response)

VAS Scale (100 mm)*		OXYCONTIN (finely crushed)	Original OxyContin (finely crushed)	Oxycodone HCl (powdered)
Drug Liking	Mean (SE)	80.4 (3.9)	94.0 (2.7)	89.3 (3.1)
	Median (Range)	88 (36-100)	100 (51-100)	100 (50-100)
Take Drug Again	Mean (SE)	64.0 (7.1)	89.6 (3.9)	86.6 (4.4)
	Median (Range)	78 (0-100)	100 (20-100)	100 (0-100)

Figure 1 [as numbered within the Full Prescribing Information] demonstrates a comparison of drug liking for finely crushed OXYCONTIN compared to powdered oxycodone HCl in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in drug liking for OXYCONTIN vs. oxycodone HCl powder greater than or equal to the value on the X-axis. Approximately 44% (n = 12) had no reduction in liking with OXYCONTIN relative to oxycodone HCl. Approximately 56% (n = 15) of subjects had some reduction in drug liking with OXYCONTIN relative to oxycodone HCl. Thirty-three percent (n =

9) of subjects had a reduction of at least 30% in drug liking with OXYCONTIN compared to oxycodone HCl, and approximately 22% (n = 6) of subjects had a reduction of at least 50% in drug liking with OXYCONTIN compared to oxycodone HCl.

Figure 1: Percent Reduction Profiles for Emax of Drug Liking VAS for OXYCONTIN vs. oxycodone HCl, N=27 Following Intranasal Administration
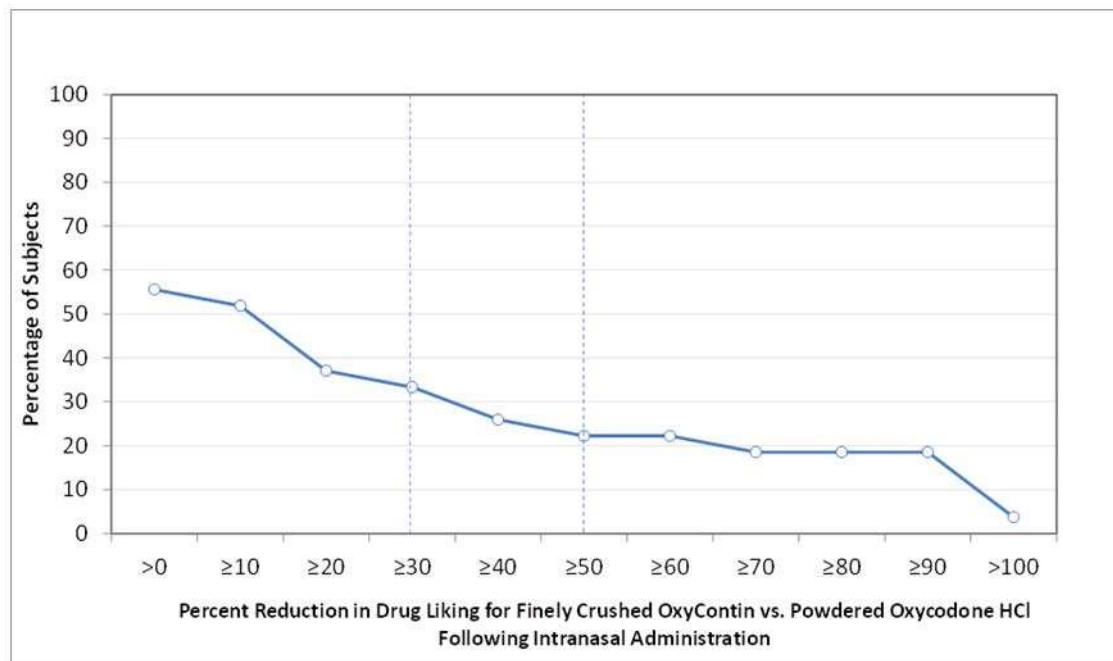
The results of a similar analysis of drug liking for finely crushed OXYCONTIN relative to finely crushed original OxyContin were comparable to the results of finely crushed OXYCONTIN relative to powdered oxycodone HCl. Approximately 43% (n = 12) of subjects had no reduction in liking with OXYCONTIN relative to original OxyContin. Approximately 57% (n = 16) of subjects had some reduction in drug liking, 36% (n = 10) of subjects had a reduction of at least 30% in drug liking, and approximately 29% (n = 8) of subjects had a reduction of at least 50% in drug liking with OXYCONTIN compared to original OxyContin.

Summary

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.

OXYCONTIN contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. OXYCONTIN can be abused and is subject to misuse, addiction, and criminal diversion.

10 APPENDIX 3: POLYETHYLENE OXIDE AND THROMBOTIC MICROANGIOPATHY

10.1 Background

Polyethylene oxide (PEO) is an inert excipient used in oral medications for decades. PEO content and form varies among products and the technologies they employ. In the OxyContin reformulation, PEO imparts both abuse-deterrent properties and controls the release rate of oxycodone to ensure bioequivalence to original OxyContin.

10.2 Thrombotic microangiopathy

Thrombotic microangiopathies are a group of disorders characterized by fragmentation of red blood cells (microangiopathic hemolytic anemia); low platelet counts (thrombocytopenia); and microthrombi that form in small blood vessels (Moake 2002, Arnold 2017). A thrombotic microangiopathy may lead to ischemic tissue damage and is potentially life-threatening.

Thrombotic microangiopathy examples include thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome. Multiple drugs have also been associated with cases of TMA (Al-Nouri 2015, Saleem 2018), and there are several TMA registries established in the United States, including TMA Registry of North America (Metjian 2016) and the Oklahoma Registry (Reese 2015).

10.3 Drug-induced TMA and Reformulated Opana ER

Opana ER is an orally administered opioid analgesic that was marketed in the US for the management of chronic pain. Opana ER was reformulated to include high molecular weight PEO in a novel dosage form intended to provide increased resistance to physical and chemical manipulation. In 2011, reformulated Opana ER was approved by FDA,but did not receive labeling indicating that it had abuse-deterrent properties.

Reformulated-Opana ER was introduced in 2012. Subsequently, cases of potentially life-threatening TMA were attributed to IV abuse of the product and FDA determined that the risks of reformulated Opana ER outweighed its benefits and the drug was withdrawn from the market (MMWR Jan2013, FDA 2017c, FDA 2017d, FDA 2017e,).

In guinea pigs, the IV administration of the inert ingredients including PEO from Opana-ER (primarily composed of PEO with a higher molecular weight of 7 million Daltons) elicited the hallmarks features of TMA, namely microangiopathic hemolytic anemia, decreased platelet counts, and renal injury that were observed in a dose-dependent manner (Hunt 2017). This study also showed that multiple injections at short intervals (5 injections spaced 1.5h apart) resulted in accumulation of PEO. Other studies in animals have shown that toxicity of PEO administered

intravenously is dependent on concentration, polymer size, and viscosity, in addition to dose (Karpova 2004, Smyth 1970).

Consistent with the concept that higher molecular weight PEO produces sheer stress leading to mechanical damage of red blood cells, an *in vitro* study using red blood cells isolated from human volunteers (Persich 2020) demonstrated that PEO-induced hemolysis requires flow (i.e., does not occur in a static system) and that higher rates of hemolysis are correlated with higher PEO concentrations and with higher PEO molecular weight. A greater than 2-fold higher level of free hemoglobin was produced from the sample containing 7 million dalton molecular weight PEO as compared to the sample containing 4 million dalton molecular weight PEO. These results are consistent with findings reported in the briefing document submitted by Intellipharmaceutics for Aximris XR (oxycodone hydrochloride). Using syringed solutions extracted from a single pretreated ground Aximris XR tablet, the sponsors reported that no mortality, morbidity, or evidence of overt toxicity or tissue damage associated with TMA, retinal damage, or acute kidney injury resulted from IV administration of a slow bolus of syringeable solution once per day for a total of 3 days. *In vivo* nonclinical studies that directly compare PEO of different molecular weights have not been conducted. However, the above-mentioned studies provide evidence of acute/short term toxicity in animals following IV administration of PEO, with higher molecular weight higher concentrations and repeat administration correlated with greater and/or faster onset toxicity.

Additionally, in-depth interviews with intravenous Opana ER users in Scott County, Indiana revealed that they had been using an injection preparation procedure that allowed them to take a single 40-mg tablet of reformulated Opana ER and convert it to an injectable form that provided up to 8-16 injections of 2.5-5 mg oxymorphone (75-150 MME) using common 1 mL syringes (Broz 2018, Iwanicki 2019a, Iwanicki 2019b, FDA 2019). A 40-mg tablet taken orally provides approximately 120 milligrams morphine equivalents (MME); however, when administered IV the bioavailability increases 10-fold, thus providing approximately 1200 MME (Dowell 2016, Iwanicki 2019b). Increased injection episodes and frequency may lead to increased exposure to PEO and risk for TMA as demonstrated in guinea pigs (Hunt 2017).

10.4 Differences Between Reformulated Opana ER and Reformulated OxyContin

Abuse-deterrent opioid products containing PEO are not identical to one another and potentially may have differential risk of TMA associated with injection abuse. Product dissimilarities might include: differences in patterns of abuse (related to opioids moiety or product formulation); differences in preferred routes of administration for abuse; differences in methods of preparation for injection abuse; differences in excipient characteristics (such as the molecular weight and viscosity of the PEO); and differences in manufacturing processes (D'Agostino 2020).

There are notable differences in the excipients and manufacturing process of reformulated-Opana ER (oxymorphone) and reformulated-OxyContin (oxycodone). Reformulated OxyContin is manufactured using either Dow Polyox WSR-301, or PEO-15 manufactured by Sumitomo Seika, and a manufacturing process that includes direct compression and subsequent heating of the tablet cores. Opana ER has a higher molecular weight PEO, which has a higher viscosity and undergoes hot-melt extrusion and shaping to form a tablet (Table 11).

Table 11.   Differences in Chemistry and Manufacturing

	Reformulated Opana ER	**Reformulated OxyContin**
PEO molecular weight (Daltons)	~7,000,000[1]	~3,300,000 to 4,000,000[2,3]
PEO viscosity 1% solution (cP at 25°C)	7500-10000[2]	1650-5500[2]
Manufacturing process	Hot-Melt Extrusion + shaping[4,5]	Direct compression + heat

PEO= polyethylene oxide. [1] Hunt 2017. [2] Dow Polyox Product Information. [3] Sumitomo 15-NF Product Information. [4] FDA 2017e (FDA Advisory Committee Briefing Materials, Mar 13–14, 2017; Opana ER). [5] Grünenthal Technology Forum presentation. INTAC. July 17, 2016.

There are also notable differences in opioid pharmacology and formulation PK profile of the active ingredients in reformulated-Opana ER (oxymorphone) and reformulated-OxyContin (oxycodone). Oxymorphone (Opana ER) has an oral bioavailability relative to IV of 10%, whereas the oral bioavailability of oxycodone from OxyContin relative to IV is 60-87%. The 10% oral bioavailability of oxymorphone means that IV administration leads to a 10-fold increase in dose for the abuser compared to the administration of the same dose orally. This intrinsic potency and shift in potency following IV administration likely contributed to driving abuse by the IV route; multiple abusers could share solutions prepared from a single Opana ER tablet. In contrast to oxymorphone, oxycodone delivered by IV administration results in a 1.1-1.7-fold increase in potency compared to the same dose administered orally (Table 12).

Table 12.   Differences in Pharmacology

	Reformulated Opana ER[6]	Reformulated OxyContin[7]
Active pharmaceutical ingredient	oxymorphone HCl	oxycodone HCl
MME of 40 mg oral dose	120 MME	60 MME
Oral bioavailability	~10%	60–87%
Potency Shift, IV vs PO (MME IV)	10-fold increase (1200 mg)	1.1 to 1.7-fold increase (66–102 mg)

HCl= hydrochloride, MME=milligram morphine equivalent, Oral = taken by mouth, IV=intravenous.
[6] FDA Opana ER Prescribing information.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021610s027lbl.pdf.
[7] FDA OXYCONTIN ER tablets prescribing information.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022272s043lbl.pdf.

10.5   TMA and Reformulated OxyContin

In 2017, Purdue voluntarily submitted an update to the OxyContin Full Prescribing Information to include the risk of TMA, based in part on three case reports associated with IV injection of OxyContin that occurred in Australia (Tate 2015, Nataatmadja 2016, Robson 2017).

The occurrence of TMA associated with reformulated OxyContin is under continual pharmacovigilance surveillance by the sponsor and includes assessment of information from published literature and the FDA Adverse Events Reporting System (FAERS) database.

A search of the FAERS database in June 2020 was conducted to identify potential TMA-related events (thrombotic microangiopathy, thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome) where OxyContin was categorized as a suspect drug. An identical search was conducted for Opana ER. Original formulation and reformulated products were delineated by case receipt date; cases received *before* the market launch date of a reformulated product were classified as original product (not containing PEO), and those received *after* the launch date were classified as reformulated product (containing PEO). The search, which included data collected up to October 2019, identified 6 total OxyContin cases with 0 received before, and 6 received after the market launch of reformulated OxyContin. In contrast, the search identified 80 total Opana ER cases with 1 received before, and 79 received after market launch of reformulated Opana ER. Notably, the number of prescriptions in the US for OxyContin was approximately 16-fold higher during this time than the number of prescriptions for Opana ER. Despite much higher availability of OxyContin, the number of reported cases of potential TMA events was much lower than for Opana ER (Table 13).

A limitation of FAERS data is uncertainty that the reported event is due to the product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Reports do not always contain enough detail to properly evaluate an event. FDA does not receive reports for every adverse event or medication error that occurs with a product, nor does it require that a causal relationship between a product and event be proven.

Table 13.   Reports of Thrombotic Microangiopathy, Thrombotic Thrombocytopenic Purpura, and/or Hemolytic Uremic Syndrome in the FAERS Database With OxyContin or Opana ER Categorized as Suspect Drug

	Opana ER	OxyContin
Reformulated product containing PEO		
Earliest availability in market [a]	Jan 2012	Aug 2010
Estimated prescriptions [b]	x million	16x million
Cases received before reformulation [c]	1	0
Cases received after reformulation [c]	79	6[D]

FAERS = FDA Adverse Event Reporting System Database, includes data up to 01Oct2019.
[A] Market launch of reformulated OxyContin was 08Aug2010 (USA), 01Mar2012 (Canada), 01Apr2014 (Australia) and Japan (12Dec2017) and Opana ER was 01Jan2012 (USA).
[B] Estimated number of Prescription in the Unites States from IQVIA National Prescription Audit as of Oct 2019. (OxyContin was 16-fold higher than Opana ER)
[C] Cases with any one or more of the following adverse event preferred terms: thrombotic microangiopathy, thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome.
[D] Includes 4 cases from Australia and 2 from the United States. In 2017, the sponsor voluntarily submitted an update to the OxyContin Full Prescribing Information (FPI) to include the statement: "Cases of thrombotic microangiopathy (a condition characterized clinically by thrombocytopenia and microangiopathic hemolytic anemia) associated with parenteral abuse have been reported."

In summary, the differences in excipients and manufacturing processes between Opana ER and OxyContin formulations, and the differences in pharmacology between oxymorphone and oxycodone may explain the differences in incidence of reported TMA. Opana ER may be more desired by IV drug abusers owing to its 10-fold increase in potency; and when used intravenously, manipulated Opana ER exposes the user to higher molecular weight PEO in a potentially more viscous preparation that may damage red blood cells. Finally, reformulated OxyContin has been associated with a low incidence of TMA cases, especially compared to reformulated Opana ER.

11   APPENDIX 4: LITERATURE SEARCH

11.1 Reformulated OxyContin Real World Literature Review Search Strategy

11.1.1 Objective

To search and provide a descriptive review of the identified published literature that informs the question of the impact of reformulated OxyContin with abuse-deterrent properties on abuse and related outcomes evaluated in real-world settings. When combined with the results of the PMR studies, this information provides insight into the totality of evidence describing the impact of the reformulation of OxyContin.

11.1.2 Methods

A comprehensive search was conducted of the electronically-accessible scientific literature for publications evaluating the effectiveness and outcomes of reformulated OxyContin with abuse-deterrent properties in real-world settings in the US and ex-US.

Publications were searched in electronic databases Medline, EMBASE, Biosis Previews, PsychINFO, EconLit and Derwent Drug Files, and identified using the following search terms including: "oxycodone", "OxyContin", "drug abuse", "drug misuse", "tamper resist*", "tamper deter*", "abuse deter*", "abuse resist*", "drug abuse prevention", "drug abuse", "abuse deterrent formulation", "abuse*", "tamper*", "crush*", "misuse*", "deter*", "resist*", "reformulat*", "new formulat*", "nonmedical", "extramedical", "opioid*" or "opiate*" from January 1, 2010 through February 29, 2020.

Publications of interest included those reporting data specific to reformulated OxyContin since its introduction to the market in August 2010 and assessed any of the following:

- Effectiveness with outcome measures including abuse, misuse, addiction, OD, and death.

- Potential unintended consequences (e.g., change to more risky routes of abuse such as IV or nasal insufflation; transition to other pharmaceutical opioids and/or illicit opioids, heroin; and published PEO-related items such as GI obstruction, blood dyscrasia).

- Potential impact to public health (e.g., injection-related injuries and diseases like hepatitis, HIV).

Publications that were deemed out of scope and excluded included those that did not report data specific to reformulated OxyContin, only reported OxyContin data prior to August 2010 (i.e., relevant to original formulation only), reported data on the opioid or oxycodone landscape and did not specify ER oxycodone, OxyContin or OXYCONTIN.

The initial search strategy yielded 1,787 results (Table 14), and included all publication types such as original articles, review articles, editorials, book chapters, case reports, and conference abstracts.

Search results were further evaluated and limited to full-text articles reporting primary/original research. Select non-peer-reviewed publications were also included if cited by the relevant peer-reviewed literature (National Bureau of Economic Research Working Paper, Powell 2020)
. After applying these criteria, a total of 37 articles examining the impact of reformulated OxyContin on abuse and related outcomes in real-world settings are included in this descriptive review (Table 14).

Tables 15-22 provide additional details for each of the included publications, such as population, sample characteristics, and findings for the primary outcomes for OxyContin and comparator opioids, where applicable, grouped by abuse outcomes. Outcomes include abuse, misuse, non-oral abuse, oral abuse, diversion and related outcomes, OD, and death, as well as other outcomes.

Table 14.   Final Search Strategy

Search	Strategy
S1	EMB.EXACT("oxycodone") OR MESH.EXACT("Oxycodone") OR SU.EXACT("Oxycodone")
S2	oxycontin or "oxy contin" or oxycodone
S3	su.exact("oxycodone hydrochloride" OR "oxycodone") and fdb(psycinfo or derwentdrugfile or biosispreviews)
S4	s1 or s2 or s3
S5	(MESH.EXACT.EXPLODE("Drug Misuse")) OR (EMB.EXACT.EXPLODE("drug abuse"))
S6	su("tamper resist*" or "tamper deter*" or "abuse deter*" or "abuse resist*" or "drug abuse prevention" or "drug abuse") and fdb(psycinfo or derwentdrugfile or biosispreviews)
S7	(EMB.EXACT.EXPLODE("abuse deterrent formulation")) OR (MESH.EXACT("Abuse-Deterrent Formulations"))
S8	ti,ab(((abuse* or tamper* or crush* or misuse*) n/3 (deter* or deterr* or resist*)) or adf)
S9	ti,ab((reformulat* or "new formulat*" or nonmedical or "non medical" or extramedical or "extra medical" or abuse* or tamper*) n/3 (oxycodone or oxycontin or "oxy contin" or opioid* or opiate*))
S10	s5 or s6 or s7 or s8 or s9
S11	s4 and s10
S12	su.exact("medline")
S13	s11 not s12
S14	(s13) and (pd(20100101-20201231)) and (human(yes) AND human(yes) AND human(yes) AND human(yes)) and (la.exact("English"))

Purdue Pharma L.P.

OxyContin® (oxycodone hydrochloride) Extended-Release Tablets Advisory Committee (September 10-11, 2020) Briefing Document

Table 15. **Summary of Characteristics of Studies Examining the Impact of Reformulated OxyContin on Abuse, Misuse, and Other Outcomes in Real-World Settings**

Author (year)	Country	Data sources	Sample size	Outcome(s) evaluated	Sponsor / funding affiliations
Alpert et al. (2018)	US	• NVSS Multiple Cause of Death mortality files • NSDUH	50 US States and District of Columbia	Overdose/death	Non-profit institution(s)
Beheshti (2019)	US	• NCHHSTP • NSDUH	50 US States and District of Columbia	Other outcomes	Non-profit institution(s)
Buer et al. (2014)	US	Primary data collected (interviews)	25 individuals	Misuse, oral ROA, non-oral ROA, diversion	Purdue Pharma L.P.
Butler et al. (2013)	US	• NAVIPPRO • ASI-MV	140,496 individuals from 357 facilities	Abuse, oral ROA, non-oral ROA	Purdue Pharma L.P. Other industry
Cassidy et al. (2014)	US	• NAVIPPRO • ASI-MV	232,874 individuals from 437 facilities in 33 US States	Abuse, oral ROA, non-oral ROA	Other industry
Cassidy et al. (2017)	US	• NAVIPPRO • ASI-MV	72,060 individuals from 874 facilities in 39 US states	Abuse	Purdue Pharma L.P.
Cheng and Coplan (2018)	US	NSDUH	• 652,602 individuals for OxyContin incidence, after excluding past-onset extra-medical OxyContin users • 578,538 individuals for non-OxyContin opioid pain reliever incidence	Misuse	Purdue Pharma L.P.
Chilcoat et al. (2016)	US	IMS LRx	Open cohort; over 150 million patients in the database	Diversion	Purdue Pharma L.P.
Cicero and Ellis (2015)	US	RADARS (SKIP and RAPID)	11,028 individuals • SKIP: 10,784 • RAPID: 244	Abuse, oral ROA, non-oral ROA	Non-profit institution(s)
Cicero et al. (2012)	US	RADARS (SKIP)	• Survey: 2,566 individuals • Qualitative study: 103 individuals	Abuse	Government, Non-profit institution(s)
Cicero et al. (2016)	US	RADARS (SKIP and RAPID)	• SKIP respondents: 12,124 • Subsample for RAPID interview: 129	Abuse, oral ROA, non-oral ROA	Non-profit institution(s)

Author (year)	Country	Data sources	Sample size	Outcome(s) evaluated	Sponsor / funding affiliations
Coplan et al. (2013)	US	National Poison Data System (NPDS)	N/A	Abuse, misuse	Purdue Pharma L.P.
Dart et al. (2015)	US	RADARS (Poison Centers, Drug Diversion Program, OTP, SKIP, College Survey)	N/A	Abuse, misuse, diversion	Non-profit institution(s)
Degenhardt et al. (2015)	Australia	• NOMAD • IDRS • MSIC • NSPs	606 individuals	Abuse, misuse, non-oral ROA, diversion, overdose/death	Other industry, Government
Erensen et al. (2018)	US	RxPATROL®	6,905 incidents	Diversion	Purdue Pharma L.P.
Evans et al. (2019)	US	• DEA ARCOS • CDC Multiple Cause of Death database • NSDUH • Truven Marketscan Research Database	50 US States and District of Columbia	Overdose/death	Non-profit institution(s)
Havens et al. (2014)	US	Primary data collected (interviews)	189 individuals	Abuse, oral ROA, non-oral ROA	Purdue Pharma L.P.
Jauncey et al. (2018)	Australia	Sydney Medically Supervised Injecting Centre (MSIC)	Not reported	Non-oral ROA, overdose/death	Non-profit institution(s)
Jones et al. (2017)	US	NSDUH	Sample size ranging from 67,400 to 70,100 per survey year during the period from 2006 to 2013	Misuse	Government
Lam et al. (2020)	Australia	State-level data on opioid-related health resource utilization	• 30,045 ambulance attendances • 10,113 ED presentations	Overdose/death	Non-profit institution(s)
Larance et al. (2018)	Australia	• NOMAD • MSIC • NSPs • State-level data on opioid-related health resource utilization	NOMAD Cohort: 499 individuals who completed three waves of interviews; other data sources not reported	Non-oral ROA, diversion, overdose/death	Mundipharma Australia; Government
Larochelle et al. (2015)	US	Optum commercial claims data	Open cohort; 31.3 million patients in the database	Overdose/death, other consequences	Government, Non-profit institution(s)

Author (year)	Country	Data sources	Sample size	Outcome(s) evaluated	Sponsor / funding affiliations
McNaughton et al. (2014)	US	Primary data collected (internet posts copied from 7 publicly accessible message boards)	• Entire study period: 45,936 posts on OxyContin • Post-reformulation: 19,659 posts on OxyContin; 5677 confirmed posts on reformulated OxyContin	Oral ROA, non-oral ROA	Purdue Pharma L.P., Other industry, Government
Michna et al. (2014)	US	Truven MarketScan claims data	• 15,162 continuous users of ER oxycodone • 2,285 continuous users of ER oxymorphone	Abuse	Purdue Pharma L.P.
Peacock et al. (2015a)	Australia	NOMAD	• Before reformulation: 606 individuals • After reformulation: 547 individuals	Misuse; other outcomes	Other industry, Government
Peacock et al. (2015b)	Australia	NOMAD	522 individuals who completed Wave 1 and 2 interviews	Misuse	Other industry, Government
Petrilla et al. (2020)	US	Inovalon MORE Registry multipayer claims data	1,350,607 members	Abuse, overdose/death	Other industry
Powell et al. (2019)	US	• NSDUH • NNDSS • NVSS	50 US States and District of Columbia	Other outcomes	Government, Other industry
Powell and Pacula (2020)	US	• NVSS Multiple Cause of Death mortality files • NSDUH	50 US States and District of Columbia	Overdose/death	Government
Rossiter et al. (2014)	US	Truven MarketScan claims data	Before reformulation • Commercially insured: 69,315 individuals • Medicare-eligible: 17,899 individuals • Medicaid: 11,883 individuals • Total: 99,097 individuals After reformulation • Commercially insured: 14,480 individuals • Medicare-eligible: 3,680 individuals • Medicaid: 2,490 individuals • Total: 20,650 individuals	Abuse	Purdue Pharma L.P.
Sankey et al. (2016)	Canada	Primary data collected (chart review)	250 patients	Abuse, misuse, diversion	Purdue Pharma L.P.
Schaffer et al. (2018)	Australia	• Calls to New South Wales Poison Information Centre • Dispensing records from the Pharmaceutical Benefits Scheme	• Dispensing records: 6,702 participants in the pre-cohort, and 6,195 participants in the post-cohort • Poison center calls: N/A	Overdose/death, other outcomes	Government

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Author (year)	Country	Data sources	Sample size	Outcome(s) evaluated	Sponsor / funding affiliations
Sessler et al. (2014)	US	Manufacturer's adverse event reporting database	326 cases	Overdose/death	Purdue Pharma L.P.
Severtson et al. (2013)	US	RADARS (Poison Centers and Drug Diversion Program)	N/A	Abuse, diversion, other outcomes	Purdue Pharma L.P.
Severtson et al. (2016)	US	RADARS (Poison Centers, Drug Diversion Program, OTP, SKIP, StreetRx)	• Poison Centers: 2,159 OxyContin cases and 19,815 other opioid cases • Drug Diversion Program: 4,142 OxyContin cases and 57,135 other opioid cases • OTP: 8,176 OxyContin cases and 15,873 other opioid cases • SKIP: 987 OxyContin cases and 8,451 other opioid cases	Abuse, oral ROA, non-oral ROA, diversion	Non-profit institution(s)
Vosburg et al. (2017)	US	RADARS Web Monitoring data	1,815 Internet posts	Diversion	Non-profit institution(s)
Wolff et al. (2020)	US	NSDUH	• Total: 81,400 individuals • Pre- reformulation Exposed (misuse of non-abuse deterrent OxyContin): 10,200 Unexposed (misuse of other prescription pain relievers): 42,000 • Post- reformulation Exposed (misuse of abuse-deterrent OxyContin): 6,800 Unexposed (misuse of other prescription pain relievers): 22,400	Misuse, other outcomes	Government

Abbreviations: ASI-MV = Addiction Severity Index-Multimedia Version; CDC = Centers for Disease Control and Prevention; DEA ARCOS = Drug Enforcement Administration Automation of Reports and Consolidated Orders System; ED = emergency department; ER = emergency room; HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome; IDRS = Illicit Drug Reporting System; MORE = Medical Outcomes Research for Effectiveness and Economics; MSIC; MSIC = Medically supervised injecting center; NAVIPPRO = National Addictions Vigilance Intervention and Prevention Program; NCHHSTP = National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention; NNDSS = National Notifiable Diseases Surveillance System; NOMAD = National Opioid Medications Abuse Deterrence; NPDS = National Poison Data System; NSDUH = National Survey on Drug Use and Health; NSP = needle–syringe program; NVSS = National Vital Statistics System; N/A = not applicable; OTP = Opioid Treatment Program; RADARS = Researched, Abuse, Diversion, and Addiction Related Surveillance; RAPID = Researchers and Participants Interacting Directly; ROA = route of administration; RxPATROL = Pattern Analysis Tracking Robberies and Other Losses; SKIP = Survey of Key Informants' Patients; STD = sexually transmitted disease; TB = tuberculosis; US = United States.

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Table 16. **Summary of Outcomes Reported by Studies Examining the Impact of Reformulated OxyContin on Abuse-Related Outcomes[1] in Real-World Settings**

Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary abuse-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Butler et al. (2013)	NAVIPPRO ASI-MV	Jun 2009 – Aug 2010	Aug 2010 – Mar 2012	Population Individuals entering substance abuse treatment programs Age • 9.9% <21 years • 53.9% 21-34 years • 32.6% 35-54 years • 3.7% ≥55 years[5] Sex 55.6% male Race 66.2% White	Self-reported past-month abuse, among all assessed and among prescription opioid abusers, unadjusted and prescription-adjusted (per 10,000 prescriptions dispensed per month)	All individuals – unadjusted −41%*** All individuals – adjusted −33%*** Abusers – unadjusted −49%*** Abusers –adjusted −42%***	All individuals – unadjusted: • ER morphine: +2 NS • ER oxymorphone: +246%*** All individuals – adjusted: • ER morphine: +1% NS • ER oxymorphone: +111%*** Abusers – unadjusted • ER morphine: −12%* • ER oxymorphone: +196%*** Abusers – adjusted • ER morphine: −13%* • ER oxymorphone: +80%***
Cassidy et al. (2014)	NAVIPPRO ASI-MV	Jan 2008 – Aug 2010	Aug 2010 – Dec 2011	Population Individuals entering substance abuse treatment programs Age Median 32 years Sex 64.5% male Race 54.2% White	Self-reported past-month abuse among total population, and adjusted for regional variation in prescription volume	Unadjusted −21.7%*** Adjusted −1.0% NS	Unadjusted • ER morphine: No change • ER oxymorphone: +190.9%*** • Buprenorphine: +84.7*** • Heroin: −10.99%*** Adjusted • ER morphine: −7.5% NS • ER oxymorphone: +45.0%*** • Buprenorphine: +18.7***

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary abuse-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Cassidy et al. (2017)	NAVIPPRO ASI-MV	Sep 2009 – Jun 2010	Post-period 1 Jan 2011 – Dec 2011 Post-period 2 Apr 2015 – Dec 2015	Population Individuals entering substance abuse treatment programs Age • 24.0% 18-24 years • 40.0% 25-34 • 32.3% 35-54 • 3.7% 55+ Sex 52.4% male Race 72.4% White	Percent change in self-reported past-month abuse	Post-period 1 • Reformulated OxyContin (post) vs original OxyContin (pre): −41%*** • Original OxyContin: −40%*** Post-period 2 Reformulated OxyContin (post) vs original OxyContin (pre): −52%*** • Original OxyContin: −92%***	Post-period 1 • ER morphine: +6% NS • ER oxymorphone: +196%*** • IR hydrocodone: −4%** • IR Oxycodone SE and combination: +21%*** Post-period 2 • ER morphine: +54%*** • ER oxymorphone: +441%*** • IR hydrocodone: 14%*** • IR Oxycodone SE and combination: +35%***
Cicero et al. (2012)	RADARS (SKIP)	Jul 2009 – Aug 2010	Aug 2010 – Mar 2012	Population Patients with opioid dependence entering treatment programs in the US for whom a prescription opioid was the primary drug of abuse; *characteristics N/A*	• Choice of primary drug of abuse • Drug chosen to get high in past month	Primary drug of abuse: pre-period 35.6% (ref) [a] Primary drug of abuse: post-period 12.8%** [a] Drug used to get high: pre-period 47.4% (ref) [a] Drug used to get high: post-period 30.0%** [a]	Primary drug of abuse: pre-period Fentanyl and hydromorphone: 20.1% (ref) [a] Primary drug of abuse: post-period Fentanyl and hydromorphone: 32.3%* [a] Drug used to get high Heroin: use nearly doubled in pre vs post period (no numerical results)
Cicero et al. (2016)	RADARS SKIP	OxyContin Jan 2009 – Aug 2010 Opana ER Mar 2011 – Feb 2012	OxyContin Aug 2010 – Dec 2014 Opana ER Feb 2012 – Dec 2014	Population Key informants recruited clients, who were individuals entering substance abuse treatment programs OxyContin abusers	Self-reported past-month abuse	Pre-period 44.2% (ref) Post-period 29.2%, OR: 0.5**	Opana ER Pre-period 5.5% (ref) Opana ER Post-period 7.6%, OR: 1.45**

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary abuse-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
				Age Mean 32.8 years *Sex* 56.2% male *Race/ethnicity* 75.4% White Opana ER abusers *Age* Mean 29.9 years *Sex* 58.4% male *Race/ethnicity* 84.9% White			
Cicero and Ellis (2015)	RADARS SKIP	Jan 2009 – Aug 2010	Aug 2010 – Jun 2014	Population Key informants recruited clients, who were individuals entering substance abuse treatment programs Age Mean 34.1 years Sex 50.6% male Race 78.4% White	Self-reported past-month abuse	Pre-period 45.1% (ref) [a] Post-period 26.0%** [a]	Pre-period Heroin: ~26.0% (ref) [a b] Post-period Heroin: ~50.0%** [a b]

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary abuse-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Coplan et al. (2013)	NPDS	Jul 2009 – Jun 2010	Oct 2010 – Sep 2012	Population Poison exposures reported to US poison centers; *characteristics N/A*	Reported exposures due to intentional abuse, unadjusted and adjusted for population size and prescriptions dispensed	Unadjusted −36%*** Population-adjusted −37%[c] Prescription-adjusted −31%***	Unadjusted • Other SE oxycodone (excludes OxyContin): +20%*** • Heroin: +42%*** Population-adjusted Other SE oxycodone: results not reported in text Prescription-adjusted Other SE oxycodone: results not reported in text
Dart et al. (2015)	RADARS (OTP, SKIP)	Jan 2002 – Aug 2010	Sep 2010 – Dec 2013	Patients entering substance abuse treatment program; *Characteristics N/A*	Rate of prescription opioid abuse (Reported use of drugs to get "high")	N/A	OTP Rate increased between 2005 and 2010, and decreased after [c] • 2005: 1.6 per 100,000 • 2010: 7.3 per 100,000 • End of 2013: 3.5 per 100,000 SKIP Rate increased between 2008 and 2011, and decreased after [c] • 2008: 1.5 per 100,000 • 2011: 3.8 per 100,000 • End of 2013: 2.8 per 100,000

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary abuse-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Degenhardt et al. (2015)	NOMAD	Jan 2014 – Mar 2014	May 2014 – Aug 2014	**Population** Individuals who use/tamper with pharmaceutical opioids monthly or more frequently; *Characteristics N/A*	Past-month use	Pre- vs post-period [a] Original OxyContin 56% vs Reformulated OxyContin 8%*	Pre- vs post-period [a] • Original OxyContin: 56% vs 16%* • Endone® 5 mg: 24% vs 10%* • Targin: 2% vs 0.4%, NS • OxyNorm tablets: 3% vs 1%* • Morphine: 65% vs 44%* • Methadone tablets: 14% vs 6%* • Methadone syrup: 51% vs 45%, NS • Fentanyl patch: 9% vs 7%, NS • Heroin: 64% vs 49%, NS
Havens et al. (2014)	Primary data collected (interviews)	Jul 2010 (past-month prior to reformulation)	Dec 2010 – Sep 2011	**Population** Adults from rural Perry County, Kentucky who had abused ER opioids in the 6 months before introduction of reformulated OxyContin **Age** Median 32 years **Sex** 54.5% male **Race** 97.9% White Median years of education: 12 Employed full-time: 23.8%	• Past-month abuse (%, and days/month)	Pre-period • Original OxyContin: 74%, 13.4 days/month Post-period • Original OxyContin: 60%, 6.8 days/month • Reformulated OxyContin: 33%, 1.9 days/month Pre vs. post, RR [e] • Prevalence: 0.45 (95% CI: 0.35 to 0.56) • Frequency: 0.14 (95% CI: 0.10 to 0.22)	Pre-period • Oxycodone IR: 74%, 12.8 days/month • Heroin: 5% Post-period • Oxycodone IR: 96%, 19.5 days/month • Heroin: 1% Pre vs. post, RR [e] • Oxycodone IR, Prevalence: 1.30 (95% CI: 1.19 to 1.42) • Oxycodone IR, Frequency: 1.53 (95% CI: 1.34 to 1.74)

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary abuse-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Michna et al. (2014)	Truven MarketScan claims data	Feb 2010 – Aug 2010	Nov 2010 – May 2011	<u>Population</u> Commercially insured adults who continuously used ER opioids during the pre-reformulation period and whose primary opioid was OxyContin; *characteristics N/A*	Diagnosed abuse during the study period, RR among those not using reformulated OxyContin vs. those using reformulated OxyContin	<u>Patients using OxyContin during the post-reformulation period</u> Rate of abuse: 3.5% (ref)	<u>Patients using non-abuse-deterrent ER opioids during the post-reformulation period</u> • Rate of abuse: 6.7% • RR: 1.89** <u>Patients using no ER opioids during the post-reformulation period</u> • Rate of abuse: 10.9% • RR: 3.08** *Subset using IR opioids* • Rate of abuse: 11.3% • RR: 3.19** *Subset using no IR opioids* • Rate of abuse: 9.7% • RR: 2.75**
Petrilla et al. (2020)	Inovalon MORE Registry multipayer claims data	N/A	2015 – 2016	<u>Population</u> Adult beneficiaries of commercial, managed Medicaid, and Medicare advantage health plans who filled ≥1 prescription for a Schedule II opioid during the study period <u>Age</u> Mean 49.6 years <u>Sex</u> 38.1% male	Opioid abuse/overdose, ORs comparing plans with different levels of <u>coverage</u> of abuse-deterrent opioids	<u>Reformulated OxyContin only vs. no abuse-deterrent opioid</u>[e] 0.91 (95% CI 0.86 to 0.95) <u>Reformulated OxyContin plus ≥ 1 other abuse-deterrent opioid vs. no abuse-deterrent opioid</u>[e] 0.70 (95% CI 0.67 to 0.73) <u>Reformulated OxyContin plus ≥ 1 other abuse-deterrent opioid vs. reformulated OxyContin only</u>[e] 0.77 (95% CI 0.73 to 0.81)	N/A

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary abuse-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Rossiter et al. (2014)	Truven MarketScan claims database	Feb 2010 – Aug 2010	Nov 2010 – May 2011	Population Adult beneficiaries of commercial, employer-sponsored Medicare Supplemental, and Medicaid health plans who continuously used ER opioids during the pre-reformulation period and whose primary opioid after reformulation was OxyContin Age Mean 48 years Sex 47% male	Rate of diagnosed abuse	Post-period: • Commercial: −22.7%** • Medicare Supplemental: +6.1% NS • Medicaid: −18.0%*	N/A
Sankey et al. (2016)	Primary data collected (chart review)	Mar 2011 – Feb 2012	Sep 2012 – Dec 2012	Population Patients diagnosed with opioid dependency receiving methadone maintenance therapy from three methadone clinics in Canada Age Mean 33.9 years Sex 55% male	Incidence of oxycodone- and morphine-positive UDSs	Transition period Oxycodone-positive UDSs: −8.7%** Post-period Oxycodone-positive UDSs: −11.9%**	Transition period Morphine-positive UDSs: +1.5% Post-period Morphine-positive UDSs: 0.0%*
Severtson et al. (2013)	RADARS Poison Centers	Oct 2008 – Sep 2010	Oct 2010 – Mar 2012	Population Poison exposures classified as intentional abuse reported to US poison centers; *characteristics N/A*	Quarterly rate of intentional abuse, per 1,000,000 population and per 10,000 URDD	Per population −38%** Per URDD −32%**	Per population All other prescription opioids: +2 NS Per URDD All other prescription opioids: −9%*

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary abuse-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Severtson et al. (2016)	RADARS Poison Centers OTP and SKIP	Jul 2009 – Jun 2010	Jan 2011 – Jun 2015	Population Poison exposures classified as intentional abuse reported to US poison centers; Key informants recruited clients, who were individuals entering substance abuse treatment programs; *characteristics N/A*	Total percent change in intentional abuse, population-adjusted and prescription-adjusted	Population-adjusted • Poison Centers: −75.0%***,d • OTP: −82.6%***,d • SKIP: −53.9%***,d Prescription-adjusted • Poison Centers: −62.3%***,d • OTP: −72.8%***,d • SKIP: −34.8%**,d	Population-adjusted, other opioids • Poison Centers: −32.8% • OTP: −32.0% • SKIP: −7.2% Prescription-adjusted, other opioids • Poison Centers: −33.7% • OTP: −30.9% • SKIP: +10.8%

Symbols: * = $p < .05$; ** = $p < .001$; *** = $p < .0001$; NS= Not significant; ref = Reference value; a Relative change was not reported, so absolute values are provided; b Values extrapolated from non-numerical data (e.g., figures); d Statistical significance is reported relative to the pre/post change in the comparator group, 'other opioids.'; e Confidence intervals reported instead of p-values

Abbreviations: ASI-MV = Addiction Severity Index-Multimedia Version; CI = confidence interval; ER = extended release; IR = immediate release; MORE = Medical Outcomes Research for Effectiveness and Economics; NAVIPPRO = National Addictions Vigilance Intervention and Prevention Program; NOMAD = National Opioid Medications Abuse Deterrence; NPDS = National Poison Data System; N/A = not applicable; OR = odds ratio; OTP = Opioid Treatment Program; RADARS = Researched, Abuse, Diversion, and Addiction Related Surveillance; RR = relative risk; SE = single-entity; SKIP = Survey of Key Informants' Patients; URDD = unique recipients of dispensed drug; UDS = urine drug screen; US = United States.

Notes:

[1] Studies operationalized abuse-related outcomes in different ways; see the 'Outcome' column for study-specific outcomes.

[2] All data sources utilized in the study are reported here, even those not utilized to evaluate abuse-related outcomes. For studies using multiple data sources, the database used to evaluate abuse-related outcomes is indicated in the 'Population and sample characteristics' column.

[3] '*Characteristics N/A*' indicates that no sample characteristics were available.

[4] Some studies reported multiple sets of results or results for multiple groups. Only information relevant to the outcome of interest (the impact of reformulated OxyContin on abuse-related outcomes) is summarized in this table. Please refer to each full text for the full context, sensitivity or subgroup analyses, or analyses of additional outcomes.

[5] The source specified 'over 55' in the text; ≥55 was inferred based on the other age groups (21-34, 35-54).

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Table 17. **Summary of Outcomes Reported by Studies Examining the Impact of Reformulated OxyContin on Misuse-Related Outcomes[1] in Real-World Settings**

Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary misuse-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Buer et al. (2014)	Primary data collected (interviews)	N/A	Apr 2011 – Jun 2011	Population Self-reported OxyContin users in a rural Appalachian county in Kentucky Age Mean 32.4 years Sex 48% male Race/ethnicity • 92% non-Hispanic White • 2% African-American • 6% other	County drug misuse patterns, qualitatively assessed perceived changes after reformulation	Reformulation deterred misuse	Misuse of other prescription opioids did not change. There were increases in misuse of other oxycodone formulations, in particular IR oxycodone
Cheng and Coplan (2018)	NSDUH	2004 – 2010	2010 – 2015	Population Non-institutionalized community residents of the US age ≥ 12 years Age (among newly incident non- or extra-medical OxyContin users) • 52% ≤ 21 years • 76% ≤ 29 years	• Incident past-year cases of OxyContin misuse (nonmedical and extra-medical use) • Change in post-period relative to predicted trend in the overall population • Change in 2012 relative to 2010 among 12-21 year-olds, adjusting for age and cohort variations	Overall population, post-vs pre period −0.05% or −137,500 incident cases[c] 12-21 year olds, 2012 vs 2010 −50%**	Overall population, post- vs pre-period Non-OxyContin prescription opioids: no change [b,c] 12-21 year olds, 2012 vs 2010 Non-OxyContin prescription opioids: lower incidence but no numerical results NS
Coplan et al. (2013)	NPDS	Jul 2009 – Jun 2010	Sep 2010 – Sep 2012	Population Poison exposures reported to US poison centers; *characteristics N/A*	Reported exposures due to intentional abuse, unadjusted and adjusted for population size and prescriptions dispensed	Unadjusted −21%* Population-adjusted −22%, NS Prescription-adjusted −15%, NS	Unadjusted • Other SE oxycodone: +15%* • Heroin: +30%* Population-adjusted Other SE oxycodone: no significant change to unadjusted results

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary misuse-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
							<u>Prescription-adjusted</u> Other SE oxycodone: results not reported in text
Dart et al. (2015)	RADARS (College Survey Program)	Jan 2002 – Aug 2010	Sep 2010 – Dec 2013	<u>Population</u> Self-identified college students; *Characteristics N/A*	Non-medical use of prescription drugs during the previous 30 days	N/A	<u>All prescription opioids</u> Rate increased between 2008 and end of 2013[c] • 2008: 0.14 per 100,000 • End of 2013: 0.35 per 100,000
Degenhardt et al. (2015)	NOMAD	Jan 2014 – Mar 2014	May 2014 – Aug 2014	<u>Population</u> Individuals who use/tamper with pharmaceutical opioids monthly or more frequently; *Characteristics N/A*	Proportion of respondents reporting strong agreement that they would tamper with the drug, change relative to pre-reformulation	<u>Post-period</u> 20% vs. Original OxyContin: 74%*	<u>Pre- vs post-period</u>[a] • Original OxyContin: 74% vs 73%, NS • Endone® 5 mg: 44% vs 49%, NS • Targin: 8% vs 0%, NS • OxyNorm tablets: 67% vs 62%, NS • Morphine: 71% vs 73%, NS • Methadone tablets: 57% vs 89%* • Methadone syrup: 44% vs 32%* • Fentanyl patch: 52% vs 67%, NS
Jones et al. (2017)	NSDUH	2006 – 2010	2011 – 2013	<u>Population</u> Non-institutionalized community residents of the US age ≥ 12 years; *Characteristics N/A*	Past-year OxyContin misuse (nonmedical and extra-medical use), change in prevalence	<u>2013 vs 2010</u> • 0.5% vs 0.7%* • - 437,000 people (- 23%) reporting nonmedical use <u>2013 vs 2006-2009</u> No significant difference <u>2013 vs. 2011 – 2012</u> No significant difference	N/A

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary misuse-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Peacock et al. (2015a)	NOMAD	Jan 2014 – Mar 2014	May 2014 – Aug 2014	Population Individuals who use/tamper with pharmaceutical opioids monthly or more frequently Age Mean 41 years Sex 69% male	Tampering with OxyContin, OR comparing reformulated vs. original OxyContin	OR: 0.47**	N/A
Peacock et al. (2015b)	NOMAD	Jan 2014 – Mar 2014	May 2014 – Aug 2014	Population Individuals who use/tamper with pharmaceutical opioids monthly or more frequently Age Mean 41 years Sex 69% male	• Proportion reporting having tampered with reformulated OxyContin • ORs comparing agreement with statements about tampering with reformulated vs. original OxyContin	Tampering with reformulated OxyContin [a] • Ever tried: 18% (95% CI: 15%-21%) • Ever successfully tampered: 12% (95% CI: 9%-15%) • Past-month tampering: 8% (95% CI: 6%-10%) Agreement with statements about "the oxycodone product," OR for reformulated vs. original OxyContin • "I would definitely tamper with [it]": OR: 0.30 NS • "[it] is unpleasant to use (tamper)": OR: 33.00*	N/A

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary misuse-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Sankey et al. (2016)	Primary data collected (chart review)	N/A	2014 – 2015	Population Patients diagnosed with opioid dependency receiving methadone maintenance therapy from three methadone clinics in Canada Age Median 33.9 years Sex 55% male	• Proportion reporting nonmedical use (to obtain a high) before and after reformulation • Proportion ever altering drugs	Non-medical use: pre-period [a] 94.4% (ref) Non-medical use: post-period [a] 34.2% Proportion who ever altered OxyContin [a] • Original OxyContin: 94.4% • Reformulated OxyContin: 22.2%	Nonmedical use, pre- vs post-period [a] • Codeine products: 39.5% vs 11.7% • Duragesic (fentanyl): 9.0% vs 1.7% • Other fentanyl patches: 22.0% vs 8.3% • Heroin: 17.5% vs 5.8% • Dilaudid: 43.5% vs 19.2% • Hydromorph Contin: 33.9% vs 17.5% • Other IR hydromorphone: 5.6% vs 1.7% • Demerol: 7.3% vs 1.7% • Kadian: 5.1% vs 2.5% • MS Contin: 16.9% vs 5.0% • MS IR or other IR morphine products: 9.0% vs 0.8% • Other morphine products: 13.6% vs 4.2% • Opium: 7.3% vs 1.7% • Oxy IR: 17.5% vs 5.0% • Percocet: 78.5% vs 28.3% • Percodan: 19.2% vs 5.8% Proportion who ever altered opioids [a] • Codeine products 23.5% • Duragesic (fentanyl): 8.0% • Other fentanyl patches: 21.0% • Dilaudid: 35.2% • Hydromorph Contin 35.2% • Percocet: 40.7%
Wolff et al. (2020)	NSDUH	2005 – 2010	2011 – 2014	Population US individuals age 18 and above who reported engaging in non-medical use of any opioid or non-opioid prescription pain	Effect of Oxycontin reformulation on the odds of self reported ast-year prescription pain reliever misuse	N/A	Past year prescription pain reliever misuse OR: 0.791** Past year heroin use

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary misuse-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
				reliever prior to the introduction of the abuse-deterrent formulation of OxyContin. Age (exposed, unexposed) *Pre-reformulation* • Mean 31.1 years, 37.7 years *Post-reformulation* • Mean 34.1 years, 40.6 years Sex (exposed, unexposed) *Pre-reformulation* • 62.7% male, 54.9% male *Post-reformulation* • 63.7% male, 55.3% male Race/ethnicity (exposed, unexposed) Pre-reformulation • 85.9% white, non-Hispanic, 75.1% white, non-Hispanic • 3.9% black, non-Hispanic, 8.8% black, non-Hispanic • 3.6% other, non-Hispanic, 4.4% other, non-Hispanic			OR: 1.014 NS <u>Past year heroin initiation</u> OR: 0.422*

Symbols: * = $p < .05$; ** = $p < .001$; *** = $p < .0001$; NS= Not significant; ref = Reference value; a Relative change was not reported, so absolute values are provided.

[a] Relative change was not reported, so absolute values are provided; [b] Values extrapolated from non-numerical data (e.g., figures); [c] Significance not reported; [d] Statistical significance is reported relative to the pre/post change in the comparator group, 'other opioids.'; [e] Confidence intervals reported instead of p-values

Abbreviations: CI = confidence interval; IR = immediate release; NOMAD = National Opioid Medications Abuse Deterrence; NPDS = National Poison Data System; NSDUH = National Survey on Drug Use and Health; N/A = not applicable; OR = odds ratio; RADARS = Researched, Abuse, Diversion, and Addiction Related Surveillance; SE = single-entity; US = United States.
Notes:
[1] Studies operationalized misuse-related outcomes in different ways; see the 'Outcome' column for study-specific outcomes.
[2] All data sources utilized in the study are reported here, even those not utilized to evaluate misuse-related outcomes. For studies using multiple data sources, the database used to evaluate misuse-related outcomes is indicated in the 'Population and sample characteristics' column.
[3] '*Characteristics N/A*' indicates that no sample characteristics were available.
[4] Some studies reported multiple sets of results or results for multiple groups. Only information relevant to the outcome of interest (the impact of reformulated OxyContin on misuse-related outcomes) is summarized in this table. Please refer to each full text for the full context, sensitivity or subgroup analyses, or analyses of additional outcomes.

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Table 18. **Summary of Outcomes Reported by Studies Examining the Impact of Reformulated OxyContin on Oral Route of Administration (ROA)-Related Outcomes[1] in Real-World Settings**

Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary oral ROA-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Buer et al. (2014)	Primary data collected (interviews)	N/A	Apr 2011 – Jun 2011	<u>Population</u> Self-reported OxyContin users in a rural Appalachian county in Kentucky <u>Age</u> Mean 32.4 years <u>Sex</u> 48% male <u>Race/ethnicity</u> • 92% non-Hispanic White • 2% African-American • 6% other	County drug misuse patterns, qualitatively assessed perceived changes after reformulation	Participants who swallowed reformulated OxyContin suggested that it was not as potent and did not last as long as original OxyContin	N/A
Butler et al. (2013)	NAVIPPRO ASI-MV	Jun 2009 – Aug 2010	Aug 2010 – Mar 2012	<u>Population</u> Individuals entering substance abuse treatment programs <u>Age</u> • 9.9% <21 years • 53.9% 21-34 years • 32.6% 35-54 years • 3.7% ≥55 years[5] <u>Sex</u> 55.6% male <u>Race</u> 66.2% White	Self-reported past-month abuse via oral ROA among all assessed and among prescription opioid abusers. Additionally, self-reported past-month abuse via oral ROA for a product, among those reporting abuse of that product.	<u>All individuals – unadjusted</u> −17%*** <u>Abusers – unadjusted</u> −27%*** <u>Among ER oxycodone abusers</u> <u>All oral [a]</u> • Pre-period: 55% • Post-period: 76%***	<u>Among ER oxymorphone abusers</u> <u>All oral [a]</u> • Pre-period: 38% • Post-period: 30%* <u>Among ER morphine abusers</u> <u>All oral [a]</u> • Pre-period: 47% • Post-period: 46%[c]
Cassidy et al. (2014)	NAVIPPRO ASI-MV	Jan 2008 – Aug 2010	Aug 2010 – Dec 2011	<u>Population</u> Individuals entering substance abuse treatment programs	Self-reported past-month abuse among prescription	<u>All oral - unadjusted [e]</u> • 12.9% vs. 17.5%, RR = 0.7 (95% CI: 0.7, 0.8)	<u>All oral - unadjusted [e]</u> • ER oxymorphone:

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				<u>Age</u> Median 32 years <u>Sex</u> 64.5% male <u>Race</u> 54.2% White	opioid abusers who reported abuse of any prescription opioid exclusively via oral ROA, among total population, and adjusted for regional variation in prescription volume	<u>All oral - prescription-adjusted</u> [e] • 2.5% vs. 2.5%, RR = 1.0 (95% CI: 0.9, 1.1)	0.2% vs. 0.4%, RR = 2.5 (95% CI: 1.6, 3.8) • ER Morphine: 1.3% vs. 1.3%, RR = 1.0 (95% CI: 0.8, 1.2) • Buprenorphine: 5.8% vs. 15.3%, RR = 2.6 (95% CI: 2.4, 2.9) <u>All oral - prescription-adjusted</u> [e] • ER oxymorphone: 0.4% vs. 0.4%, RR = 1.3 (95% CI: 0.8, 2.0) • ER Morphine: 0.3% vs. 0.3%, RR = 1.0 (95% CI: 0.8, 1.2) • Buprenorphine: 1.2% vs. 2.1%, RR = 1.7 (95% CI: 1.6, 1.9)
Cicero and Ellis (2015)	RAPID		<u>RAPID interview</u> May 2014 – Jun2014	<u>Population</u> Subset of individuals entering substance abuse treatment programs who agreed to participate in the interview-based RAPID <u>Age</u> Mean 35.9 years <u>Sex</u> 46.4% male <u>Race</u> 90.4% White	Self-reported lifetime abuse of OxyContin including ROA and effects of introduction of ADF	<u>Among 88 responders who reported using both formulations of OxyContin to "get high"</u> • 38 (43%) switched from injecting/inhaling to swallowing whole • 20 (23%) continued oral abuse • More individuals selected oral as ROA (55% vs. 81%)**	N/A
Cicero et al. (2016)	RAPID	<u>Opana ER</u>	<u>RAPID interview:</u> OxyContin May 2014 – Sep 2014 <u>RAPID interview:</u> Opana ER	<u>Population</u> Individuals, aged above 18 years, entering substance abuse treatment programs <u>OxyContin abusers</u> *Age* Mean 32.8 years *Sex* 56.2% male	Self-reported lifetime abuse; ROA used	<u>Overall</u> • Original: 53.8% • Reformulated: 80.3% • OR: 3.50** <u>Swallowed</u> • Original: 44.4% • Reformulated: 59.8% • OR: 1.86*	<u>Overall (Opana ER)</u> • Original: 57.1% • Reformulated: 60.0% • OR: 1.13, NS <u>Swallowed (Opana ER)</u> • Original: 48.6% • Reformulated: 51.4% • OR: 1.12, NS

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			Dec 2014 – Feb 2015	*Race/ethnicity* 75.4% White **Opana ER abusers** *Age* Mean 29.9 years *Sex* 58.4% male *Race/ethnicity* 84.9% White		Chewed • Original: 36.8% • Reformulated: 49.6% • OR: 1.69* Sublingual • Original: 8.5% • Reformulated: 13.7% • OR: 1.70, NS	Chewed (Opana ER) • Original: 40.0% • Reformulated: 40.0% • OR: 1.00, NS Sublingual (Opana ER) • Original: 11.4% • Reformulated: 14.3% • OR: 1.29, NS
Havens et al. (2014)	Primary data collected (interviews)	Jul 2010 (past-month prior to reformulation)	Dec 2010 – Sep 2011	Population Adults from rural Perry County, Kentucky who had abused ER opioids in the 6 months before introduction of reformulated OxyContin Age Median 32 years Sex 54.5% male Race 97.9% White	Past-month prevalence of abuse	Pre-period [b,c] • Original OxyContin: ~2% Post-period [b] • Original OxyContin: ~8% • Reformulated OxyContin: ~22%	Pre-period [b,c] • Oxycodone IR: ~9% Post-period [b] • Oxycodone IR: ~30%
McNaughton et al. (2014)	Primary data collected (internet posts copied from 7 publicly accessible message boards)	Jan 2008 – Jul 2010	Aug 2010 – Sep 2013	Population Drug abusers; *characteristics N/A*	Mention of any oral use of reformulated OxyContin following the use of recipes that allow for the feasible manipulation of reformulated OxyContin (i.e., use of the product other than swallowing the tablet whole) among all reformulated OxyContin-related discussions	Post-period [c] 4.58% (260/5677)	N/A
Severtson et al. (2016)	RADARS Poison Centers	Jan 2010 – Jun 2010	Jan 2011 – Jun 2015	Population Poison exposures classified as intentional abuse (by route of abuse) reported to US poison centers; *characteristics N/A*	Quarterly rate of intentional abuse by route of abuse	−71% (95% CI: −76.9, −63.7)[c]	N/A

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Symbols: * = p < .05; ** = p < .001; *** = p < .0001; NS= Not significant; ref = Reference value; a Relative change was not reported, so absolute values are provided; b Values extrapolated from non-numerical data (e.g., figures); [c] Significant not reported; [d] Statistical significance is reported relative to the pre/post change in the comparator group, 'other opioids.'; [e] Confidence intervals reported instead of p-values

Abbreviations: ADF = abuse-deterrent formulation; ASI-MV = Addiction Severity Index-Multimedia Version; CI = confidence interval; ER = extended release; IR = immediate release; NAVIPPRO = National Addictions Vigilance Intervention and Prevention Program; N/A = not applicable; OR = odds ratio; RADARS = Researched, Abuse, Diversion, and Addiction Related Surveillance; RAPID = Researchers and Participants Interacting Directly; ROA = routes of abuse; RR = relative risk; US = United States.

Notes:

[1] Studies operationalized oral ROA-related outcomes in different ways; see the 'Outcome' column for study-specific outcomes.

[2] All data sources utilized in the study are reported here, even those not utilized to evaluate oral ROA-related outcomes. For studies using multiple data sources, the database used to evaluate oral ROA-related outcomes is indicated in the 'Population and sample characteristics' column.

[3]*Characteristics N/A*' indicates that no sample characteristics were available.

[4] Some studies reported multiple sets of results or results for multiple groups. Only information relevant to the outcome of interest is summarized in this table. Please refer to each full text for the full context, sensitivity or subgroup analyses, or analyses of additional outcomes.

[5] The source specified 'over 55' in the text; ≥55 was inferred based on the other age groups (21-34, 35-54).

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Table 19.   Summary of Outcomes Reported by Studies Examining the Impact of Reformulated OxyContin on Non-Oral Route of Administration Related-Outcomes in Real-World Settings

Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary non-oral ROA-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Buer et al. (2014)	Primary data collected (interviews)	N/A	Apr 2011 – Jun 2011	Population Self-reported OxyContin users in a rural Appalachian county in Kentucky Age Mean 32.4 years Sex 48% male Race/ethnicity • 92% non-Hispanic White • 2% African-American • 6% other	County drug misuse patterns, qualitatively assessed perceived changes after reformulation	• Participants uniformly disliked reformulated OxyContin because of a perceived inability to inject or snort it • Participants who claimed not to be able to inject or snort it also suggested that it was not as potent and did not last as long as original OxyContin • Of 25 participants, 3 claimed they could inject and 6 claimed they could snort reformulated OxyContin	N/A
Butler et al. (2013)	NAVIPPRO ASI-MV	Jun 2009 – Aug 2010	Aug 2010 – Mar 2012	Population Individuals entering substance abuse treatment programs Age • 9.9% <21 years • 53.9% 21-34 years • 32.6% 35-54 years • 3.7% ≥55 years[5] Sex 55.6% male Race 66.2% White	Self-reported past-month abuse via non-oral ROA among all assessed and among prescription opioid abusers. Additionally, self-reported past-month abuse via non-oral ROA for a product, among those reporting abuse of that product.	All individuals – unadjusted −66%*** Abusers – unadjusted −71%*** Among ER oxycodone abusers Injection [a] • Pre-period: 36% • Post-period: 16%** Snorting [a] • Pre-period: 53% • Post-period: 25%*** Smoking [a] • Pre-period: 6% • Post-period: 4%*	Among ER Oxymorphone abusers Injection [a] • Pre-period: 9% • Post-period: 16%* Snorting [a] • Pre-period: 62% • Post-period: 69%* Smoking [a] • Pre-period: 0% • Post-period: 2%, NS Among ER Morphine abusers

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary non-oral ROA-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
							Injection [a,c] • Pre-period: 46% • Post-period: 46% Snorting [a] • Pre-period: 25% • Post-period: 26%, NS Smoking [a] • Pre-period: 1% • Post-period: 2%, NS
Cassidy et al. (2014)	NAVIPPRO ASI-MV	Jan 2008 – Aug 2010	Aug 2010 – Dec 2011	Population Individuals entering substance abuse treatment programs Age Median 32 years Sex 64.5% male Race 54.2% White	Self-reported past-month abuse among prescription opioid abusers who reported abuse of any prescription opioid exclusively via non-oral ROA, among total population, and adjusted for regional variation in prescription volume	Snort - unadjusted [e] • 55.4% vs. 33.7%, RR = 0.6 (95% CI: 0.5, 0.8) Snort- prescription-adjusted [e] • 8.5% vs. 5.7%, RR = 0.7 (95% CI: 0.5, 0.9) Inject - unadjusted [e] • 50.9% vs. 41.5%, RR = 0.8 (95% CI: 0.7, 1.0) Inject - prescription-adjusted [e] • 7.8% vs. 7.9%, RR = 1.0 (95% CI: 0.8, 1.2)	Snort - unadjusted [e] • ER oxymorphone: 3.4% vs. 13.2%, RR = 3.9 (95% CI: 2.4, 6.2) • ER Morphine: 3.6% vs. 2.6%, RR = 0.7 (95% CI: 0.4, 1.4) • Buprenorphine: 6.4% vs. 16.9%, RR = 2.7 (95% CI: 1.8, 4.0) Snort - prescription-adjusted [e] • ER oxymorphone: 7.6% vs. 12.5%, RR = 1.7 (95% CI: 1.0, 2.7) • ER Morphine: 0.8% vs. 0.5%, RR = 0.6 (95% CI: 0.3, 1.1) • Buprenorphine: 1.4% vs. 2.1%, RR = 1.5 (95% CI: 1.0, 2.3) Inject - unadjusted [e] • ER oxymorphone: 0.7% vs. 5.3%, RR = 7.8 (95% CI: 1.7, 35.1) • ER Morphine:

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary non-oral ROA-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
							14.8% vs. 25.2%, RR = 1.7 (95% CI: 1.2, 2.4) • Buprenorphine: 2.1% vs. 13.0%, RR = 6.4 (95% CI: 2.7, 15.1) Inject - prescription-adjusted [e] • ER oxymorphone: 1.5% vs. 5.6%, RR = 3.7 (95% CI: 0.8, 16.2) • ER Morphine: 3.5% vs. 5.4%, RR = 1.5 (95% CI: 1.1, 2.2) • Buprenorphine: 0.5% vs. 1.8%, RR = 3.9 (95% CI: 1.7, 9.2)
Cicero and Ellis (2015)	RAPID		RAPID interview May 2014 – Jun 2014	Population Subset of individuals entering substance abuse treatment programs who agreed to participate in the interview-based RAPID Age Mean 35.9 years Sex 46.4% male Race 90.4% White	Self-reported lifetime abuse of OxyContin including ROA and effects of introduction of ADF	Among 88 responders who reported using both formulations of OxyContin to "get high" • 30 (34%) defeated ADF and continued injecting/inhaling • Less individuals selected non-oral as ROA (93% vs. 51%)**	N/A

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary non-oral ROA-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Cicero et al. (2016)	RAPID		RAPID interview: OxyContin May 2014 – Sep 2014 RAPID interview: Opana ER Dec 2014 – Feb 2015	Population Individuals, aged above 18 years, entering substance abuse treatment programs OxyContin abusers *Age* Mean 32.8 years *Sex* 56.2% male *Race/ethnicity* 75.4% White Opana ER abusers *Age* Mean 29.9 years *Sex* 58.4% male *Race/ethnicity* 84.9% White	Self-reported lifetime abuse; ROA used	Overall • Original: 91.5% • Reformulated: 47.9% • OR: 0.09** Injected • Original: 42.7% • Reformulated: 21.4% • OR: 0.36** Snorted • Original: 78.6% • Reformulated: 28.2% • OR: 0.11** Smoked • Original: 17.9% • Reformulated: 7.7% • OR: 0.38*	Overall (Opana ER) •Original: 94.3% • Reformulated: 77.1% • OR: 0.21, NS Injected (Opana ER) • Original: 60.0% • Reformulated: 51.4% • OR: 0.71, NS Snorted (Opana ER) • Original: 80.0% • Reformulated: 37.1% • OR: 0.15** Smoked (Opana ER) • Original: 20.0% • Reformulated: 2.9% • OR: 0.12, NS
Degenhardt et al. (2015)	• NOMAD • IDRS • MSIC • NSPs	• NOMAD: Jan 2014 – Mar 2014 • IDRS: 2013 • MSIC: Nov 2013 – Mar 2014 • NSPs: Nov 2013 – Mar 2014	• NOMAD: May 2014 – Aug 2014 • IDRS: 2014 • MSIC: Apr 2014 – Aug 2014 • NSPs: Apr 2014 – Aug 2014	Population • NOMAD: Individuals who use/tamper with pharmaceutical opioids monthly or more frequently; *Characteristics N/A* • IDRS: People who inject drugs regularly across Australia; *Characteristics N/A* • MSIC: Individuals attending a safer injecting facility in Sydney; *Characteristics N/A* • NSPs: Individuals attending two needle-syringe programs in inner-city Sydney; *Characteristics N/A*	• NOMAD: Proportion injecting in the past month pre vs post; Proportion of those who injected strongly agreed the drug was difficult to inject pre vs post; Median proportion of days injected during past 6 months pre vs during past month post • IDRS: Proportion reporting injecting the drug at least once in the past 6 months, pre vs post • MSIC: Proportion of overall client visits during pre vs post where the drug were injected; Number of client visits per month where the drug were	NOMAD • Past-month original OxyContin injection: 55% vs 15%* • Past-month reformulated OxyContin injection: 3%* • Agreed original OxyContin was difficult to inject: 7% vs 3% • Agreed reformulated OxyContin was difficult to inject: 50% IDRS [c] • All oxycodone: 31% (pre) vs OxyContin: 5% (post) MSIC [c] • Oxycodone: 62% vs 5%; 3,370 vs 789 visits per month • Reformulated OxyContin: 26 visits per month (post)	NOMAD *Past-month injection* • Endone: 13% vs 4%* • Targin: 1% vs 0.2%, NS • OxyNorm: 3% vs 1%* • Morphine: 63 vs 42%* • Methadone syrup: 28% vs 17%* • Methadone tablets: 12% vs 6%* • Buprenorphine: 16% vs 7%* • Buprenorphine patch: 2% vs 1%, NS • Codeine: 2% vs 1%, NS • Fentanyl: 8% vs 6%, NS • Tramadol: <1% vs 0%, NS • Hydromorphone: 1% vs 0.2%* • Dextropropoxyphene: 1% vs 0.2%*

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary non-oral ROA-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
					injected during pre vs post; Change in overall visits pre vs post • NSPs: Change in overall or drug-specific visits pre vs post; Proportion of overall visits where the specific drug was the last drug injected		• Tapentadol: 0% vs 0%, NS *Median % of days injected[c]* • Methamphetamine injection: 7% (IQR 25) vs 14% (IQR 21) of days • Heroin injection: 27% (IQR 63) vs 36% (IQR 61) of days *Agreed drug was difficult to inject [c]* • Endone: 16% vs 4% • Targin: 48% vs 0% • OxyNorm: 8% vs 0% • Morphine: 10 vs 6% • Methadone syrup: 9% vs 5% • Methadone tablets: 7% vs 0% • Fentanyl patch: 17% vs 12% MSIC [c] • Overall visits: -23% • Heroin: 905 vs 1,422 visits per month • Fentanyl: 16 vs 75 visits per month • Morphine: 229 vs 799 visits per month NSPs [c] • Overall visits: -10% • Overall pharmaceutical opioids were the last drug injected: -51% • Pharmaceutical opioids other than methadone, buprenorphine, or methamphetamine were the last drug injected 10% vs 6%

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary non-oral ROA-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Havens et al. (2014)	Primary data collected (interviews)	Jul 2010 (past-month prior to reformulation)	Dec 2010 – Sep 2011	Population Adults from rural Perry County, Kentucky who had abused ER opioids in the 6 months before introduction of reformulated OxyContin Age Median 32 years Sex 54.5% male Race 97.9% White	• Past-month prevalence of abuse • Past-month frequency of abuse (days/month)	Pre-period Snorting • Original OxyContin: 39%, 6.0 days/month (95% CI: 4.6 to 7.3) Injecting • Original OxyContin: 41%, 8.6 days/month (95% CI: 6.8 to 10.4) Post-period Snorting • Original OxyContin: 39%, 3.3 days/month (95% CI: 2.3 to 4.4) • Reformulated OxyContin: 5%, 0.2 days/month (95% CI: 0.02 to 0.4) Injecting • Original OxyContin: 30%, 3.6 days/month (95% CI: 2.4 to 4.8) • Reformulated OxyContin: 0.5%, <0.1 days/month (95% CI: 0.00 to 0.02) Pre vs. post, RR [e] • Snorting, Prevalence: 0.14 (95% CI: 0.07 to 0.26) • Snorting, Frequency: 0.04 (95% CI: 0.01 to 0.10) • Injecting Prevalence: 0.01 (95% CI: 0.002 to 0.09) • Injecting, Frequency: 0.001 (95% CI: 0.0001 to 0.004)	Pre-period Snorting • Oxycodone IR: 47%, 7.4 days/month (95% CI: 5.9 to 8.9) Injecting • Oxycodone IR: 31%, 5.7 days/month (95% CI: 4.3 to 7.2) Post-period Snorting • Oxycodone IR: 70%, 10.3 days/month (95% CI: 8.7 to 11.9) Injecting • Oxycodone IR: 51%, 10.5 days/month (95% CI: 8.6 to 12.4) Pre vs. post, RR [e] Snorting • Oxycodone IR, Prevalence: 1.50 (95% CI: 1.31 to 1.72) • Oxycodone IR, Frequency: 1.38 (95% CI: 1.16 to 1.66) Injecting • Oxycodone IR, Prevalence: 1.64 (95% CI: 1.36 to 1.99) • Oxycodone IR, Frequency: 1.83 (95% CI: 1.46 to 2.30)

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary non-oral ROA-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Jauncey et al. (2018)	Sydney Medically Supervised Injecting Centre (MSIC)	Feb 2007 – Mar 2014	Apr 2014 – Feb 2016	<u>Population</u> Adults with a history of injecting drug use who visited MSIC to legally inject drugs under supervision of trained health professionals <u>Age</u> Majority >30 years <u>Sex</u> Majority male	Visits per month, overall and by self-reported injected drug, change relative to pre-reformulation	<u>Pre vs. post-period monthly visits to injection facilities</u> OxyContin: −1,745 *	<u>Pre vs. post-period monthly visits to injection facilities</u> • Overall: −1,061 * • Morphine: +1,083 * • Fentanyl: +57 * • Heroin: +344 NS
Larance et al. (2018)	• NOMAD • MSIC • NSPs • State-level data on opioid-related health resource utilization	•NOMAD:Dec 2013– Mar 2014 • MSIC: Jul 2009 – Mar 2014 • NSPs: Jul 2009 – Mar 2014	•NOMAD: May 2014 – Aug 2014; Apr 2015 – Aug 2015 • MSIC: Apr 2014 – Nov 2015 • NSPs: Apr 2014 – Nov 2015	<u>Population</u> • NOMAD: Individuals who regularly tamper with pharmaceutical opioids; *Characteristics N/A* • MSIC: Individuals attending a safer injecting facility in Sydney; *Characteristics N/A* • NSPs: Individuals attending two needle-syringe programs in inner-Sydney and Queensland; *Characteristics N/A*	Effect of the tamper-resistant formulation of controlled-release oxycodone in Australia, reported as Z score and p-value, negative value representing decrease from pre period	<u>NOMAD</u> • Oxycodone injection: −16.41*** • ER Oxycodone 80 mg injection: −14.64*** <u>MSIC:</u> • Oxycodone: −5.29***	<u>NOMAD</u> • Any pharmaceutical opioid injection: −5.23*** • Other pharmaceutical opioid injection (excluding oxycodone): −5.49*** <u>MSIC:</u> • Other pharmaceutical opioid (excluding oxycodone): 2.57* <u>NSP:</u> • Any pharmaceutical opioid: −5.58*** • Amphetamine: −0.48 NS • Heroin: −2.02*

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary non-oral ROA-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
McNaughton et al. (2014)	Primary data collected (internet posts copied from 7 publicly accessible message boards)	Jan 2008 – Jul 2010	Aug 2010 – Sep 2013	Population Drug abusers; *characteristics N/A*	Mention of snorting, injecting, smoking, or rectal administration of reformulated OxyContin following the use of recipes that allow for the feasible manipulation of reformulated OxyContin (i.e., use of the product other than swallowing the tablet whole) among all reformulated OxyContin-related discussions	Post period [c] • Snorting: 2.25% (128/5677) • Injecting: 0.72% (41/5677) • Smoking: 0.12% (7/5677) • Rectal administration: 0.11% (6/5677)	N/A
Severtson et al. (2016)	RADARS Poison Centers	Jan 2010 – Jun 2010	Jan 2011 – Jun 2015	Population Poison exposures classified as intentional abuse (by route of abuse) reported to US poison centers; *characteristics N/A*	Quarterly rate of intentional abuse by route of abuse	• −86.7% (95% CI: −91.9%, −78.0%) [e] • The decline in non-oral abuse was greater than the decline in oral abuse*	N/A

Symbols: * = p < .05; ** = p < .001; *** = p < .0001; NS= Not significant; ref = Reference value; a Relative change was not reported, so absolute values are provided; b Values extrapolated from non-numerical data (e.g., figures); [c] Significance not reported; [d] Statistical significance is reported relative to the pre/post change in the comparator group, 'other opioids.'; [e] Confidence intervals reported instead of p-values

Abbreviations: ADF = abuse-deterrent formulation; ASI-MV = Addiction Severity Index-Multimedia Version; Confidence Interval = CI; ER = extended release; IDRS = Illicit Drug Reporting System; IQR = interquartile range; IR = immediate release; MSIC = Medically Supervised Injecting Centre; NAVIPPRO = National Addictions Vigilance Intervention and Prevention Program; NOMAD = National Opioid Medication Abuse Deterrence; NSPs = needle-syringe programs; N/A = not applicable; RADARS = Researched, Abuse, Diversion, and Addiction Related Surveillance; RAPID = Researchers and Participants Interacting Directly; ROA = routes of administration; RR = relative risk

Notes:

[1] Studies operationalized non-oral ROA-related outcomes in different ways; see the 'Outcome' column for study-specific outcomes.

[2] All data sources utilized in the study are reported here, even those not utilized to evaluate non-oral ROA-related outcomes. For studies using multiple data sources, the database used to evaluate non-oral ROA-related outcomes is indicated in the 'Population and sample characteristics' column.

[3] '*Characteristics N/A*' indicates that no sample characteristics were available.

[4] Some studies reported multiple sets of results or results for multiple groups. Only information relevant to the outcome of interest is summarized in this table. Please refer to each full text for the full context, sensitivity or subgroup analyses, or analyses of additional outcomes.

[5] The source specified 'over 55' in the text; ≥55 was inferred based on the other age groups (21-34, 35-54).

Table 20.   Summary of Outcomes Reported by Studies Examining the Impact of Reformulated OxyContin on Diversion-Related Outcomes[1] in Real-World Settings

Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary diversion-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Buer et al. (2014)	Primary data collected (interviews)	N/A	Apr 2011 – Jun 2011	Population Self-reported OxyContin users in a rural Appalachian county in Kentucky Age Mean 32.4 years Sex 48% male Race/ethnicity • 92% non-Hispanic White • 2% African-American • 6% other	Qualitatively assessed perceived changes in sources and use/misuse of prescription drugs after reformulation	• The unpopularity of reformulated OxyContin made it difficult to sell and cheaper than original OxyContin • People therefore stopped requesting prescriptions for reformulated OxyContin	N/A
Chilcoat et al. (2016)	IMS LRx; individuals with retail prescription fills	Jul 2009 – Jun 2010	Jan 2011 – Jun 2013	Population Open cohort of over 150 million patients in the IMS LRx database (~65% of retail prescriptions filled in the US); Characteristics N/A	Average rates of doctor shopping rate by drug, change after reformulation	Overall [e] −50% (95% CI: −53% to −47%); RR: 0.49 Subgroups [e] By age • 18-29 years: −73% • 30-44 years: −51% • 45-54 years: −46% Cash payment −61% Highest dosage (80 mg) −62% Cash payment + highest dosage −70% 18-29 years of age + cash payment −81% 18-29 years of age + highest dosage −86%	Pre-to-post change and RORR (OxyContin vs. comparator) [e] IR hydromorphone • −25% (95% CI: −31% to −17%) • RORR: 0.66 (95% CI: 0.59 to 0.74) IR oxycodone APAP • −23% (95% CI: −25% to −21%) • RORR: 0.65 (95% CI: 0.61 to 0.69) IR hydrocodone APAP • −13% (95% CI: −14% to −12%) • RORR: 0.58 (95% CI: 0.54 to 0.61) ER Morphine • +4% (95% CI: −5% to +14%)

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary diversion-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
						18-29 years of age + cash payment + highest dosage −90%	• RORR: 0.48 (95% CI: 0.43 to 0.53) *IR oxycodone SE* • +5% (95% CI: +2% to +9%) • RORR: 0.47 (95% CI: 0.44 to 0.51) *ER oxymorphone* • +66% (95% CI: +34% to +106%) • RORR: 0.30 (95% CI: 0.24 to 0.37)
Dart et al. (2015)	RADARS (Drug Diversion Program)	Jan 2002 – Aug 2010	Sep 2010 – Dec 2013	<u>Population</u> Quarterly reports from drug diversion officers across the US on new incidents of documented diverted drug products; *Characteristics N/A*	Rate of drug diversion cases opened per 100,000 population, trend over time	N/A	<u>All prescription opioids</u> Rate increased before mid-2010 and trended downward by 2013[c] • 2002: 1.5 per 100,000 • 2012: 2.9 per 100,000 • End of 2013: 2.5 per 100,000
Degenhardt et al. (2015)	NOMAD	Jan 2014 – Mar 2014	May 2014 – Aug 2014	<u>Population</u> Individuals who use/tamper with pharmaceutical opioids monthly or more frequently; *Characteristics N/A*	Median price on the illicit market, change after reformulation	<u>Price per 80 mg tablet</u> • Original OxyContin: $50 • Reformulated OxyContin: $30*	Comparators: no change or insufficient sample to assess change

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary diversion-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Erensen et al. (2018)	RxPATROL	Jan 2007 – Dec 2010	Jan 2011 – Dec 2016	Population Pharmacy thefts reported to a web-based repository	Pharmacy thefts, change after reformulation	Total pharmacy thefts (robberies + burglaries) [a] • Pre-period: 771 (192.75/year) • Post-period: 366 incidents (61/year)	Total pharmacy thefts, other oxycodone products [a] • Pre-period: 202 (50.5/year) • Post-period: 817 incidents (136.2/year)
Larance et al. (2018)	NOMAD	Dec 2013 – Mar 2014	May 2014 – Aug 2014; Apr 2015 – Aug 2015	Population Individuals who regularly tamper with pharmaceutical opioids ; *Characteristics N/A*	Median price on the illicit market, change after reformulation	Price per 80 mg tablet • Original OxyContin: $50 • Reformulated OxyContin: $30***	N/A
Sankey et al. (2016)	Primary data collected (chart review)	Mar 2011 – Feb 2012	Sep 2012 – Dec 2012	Population Patients diagnosed with opioid dependency receiving methadone maintenance therapy from three methadone clinics in Canada Age Mean 33.9 years Sex 55% male	Self-reported sources of OxyContin used to get high, change after reformulation	Reported sourcing of original vs. reformulated OxyContin [a,c] • Buying or trading from a stranger/dealer: 74.2% vs. 59.3% • Receiving it free from a stranger/dealer: 9.4% vs. 5.6% • Buying or trading from friends/family: 34.4% vs. 35.2% • Receiving it free from friends/family: 20.3% vs. 16.7% • Prescription from one doctor: 38.3% vs. 14.8% • Prescription from more than one doctor: 5.5% vs. 1.9% • Stealing: 4.7% vs. 1.9%	N/A

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary diversion-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Severtson et al. (2013)	RADARS Drug Diversion Program	Oct 2008 – Sep 2010	Oct 2010 – Mar 2012	**Population** Quarterly reports from drug diversion officers across the US on new incidents of documented diverted drug products; *Characteristics N/A*	• Quarterly rate of drug diversion cases opened, per 1,000,000 population and per 10,000 URDD, change after reformulation • Average street price for OxyContin, change after reformulation	<u>Rate of diversion</u> *Per population* −53%** *Per URDD* −50%** <u>Average street price per mg</u> −22%*	<u>Rate of diversion, other prescription opioids</u> *Per population* −6% NS *Per URDD* −15% NS
Severtson et al. (2016)	RADARS Drug Diversion Program	Jul 2009 – Jun 2010	Apr 2015 – Jun 2015	**Population** Quarterly reports from drug diversion officers across the US on new incidents of documented diverted drug products; *Characteristics N/A*	Total percent change in drug diversion cases opened, population-adjusted and prescription-adjusted	<u>Population-adjusted</u> −89.4%***,d <u>Prescription-adjusted</u> −85.8%***,d	<u>Population-adjusted</u> −26.8% <u>Prescription-adjusted</u> −31.7%
Vosburg et al. (2017)	RADARS Web Monitoring data	Oct 2009 – Aug 2010	Aug 2010 – Dec 2014	**Population** Posts about prescription drugs from over 150 million social media websites, blogs, and web forums; *Characteristics N/A*	Drug use patterns reported on the web, change after reformulation	Some posts described reduced availability of OxyContin after reformulation	N/A

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary diversion-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)

Symbols: * = p < .05; ** = p < .001; *** = p < .0001; NS= Not significant; ref = Reference value; [a] Relative change was not reported, so absolute values are provided; [b] Values extrapolated from non-numerical data (e.g., figures); [c] Significance not reported; [d] Statistical significance is reported relative to the pre/post change in the comparator group, 'other opioids.'; [e] Confidence intervals reported instead of p-values

Abbreviations: APAP = acetaminophen; CI = confidence interval; ER = extended release; IR = immediate release; NOMAD = National Opioid Medication Abuse Deterrence; N/A = not applicable; RADARS = Researched, Abuse, Diversion, and Addiction Related Surveillance; RR = relative risk; RORR = ratio of RRs; RxPATROL® = Rx Pattern Analysis Tracking Robberies and Other Losses; SE = single-entity; URDD = unique recipients of dispensed drug; US = United States.

Notes:

[1]Studies operationalized diversion-related outcomes in different ways; see the 'Outcome' column for study-specific outcomes.

[2]All data sources utilized in the study are reported here, even those not utilized to evaluate diversion-related outcomes. For studies using multiple data sources, the database used to evaluate diversion-related outcomes is indicated in the 'Population and sample characteristics' column.

[3]*Characteristics N/A'* indicates that no sample characteristics were available.

[4]Some studies reported multiple sets of results or results for multiple groups. Only information relevant to the outcome of interest is summarized in this table. Please refer to each full text for the full context, sensitivity or subgroup analyses, or analyses of additional outcomes.

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Table 21. **Summary of Outcomes Reported by Studies Examining the Impact of Reformulated OxyContin on Overdose and Death Outcomes[1] in Real-World Settings**

Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary overdose or death-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Alpert et al. (2018)	NVSS Multiple Cause of Death mortality files NSDUH	2008 – 2010	2011 – 2013	Population 50 US states and District of Columbia 2000-2009 Population-weighted characteristics (states with low vs high OxyContin misuse rates) •Age • 0-17: 25.98% vs 24.88% • 18-64: 62.08% vs 61.55% • 65+: 11.94% vs 13.57% Race • White: 78.64% vs 86.45% • Black: 14.41% vs 8.70% • Other: 6.94% vs 4.85%	Effect of pre-reformulation OxyContin misuse on changes in heroin deaths, opioid deaths, and total overdose deaths (per 100,000 population per year)	N/A	(Heroin deaths (per 100,000 population per year; with vs without adjustment for initial pain reliever use) • Total heroin deaths: 3.581* vs 2.523* • Heroin-only deaths: 2.694* vs 1.849* • Opioid deaths (per 100,000 population per year; with vs without adjustment for initial pain reliever use) • Total opioid deaths: 0.789 NS vs −0.420 NS • Total natural opioid deaths: −1.700 NS vs −2.388 NS • Natural opioid-only deaths: −2.337 NS vs −2.742 NS • Total synthetic opioid deaths: 0.869 NS; 0.641 NS • Synthetic opioid-only: 0.363 NS vs 0.267 NS Total overdose deaths (per 100,000 population per year; with vs without adjustment for initial pain reliever use) • Opioid and heroin deaths: 3.483 NS vs 1.429 NS • All overdoses: 3.713 NS vs 1.322 NS

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary overdose or death-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Degenhardt et al. (2015)	NOMAD	Jan 2014 – Mar 2014	May 2014 – Aug 2014	Population Individuals who use/tamper with pharmaceutical opioids monthly or more frequently; *Characteristics N/A*	• Proportion of respondents reporting overdosing in the past month • Proportion of reported overdoses in which specific drugs were mentioned	% of overdoses involving oxycodone, pre vs post • 8% vs 6%	% respondents reporting overdoses, pre vs post • 4% vs 3% NS % of overdoses involving specific drugs, pre vs post • Any pharmaceutical opioid: 32% vs 30% NS • Morphine: 8% vs 6% • Methadone: 12% vs 6% • Codeine: 4% vs 0% • Buprenorphine/buprenorphine-naloxone: 4% vs 6% • Fentanyl: 4% vs 6% • Tramadol: 4% vs 0% • Heroin: 68% vs 77% NS
Evans et al. (2019)	CDC Multiple Cause of Death database DEA ARCOS Truven Marketscan Research Database	Identify national structural breaks N/A State-level interrupted time series Jan 2004 – Jul 2010	Identify national structural breaks N/A State-level interrupted time series Aug 2010 – Dec 2012	Population 50 US states and District of Columbia; *Characteristics N/A*	Identify national structural breaks • Quarter most indicative of a break in the trend in oxycodone shipments • Month most indicative of a break in the trend in oxycodone prescriptions • Quarter most indicative of a break in the trend in past-month recreational pain-medication use • Months most indicative of breaks in trends in national heroin encounters and deaths per 100,000 State-level interrupted time series • Change in monthly trend in state-level death rate (per 100,000)	N/A	Identify national structural breaks • Oxycodone shipments: 2010Q3 • Oxycodone prescriptions: Aug 2010 • Past-month recreational use of pain medication: 2010Q2, NS • Heroin poisoning encounters per 1,000: Sep 2010, NS • Heroin deaths per 100,000: Sep 2010 State-level interrupted time series 1. Low oxycodone & low heroin • Heroin death rate: 0.0008, NS • Opioid death rate: −0.0054**

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary overdose or death-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
					• Change in monthly trend in death rate, less the corresponding change in "low oxycodone and low heroin" states (i.e., states below median pre-reformulation per capita heroin death rate and oxycodone consumption)		• Heroin + opioid death rate: −0.0045[*] • Relative heroin death rate: ref • Relative opioid death rate: ref • Relative heroin + opioid death rate: ref 2. High oxycodone & low heroin • Heroin death rate: 0.0024[8] • Opioid death rate: −0.0096[***] • Heroin + opioid death rate: −0.0075[*] • Relative heroin death rate: 0.0017, NS • Relative opioid death rate: −0.0043, NS • Relative heroin + opioid death rate: −0.0030, NS 3. Low oxycodone & high heroin • Heroin death rate: 0.0010, NS • Opioid death rate: −0.0056[***] • Heroin + opioid death rate: −0.0044[*] • Relative heroin death rate: 0.0003, NS • Relative opioid death rate: −0.0003, NS • Relative heroin + opioid death rate: 0.0001, NS 4. High oxycodone & high heroin

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary overdose or death-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
							• Heroin death rate: 0.0049** • Opioid death rate: −0.0035* • Heroin + opioid death rate: 0.0010, NS • Relative heroin death rate: 0.0042* • Relative opioid death rate: 0.0019, NS • Relative heroin + opioid death rate: 0.0055*
Jauncey et al. (2018)	Sydney Medically Supervised Injecting Centre (MSIC)	Feb 2007 –Mar 2014	Apr 2014 – Feb 2016	Population Adults with history of injecting drug use who visited MSIC to legally inject drugs under supervision of trained health professionals Age Majority >30 years Sex Majority male	Onsite opioid overdoses per month, overall and by self-reported injected drug, change relative to pre-reformulation	Pre vs. post-period monthly overdoses • OxyContin: −17.1*	• Pre vs. post-period monthly overdoses • Overall: +15.9 NS • Morphine : +12.4* • Heroin : +22.4*
Lam et al. (2020)	State-level data on opioid-related health resource utilization	Ambulance data: • Jan 2012 – Mar 2014 ED data: • Jul 2008 – Mar 2014	Ambulance data: • Jul 2014 – Oct 2018 ED data: • Jul 2014 – June 2018	Population Patients aged ≥ 12 using state healthcare resources ambulances, EDs) related to extramedical opioid use in Victoria, Australia Sex *Ambulance attendances* • Heroin-related: 71% male • Pharmaceutical opioid-related: 45% male *ED presentations* • Heroin-related: 69% male • Pharmaceutical opioid-related: 39% male	Opioid-related events per 100,000 people per quarter, post-slope change in expected time trend relative to pre-reformulations	N/A	Ambulance attendances • Any opioid: +0.237 NS • Pharmaceutical opioid: −0.050 NS • Heroin: +0.296* ED presentations • Any opioid: −0.056** • Pharmaceutical opioid: −0.083** • Heroin: +0.026*

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary overdose or death-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Larance et al. (2018)	State-level data on opioid-related health resource utilization	• Ambulance data: 2001 – Mar 2014 • Hospital separation data: 2001 – Mar 2014 • ED data: 2002 – Mar 2014	• Ambulance data: Apr 2014 – 2015 • Hospital separation data: Apr 2014 – -2015 • ED data: Apr 2014 – 2015	Population Patients using state healthcare resources (e.g., ambulances, hospitals, EDs) due to drug-related overdoses/events in selected states in Australia; *Characteristics N/A*	Z-scores for changes in monthly state-level data on ambulance call outs for opioid overdose, drug-related hospital separations, and drug-related ED admissions	N/A	• All drug overdose: +0.32 NS • Opioid overdose or poisoning: +0.53 NS • Other drug overdose or poisoning: −0.55 NS
Larochelle et al. (2015)	Optum commercial claims data	Jan 2003 – Jul 2010	Jan 2011-Dec 2012	Population Members aged 18 – 64 years enrolled in a commercial health plan between January 2003 and December 2012 Characteristics • Male: ~49% • Age 18 – 24: ~13% • Age 25 – 34: ~22% • Age 35 – 44: ~25% • Age 45 – 54: ~24% • Age 55 – 64: ~16% • White: ≥66%	• Change in quarterly trend in prescription opioid overdose rate episodes per 100,000 members • Change in quarterly trend in prescription opioid overdose rate (episodes per 100,000 members), adjusted for prescription opioids dispensed • Change in quarterly trend in heroin overdose rate (episodes per 100,000 members)	N/A	Prescription opioid overdose rate [e] • Change in linear trend: −0.14 (−0.18 to −0.09) Prescription opioid overdose per million mg morphine-equivalent dose dispensed • Change in linear trend: −0.0067 (−0.0133 to −0.0002) Heroin overdose rate • Change in quadratic trend: 0.0041 (−0.0003 to 0.0085)

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary overdose or death-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Petrilla et al. (2020)	Inovalon MORE Registry multi-payer claims data	N/A	2015-2016	**Population** Members aged 18 and up continuously enrolled in a health plan **Age** Mean 49.6 years **Sex** 38.1% male	Adjusted associations (ORs) between plan formulary coverage of abuse-deterrent opioids and opioid abuse/overdose	Reformulated OxyContin only vs. no abuse-deterrent opioid [e] 0.91 (95% CI: 0.86, 0.95) Reformulated OxyContin only plus at least one other abuse-deterrent opioid vs. no abuse-deterrent opioid [e] 0.70 (95% CI: 0.67, 0.73) Reformulated OxyContin only plus at least one other abuse-deterrent opioid vs. reformulated OxyContin only [e] 0.77 (95% CI: 0.73, 0.81)	N/A
Powell and Pacula (2020)	NVSS Multiple Cause Death mortality files NSDUH	1999 – 2010	2011- 2017	**Population** 50 US states and District of Columbia 2004-2009 Population-weighted characteristics (states with low vs high OxyContin misuse rates) **Age** • 25-44: 27.89% vs 26.78% • 45-64: 25.03% vs 25.96% • 65+: 12.11% vs. 13.64% **Race** • White: 77.82% vs 85.71% • Black: 15.02% vs 9.67%	Effect of pre-reformulation OxyContin misuse on heroin deaths, opioid deaths, cocaine deaths, psychostimulant deaths, and total overdose deaths (100,000 population per year)	N/A	**Heroin deaths** • Heroin + opioid deaths: No trend during the pre-reformulation period, upwards trend beginning in 2011 and through 2016, before first decrease is observed in 2017 • Heroin-only deaths: Generally, no trend during the pre-reformulation period, upwards trend beginning in 2011 and through 2015, then downwards trend through 2017 **Opioid deaths** • Total opioid deaths: No trend during the pre-reformulation period, upwards trend beginning in 2011 and through 2017

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary overdose or death-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
							• Synthetic opioid deaths: No trend from pre-reformulation period through 2012. Upward trend beginning in 2013 and through 2017 • Natural/semi-synthetic + other opioid deaths: Generally upward trend during the pre-reformulation trend, but flattens around the time of reformulation with little evidence of a return to the pre-reformulation trend Natural/semi-synthetic-only opioid deaths: Generally upward trend during the pre-reformulation period, downward trend during post-reformulation period Cocaine deaths • Cocaine + opioid deaths: No trend during pre-reformulation period through 2012. First rise in estimates is observed in 2013 and continues through 2017 • Cocaine-only deaths: Generally, no trends during the pre- and post-reformulation periods Psychostimulant deaths • Psychostimulant + opioid deaths: Slightly downward trend during pre-reformulation period through 2015, upwards trend from 2016-2017

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary overdose or death-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
							• Psychostimulant-only deaths: Downward trend observed for both the pre- and post-reformulation periods
Schaffer et al. (2018)	Call to New South Wales Poison Information Centre	Poison center calls Jul 2012 - Mar 2014	Poison center calls Apr 2014 - Dec 2016	Age Median 57 years (IQR: 46, 70) Sex 44% male	Number of calls reporting intentional poisoning to poison centers and mean level of dispensing, post- to pre-reformulation periods comparison, adjusted for oral morphine equivalents dispensed	Change in number of calls [e] • Oral oxycodone, IRR: 1.01 (95% CI: 0.96, 1.06) • Injected oxycodone, IRR: 0.93 (95% CI: 0.79, 1.10) • Oxycodone/naloxone, IRR: 1.16 (95% CI: 1.01, 1.34) Change in the mean level of dispensing [e] • Oral oxycodone, IRR: 1.3 (95% CI: 1.05, 1.64) • Injected oxycodone, IRR: 1.07 (95% CI: 0.51, 2.22) • Oxycodone/naloxone, IRR: 1.52 (95% CI: 0.87, 2.65)	Change in number of calls [e] • Morphine, IRR: 1.04 (95% CI: 0.92, 1.18) • Other opioids, IRR: 0.96 (95% CI: 0.92, 1.00) • Heroin, IRR [unadjusted]: 1.08 (95% CI: 0.87, 1.32) Change in the mean level of dispensing [e] • Morphine, IRR: 0.82 (95% CI: 0.45, 1.47) • Other opioids, IRR: 1.05 (95% CI: 0.87, 1.27) • Heroin, IRR [unadjusted]: 0.90 (95% CI: 0.36, 2.25)

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary overdose or death-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids)
Sessler et al. (2014)	Manufacturer's adverse event reporting database	3Q2009-2Q2010	First 3Q2010-2Q2011 Second 3Q2011-2Q2012 Third 3Q2012-2Q2013	Reports of US fatalities involving ER oxycodone that included date of death (n=326) Age Majority 18-64 years Sex Mostly male (63% vs. 66%)	Change in number of fatality cases per quarter	Mean number of ER oxycodone fatality reports per quarter • Pre-period: 32.8 [f] • Post period year 1: 30.5 • Post period year 2: 12.5 • Post period year 3: 5.8 Percent change in number of ER oxycodone fatality reports per quarter [e] • Change in post year 1: -7% (95% CI: -27, 19) • Change in post year 2: -62% (95% CI: -72, -47) • Change in post year 3: -82% (95% CI: -89, -73)	N/A

Symbols: * = p < .05; ** = p < .001; *** = p < .0001; NS= Not significant; ref = Reference value; [a] Relative change was not reported, so absolute values are provided; [b] Values extrapolated from non-numerical data (e.g., chart bars); [c] Significance not reported; [d] Statistical significance is reported relative to the pre/post change in the comparator group, 'other opioids.'; [e] Confidence intervals reported instead of p-values; [f] Mean number of fatality case per quarter with values round up to one decimal.

Abbreviations: CDC = Centers for Disease Control and Prevention; CI = confidence interval; DEA ARCOS = Drug Enforcement Administration Automation of Reports and Consolidated Orders System; ED = emergency department; IRR = incidence of rate ratio; NOMAD = National Opioid Medications Abuse Deterrence; NSDUH = National Survey on Drug Use and Health; NVSS=National Vital Statistics System; N/A = not applicable; OR = odds ratio US = United States.

Notes:

[1] Studies operationalized overdose and death in different ways; see the 'Outcome' column for study-specific outcomes.

[2] All data sources utilized in the study are reported here, even those not utilized to evaluate overdose and death-related outcomes. For studies using multiple data sources, the database used to evaluate overdose and death-related outcomes is indicated in the 'Population and sample characteristics' column.

[3] *'Characteristics N/A'* indicates that no sample characteristics were available.

[4] Some studies reported multiple sets of results or results for multiple groups. Only information relevant to the outcome of interest (the impact of reformulated OxyContin on overdose and death) is summarized in this table. Please refer to each full text for the full context, sensitivity or subgroup analyses, or analyses of additional outcomes.

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Table 22. **Summary of outcomes reported by studies examining the impact of reformulated OxyContin on outcomes related to other consequences[1] in real-world setting**

Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary unintended consequences-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids, other)
Beheshti (2019)	NCHHSTP NSDUH	2004 – 2009	2010 – 2015	<u>Population</u> 50 US states and District of Columbia <u>2004 – 2009 Characteristics (Population-weighted)</u> Average OxyContin misuse: 57%	Changes in the number of blood-borne disease diagnoses per 100,000 population (for each year vs 2009) for a 1 percentage point increase in pre-period OxyContin misuse	<u>Hepatitis C</u> • 2004: −5.8 NS • 2005: −4.0 NS • 2006: −0.3 NS • 2007: −3.0 NS • 2008: −1.1 NS • 2010: 3.8 NS • 2011: 13.8* • 2012: 16.9* • 2013: 23.4* • 2014: 24.6* • 2015: 21.4* <u>Hepatitis B</u> • 2004: −1.2 NS • 2005: −4.8 NS • 2006: −1.0 NS • 2007: −0.3 NS • 2008: −0.2 NS • 2010: 3.9* • 2011: 5.1* • 2012: 8.4* • 2013: 12.1 NS • 2014: 11.0 NS • 2015: 15.4 NS	/A
Coplan et al. (2013)	NPDS	Jul 2009 – Jun 2010	Oct 2010 – Sep 2012	<u>Population</u> Poison exposures reported to US poison centers; *characteristics N/A*	Reported exposures due to unintentional misuse or therapeutic errors, unadjusted and adjusted for population size and prescriptions dispensed	<u>Unadjusted</u> −25%*** <u>Population-adjusted unintentional therapeutic errors</u> -21%ᶜ <u>Population-adjusted unintentional general/accidental exposures</u> -40%ᶜ	<u>Unadjusted</u> • Other SE oxycodone (excludes OxyContin): +10%** • Heroin: +23%, NS <u>Population-adjusted</u> Other SE oxycodone: results not reported in text; appears to increase in post-period <u>Prescription-adjusted</u>

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary unintended consequences-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids, other)
					Prescription-adjusted unintentional therapeutic errors -14%* Prescription-adjusted unintentional general/accidental exposures -34%***		Other SE oxycodone: results not reported in text; appears to decline in post-period
Larochelle et al. (2015)	Optum commercial claims data	2003Q1 – 2010Q2	2011Q1 – 2012Q4	Population Members aged 18 – 64 years enrolled in a commercial health plan between January 2003 and December 2012 Characteristics • Male: ~49% • Age 18 – 24: ~13% • Age 25 – 34: ~22% • Age 35 – 44: ~25% • Age 45 – 54: ~24% • Age 55 – 64: ~16% • White: ≥66%	• Instantaneous change in quarterly opioid prescribing rate in mg MED per member • Changes in linear and/or quadratic trends in opioid prescribing	N/A	All opioids[e] • Instantaneous change: −14.8 (95% CI: −19.3 to −10.4) • Change in linear trend: −2.17 (95% CI: −2.95 to 1.39) Extended-release oxycodone[e] • Instantaneous change: −4.56 (95% CI: −5.91 to −3.21) • Change in linear trend: −1.35 (95% CI: −2.03 to −0.67) • Change in quadratic trend: 0.064 (95% CI: −0.009 to 0.137) Other long-acting opioids[e] • Instantaneous change: 1.09 (95% CI: −0.27 to 2.46) • Change in linear trend: 0.27 (95% CI: 0.03 to 0.51) Propoxyphene[e] • Instantaneous change: −12.2 (95% CI: −12.9 to −11.4) • Change in linear trend: 0.50 (95% CI: 0.36 to 0.64) Other immediate-release opioids[e]

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary unintended consequences-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids, other)
							• Change in linear trend: −1.01 (95% CI: −1.96 to −0.05) • Change in quadratic trend: −0.13 (95% CI: −0.24 to −0.01)
Peacock et al. (2015a)	NOMAD	Jan 2014 – Mar 2014	May 2014 – Aug 2014	Population Individuals who use/tamper with pharmaceutical opioids monthly or more frequently Age Median 31 years Sex 69% male	ORs comparing past-month harms experienced in the post- vs. pre-period	• Injecting any drug: 0.19** • Daily injection: 0.56* • Using a needle after someone else: 0.76 NS • Non-serious IRID: 0.15** • Potentially serious IRID: 0.19** • Serious IRID: 0.15**	N/A
Powell et al. (2019)	NNDSS NSDUH	2004 – 2009	2011 – 2015	Population 50 US states and District of Columbia 2004 – 2009 Characteristics (Below-median Initial Misuse; Above-median Initial Misuse) • Female: 50.9; 50.8 • Age 0-11: 16.2; 15.5 • Age 12-17: 8.7; 8.3 • Age 18-24: 10.0; 9.8 • Age 25-44: 27.9; 26.8 • Age 45-64: 25.0; 26.0 • Age 65+: 12.1; 13.6 • High school diploma or less: 51.9; 50.9 • Some college: 29.0; 30.9 • College degree: 19.1; 18.2 • White: 61.9; 75.7	Stratified Analysis Additional Hepatitis C diagnoses per 100,000 population among states with above-median levels of initial OxyContin misuse Event Study Effect of 1pp increase in initial OxyContin misuse on number of new Hepatitis C diagnoses per 100,000 population (relative to 2009 levels)	N/A	Stratified Analysis Additional Hepatitis C diagnoses per 100,000 population: 0.673* Event Study No significant differential impact between 2004 and 2010.

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary unintended consequences-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids, other)
				• Population: 8,343,030; 3,580,615 • Unemployment rate: 5.94; 5.64 • Heroin deaths (per 100,000 population): 0.847; 0.859 • Other opioid deaths (per 100,000 population): 3.683; 6.726			
Schaffer et al. (2018)	Dispensing records from the Pharmaceutical Benefits Scheme	Dispensing records Apr 2013 - Nov 2013	Dispensing records Apr 2014 - Nov 2014	Population Australian residents who were dispensed oxycodone ER through during Feb-Mar in 2013 or 2014 through the Pharmaceutical Benefits Scheme Characteristics, pre vs post cohorts • Male: 49% vs 49% • Age < 45: 20% vs 20% • Age 45 – 64: 39% vs 42% • Age 65 – 79: 26% vs 25% • Age ≥ 80: 14% vs 13%	HR (95% CI)[b] for switching to other opioids in the 8 months after Apr 1, 2014, compared to the same time period in 2013	Switching to any strong opioid [e] • < 45 years: 1.79 (95% CI: 1.40, 2.28) • 45-64 years: 1.44 (95% CI: 1.22, 1.69) • 65-79 years: 1.20 (95% CI: 1.01, 1.42) • ≥ 80 years: 1.10 (95% CI: 0.88, 1.37) Switching to buprenorphine [e] • Overall: 0.93 (95% CI: 0.72, 1.19) Switching to fentanyl [e] • Overall: 0.74 (95% CI: 0.55, 1.00) Switching to morphine [e] • < 45 years: 4.33 (95% CI: 2.13, 8.80) • 45-64 years: 1.73 (95% CI: 1.13, 2.67) • 65-79 years: 1.26 (95% CI: 0.80, 1.97) • ≥ 80 years: 0.70 (95% CI: 0.41, 1.19)	N/A

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary unintended consequences-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids, other)
						Switching to oxycodone / naloxone[e] • Overall: 1.54 (95% CI: 1.32, 1.79) Switching to other strong opioids (i.e., oxycodone IR, methadone, hydromorphone)[e] • Overall: 1.21 (95% CI: 0.95, 1.55)	
Severtson et al. (2013)	RADARS Drug Diversion Program	Oct 2008 – Sep 2010	Oct 2010 – Mar 2012	Population Quarterly reports from drug diversion officers across the US on new incidents of unintentional therapeutic error; *Characteristics N/A*	• Quarterly rate of unintentional therapeutic error, per 1,000,000 population and per 10,000 URDD, change after reformulation	Rate of therapeutic error *Per population* −24%** *Per URDD* −15%*	Rate of therapeutic error Other prescription opioids: *Per population* +2% NS *Per URDD* −8%*
Wolff et al. (2020)	NSDUH	2005 – 2010	2011 – 2014	Population Non-institutionalized community residents of the US individuals age 18 and above who reported engaging in non-medical use of any opioid or non-opioid prescription pain reliever prior to the introduction of the abuse-deterrent formulation of OxyContin. Age (exposed, unexposed) *Pre-reformulation* • Mean 31.1 years, 37.7 years *Post-reformulation* • Mean 34.1 years, 40.6 years Sex (exposed, unexposed)	Effect of OxyContin reformulation on the odds of self-reported past-year heroin use, heroin use disorder, and heroin initiation	N/A	Heroin use OR: 1.014 NS Heroin use disorder OR: 1.063 NS Heroin initiation OR: 0.422*

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Author (year)	Data source[2]	Pre period	Post period	Population and sample characteristics[3]	Primary unintended consequences-related outcome(s)[4]	Findings (OxyContin)	Findings (Comparators, non-specific opioids, illicit opioids, other)
				Pre-reformulation • 62.7% male, 54.9% male *Post-reformulation* • 63.7% male, 55.3% male Race/ethnicity (exposed, unexposed) *Pre-reformulation* • 85.9% white, non-Hispanic, 75.1% white, non-Hispanic • 3.9% black, non-Hispanic, 8.8% black, non-Hispanic • 3.6% other, non-Hispanic, 4.4% other, non-Hispanic • 6.5% Hispanic, 11.8% Hispanic *Post-reformulation* • 84.5% white, non-Hispanic, 71.4% white, non-Hispanic • 3.6% black, non-Hispanic, 9.8% black, non-Hispanic • 4.1% other, non-Hispanic, 5.3% other, non-Hispanic • 7.8% Hispanic, 13.5% Hispanic			

Symbols**:** * = p < .05; ** = p < .001; *** = p < .0001; NS= Not significant; ref = Reference value; [a] Relative change was not reported, so absolute values are provided; [b] Values extrapolated from non-numerical data (e.g., figures); [c] Significance not reported; [d] Statistical significance is reported relative to the pre/post change in the comparator group, 'other opioids.'; [e] Confidence intervals reported instead of p-values

Abbreviations**:** CI = confidence interval; ER = extended release; HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome; IR = immediate release; IRID = injection-related injury and disease; HR = hazard ratio; MED = morphine-equivalent dose; NCHHSTP = National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention; NNDSS = National Notifiable Diseases Surveillance System; NOMAD = National Opioid Medications Abuse Deterrence; NPDS = National Poison Data System; NSDUH = National Survey on Drug Use and Health; N/A = not applicable; OR = odds ratio; RADARS = Researched, Abuse, Diversion, and Addiction Related Surveillance; SE = single-entity; STD = sexually transmitted disease; TB = tuberculosis; URDD = unique recipients of dispensed drug; US = United States.

Notes**:**

[1] Studies operationalized other consequences in different ways; see the 'Outcome' column for study-specific outcomes.

[2] All data sources utilized in the study are reported here, even those not utilized to evaluate unintended consequences-related outcomes. For studies using multiple data sources, the database used to evaluate unintended consequences-related outcomes is indicated in the 'Population and sample characteristics' column.

[3] '*Characteristics N/A*' indicates that no sample characteristics were available.

[4] Some studies reported multiple sets of results or results for multiple groups. Only information relevant to the outcome of interest (the impact of reformulated OxyContin on unintended consequences) is summarized in this table. Please refer to each full text for the full context, sensitivity or subgroup analyses, or analyses of additional outcomes.

12 APPENDIX 5: GLOSSARY OF TERMS

Term	Definition
3-digit ZIP	Determined by the respondents' residence
Abuse-deterrent properties	In reformulated OxyContin, abuse-deterrent properties include hardness and gelling, which are intended to deter manipulation of the tablet for abuse and unintentional misuse.
All OxyContin	Original and reformulated OxyContin combined
All oxycodone excluding OxyContin	Any oxycodone endorsement other than OxyContin
Bioequivalence	No significant difference in the rate and extent of absorption of the active pharmaceutical ingredient
Dosage units dispensed	Tablets or capsules dispensed as estimated using IQVIA data
ER oxycodone	Any ER oxycodone endorsement including OxyContin
General oxycodone	Oxycodone category for unknown formulation (oxycodone that was not assigned to a formulation [IR or ER] but was known to be oxycodone)
Immediate shift	Difference between last quarter of pre-reformulation period and first quarter of post-reformulation period
Intentional abuse	In the RADARS Poison Centers Study, an exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect or some other psychotropic effect
Inhalation abuse	Includes snorting and smoking routes
IR oxycodone products	All known IR oxycodone products (combined combination products and single-entity products, because they were not distinguished in the survey)
IR oxycodone or unknown oxycodone	Include both IR oxycodone products and general oxycodone
Medicaid data	In the Insured Populations Study, Medicaid data represents individuals with lower socioeconomic status than commercially-insured individuals in other data sets

Misuse	An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect
New user	The new (incident) user design is based on the first exposure to the drug of interest
Non-oral abuse	Injecting, snorting, smoking and "other" routes of administration, other than an oral route
Number of respondents	Number of respondents who completed surveys
Original OxyContin	The formulation of OxyContin without abuse-deterrent properties that was distributed by Purdue Pharma L.P. between January 1996 and August 2010
Other opioid	All non-comparator Schedule II and III opioid analgesics and tramadol, excluding narcotic antitussives and opioids used to treat opioid dependence/addiction (i.e., methadone solutions, buprenorphine/naloxone, and buprenorphine/naltrexone sublingual tablets)
Other Schedule II opioids	Schedule II opioid analgesic tablets and capsules: IR hydrocodone combination products, ER oxymorphone, ER hydromorphone, ER morphine and IR oxycodone products. Excludes OxyContin (and generic ER oxycodone), methadone, TD fentanyl, and ER tapentadol (because it entered the market after the reformulation of OxyContin)
Overall abuse	In the RADARS Treatment Center Study: past-month abuse including all routes of abuse, as the data do not distinguish between routes of abuse
Overdose	An overdose is the ingestion or application of a medication or other substance in quantities greater than are recommended or generally practiced that has a harmful effect on a body's functions (i.e., poisoning)
OxyContin	Original and reformulated OxyContin combined
Post-period	The timeframe of analysis after the introduction of reformulated OxyContin and the transition period
Post-reformulation period	1Q2011 to 4Q2015 (5 years after the introduction of reformulated OxyContin and the transition period); or 1Q2011 to 4Q2013 (3 years after the introduction of reformulated OxyContin and the transition period)

Pre-period	The timeframe of analysis before the introduction of reformulated OxyContin
Pre-reformulation period	3Q2008 to 2Q2010 (2 years before the introduction of reformulated OxyContin); or 3Q2009 to 2Q2010 (1 year before the introduction of reformulated OxyContin)
Reformulated OxyContin	The reformulated version of OxyContin with abuse-deterrent properties that entered the market in August 2010 and substantially replaced the original OxyContin in pharmacies by January 2011
Transition period	3Q2010 to 4Q2010 (from introduction of reformulated OxyContin until the original formulation was substantially no longer available in pharmacies)
Treatment episode	A continuous segment of an opioid exposure in which the drug dispensings are in continuity with previous dispensings. A treatment episode will end if there is one or more days of discontinuity between dispensings. A treatment episode was censored if an individual discontinued use of any of the study drugs, initiated another study drug, terminated their health plan, died, or reached the end of a study period (i.e., 6/30/2010, 12/31/2010, 09/30/2015). This analysis was conducted on the treatment episode level, as individuals could have multiple treatment episodes over the course of the study that fell into different exposure categories.
Unintentional general exposures	A measure of accidental exposures severe enough to warrant a call to a poison center
Unintentional therapeutic error	A measure of medication errors severe enough to warrant a call to a poison center