Postmarketing Study Results: The Impact of the Abuse Deterrent Reformulation of OxyContin on Abuse and Overdose

Joint Meeting of the Drug Safety and Risk Management and Anesthetic and Analgesic Drug Products Advisory Committees

September 10-11, 2020

PURDUE

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Introduction

Craig Landau, M.D.

Craig Landau, MD

President & Chief Executive Officer
Purdue Pharma L.P.

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Presentation Purpose

- **Purdue is here today to discuss findings related to the FDA-required postmarketing requirement epidemiology studies concerning reformulated OxyContin**
- **Purdue is not seeking new labeling claims for OxyContin related to these studies**
  - If FDA determines that it is important for prescribers and the public to be informed by additional information in OxyContin's label regarding the results of these studies, Purdue will discuss with the Agency

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Reasons for Reformulating OxyContin

- **OxyContin is a mu-opioid agonist that is indicated 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**
- **The original formulation was being abused**
  - Individuals would manipulate the tablet (e.g., crushing) into small particles which they then would snort and inject
- **To address this serious problem, Purdue reformulated to:**
  1) Make the tablets more difficult to manipulate, snort, and inject
  2) Achieve bioequivalence to the original formulation

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Reformulated OxyContin Is Harder, Making It More Difficult to Crush Into Powder

Original Formulation

Reformulated OxyContin

FDA approved reformulated OxyContin in 2010

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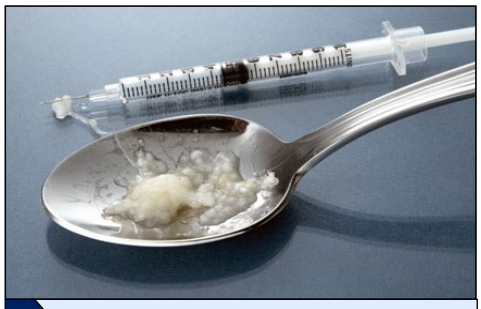
Reformulated OxyContin Becomes Viscous in Water, Making It Difficult to Inject and Less Attractive to Snort

Original Formulation



Reformulated OxyContin

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Characterization of Reformulated OxyContin Based on FDA Testing Framework

Extensive laboratory and clinical testing was conducted to establish that reformulated OxyContin:

- **Is hard to crush**
- **Becomes viscous when mixed with water**
- **Is less "liked" for intranasal abuse**
- **Is bioequivalent to the original formulation**

Expected abuse reduction via routes requiring manipulation

Laboratory Manipulation and Extraction Studies	Clinical Pharmacokinetic Studies	Clinical Abuse Potential Studies
Physical and chemical properties, intact/manipulated	Oral/intranasal bioavailability/PK intact/manipulated	Subjective liking and abuse via potential routes

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Expectations for Reformulated OxyContin

- **Reformulated OxyContin would provide a meaningful incremental improvement over the original formulation**
  - Would likely reduce abuse by injection
  - Would likely reduce intranasal abuse
- **Reformulated OxyContin would have its limitations**
  - Would not make the medication abuse-proof
  - With sufficient time and effort would likely still be subject to manipulation
  - Would present no barriers to intact oral abuse (swallowed whole)
  - Would likely result in some switching to other opioids without abuse deterrent properties

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Evolution of Postmarketing Requirements

OxyContin reformulation approved

Advisory Committee meeting on PMR study designs

2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019

1st annual report with postmarketing data sent to FDA

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Evolution of Postmarketing Requirements

OxyContin reformulation approved

Advisory Committee meeting on PMR study designs

ADF labeling approved based in part on post marketing data to date

2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019

1st annual report with postmarketing data sent to FDA

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Evolution of Postmarketing Requirements

OxyContin Current Label Section 9.2

"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."

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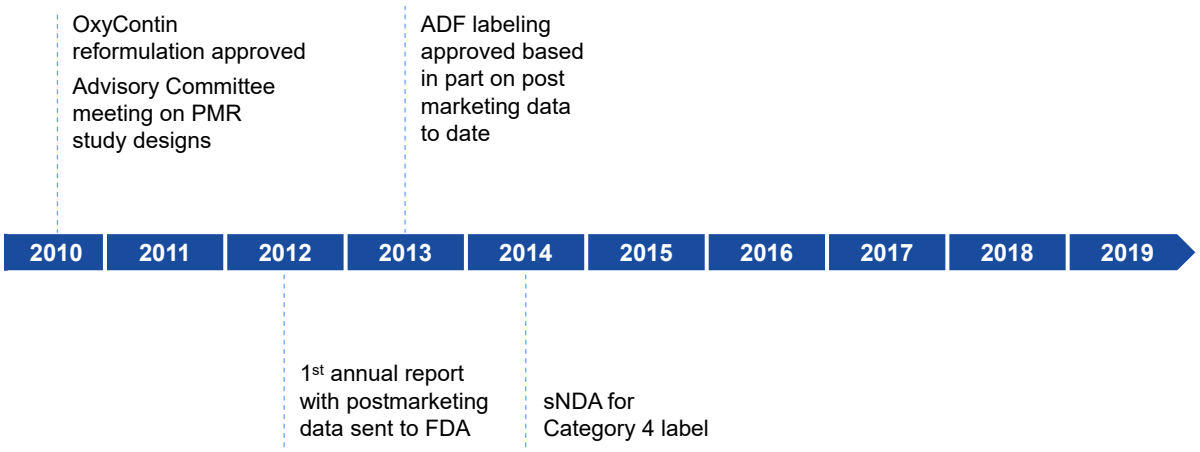
Evolution of Postmarketing Requirements



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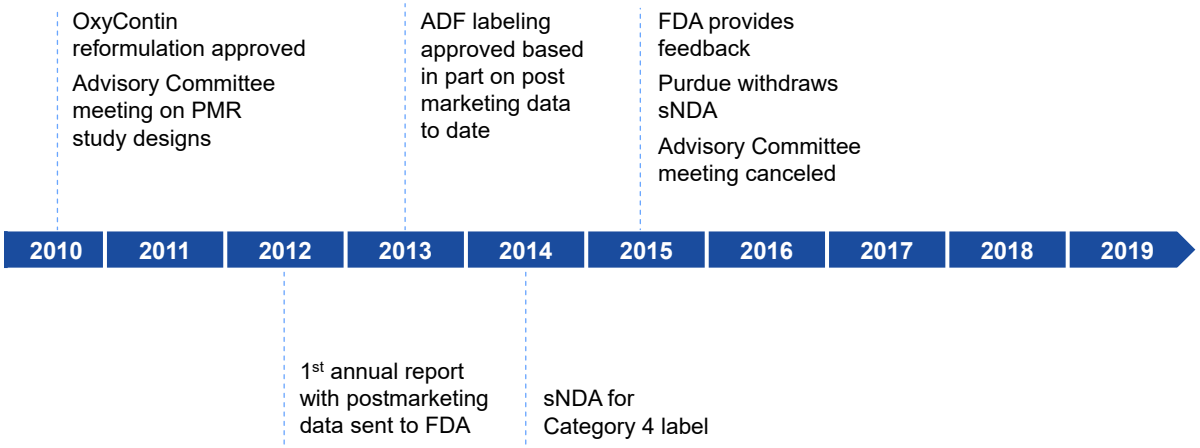
Evolution of Postmarketing Requirements



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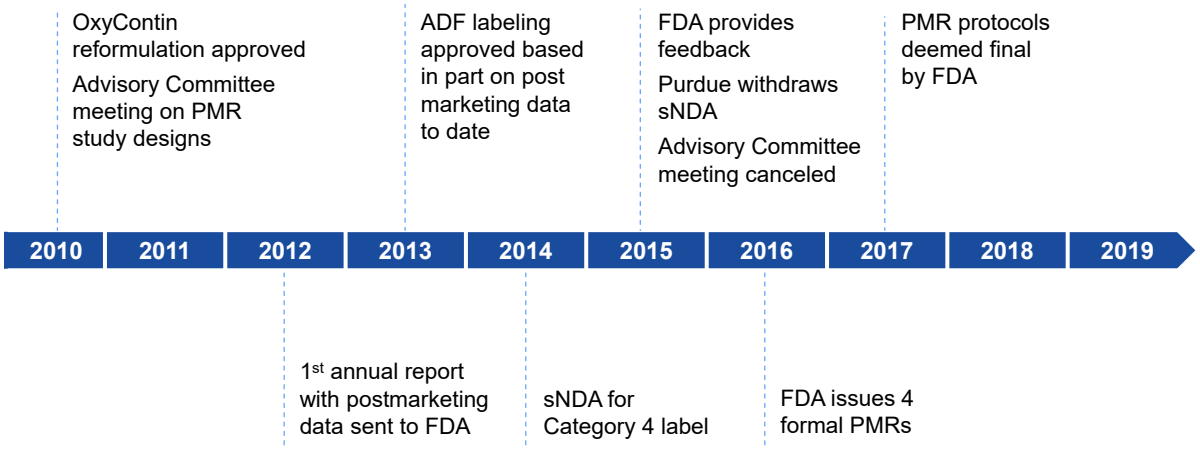
Evolution of Postmarketing Requirements



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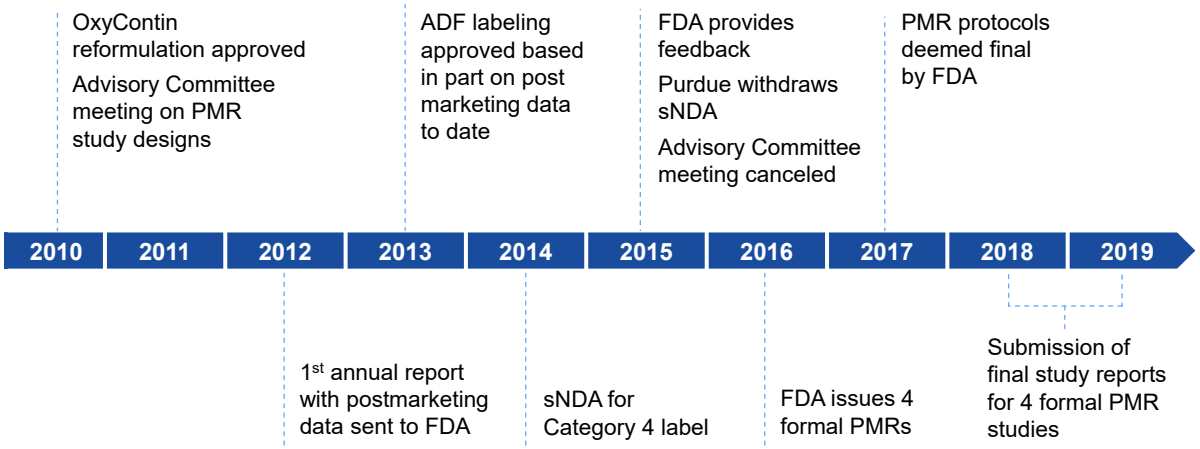
Evolution of Postmarketing Requirements



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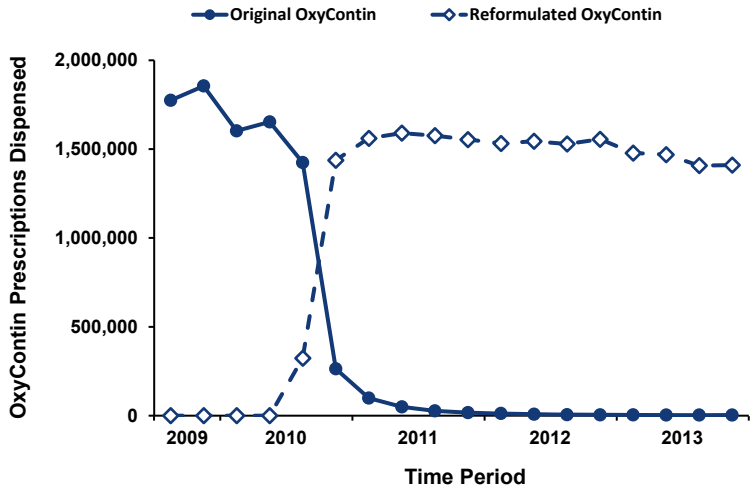
The Transition to Reformulated OxyContin Presented a Rare Opportunity



Source: IMS Xponent data

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Conclusions

- **Totality of evidence shows:**
  - The reformulation succeeded in reducing non-oral abuse of OxyContin, including snorting and injection
  - The reformulation is a meaningful incremental improvement over original OxyContin

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Overview of Today's Agenda

Introduction	**Craig Landau, MD** President & Chief Executive Officer Purdue Pharma L.P.
Overview and Results of Postmarketing Studies 1-4	**Alexander M. Walker, MD, DrPH** Principal, World Health Information Science Consultants
Real World Evidence for Opioid Analgesics with Abuse Deterrent Properties	**Richard C. Dart, MD, PhD** Director, Rocky Mountain Poison and Drug Safety Executive Director, RADARS System Professor, University of Colorado School of Medicine
Closing Remarks	**Craig Landau, MD** President & Chief Executive Officer Purdue Pharma L.P.

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Overview and Results of Postmarketing Studies 1-4

Alexander M. Walker, MD, DrPH

Alexander M. Walker, MD, DrPH
Principal, World Health Information Science Consultants

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Positions and COI

- **Present**
  - Principal, World Health Information Science Consultants
  - Adjunct Professor of Epidemiology, Harvard TH Chan School of Public Health
- **Prior**
  - Professor (1991-2002) and Chair (1996-2000), Department of Epidemiology, Harvard TH Chan School PH
- **Commercial interests – current and recent**
  - Research contracts with Opioid Postmarketing Consortium
    - Consulting on OPC PMR 3033-5, -6
    - Conduct of OPC PMR 3033-8
    - Coordination of OPC PMR 3033-2
  - Consulting to Purdue
    - Advice on design and conduct of Purdue PMR 3051-4
    - Advice on interpretation and presentation of Purdue PMRs 3051-1, -2, -3, -4
    - Preparation for this meeting
  - Financial relationships with other pharmaceutical clients to conduct or advise about drug safety studies
    - Astellas, Daichi-Sankyo, Endo, MannKind, Pfizer
  - Other – High Temperature Insultation Wool Coalition
  - Stock holdings in retirement portfolio

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Drug Safety in Well-Controlled Studies

- **Appropriate patients**
  - No contraindications
  - Concomitant exposures minimal and well understood
- **Investigator control of treatment regimens**
  - Assignment to patients
  - Management per protocol
- **Blinding of treatment assignment**
  - Investigators
  - Patients
  - Caregivers
  - Assessors

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Drug Safety in the Real Word

- **Short of extrapolation, you don't know what to expect**
  - Longer treatment duration
  - Variable treatment and not given in isolation
- **Basis for extrapolation may be weak**
  - Patients are complex
  - Patients are not always like those studied pre-authorization
- **Extraneous factors can lead to artifacts**
  - Drug choice
  - Adherence
  - Outcomes

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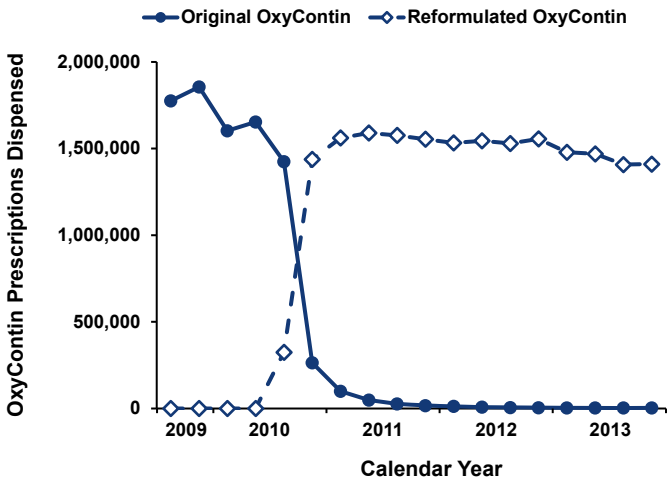
A Real World Experiment

- **Purposeful Intervention**
  - Purdue
  - FDA
- **Comparison**
  - Pre-post
    - Not concurrent
  - Clean
    - Outside of the transition period
- **Confounding**
  - NOT by individual characteristics
  - Concurrent temporal changes
    - Regulation, guidelines
    - New products
    - Assessment



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Considerations for a Pre-post Study Design

- **Studies of abuse preference are not classic epidemiology**
  - No firm denominators
  - Samples of convenience
  - Numerators self-reports
- **Determinants of choice are varied, e.g.**
  - Potency
  - Ease of use
  - Price
  - Availability
  - Notoriety
- **All confounding is temporal, and therefore easy to identify as changes in, e.g.**
  - Regulation
  - Enforcement
  - Guidelines
  - Characteristics of the using population

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PMR Studies

Study Name	**NAVIPPRO Treatment Centers (PMR 3051-1)**
Population	**Individuals assessed for substance abuse treatment**
Endpoints	**Abuse**

ASI-MV=addiction severity index-multimedia version; NAVIPPRO=national addictions vigilance intervention and prevention program; PMR=postmarketing requirement; RADARS=researched abuse, diversion and addition-related surveillance.

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PMR Studies

Study Name	**NAVIPPRO Treatment Centers (PMR 3051-1)**	**RADARS Treatment Centers (PMR 3051-3)**
Population	**Individuals assessed for substance abuse treatment**	**Individuals at substance abuse treatment centers**
Endpoints	**Abuse**	**Abuse**

ASI-MV=addiction severity index-multimedia version; NAVIPPRO=national addictions vigilance intervention and prevention program; PMR=postmarketing requirement; RADARS=researched abuse, diversion and addition-related surveillance.

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PMR Studies

Study Name	NAVIPPRO Treatment Centers (PMR 3051-1)	RADARS Treatment Centers (PMR 3051-3)	RADARS Poison Centers (PMR 3051-2)
Population	Individuals assessed for substance abuse treatment	Individuals at substance abuse treatment centers	Individuals with intentional exposures reported
Endpoints	Abuse	Abuse	Abuse

ASI-MV=addiction severity index-multimedia version; NAVIPPRO=national addictions vigilance intervention and prevention program; PMR=postmarketing requirement; RADARS=researched abuse, diversion and addition-related surveillance.

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PMR Studies

Study Name	NAVIPPRO Treatment Centers (PMR 3051-1)	RADARS Treatment Centers (PMR 3051-3)	RADARS Poison Centers (PMR 3051-2)	Insured Populations (PMR 3051-4)
Population	Individuals assessed for substance abuse treatment	Individuals at substance abuse treatment centers	Individuals with intentional exposures reported	Individuals with an opioid prescription
Endpoints	Abuse	Abuse	Abuse	Fatal and non-fatal overdose

ASI-MV=addiction severity index-multimedia version; NAVIPPRO=national addictions vigilance intervention and prevention program; PMR=postmarketing requirement; RADARS=researched abuse, diversion and addition-related surveillance.

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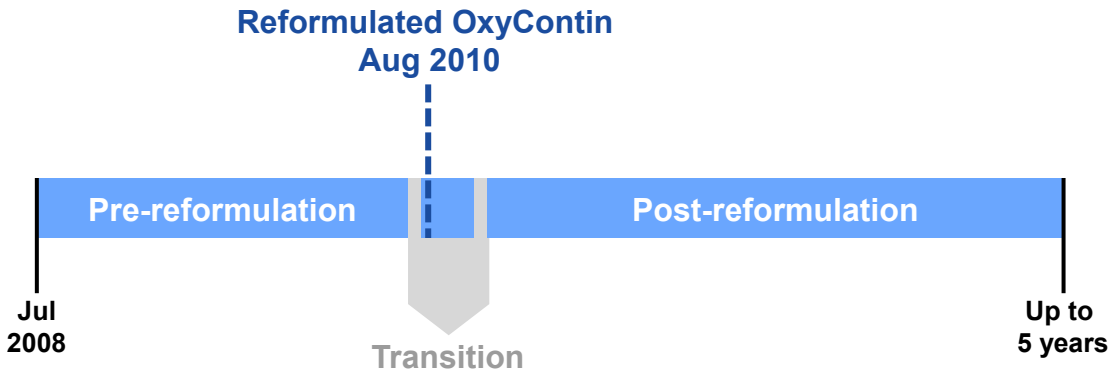
Study Time Periods



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Common Study Elements

- **Identification of specific products**
- **Primary and secondary opioid comparators**
- **Limitations**
  - Retrospective data
  - Observations at a group level may not match individual experience (ecological fallacy)
  - Possible concurrent changes (temporal confounding)
    - Drug use
    - Populations
    - Use of surveillance mechanisms (NAVIPPRO, RADARS)

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Representations of Calendar Time

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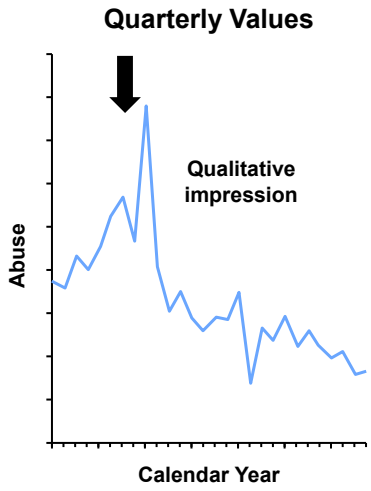
Representations of Calendar Time



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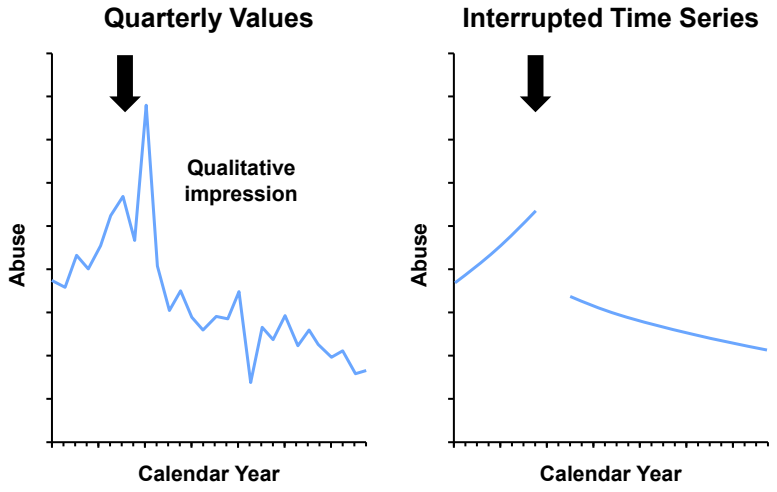
Representations of Calendar Time



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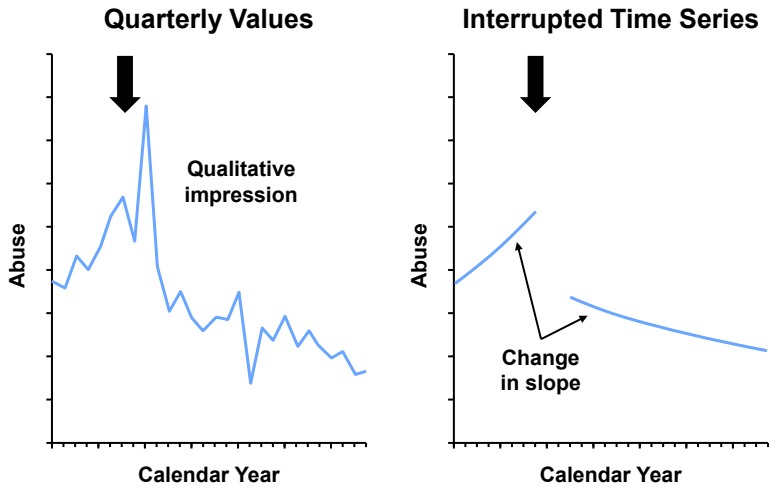
Representations of Calendar Time



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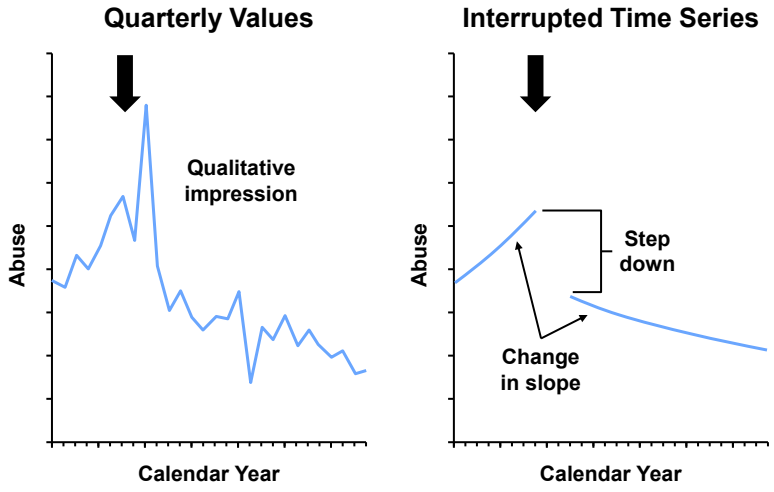
Representations of Calendar Time



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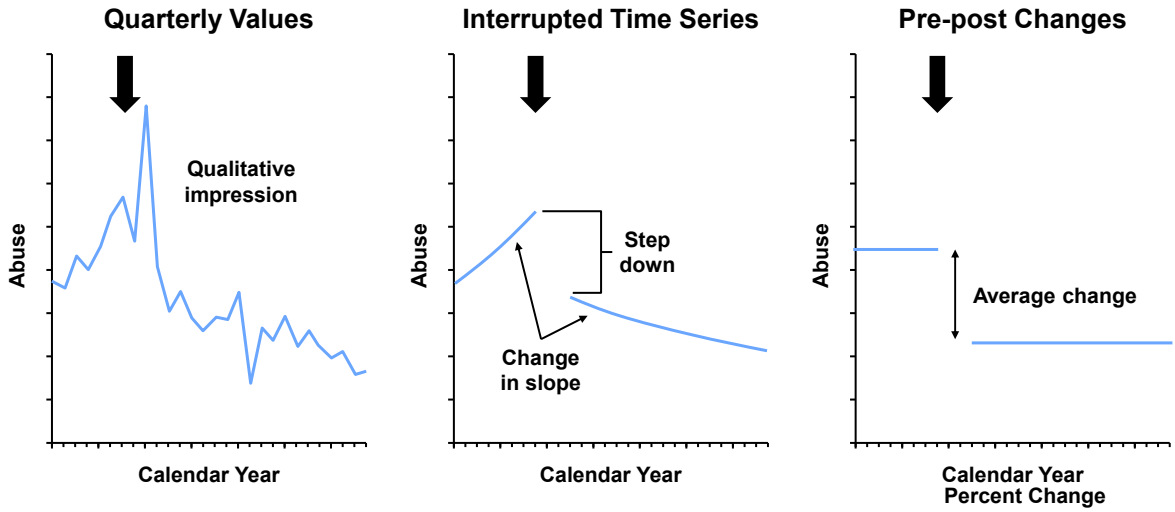
Representations of Calendar Time



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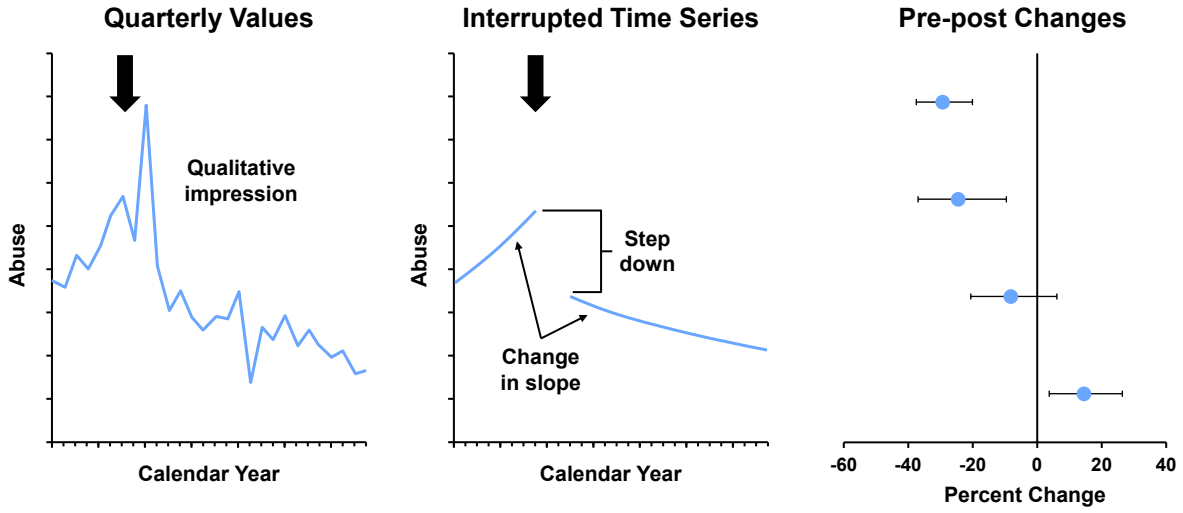
Representations of Calendar Time



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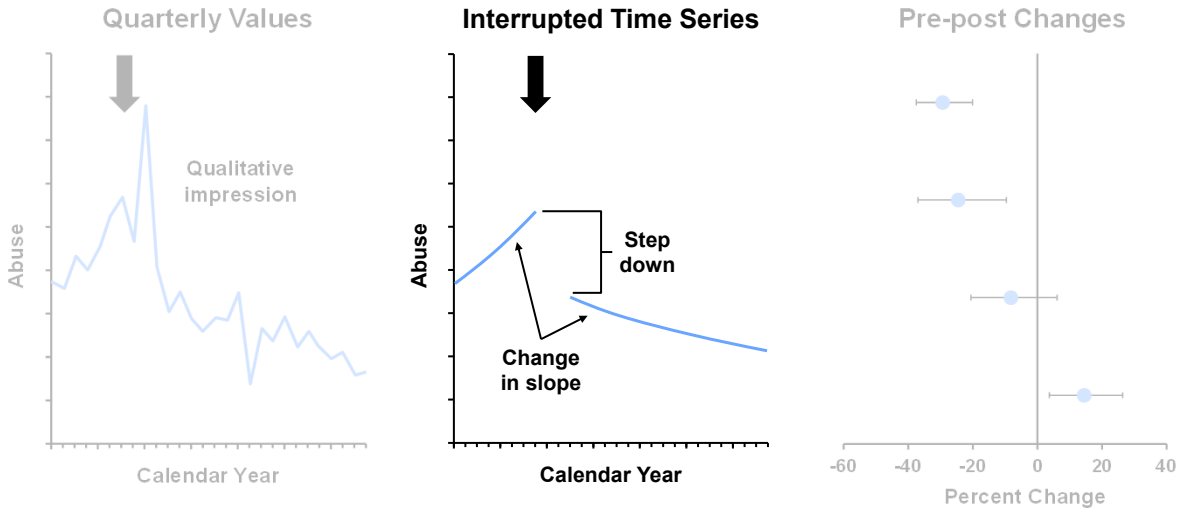
Representations of Calendar Time



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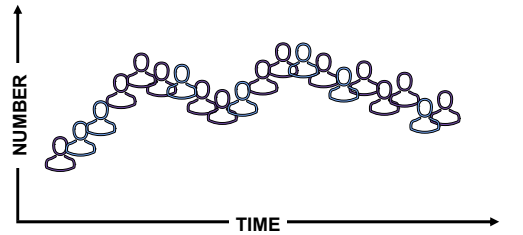
Abuse Per Individual or Per Unit Sales?

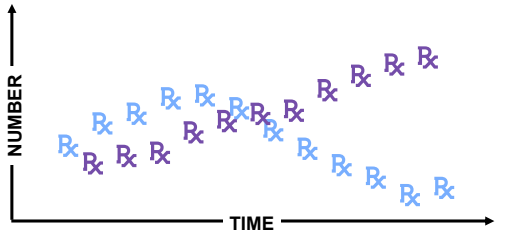
Abuse Reports for Drug A and B (Calculated each quarter)

***by* People**	VS	***by* Prescriptions**
INDIVIDUALS IN TREATMENT CENTERS		RETAIL DISPENSING VOLUME



$$\frac{\textit{Abuse Reports Drug A}}{\textit{Assessments}} \text{ v } \frac{\textit{Abuse Reports Drug B}}{\textit{Assessments}}$$

Shared denominator at every point in time



$$\frac{\textit{Abuse Reports Drug A}}{\textit{Rx Drug A}} \text{ v } \frac{\textit{Abuse Reports Drug B}}{\textit{Rx Drug B}}$$

Different time-varying denominators

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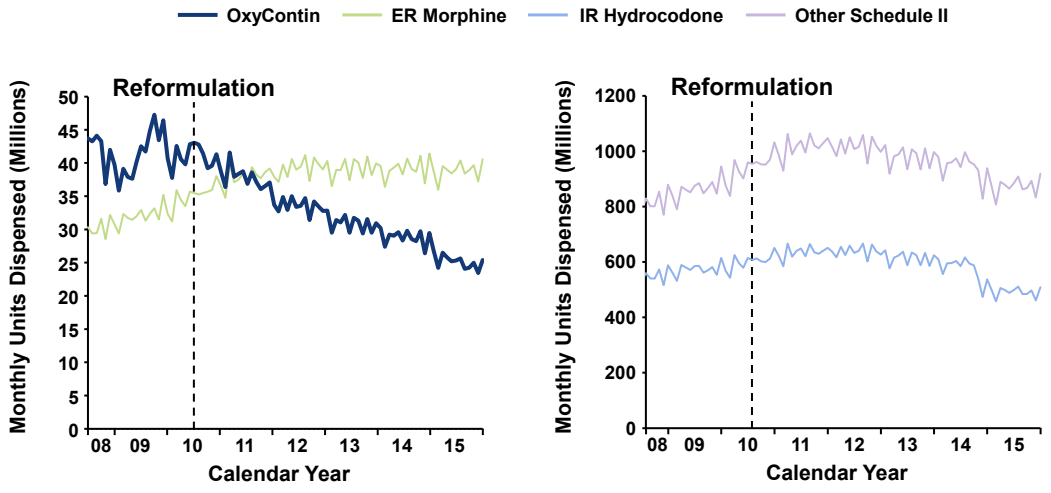
National Retail Pharmacy Unit Dispensing for OxyContin, ER Morphine, IR Hydrocodone, and Other Schedule II Opioids



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Abuse per Individual or per Unit Sales?

- **Individuals form a more interpretable "epidemiologic" denominator than does dispensing volume**
- **Dispensing volume does not directly control for non-drug factors that drive use, e.g.**
  - Availability
  - Street price
- **Reasons to doubt the proxy value of dispensing volume**
  - Use by legitimate patients drives dispensing volume but has no relation to illicit use
  - Illicit products often come from distant areas, not captured by local sales

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Abuse Report Dispensing Ratio

- **Abuse reports compared to product dispensing volume**
  - Important part of discussions between Purdue and FDA
  - Statistical models were created to estimate this ratio
- **Will be presented side by side with abuse proportions**
- **Nomenclature: ARDR (Abuse Report Dispensing Ratio)**

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Summary of Background Considerations for Surveillance of Opioid Abuse

- **Clean pre-/post- reformulation comparisons**
  - Quick changeover in OxyContin reformulation
  - Unique opportunity for epidemiologic study
  - Small range of possible confounders
- **Problems of measurement remain**
  - Limited access to abusing population
  - Uncertain choice among proxy denominators

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NAVIPPRO Treatment Centers Study

PMR 3051-1

Changes in Rates and Routes of Abuse of OxyContin after its Reformulation with Abuse Deterrent Properties among People Assessed for Treatment at Substance Abuse Treatment Centers using the NAVIPPRO® ASI-MV® System

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Key Findings
NAVIPPRO Treatment Centers

- **Abuse of OxyContin by injection and insufflation dropped abruptly by up to 52% following OxyContin reformulation**
- **Decline continued over an extended follow up period**
- **No comparator opioid showed a comparable change**
- **Abuse by swallowing intact OxyContin tablets did not decline**

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National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO)

- **NAVIPPRO aggregates data**
  - Adults entering abuse treatment centers across the US
- **Self-reported data on abuse in the past 30 days**
  - Addiction Severity Index-Multimedia Version (ASI-MV)
  - Completed at program intake
  - ASI-MV used in treatment planning and clinical care

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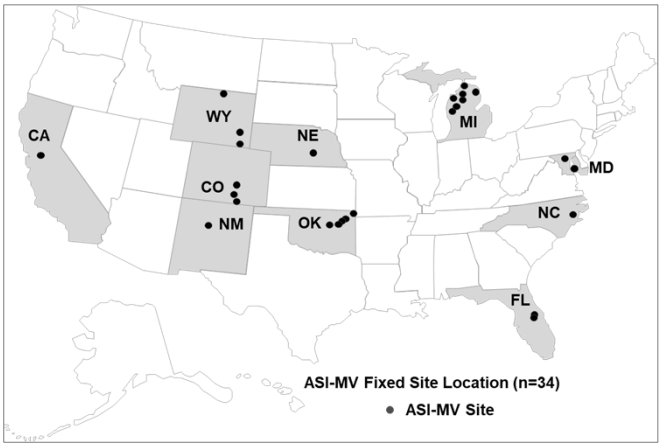
NAVIPPRO Treatment Centers Study

- **Study period**
  - Jul 2008 to Dec 2014
- **Site inclusion criterion**
  - At least quarterly submission of assessments over entire study period
- **66,897 assessments**
- **34 sites in 10 states**



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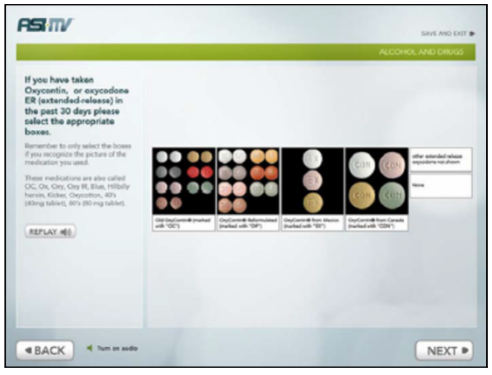
Addiction Severity Index-Multimedia Version (ASI-MV)

- **Standardized, computer-administered clinical assessment tool**
- **Uses photos as prompts**
- **Collects route of administration for each drug abused in the last 30 days**
- **Questions and photos are modified with changes in FDA drug approvals**



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Population Characteristics
NAVIPPRO Treatment Centers Study

For OxyContin users

- **Male: 57%**
- **Median age: 26 years**
- **White: 79%**
- **Residential: 55%**
- **Mean number of opioid products abused in past 30 days: 6.6**

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Variables
NAVIPPRO Treatment Centers Study

- **Primary Comparator Opioids**
  - ER morphine
  - IR hydrocodone
  - Other Schedule II opioids (excluding ER oxycodone, methadone, and transdermal patches).
- **Outcomes**
  - Reports of past 30-day abuse of OxyContin or comparators, classified by route
    - Non-oral: Injection and insufflation (target of reformulation)
    - Swallowing intact tablets
- **Denominators and covariates**
  - Number of ASI-MV assessments administered
  - Regional pharmacy dispensing volume

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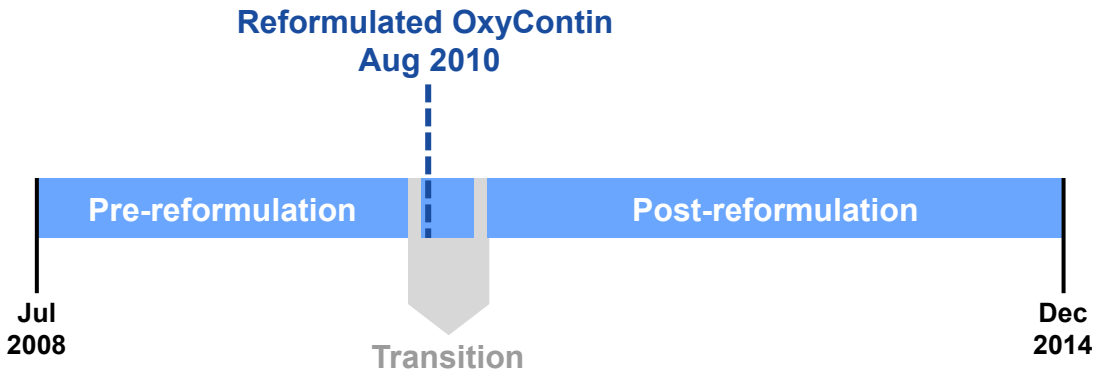
Time Periods
NAVIPPRO Treatment Centers Study



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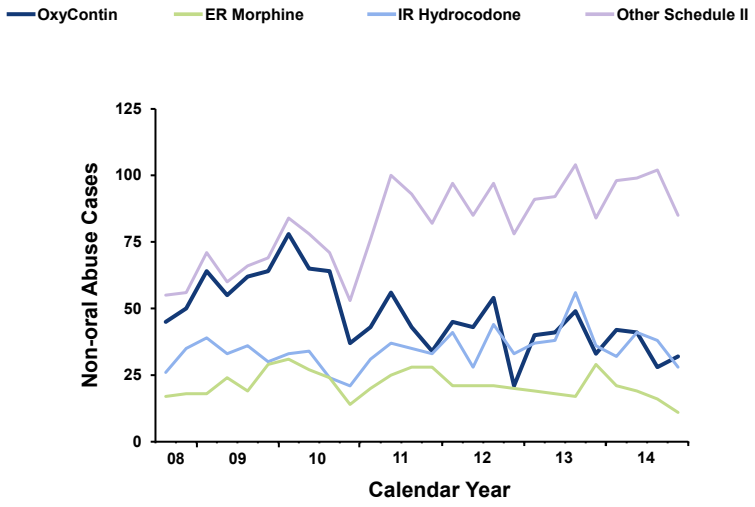
Non-oral Abuse Cases
NAVIPPRO Treatment Centers Study



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Statistical Models
NAVIPPRO Treatment Centers Study

- **Model 1: Proportion reporting abuse**
  - Dependent variable: Quarterly number of reports of abuse
  - Offset: Quarterly number of ASI-MV Assessments
- **Model 2a: ARDR in Relation to Regional Unit Dispensing**
  - Dependent variable: Quarterly number of reports of abuse
  - Offset: Quarterly dispensing volume
  - Covariate: Quarterly number of ASI-MV Assessments
- **Model 3a: Quarterly dispensing volume and number of ASI-MV Assessments, both as covariates**
  - Achieves substantially better fit than Model 2a
  - Results very similar to Model 1

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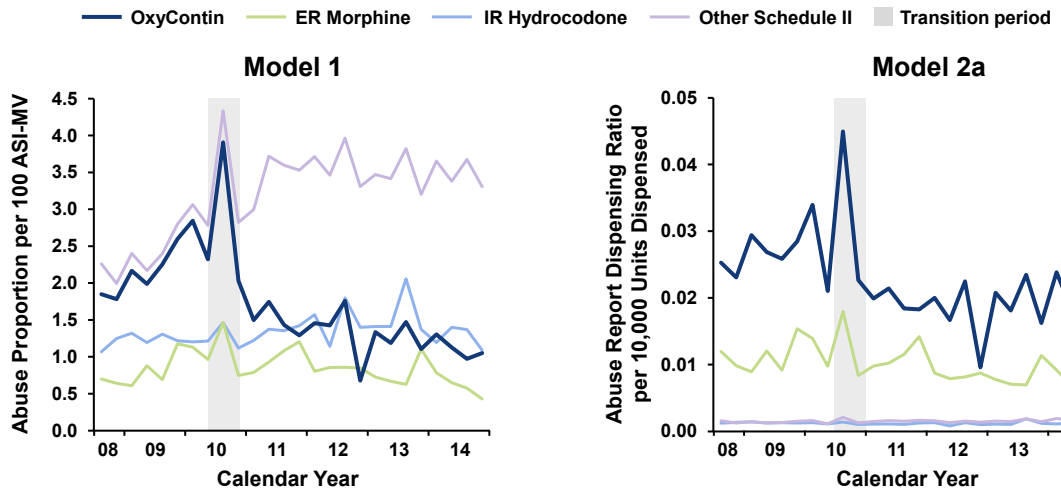
Non-Oral Abuse: Quarterly Values
NAVIPPRO Treatment Centers Study



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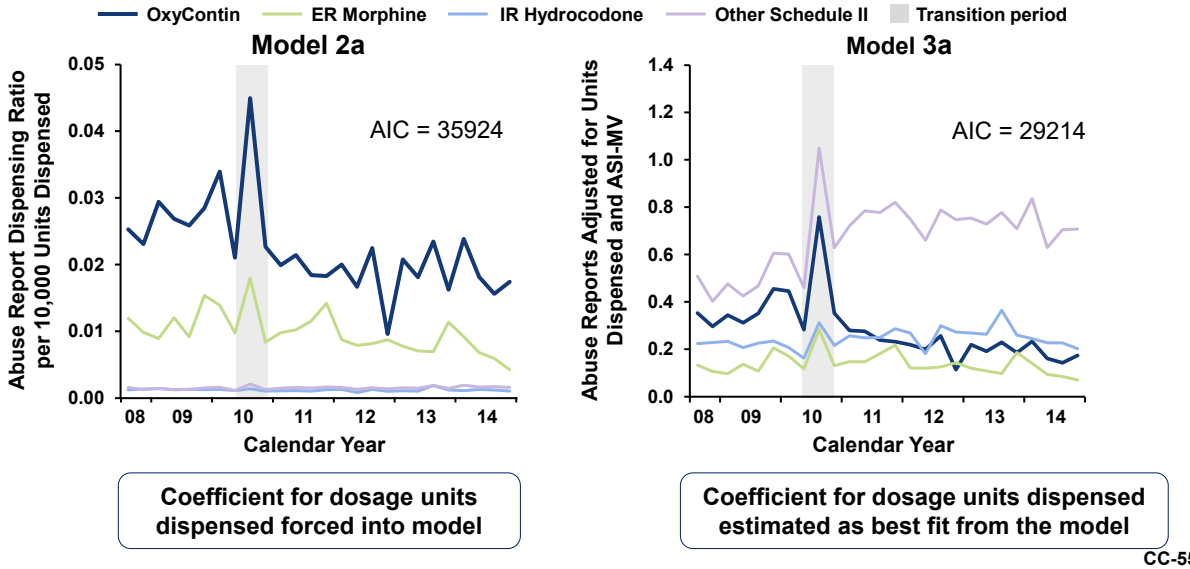
Non-Oral Abuse: Models for Dosage Units Dispensed

NAVIPPRO Treatment Centers Study



Coefficient for dosage units dispensed forced into model

Coefficient for dosage units dispensed estimated as best fit from the model

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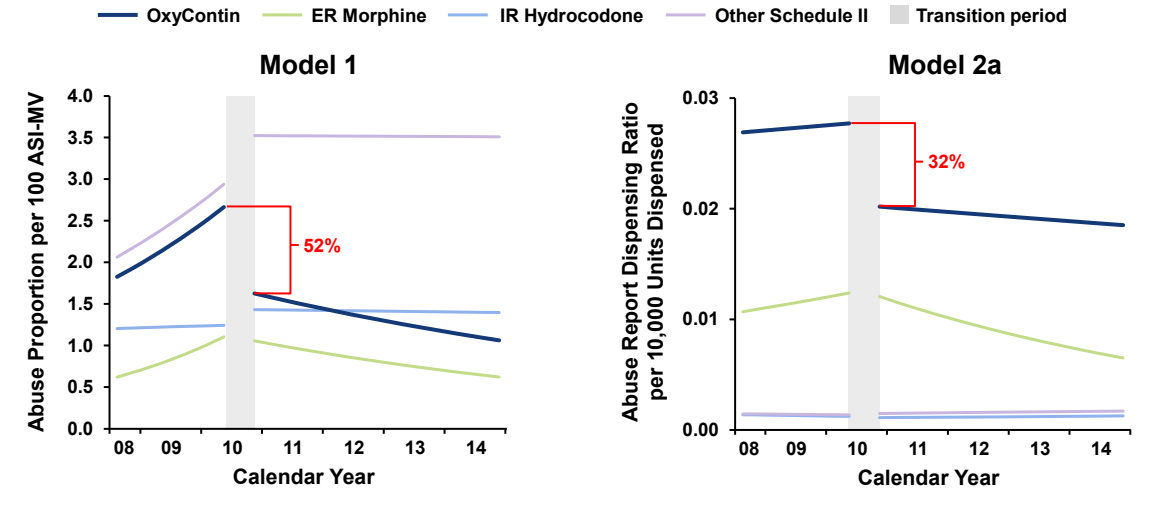
Non-Oral Abuse: Interrupted Time Series

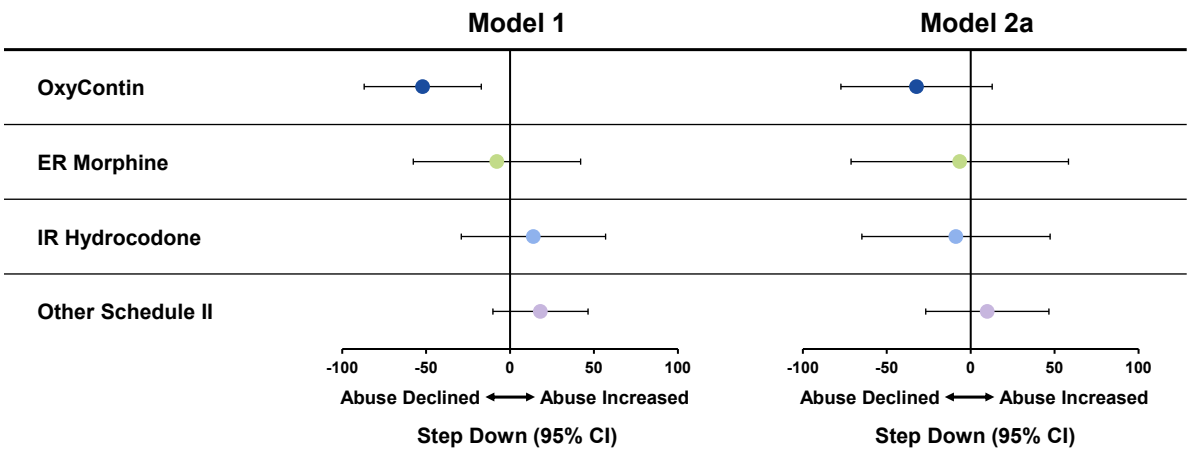
NAVIPPRO Treatment Centers Study



CC-56

56

Step Down Immediately Post-reformulation (ITS)
NAVIPPRO Treatment Centers Study (Non-oral Abuse)



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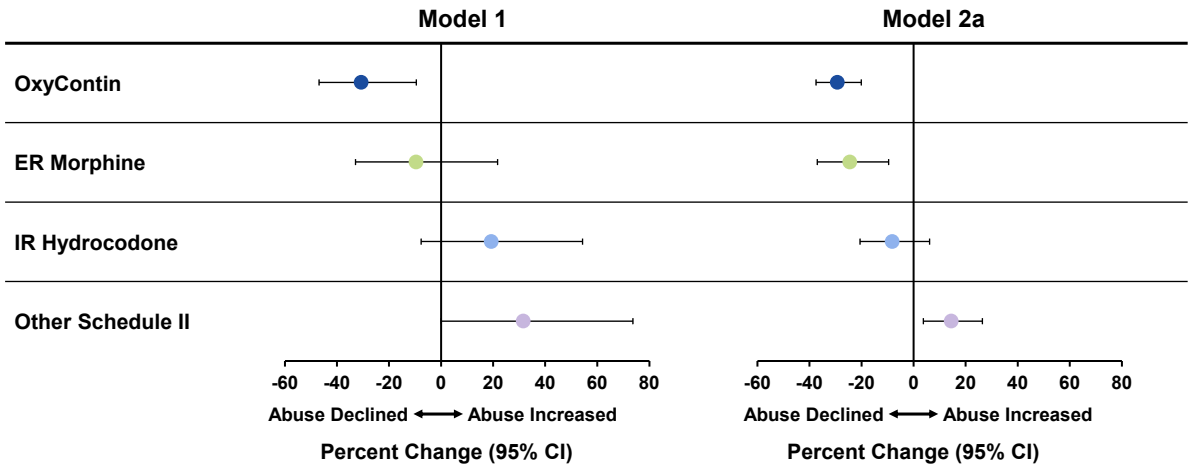
Percent Change Comparing Post-period to Pre-period
NAVIPPRO Treatment Centers Study (Non-Oral Abuse)

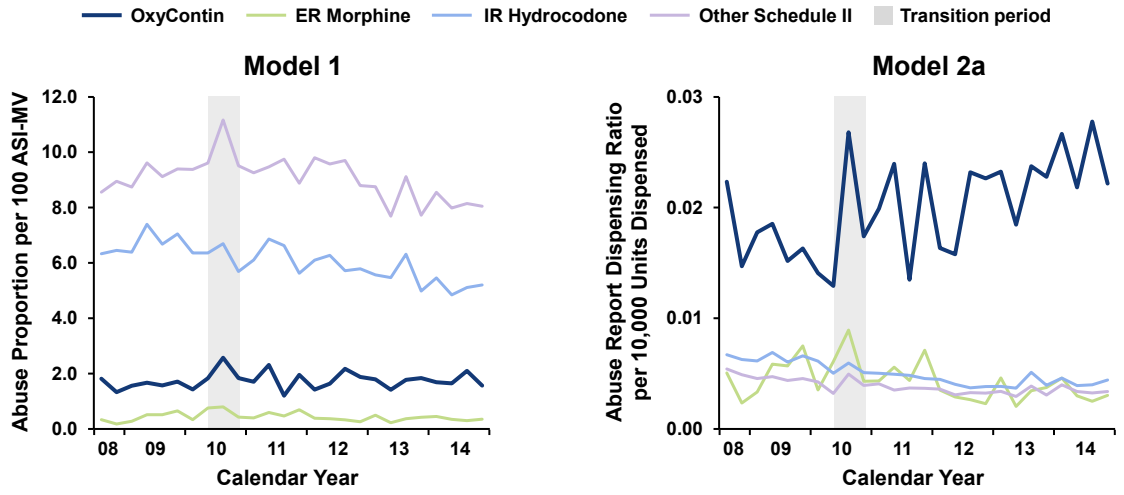


CC-58

58

Oral Swallowed Intact Abuse: Quarterly Values

NAVIPPRO Treatment Centers Study



CC-59

59

Conclusions

NAVIPPRO Treatment Centers Study

- **Abuse of OxyContin by injection and insufflation dropped abruptly by up to 52% following OxyContin reformulation**
- **Decline continued over an extended follow up period**
- **No comparator opioid showed a comparable change**
- **Abuse by swallowing intact OxyContin tablets did not decline**

CC-60

60

RADARS Treatment Centers Study

PMR 3051-3

Assessment of the Effect of Reformulated OxyContin on Reported Abuse of OxyContin among Patients Treated in Substance Abuse Treatment Centers Using the RADARS® System Treatment Center Programs Combined

CC-61

61

RADARS System Treatment Centers Combined

- **Adults treated in substance abuse treatment centers**
  - 373 sites in 49 states
  - Aggregated by 3-digit Zip Code
- **Voluntary participation (85% of eligible persons)**
- **Data collection forms were simpler than NAVIPPRO's ASI-MV**
- **Centers entered and left the RADARS system**
  - Too few centers with continuous data
- **No information on route of abuse**

CC-62

62

Key Findings
RADARS Treatment Centers Study

- **Reports of OxyContin abuse in the RADARS treatment centers showed an immediate step down of up to 27% and a continued decline after the OxyContin reformulation**
- **ER morphine and IR hydrocodone did not show a step down**
- **The group of all other Schedule II opioids showed a pattern similar to OxyContin's**

CC-63

63

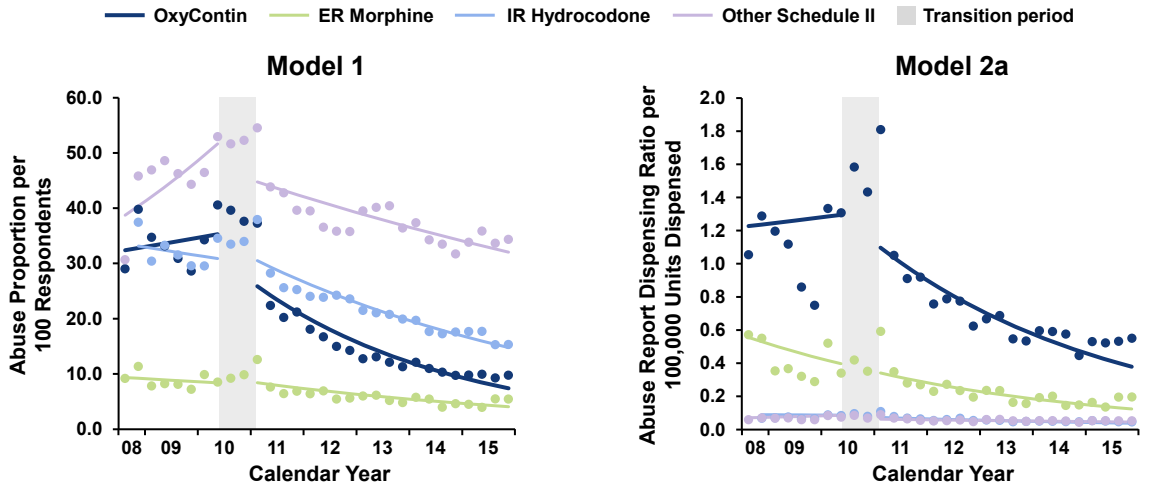
Population Characteristics
RADARS Treatment Centers Study

- **OxyContin abusers**
  - Median age: 30 years
  - Male: 54%
  - White: 88%
  - Mean opioids abused in past 30 days: 9
- **Abusers of comparator opioids were very similar**

CC-64

64

Interrupted Time Series
RADARS Treatment Centers Study (All Routes)



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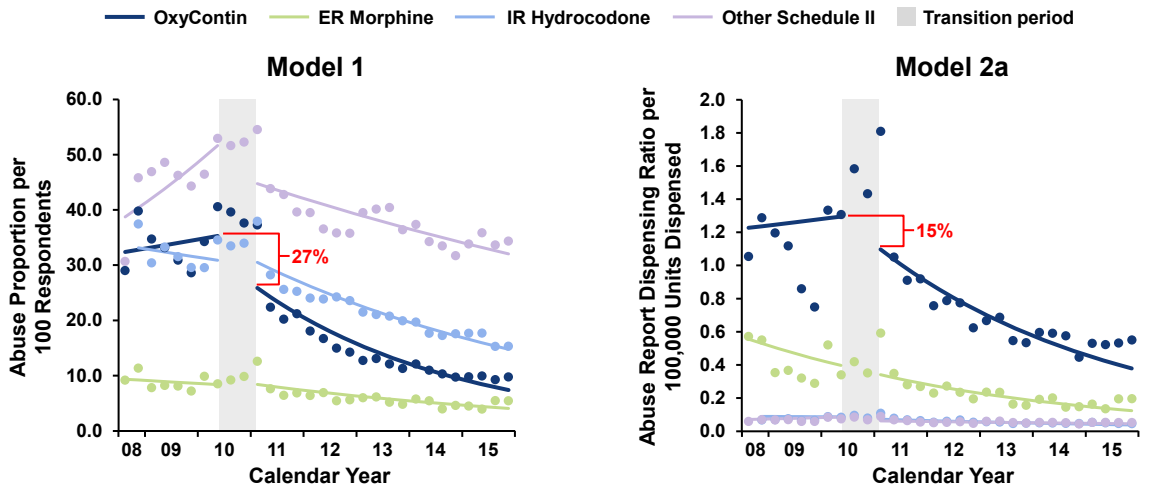
Interrupted Time Series
RADARS Treatment Centers Study (All Routes)

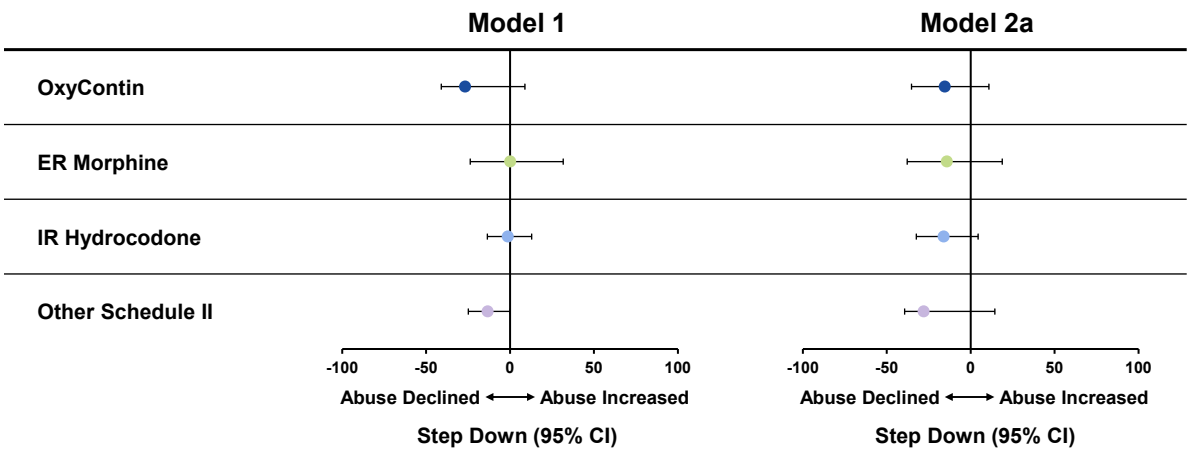


CC-66

66

Step Down Immediately Post-reformulation (ITS)

RADARS Treatment Centers Study (All Routes)



CC-67

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Conclusions

RADARS Treatment Centers Study

- **Reports of OxyContin abuse in the RADARS treatment centers showed an immediate step down up to 27% and continued decline after the OxyContin reformulation**
- **ER morphine and IR hydrocodone did not show a step down**
- **The group of all other Schedule II opioids showed a pattern similar to OxyContin in one analysis**

CC-68

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RADARS Poison Centers Study

PMR 3051-2

Changes in Abuse of OxyContin Following its Reformulation with Properties Intended to Deter Abuse as Measured by the RADARS® System Poison Center Program

CC-69

69

RADARS System Poison Center Program

- **Participating US poison centers**
  - 46-50 Centers
  - Covering 83-94% of US population
- **Medical professionals manage incoming calls**
  - Nurses, pharmacists, physician assistants and physicians
  - Trained in medical and clinical toxicology
- **Calls from users, family, friends, sometimes medical caregivers**
- **Opioid calls reflect wider spectrum of opioid abuse, including less experienced abusers**

CC-70

70

RADARS Poison Centers Study Variables

- **Outcomes**
  - Reports of intentional abuse by any route for that substance (attempting to achieve euphoric or psychotropic effect)
- **Covariates and Denominators**
  - 2010 US Census data
  - Quarterly retail pharmacy dispensing volume in the service area
  - Intentional pharmaceutical exposures
- **Primary Comparators**
  - ER morphine
  - IR hydrocodone
  - Other Schedule II opioids

CC-71

71

OxyContin Population
RADARS Poison Centers Study

- **Characteristics**
  - Mean age: 29 years
  - Male: 68%
  - Mean number of substances: 2.1
- **Medical severity**
  - Death: <1%
  - No or minor effect: 35%
  - Moderate or major effect: 39%
  - Other/unknown: 26%

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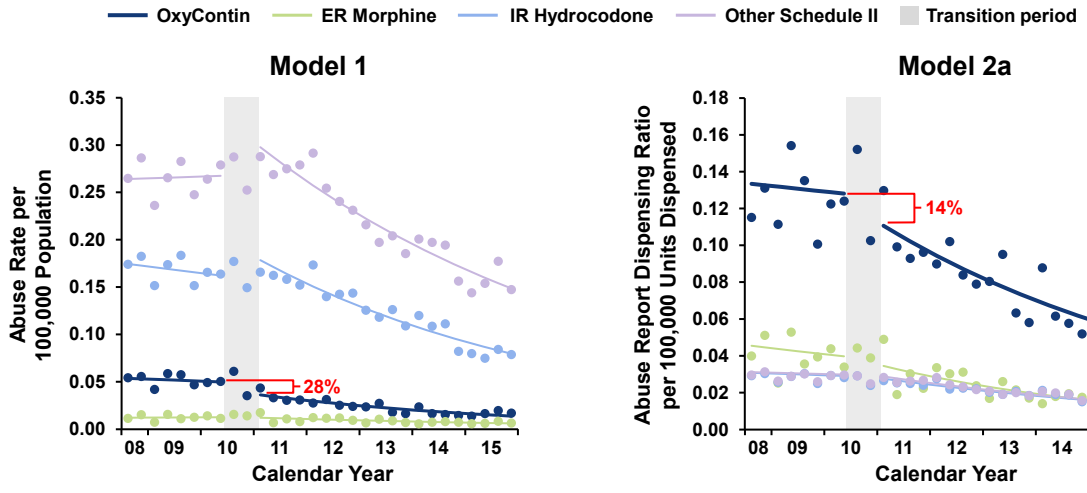
Interrupted Time Series
RADARS Poison Centers Study



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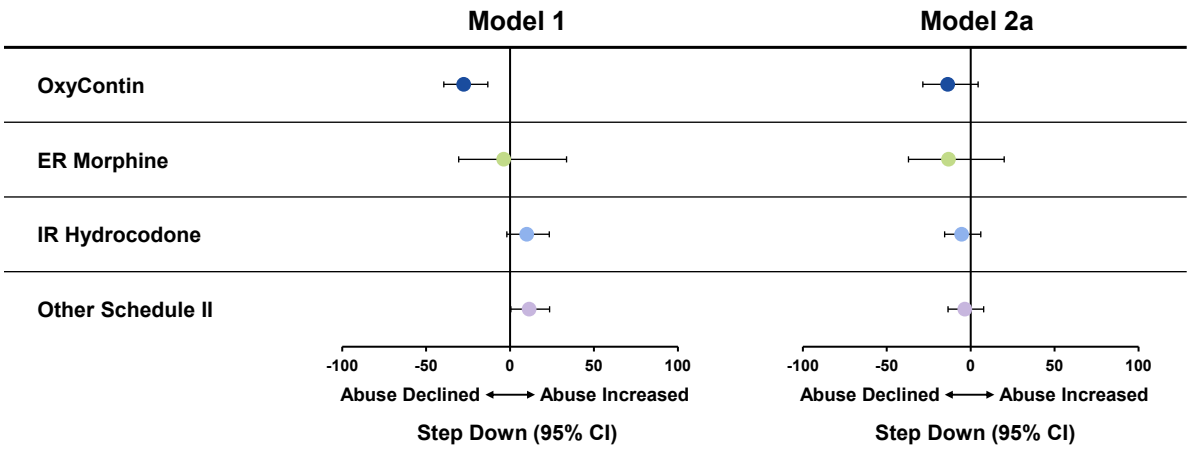
Step Down Immediately Post-reformulation (ITS)
RADARS Poison Centers Study (All Routes)



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Conclusions
RADARS Poison Centers Study

- **There was a step down of up to 28% for OxyContin calls immediately following reformulation**
  - Continued further decline during the follow-up period
- **There was no step down for any of the comparators**

CC-75

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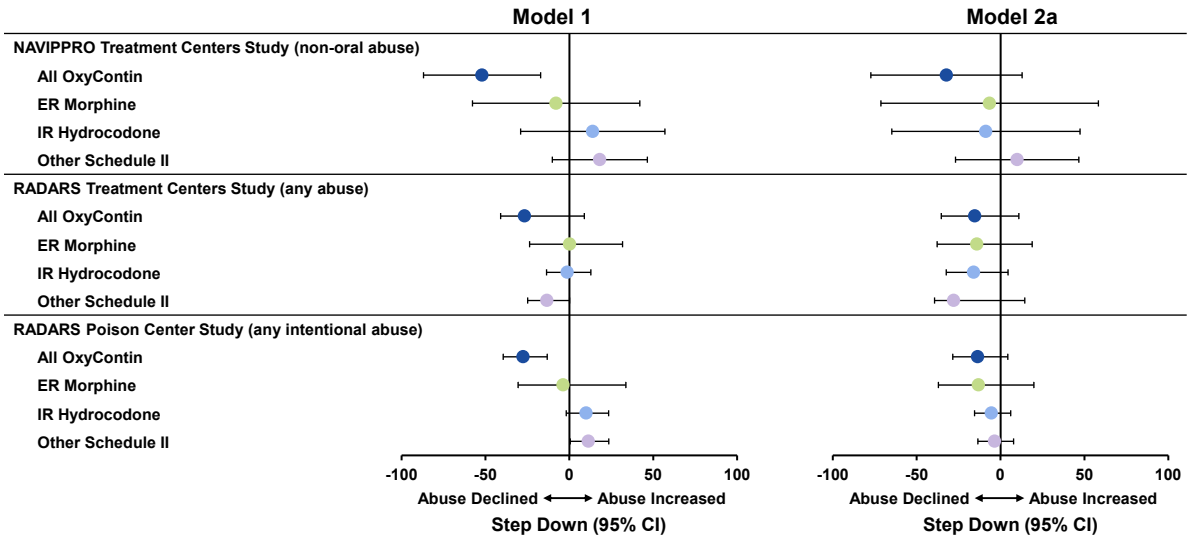
Step Down Immediately Post-reformulation (ITS)
NAVIPPRO, RADARS Treatment Centers, and RADARS Poison Centers Studies



CC-76

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Insured Populations Study

PMR 3051-4

Changes in Fatal and Non-fatal Overdose among Individuals Dispensed OxyContin® after its Reformulation with Abuse-deterrent Properties – A Healthcare Database Analysis with Linkage to the National Death Index

CC-77

77

Study Objective
Insured Populations Study

- **Estimate rates of fatal and non-fatal, non-intentional opioid overdoses during treatment**
- **Changes pre-/post-reformulation**
  - In OxyContin and in all comparators
  - OxyContin vs comparators
- **Post protocol analysis requested by FDA included all events (intentional and non-intentional)**
  - Results substantially similar

CC-78

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Distinctive Features
Insured Populations Study

- **Attention limited to times of recent prescription dispensing**
  - OxyContin and comparator opioids
- **Outcome identified from insurance claims and death certificates**
- **General population under medical care**
- **Events linked to exposure by date – not by clinical attribution**

CC-79

79

Patients in Regular Medical Care

- **Bioequivalence of reformulation to original OxyContin**
- **Expectation of no impact on care or outcomes**
- **Potential impact limited to incorrect use before reformulation**
  - Chewing tablets
  - Crushing tablets for easier administration
  - Unrecognized misuse/abuse

CC-80

80

Key Findings
Insured Populations Study

- **No evidence of an effect on OD with reformulation for individuals under regular medical care**
- **Among persons who received OxyContin alone:**
  - OD rate declined following reformulation
  - Decline was greater for OxyContin than for any comparators

CC-81

81

Study Population
Insured Populations Study

Persons filling a prescription for OxyContin or a comparator after at least three months' time in:

- **Two nationwide commercial health insurance data sources**
  - HIRD – Anthem (HealthCore)
  - MarketScan – Employer-sponsored plans (IBM)
- **Selected plans from national Medicaid (via StatInMed)**
  - Plans meeting published research quality criteria

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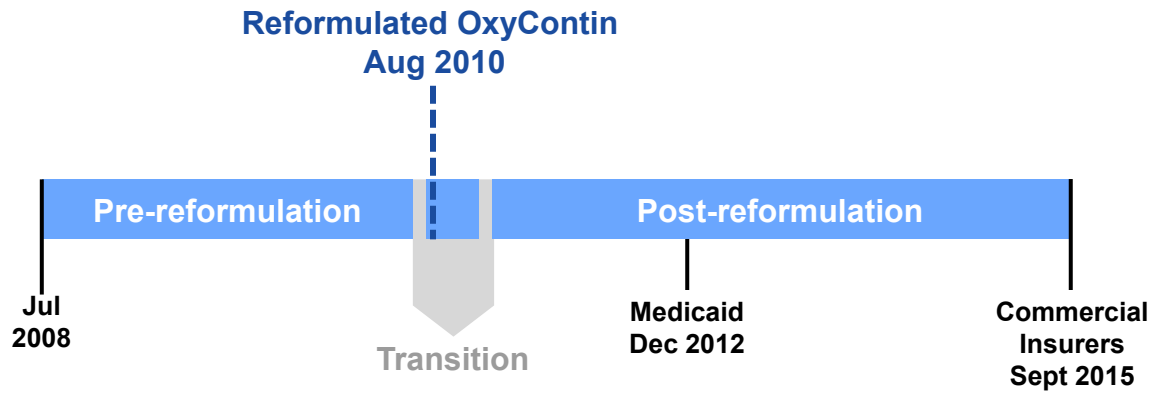
Time Periods
Insured Populations Study



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Study Drugs
Insured Populations Study

- **OxyContin**
- **Primary comparators**
  - ER morphine, transdermal (TD) fentanyl, methadone tablets/capsules
- **Secondary comparators**
  - ER oxymorphone, IR oxycodone (single entity), IR hydromorphone

CC-84

84

Exposure
Insured Populations Study

- **Evaluated as "treatment episodes" including OxyContin or a comparator opioid**
- **Exposure status on each person-day a function of recent dispensing dates and days supply**
- **Exposure for each treatment episode was classified in subcategories including:**
  - "Only use" of the drug (i.e., without concomitant use of non-study Schedule II opioids)
  - "Any use" of the drug (i.e., with or without concomitant use of non-study Schedule II opioids) and

CC-85

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Treatment Episode – One Opioid
Insured Populations Study

DAY	1	2	3	4	5	6	7
	Prescription						

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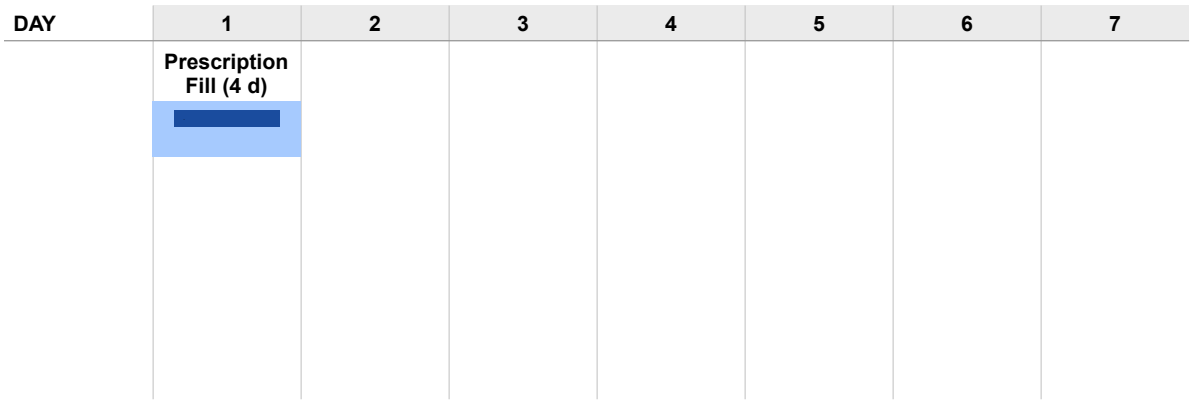
Treatment Episode – One Opioid
Insured Populations Study



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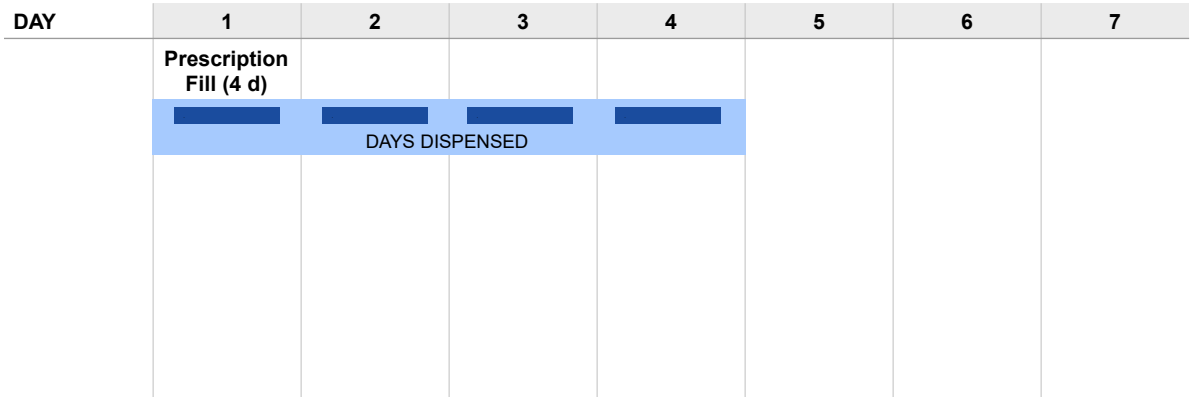
Treatment Episode – One Opioid
Insured Populations Study



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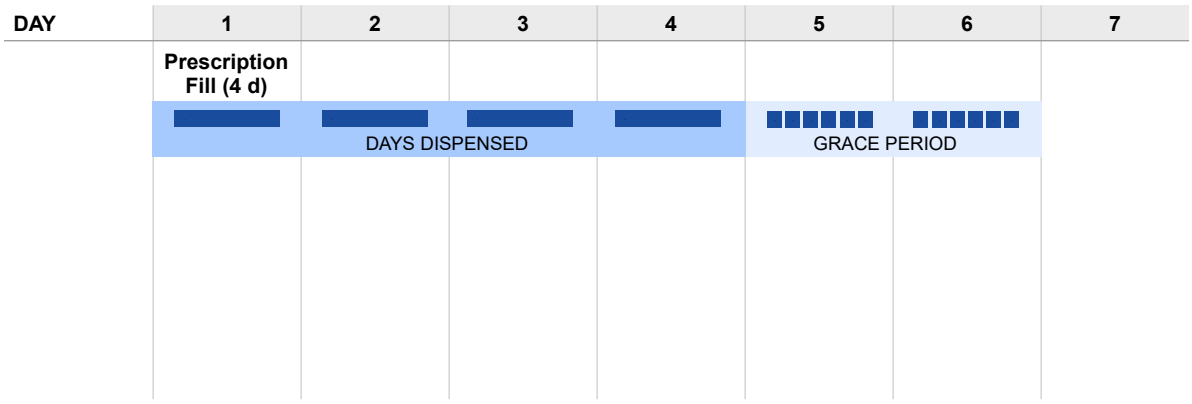
Treatment Episode – One Opioid
Insured Populations Study



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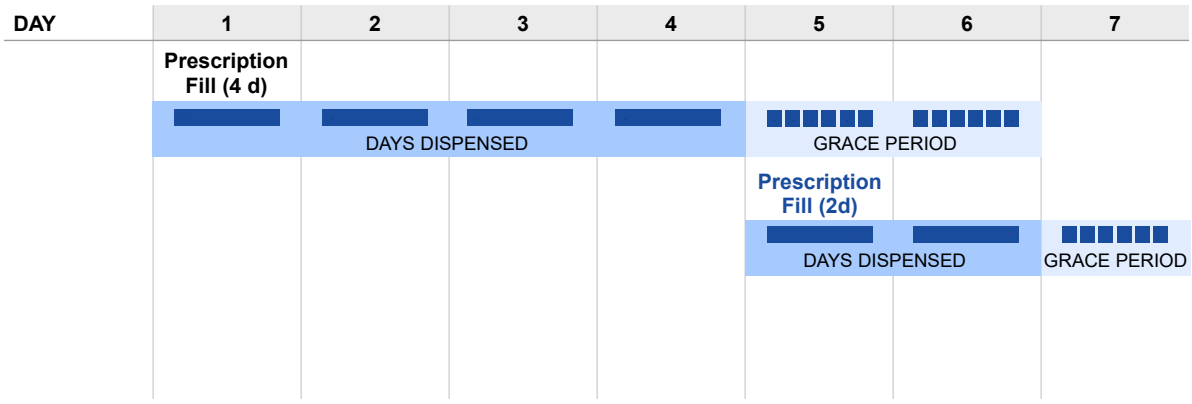
Treatment Episode – One Opioid
Insured Populations Study



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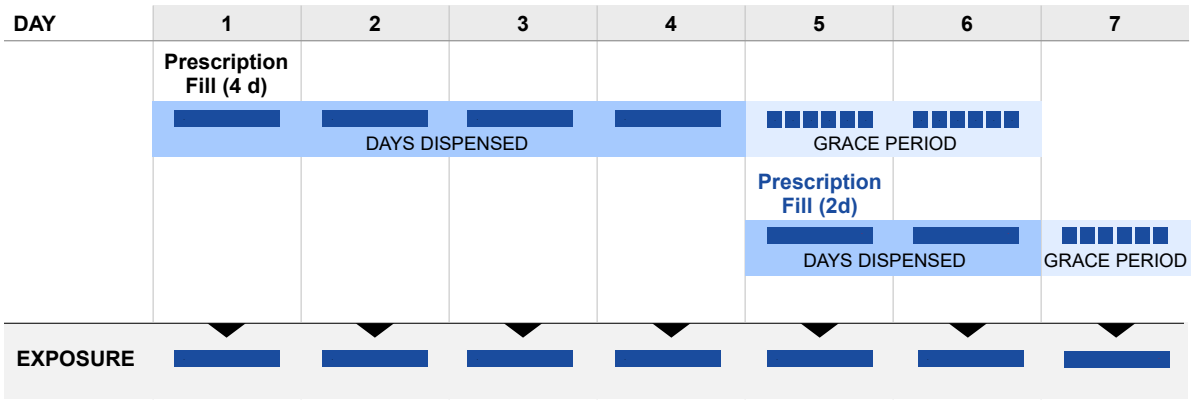
Treatment Episode – One Opioid
Insured Populations Study



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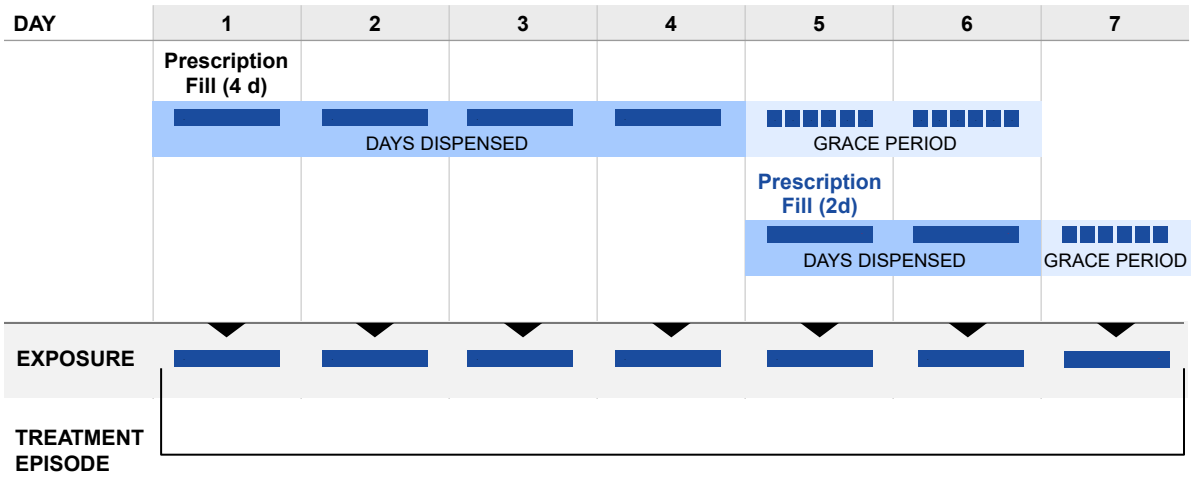
Treatment Episode – One Opioid
Insured Populations Study



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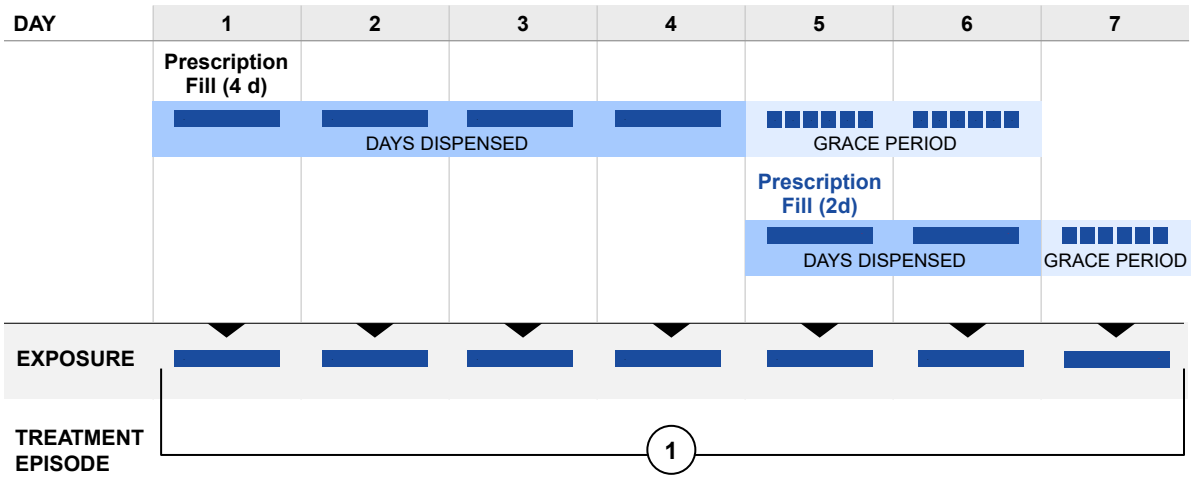
Treatment Episode – One Opioid
Insured Populations Study



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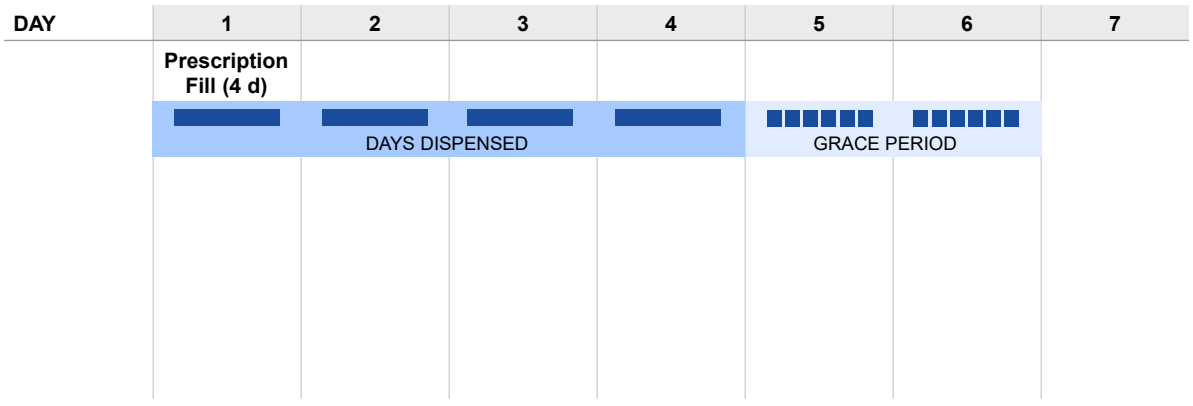
Treatment Episodes – Two Opioids
Insured Populations Study



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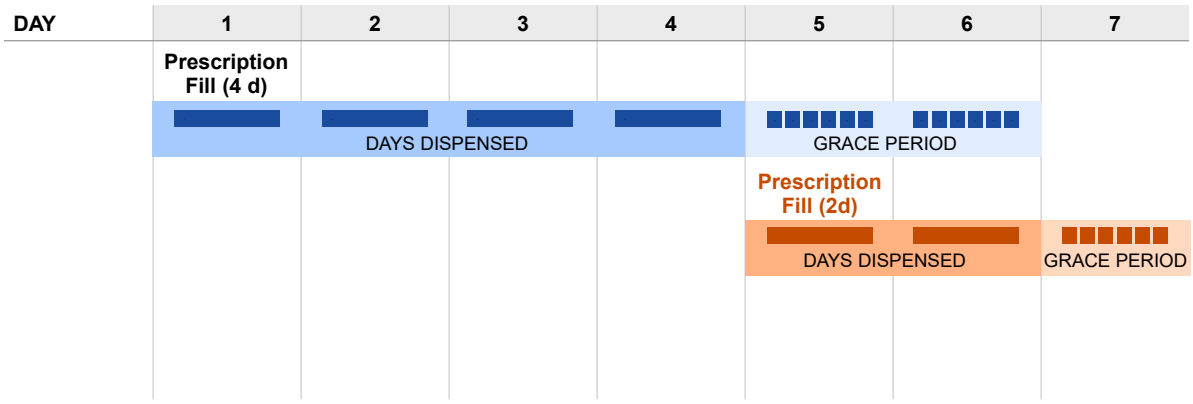
Treatment Episodes – Two Opioids
Insured Populations Study



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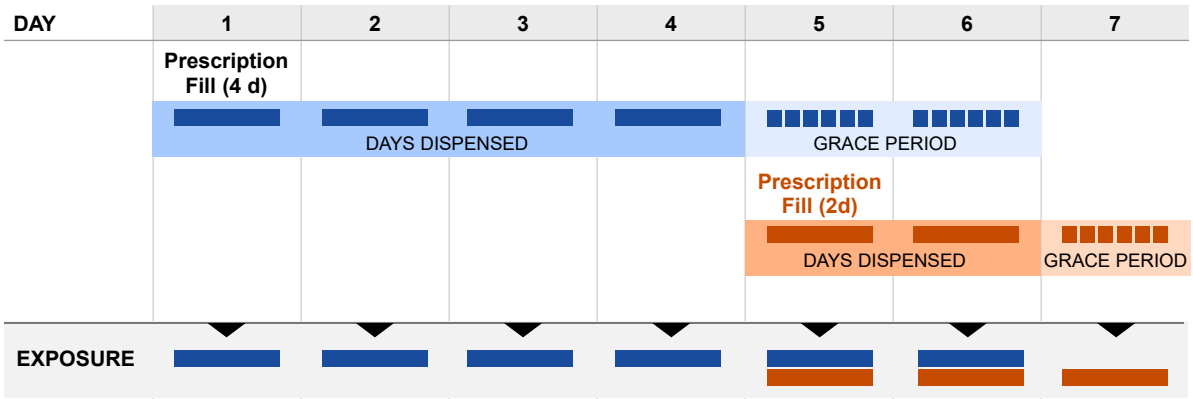
Treatment Episodes – Two Opioids
Insured Populations Study



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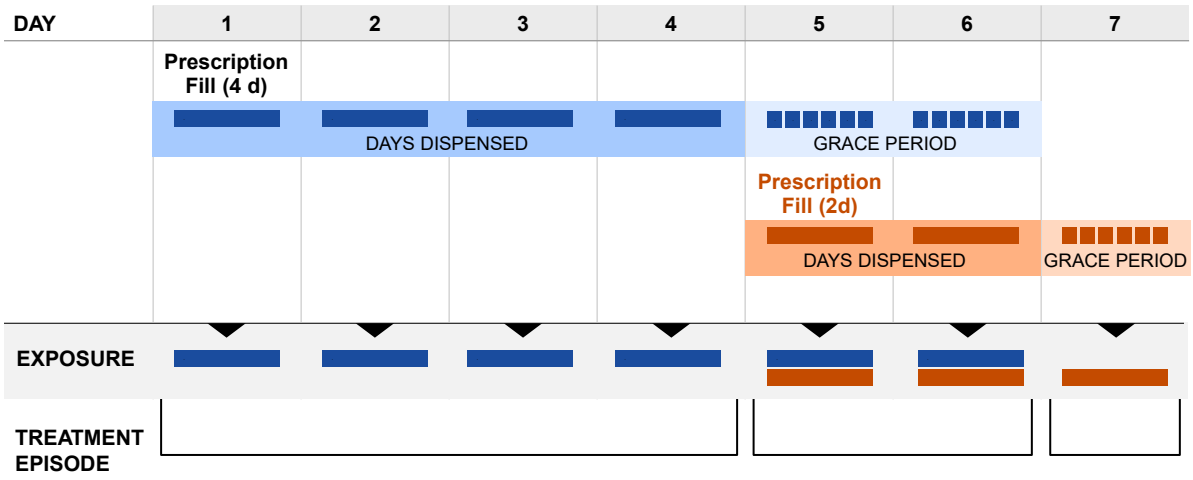
Treatment Episodes – Two Opioids
Insured Populations Study



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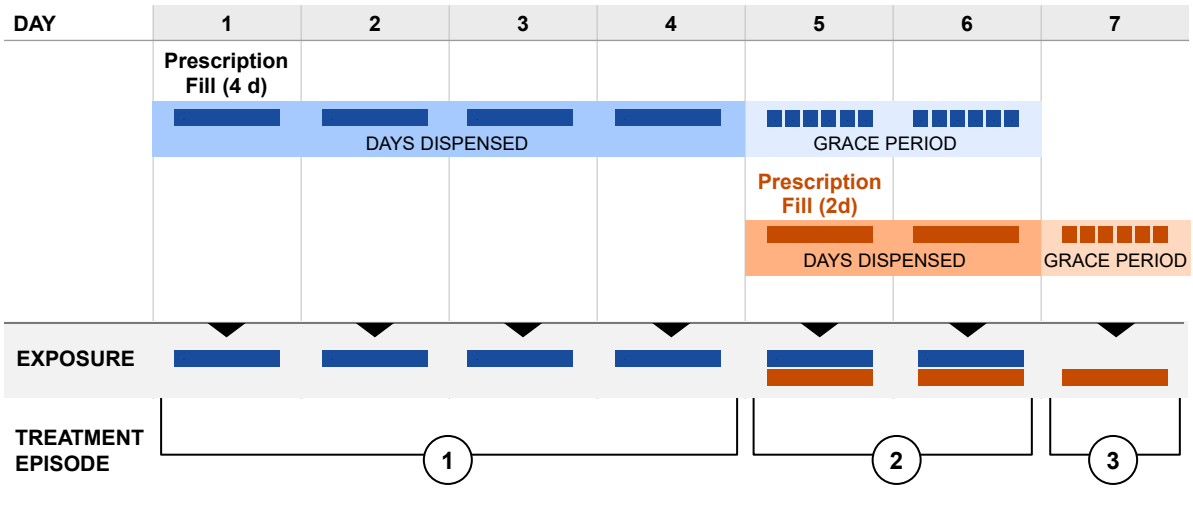
Treatment Episodes – Two Opioids
Insured Populations Study



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Outcomes
Insured Populations Study

- **The primary outcome was unintentional overdose, ascertained from insurance claims and National Death Index (NDI)**
  - Overdose and intentionality were defined with a previously validated algorithm for health insurance claims

CC-99

99

Covariates (Established at the Start of Each Treatment Episode)
Insured Populations Study

Demographic

- **Age**
- **Gender**
- **Geographic region**
- **Calendar year**
- **Type of insurance (e.g. PPO/HMO)**

Clinical

- **Pain diagnoses (14 categories)**
- **Conditions that may affect opioid metabolism (hepatic, renal)**
- **Diseases that exacerbate respiratory depression**
- **Deyo-Charlson comorbidity index**
- **Recent use of opioid analgesics**
- **Recent history of overdose**

CC-100

100

Study Design – Analytic Methods
Insured Populations Study

- **Treatment episode as the unit of analysis**
  - Characterized by exposure, demographics, medical covariates
  - Possibly ending in an overdose
- **Poisson regression for multiple determinants with covariate adjustment**
- **Drug-by-period effects modeled through interaction terms**
- **Random-effects meta-analysis for the two commercial databases**

CC-101

101

Population Characteristics
Insured Populations Study (Entire Study Period)

	Medicaid		MarketScan		HIRD	
	Any OxyContin N=94,445	Any Primary Comparator N=367,814	Any OxyContin N=122,254	Any Primary Comparator N=181,240	Any OxyContin N=81,137	Any Primary Comparator N=110,619
Total observation time per patient, months						
Mean (SD)	7.8 (10.0)	8.1 (10.3)	6.0 (10.3)	8.0 (11.9)	6.1 (11.4)	9.5 (13.9)
Treatment episodes						
n	522,775	2,039,232	561,703	975,389	378,441	654,462
Gender, %						
Female	56.6	60.9	50.8	57.4	50.2	58.5
Age, y						
Mean (SD)	46.7 (10.5)	46.9 (10.6)	53.1 (12.0)	54.6 (11.6)	51.4 (12.2)	53.4 (11.9)
Comorbidity Index (DCI)						
Mean (SD)	2.0 (2.8)	2.0 (2.8)	2.0 (3.1)	2.4 (3.3)	1.7 (2.8)	2.0 (3.0)

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Clinical and Comorbidity Characteristics
Insured Populations Study (Entire Study Period)

	Medicaid		MarketScan		HIRD	
	Any OxyContin N=94,445 %	Any Primary Comparator N=367,814 %	Any OxyContin N=122,254 %	Any Primary Comparator N=181,240 %	Any OxyContin N=81,137 %	Any Primary Comparator N=110,619 %
Abdominal pain	19.1	21.4	14.3	18.4	14.7	18.4
Chronic pain	20.0	21.0	11.7	14.7	16.8	21.1
Neuropathic pain	3.2	3.5	2.5	3.4	2.8	4.0
Joint and musculoskeletal	33.3	32.1	37.6	30.7	43.5	37.2
COPD	19.7	19.7	11.5	13.2	13.2	16.0
Major depression disorder	16.9	18.6	11.1	13.2	15.5	18.3
History of overdose	0.5	0.8	0.3	0.4	0.3	0.5
Opioid type dependence	5.8	5.9	1.7	1.9	3.0	3.6
Non-opioid drug dependence	6.2	5.9	1.4	1.5	2.3	2.9
Benzodiazepines	18.6	18.1	15.4	15.8	16.1	16.7

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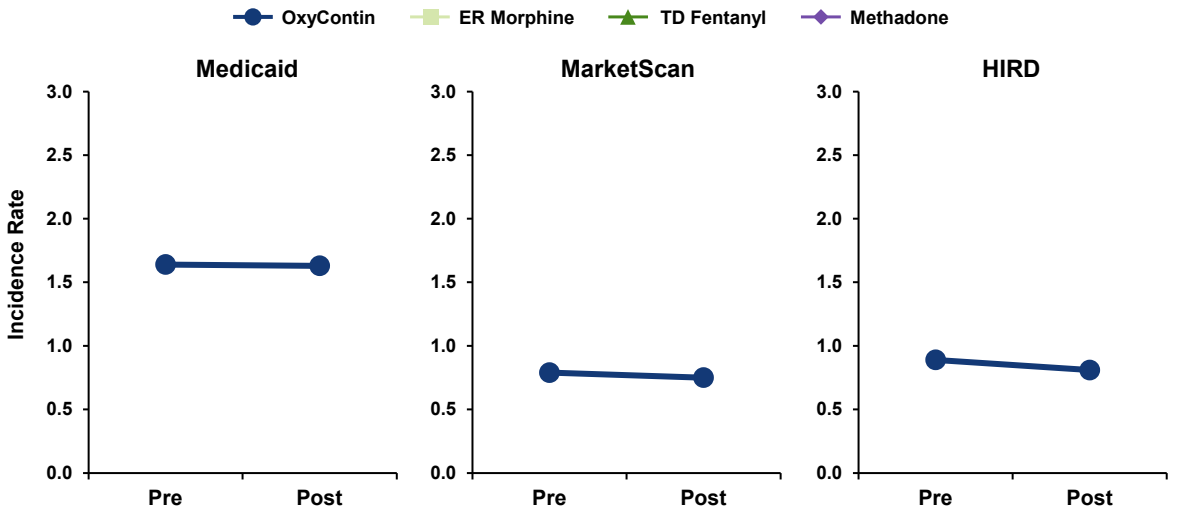
"Any Use" – Small Overall Impact on OD Rates
Insured Populations Study



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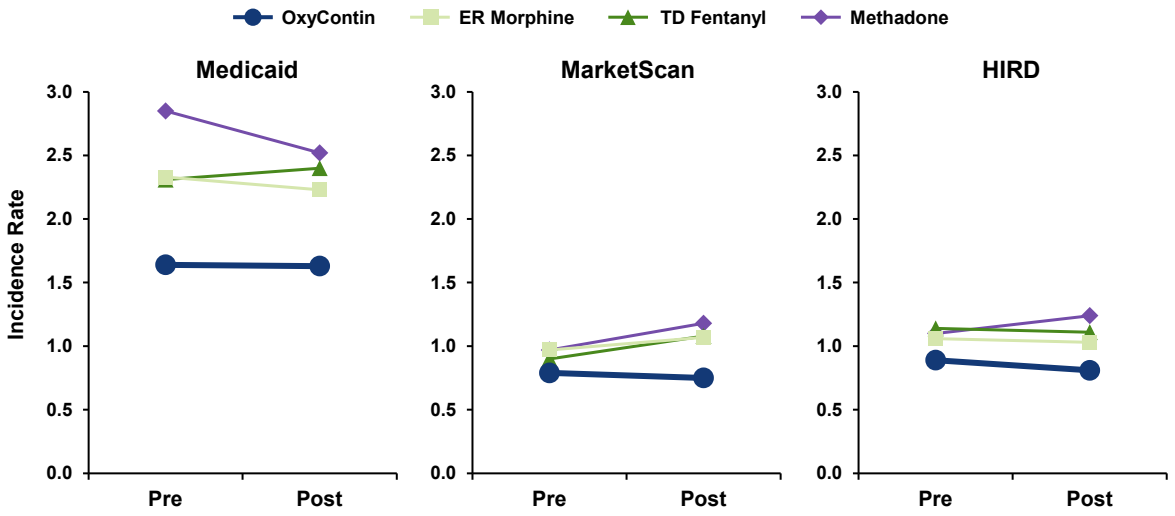
"Any Use" – Small Overall Impact on OD Rates
Insured Populations Study



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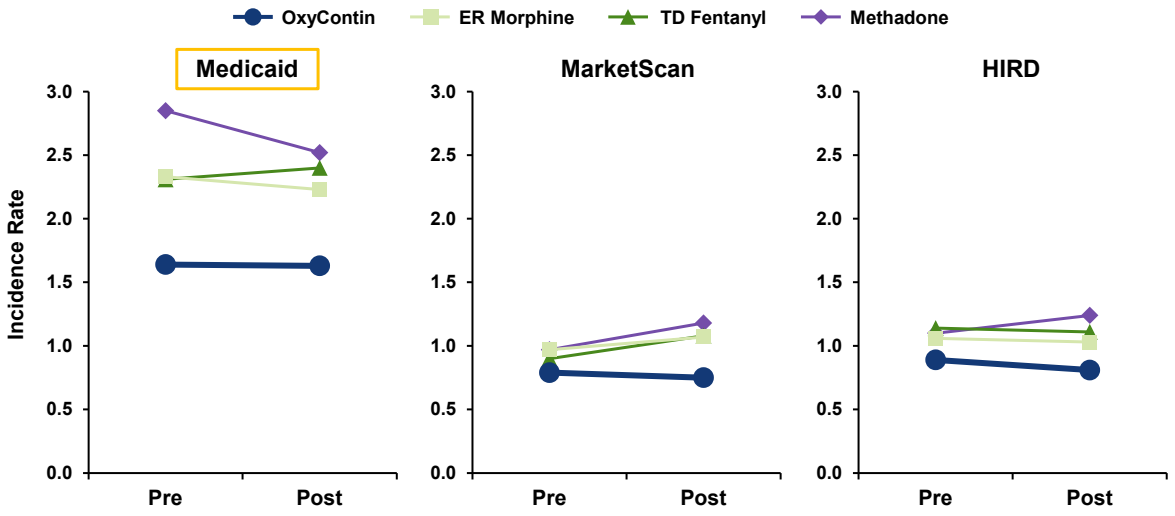
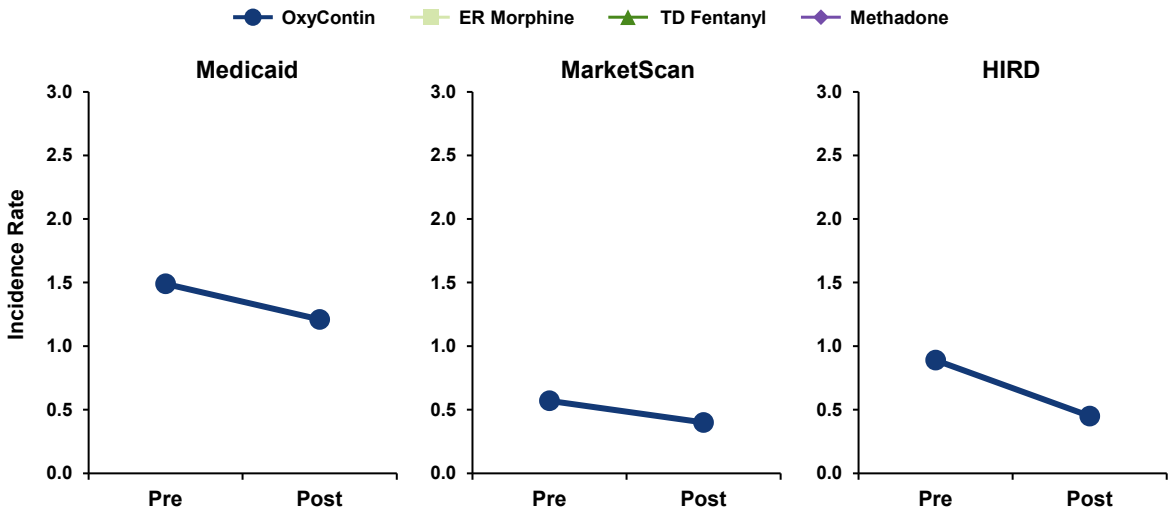
"Any Use" – Small Overall Impact on OD Rates
Insured Populations Study



106

"Only Use" – Consistent Effect of Reformulation
Insured Populations Study



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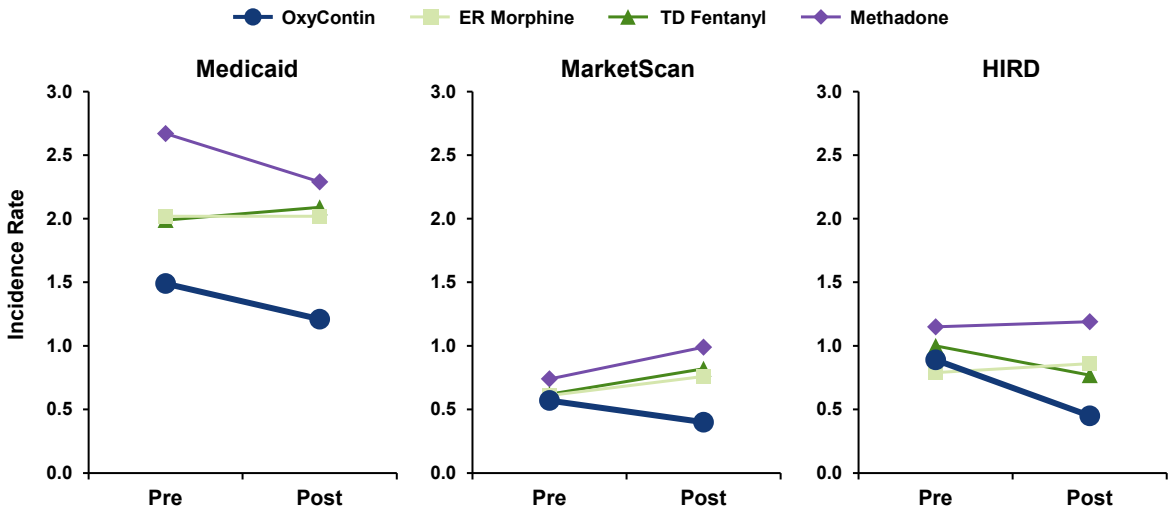
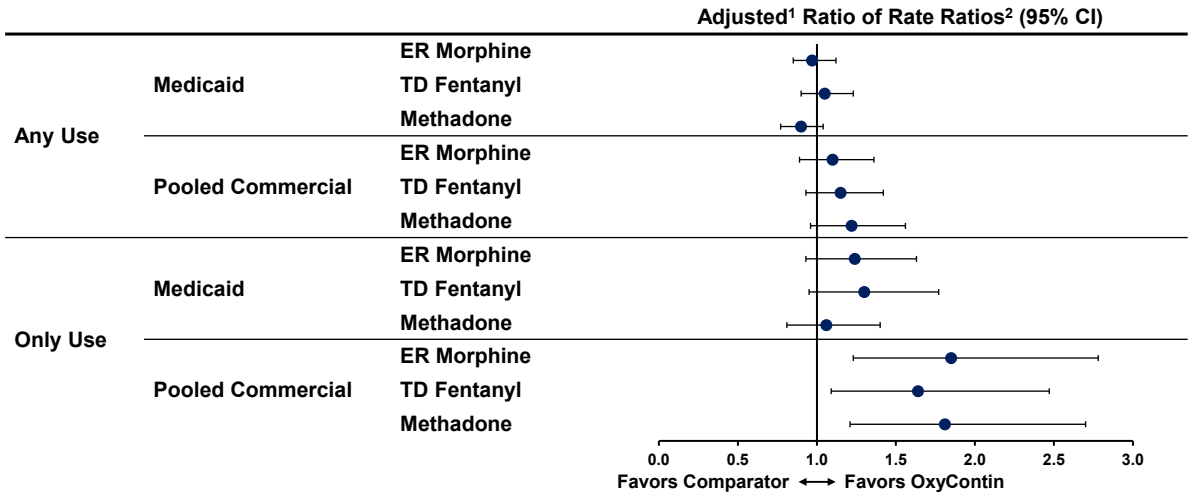
"Only Use" – Consistent Effect of Reformulation
Insured Populations Study



108

Comparison of Post vs. Pre Reformulation Overdose Rates vs. OxyContin
Insured Populations Study



1. Models adjusted for demographics and clinical characteristics.
2. Calculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

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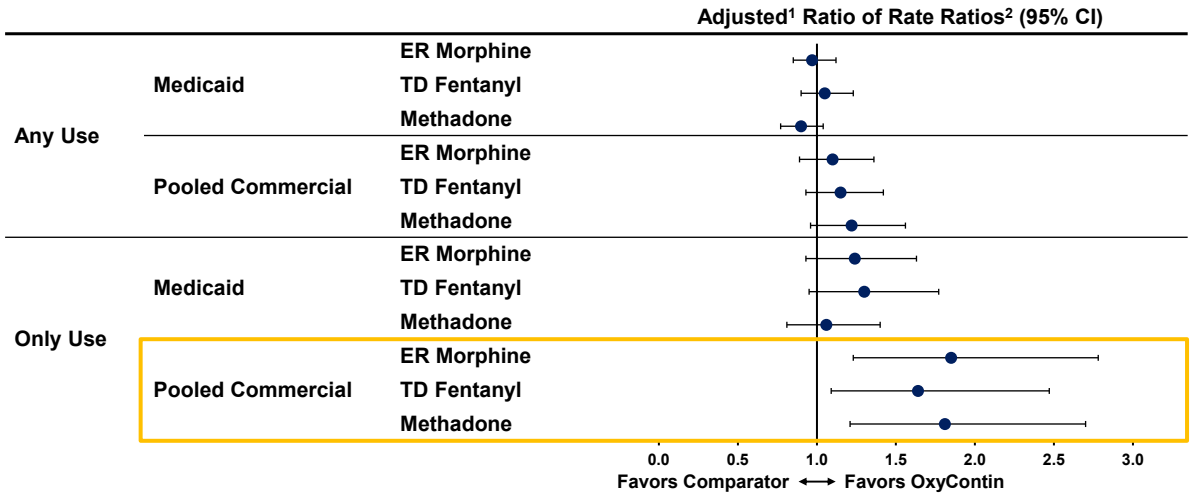
Comparison of Post vs. Pre Reformulation Overdose Rates vs. OxyContin
Insured Populations Study



1. Models adjusted for demographics and clinical characteristics.
2. Calculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

CC-110

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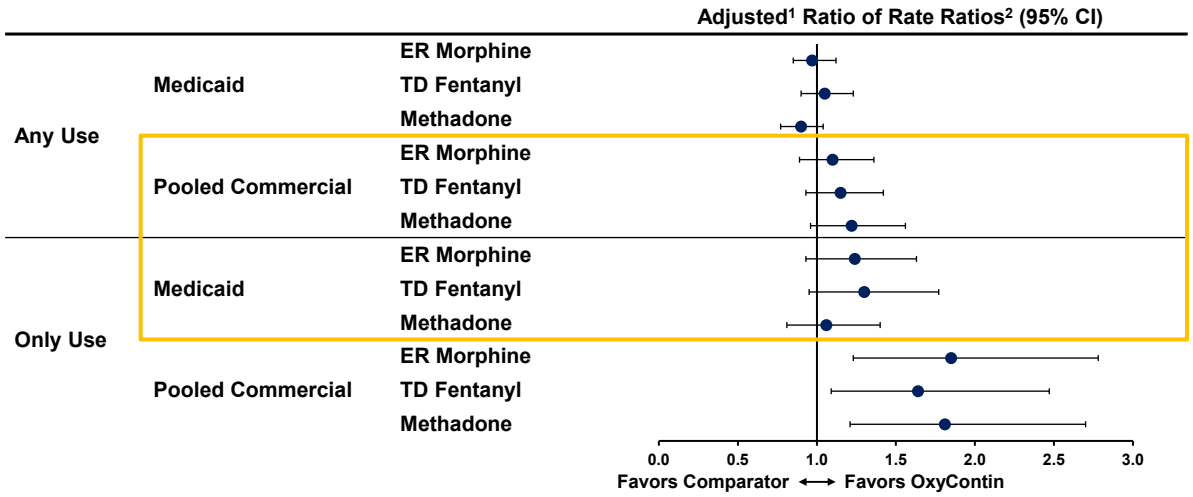
Comparison of Post vs. Pre Reformulation Overdose Rates vs. OxyContin
Insured Populations Study



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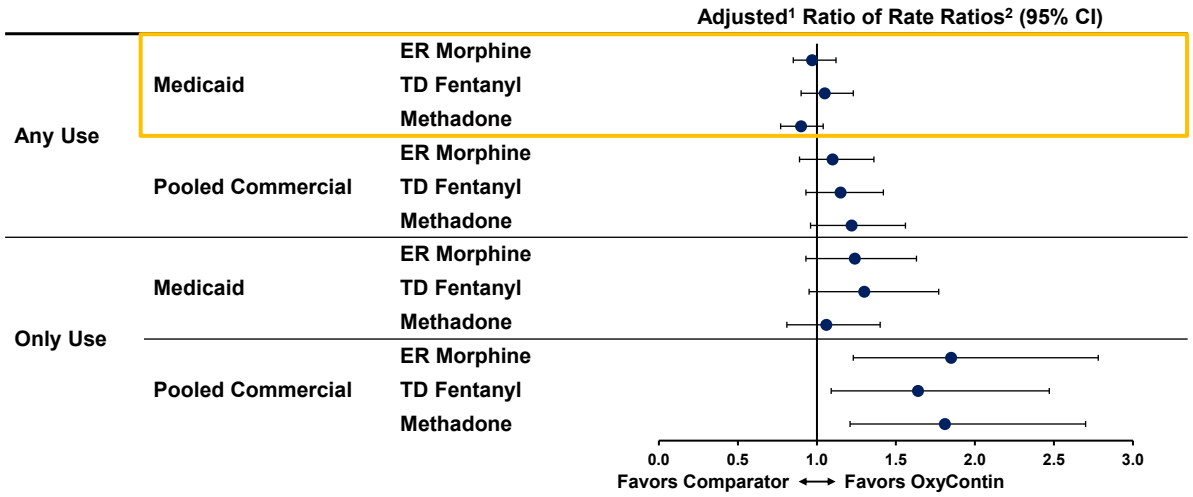
111

Comparison of Post vs. Pre Reformulation Overdose Rates vs. OxyContin
Insured Populations Study



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112

Comparison of Post vs. Pre Reformulation Overdose Rates vs. OxyContin
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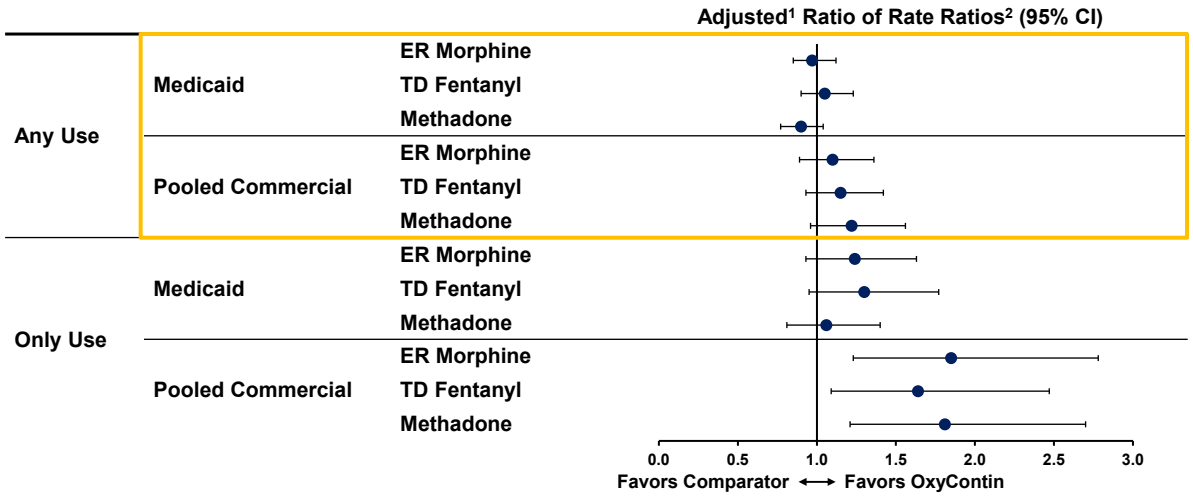

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113

Comparison of Post vs. Pre Reformulation Overdose Rates vs. OxyContin
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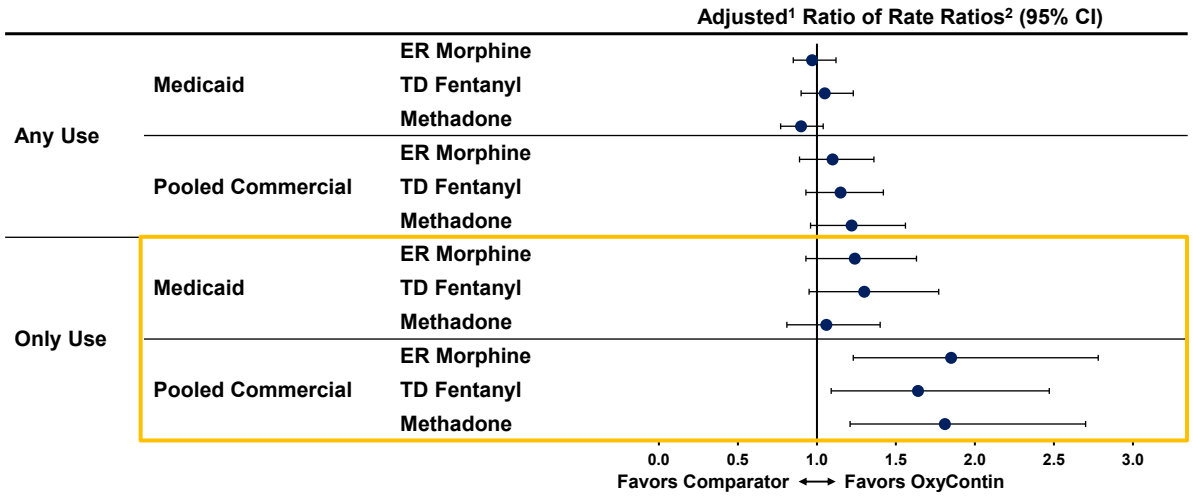

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2. Calculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

CC-114

114

Conclusions
Insured Populations Study

- **No evidence of change in OD with reformulation for individuals under regular medical care**
- **Among persons who received OxyContin alone:**
  - OD rate declined following reformulation
  - Decline was greater for OxyContin than for any comparator

CC-115

115

PMR Studies – Overall Conclusions

- **NAVIPPRO Treatment Centers Study**
  - Step down and continued decline of non-oral OxyContin abuse, more than any comparator
  - Oral abuse not reduced
- **RADARS Treatment Centers Study**
  - Step down and decline greater than some comparators
- **RADARS Poison Centers Study**
  - Step down and decline greater than some comparators
- **Insured Populations Study**
  - No overall increase in OD with reformulation for individuals under regular medical care
  - Suggestive decline in patients receiving OxyContin alone

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Real World Evidence for Opioid Analgesics with Abuse Deterrent Properties

Richard C. Dart, MD, PhD

Richard C. Dart, MD, PhD

Director, Rocky Mountain Poison and Drug Safety
Executive Director, RADARS System
Professor, University of Colorado School of Medicine

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Conflict of Interest Statement

- **History of RADARS System**
  - Acquired from Purdue Pharma in 2006, now independently owned by Denver Health and Hospital Authority
    - Denver Public Hospital for 150 years
    - State sanctioned independent authority
- **Conflict of Interest Statement**
  - Many manufacturers of prescription opioids or stimulants as well as federal agencies subscribe to RADARS System. Purdue Pharma is one of many subscribers. No company has special privileges
  - Subscribers receive information, but do not participate in developing the System, data collection, or analysis of the data. They do not have access to the raw data
  - Employees are prohibited from having personal financial relationships with any company
  - RADARS System is the property of Denver Health and Hospital Authority (DHHA), a political subdivision of the State of Colorado
  - Through my employer, DHHA, I am a consultant for Purdue on the postmarketing epidemiologic studies and preparation for this meeting
  - Denver Health and Hospital Authority has been compensated for my time
  - Consulting agreements for RADARS employees, including myself, are between Purdue and DHHA. DHHA employees fulfill the responsibilities of these contractual relationships through their employer and do not receive direct payment, incentives or other form of compensation from Purdue for their work

CC-118

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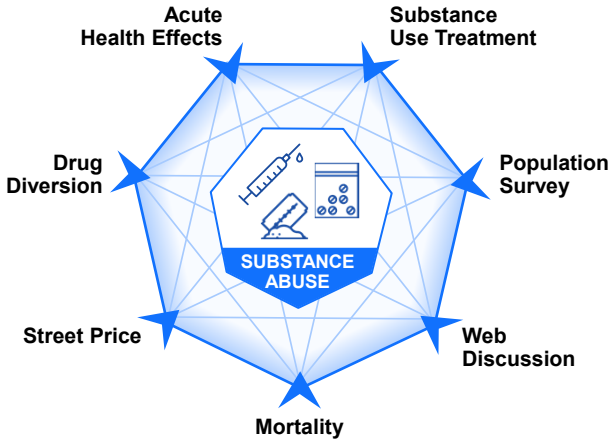
RWE and Triangulation



Lawler DA, et al. Int J Epidemiology, 2016, 1866–1886 doi: 10.1093/ije/dyw314

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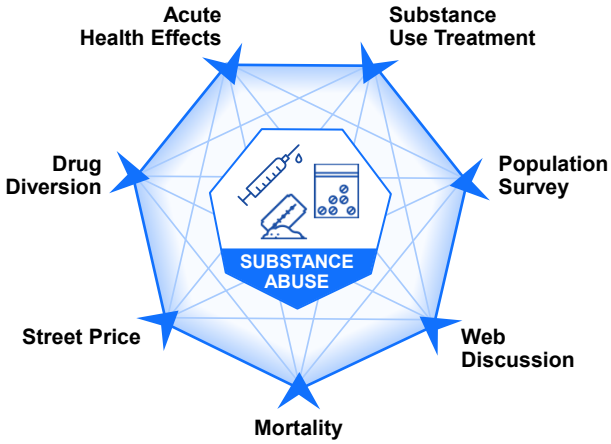
119

RWE and Triangulation

Triangulation
More reliable answers by integrating results from several different approaches, each with different and unrelated key sources of potential bias



Lawlor DA, et al. Int J Epidemiology, 2016, 1866–1886 doi: 10.1093/ije/dyw314

CC-120

120

How Does an Opioid with Abuse Deterrent Properties (ADPs) Work?

- **Can still be abused orally**
- **More difficult, but not impossible to manipulate**
  - Dedicated individuals can still extract part of the drug in tablet
- **While still abusable, the drug becomes less desirable.**

CC-121

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Abuse Deterrent Formulations (ADFs) Can Impact Different Types of Individuals

Use Without Tampering	▪ **Patients need safe and effective treatment for pain** ▪ **ADF minimizes risk of misuse and diversion**

CC-122

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Abuse Deterrent Formulations (ADFs) Can Impact Different Types of Individuals

Use Without Tampering	▪ Patients need safe and effective treatment for pain ▪ ADF minimizes risk of misuse and diversion
Primarily Oral, Occasional Tampering	▪ Novice/ Recreational use, primarily by oral route ▪ ADF decreases risk of manipulation and transition to non-oral use ▪ ADF decreases risk of medical errors

CC-123

123

Abuse Deterrent Formulations (ADFs) Can Impact Different Types of Individuals

Use Without Tampering	▪ Patients need safe and effective treatment for pain ▪ ADF minimizes risk of misuse and diversion
Primarily Oral, Occasional Tampering	▪ Novice/ Recreational use, primarily by oral route ▪ ADF decreases risk of manipulation and transition to non-oral use ▪ ADF decreases risk of medical errors
Regular Tampering and Manipulation	▪ More severe substance use disorders ▪ Polysubstance use and non-oral use common ▪ ADF decreases frequency of risky behaviors

CC-124

124

Did the Introduction of Reformulated OxyContin Result in its Reduced Overall Abuse?

- **Systematic Review**
- **Search Strategy**
  - Opioid analgesics with abuse deterrent properties (hydrocodone, morphine, oxycodone)
  - English language, use in humans, and publication years 2009-2016. Updated April 2020
  - All articles that contained data evaluating misuse, abuse, overdose, addiction, and death
- **Results categorized using Bradford-Hill framework**

Dart RC, et al, Do Abuse Deterrent Formulations Work? *J Opioid Manag*, 2017;13:365-378.
Bradford-Hill AB. The Environment and Disease: Association or Causation? *Proc Royal Soc Med.* 1965;58:295–300.

CC-125

125

Bradford-Hill Evaluation Criteria

Strength (Effect Size)	**The larger the association, the more likely that it is causal**
Consistency (Reproducibility)	**"…consistency of the observed association. Has it been repeatedly observed by different persons, in different places, circumstances and times?"**
Specificity	**A causal relationship is supported if there is a very specific population at a specific site and disease with no other likely explanation.**
Temporality	**The effect has to occur after the cause. If appropriate, the effect must occur after expected delay**
Alternative Explanations	**Plausible confounders should be controlled**
Plausibility	**A plausible mechanism between cause and effect is helpful. Fulfilled by FDA ADF Categories 1-3**
Coherence	**Coherence between epidemiological and laboratory findings increases the likelihood of an effect. Fulfilled by FDA ADF Categories 1-3**
Biological gradient	**Greater exposure should generally lead to greater incidence of the effect**
Experiment	**"… because of an observed Association some preventive action is taken. Does it in fact prevent the effect?"**
Analogy	**The effect of similar factors may be considered**

Bradford-Hill AB. The Environment and Disease: Association or Causation? *Proc Royal Soc Med.* 1965;58:295–300.

CC-126

126

Worldwide Literature on Abuse Deterrent Properties

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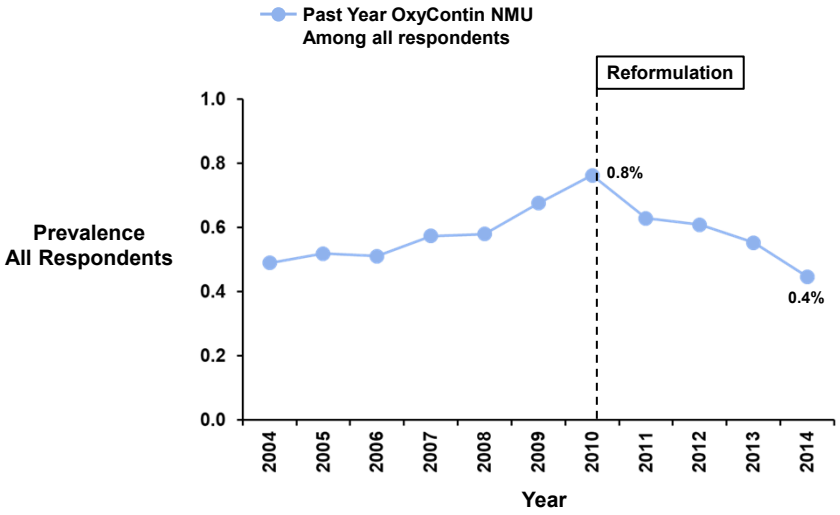
CC-127

127

Past Year Nonmedical Use (NMU) of OxyContin®
National Survey of Drug Use and Health, 2004 – 2014

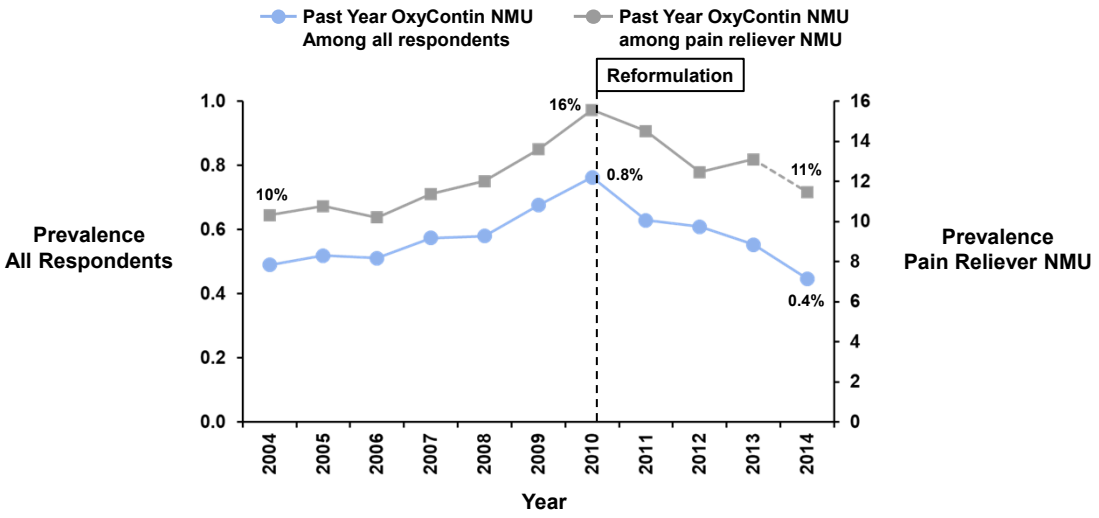


Data from National Survey on Drug Use and Health, 2004-2014.

CC-128

128

Past Year Nonmedical Use (NMU) of OxyContin®
National Survey of Drug Use and Health, 2004 – 2014



Jones C, et al. *Clin J Pain* 2017;33:452–461 [data from 2006-2013]
Data from National Survey on Drug Use and Health, 2004-2014.

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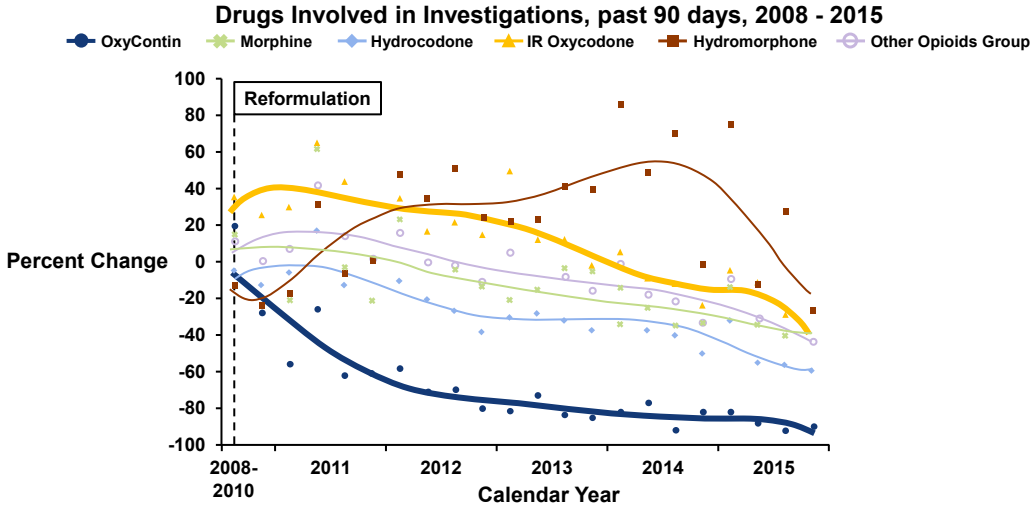
129

Diversion of OxyContin Decreased 70% within 18 Months
RADARS Drug Diversion Program



Data on file, RADARS® System

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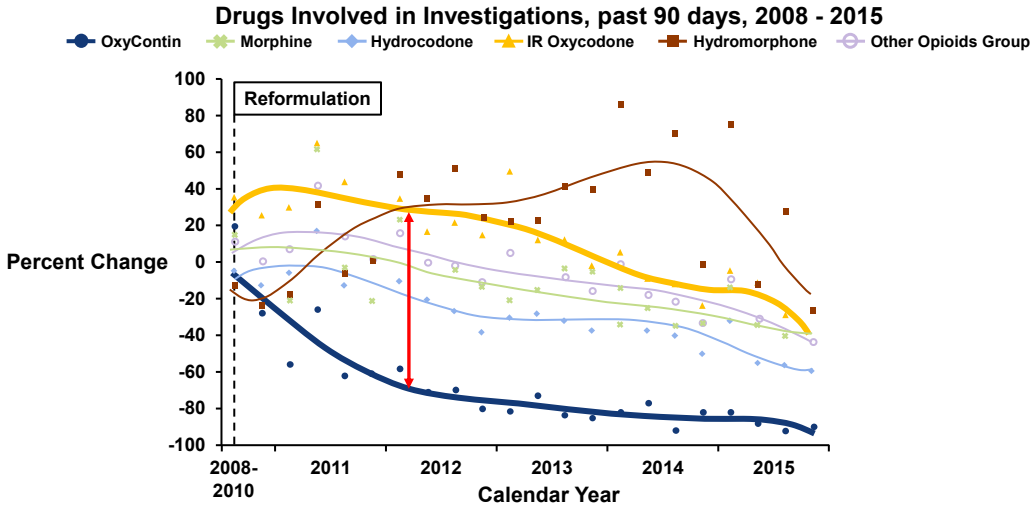
130

Diversion of OxyContin Decreased 70% within 18 Months

RADARS Drug Diversion Program



Data on file, RADARS® System

CC-131

131

Worldwide Literature on Abuse Deterrent Properties

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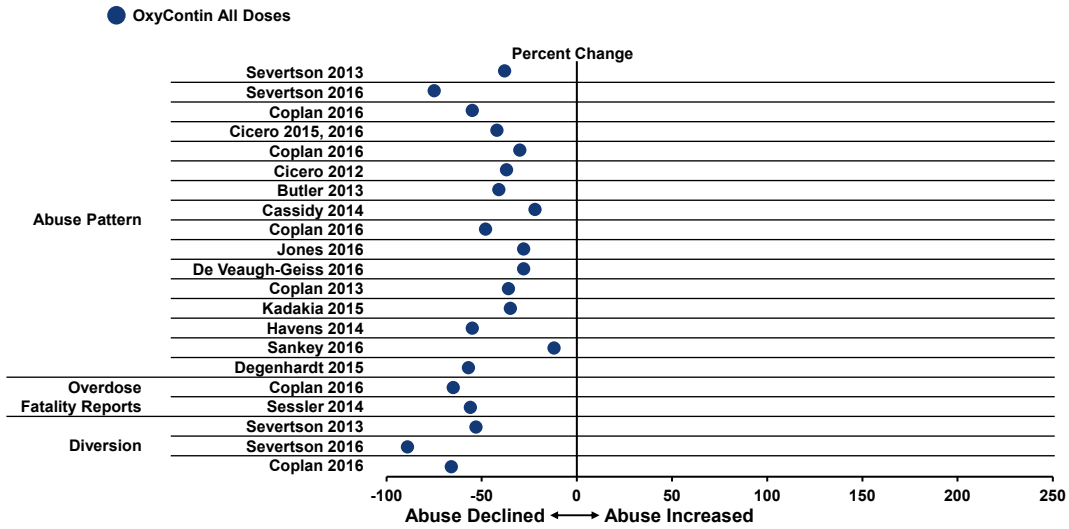
CC-132

132

ICER Assessment of Abuse Deterrent Formulations



Institute for Clinical and Economic Review (ICER). Abuse-Deterrent Formulations of Opioids: Effectiveness and Value. Final Evidence Report. August 8, 2017; graph displays numeric values from Tables 10, 11, and 12.

CC-133

133

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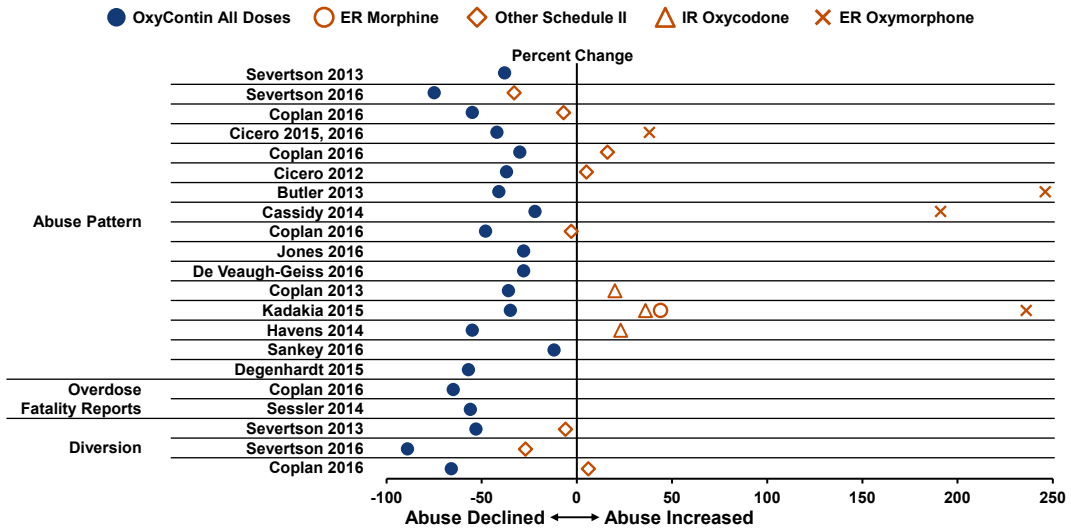
CC-134

134

ICER Assessment of OxyContin ADF



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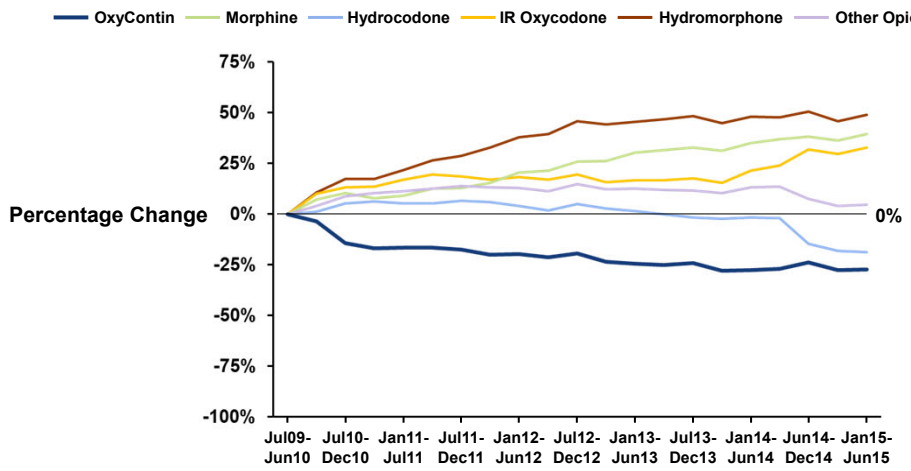
CC-135

135

Reduced Prescriptions Driven by Reduced Demand



Number of opioid analgesic prescriptions dispensed in the United States, April 1, 2009 to June 30, 2015. IMS Government Solutions, Inc., a subsidiary of IMS Health, Inc., Danbury, CT.

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136

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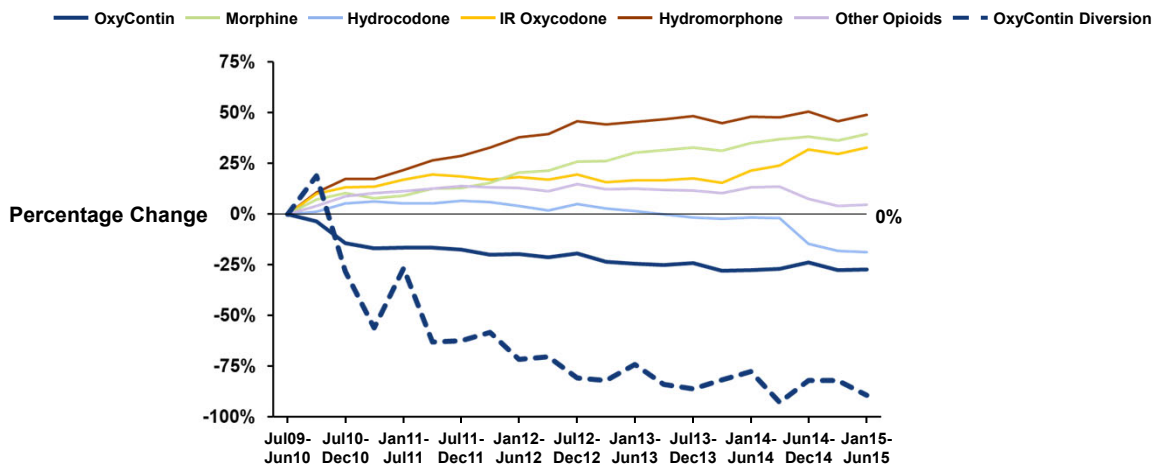

Number of opioid analgesic prescriptions dispensed in the United States, April 1, 2009 to June 30, 2015.
IMS Government Solutions, Inc., a subsidiary of IMS Health, Inc., Danbury, CT.

CC-137

137

Less than Half of People Receiving OxyContin Prescriptions Stayed on OxyContin after Reformulation

- **Prescriptions in PDMP for OxyContin 80 mg among NYC residents**
- **4,098 people filled prescriptions for oxycodone 80 mg in 3 of 4 months immediately prior to reformulation**
- **Post-reformulation (Oct-Dec 2010)**
  - 46% continued on OxyContin 80 mg
  - 40% switched to another Rx opioid
  - 14% discontinued filling opioid analgesic prescriptions
- **Of individuals switching from OxyContin 80 mg, 71% switched to oxycodone immediate release (IR), 30 mg.**

Nolan ML, et al. Reformulation of oxycodone 80 mg to prevent misuse2020 Int J Drug Policy 83 (2020) 102848

CC-138

138

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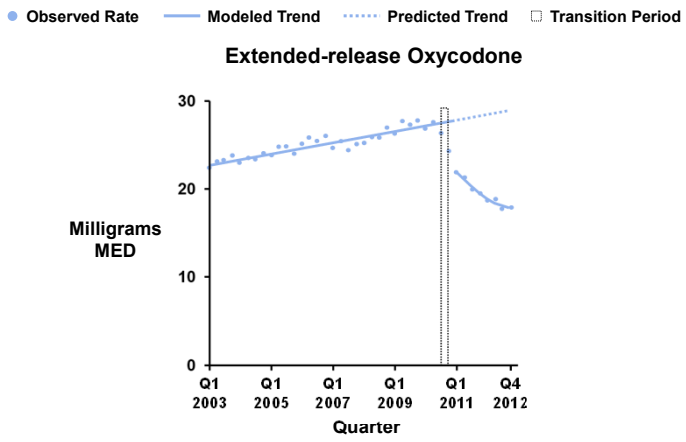
CC-139

139

Prescribing Morphine Equivalents Decreased Disproportionately After Reformulation



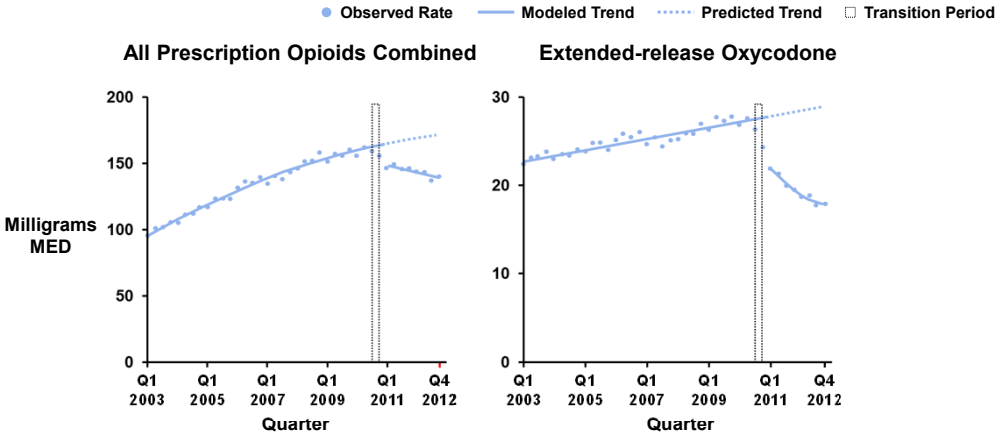
- **Optum dataset: 31 428 338 members of commercial health plans**
- **MED – Morphine equivalent dose per member per quarter**

Larochelle MR, et al. *JAMA Intern Med.* 2015

CC-140

140

Prescribing Morphine Equivalents Decreased Disproportionately After Reformulation



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141

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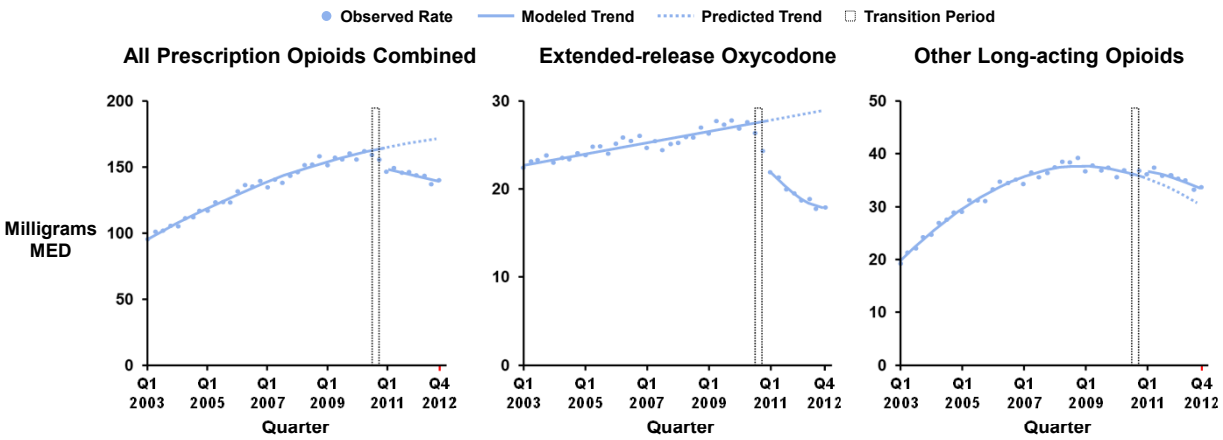

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Larochelle MR, et al. *JAMA Intern Med.* 2015

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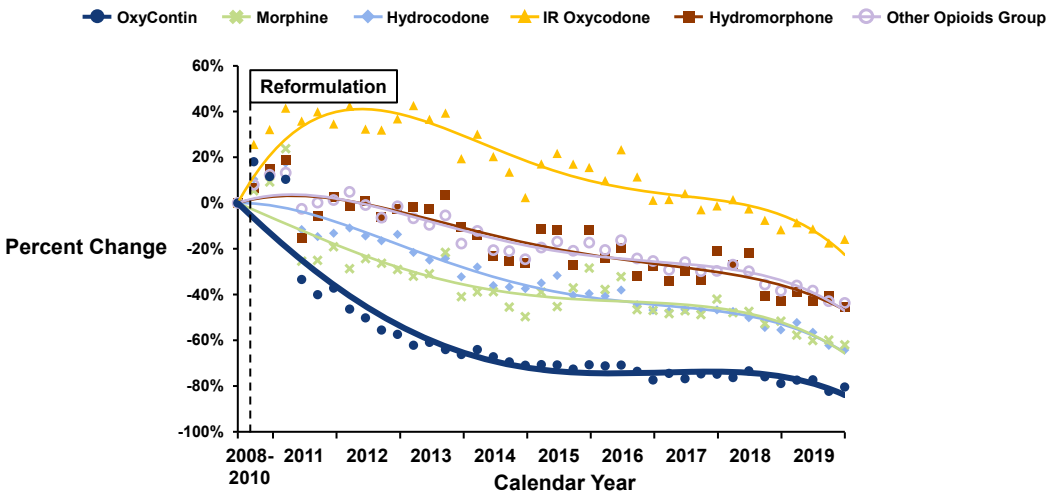
142

OxyContin Fell Sooner and Further than Other Opioids
RADARS Treatment Centers



RADARS System Data on File, 2020

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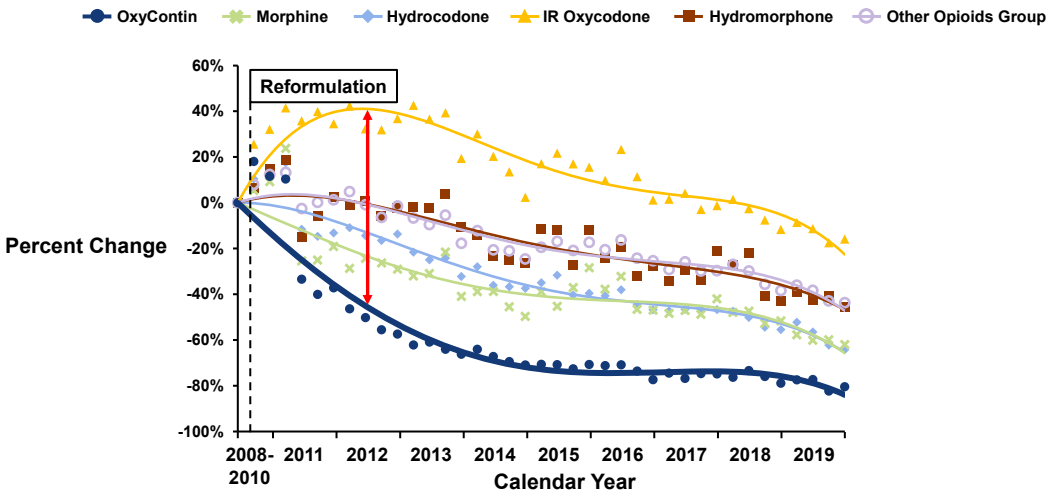
143

OxyContin Fell Sooner and Further than Other Opioids
RADARS Treatment Centers



RADARS System Data on File, 2020

CC-144

144

Worldwide Literature on Abuse Deterrent Properties

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Analogy	The effect of similar factors may be considered

CC-145

145

Do Other (Unmeasured) Factors Explain the Decrease in OxyContin Misuse, Abuse and Diversion?

- **Substantial tightening of controls over access to prescription opioids**
  - PDMP, state medical and pharmacy boards
- **Enhanced law enforcement**
  - Criminal sanctions against doctors
- **Increased public concern over pharmaceutical opioid use**
- **Clinical guidelines for treatment of chronic pain**
- **Others**

CC-146

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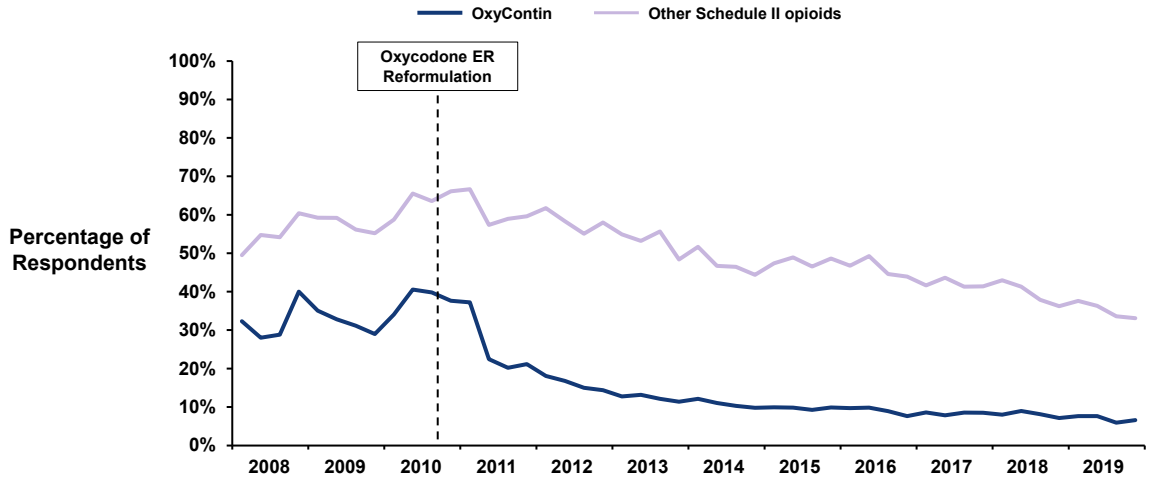
Timeline of Interventions vs. Oxycodone ER, Other Opioids
RADARS Treatment Center Program



Dart RC, et al. *J Opioid Manag* 2017;13(6):365-378.
2016-2019 data on file

CC-147

147

Timeline of Interventions vs. Oxycodone ER, Other Opioids
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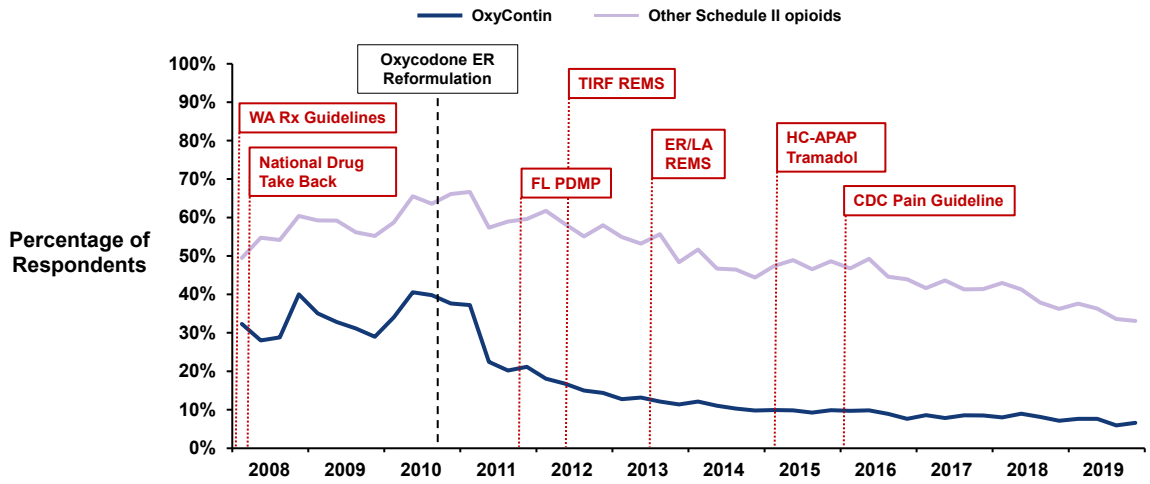

Dart RC, et al. *J Opioid Manag* 2017;13(6):365-378.
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148

Timeline of Interventions vs. Oxycodone ER, Other Opioids
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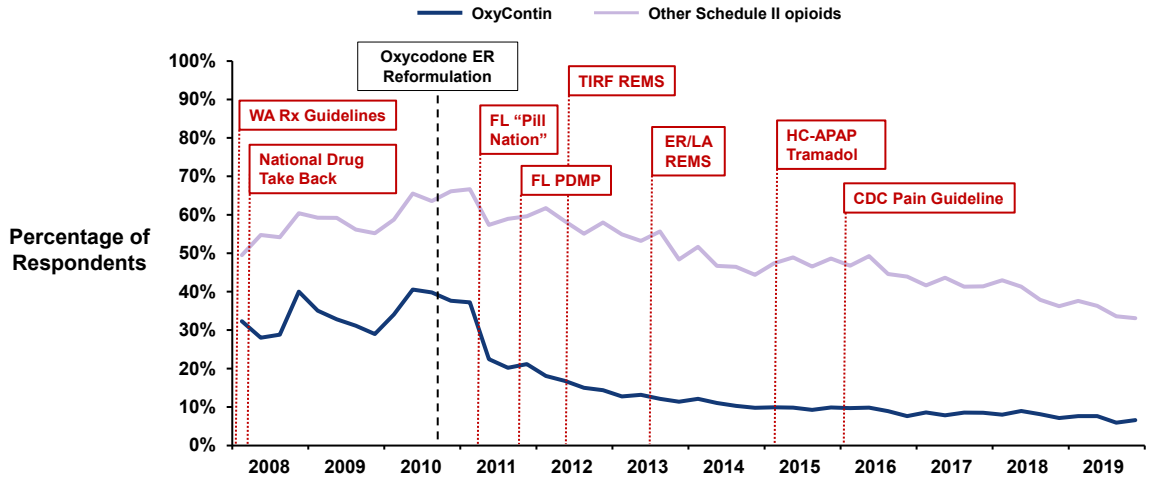

Dart RC, et al. *J Opioid Manag* 2017;13(6):365-378.
2016-2019 data on file

CC-149

149

Effect of Potentially Tamper-resistant Oxycodone Formulation on Opioid use and Harm
Main Findings of the National Opioid Medications Abuse Deterrence (NOMAD) study

- **National Drug and Alcohol Research Centre (NDARC) at the University of New South Wales in Sydney**
- **Abuse deterrent OxyContin introduced in Australia in 2014**
  - The formulations are nearly identical
- **Meta-analysis of 17 Australian data sources**
- **Populations: Total population and sentinel populations**
- **No changes**
  - Regulatory systems for pharmaceutical opioids
  - Opioid prescription guidelines
  - Limits on doctors' prescribing of opioids
  - Monitoring of patient or doctor access to opioids, or
  - Access to medicines via public subsidy

Larance B, et al. Lancet Psychiatry 2017. http://dx.doi.org/10.1016/S2215-0366(18)30003-8
Mundipharma is an independent associated company beneficially owned by the ultimate shareholders of Purdue Pharma L.P.

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Australia – Data consistent across 17 Analyses

Outcomes

- Population-level use
- Extra-medical use of the reformulation and original formulation
- Use of other pharmaceutical opioids and heroin
- Attractiveness of reformulation among people who tamper
- Methods of tampering
- Changes in opioid overdose, and help or treatment-seeking for opioids

Analyses: Z scores, interrupted time-series analysis

- Magnitude of Z score = magnitude of effect
- Positive or negative = direction of effect

Larance B, et al. Lancet Psychiatry 2017. http://dx.doi.org/10.1016/S2215-0366(18)30003-8

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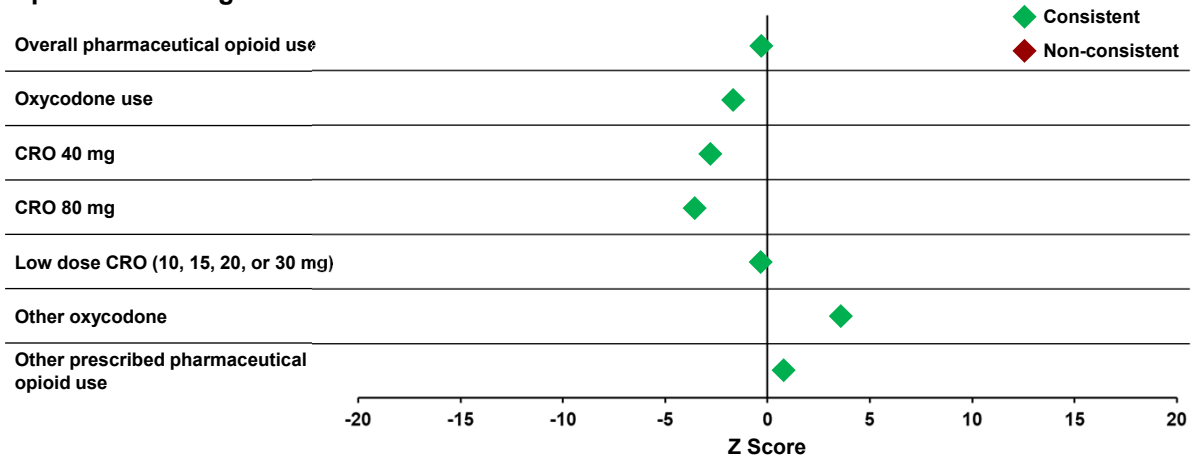
NOMAD: Prescribing for Controlled Release Oxycodone (CRO) Decreased While Other Oxycodone Increased

Question 1: Change in the population-level use of oxycodone and other pharmaceutical opioids following reformulation?



Larance B, et al. Lancet Psychiatry 2017. http://dx.doi.org/10.1016/S2215-0366(18)30003-8

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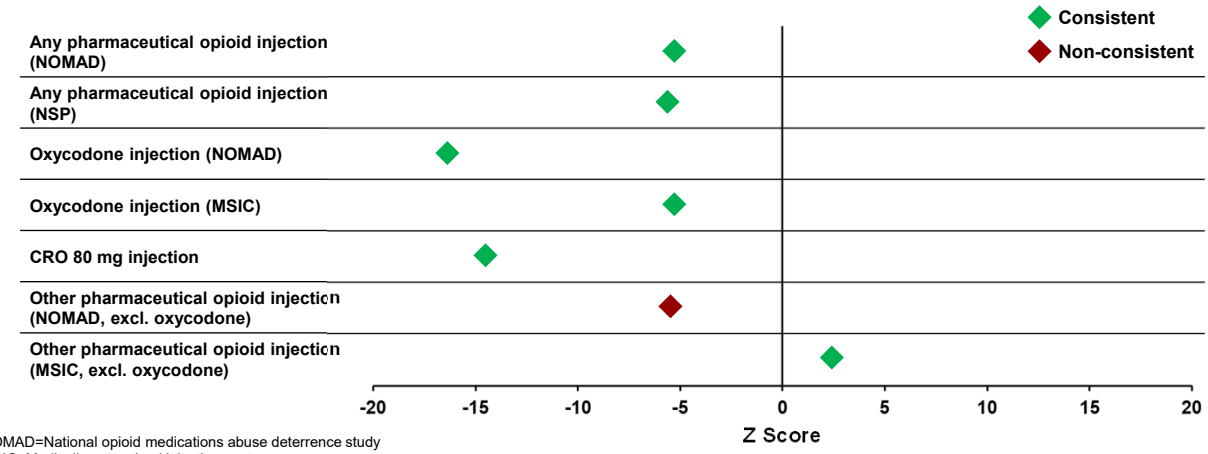
NOMAD: Extramedical Use of Rx Opioids Decreased

Question 2. Was there a reduction in the extra-medical use of the reformulation?
Question 3. Was there an impact on the extra-medical use of non-tamper resistant oxycodone formulations?



NOMAD=National opioid medications abuse deterrence study
MSIC=Medically supervised injection center
NSP=Needle and syringe program

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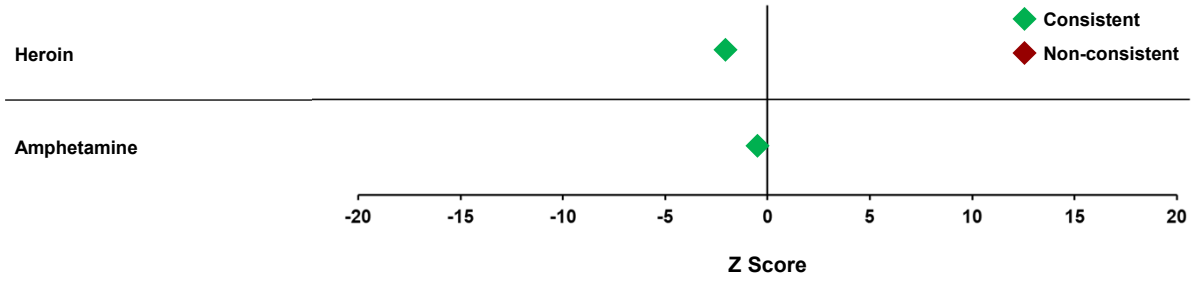
NOMAD: Heroin and Amphetamine were Unchanged

Question 4. Was there an impact on the use of other pharmaceutical opioids and heroin?



Larance B, et al. Lancet Psychiatry 2017. http://dx.doi.org/10.1016/S2215-0366(18)30003-8

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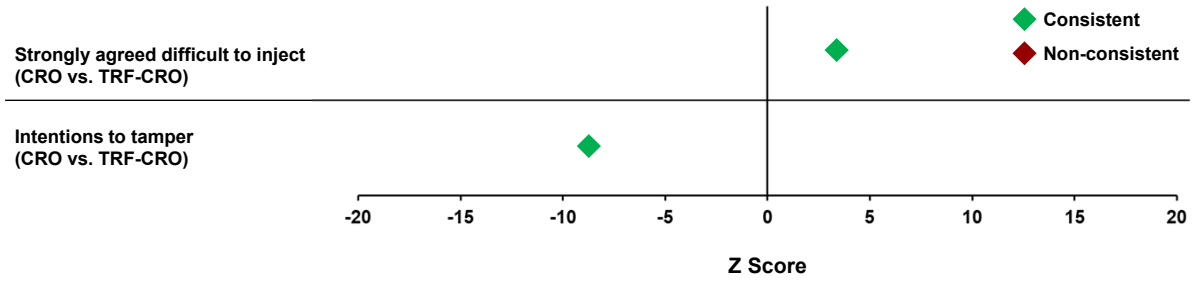
Attractiveness of CRO for Extra-medical Use

Question 5: Was the reformulation less attractive among people who tamper with pharmaceutical opioids?



TRF-CRO=Tamper resistant formulation-controlled release oxycodone

Larance B, et al. Lancet Psychiatry 2017. http://dx.doi.org/10.1016/S2215-0366(18)30003-8

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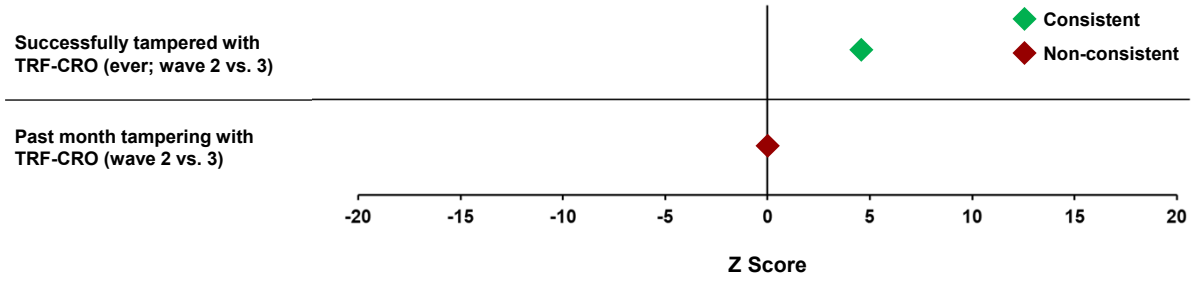
Evolution and Spread of Tampering Methods

Question 6: Did methods of tampering of tamper-resistant formulation of OxyContin evolve and become widespread?



Larance B, et al. Lancet Psychiatry 2017. http://dx.doi.org/10.1016/S2215-0366(18)30003-8

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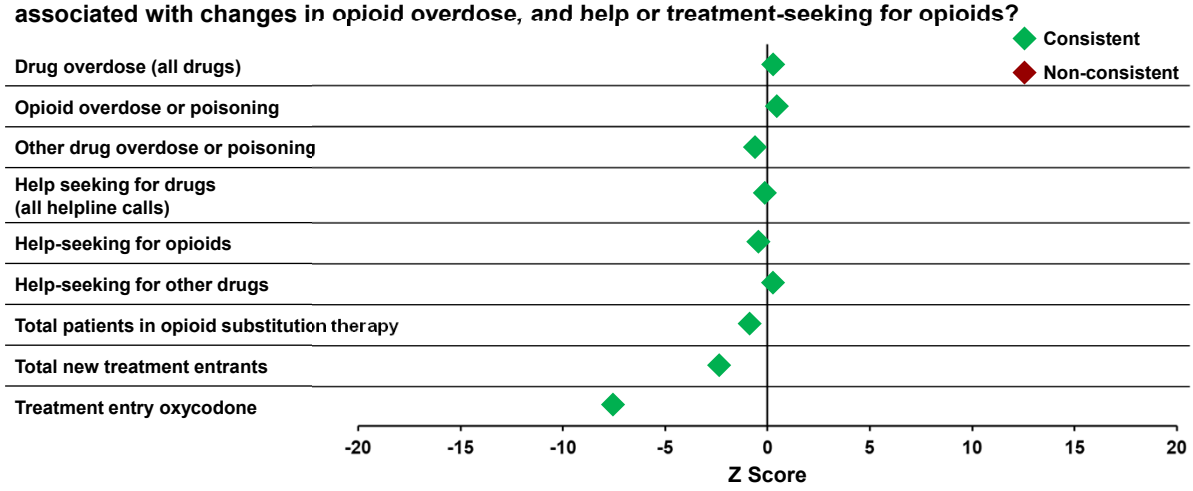
Adverse Consequences did not Appear to Increase

Question 7: Was the introduction of tamper-resistant formulation of controlled-release oxycodone associated with changes in opioid overdose, and help or treatment-seeking for opioids?



Larance B, et al. Lancet Psychiatry 2017. http://dx.doi.org/10.1016/S2215-0366(18)30003-8

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Summary

- **Information from a wide variety of sources shows that misuse, abuse and diversion of OxyContin decreased after reformulation**
- **Confounding is the biggest threat to concluding that the reformulation caused the improvements**
- **The use of triangulation shows remarkable consistency among a wide variety of studies**
- **A compelling alternate explanation has not been identified**

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The Benefits of Opioids with Abuse Deterrent Properties

Group	Group Size	Estimated Effect Size
Regular Manipulation Opioid Use Disorder	Small	Large
Occasional Misuse/Abuse Recreational abuse with occasional crushing Crushing for therapeutic use Crushing for other use	Large	Large
Use Without Tampering People with chronic pain	Very Large	Moderate (Large for vulnerable sub-populations)

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Closing Remarks

Craig Landau, M.D.

Craig Landau, MD

President & Chief Executive Officer
Purdue Pharma L.P.

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Summary of the Impact of Reformulated OxyContin

- **Laboratory and clinical studies predicted reductions in certain routes of OxyContin abuse**
- **PMR studies and published literature demonstrate impact**
  - Predicted effects were realized in the real world
  - Reductions in abuse by non-oral routes
- **Reducing non-oral abuse provides significant public health benefits**
  - While all abuse carries serious health risks, snorting and injection heighten those risks and carry additional ones

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Reformulated OxyContin Is a Meaningful Incremental Improvement

- **While reformulated OxyContin reduced abuse by certain routes, it was not expected to reduce abuse of other opioids**
  - For instance, those with severe opioid use disorder who were crushing and injecting the original tablet were not expected to cease abusing all drugs simply because Purdue reformulated OxyContin
- **The full potential public benefits of ADFs are unknown**
  - Given the small market share of ADFs, the public health benefits of converting a substantial portion of the market are not known at this time
- **Reformulated OxyContin provides an important incremental improvement over the original formulation**

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Available to Respond to Questions

Name	Affiliation	Subject Matter Expertise
Richard Fanelli, PhD	Purdue Pharma L.P.	Sponsor
Jennifer Giordano	Purdue Pharma L.P.	Sponsor
Alexander M. Walker, MD, DrPH	World Health Information Science Consultants	PMR Study Results Insured Populations Study
Richard C. Dart, MD, PhD	Rocky Mountain Poison and Drug Safety RADARS System	Real World Evidence RADARS Program (Treatment Centers & Poison Centers Studies)
Jody Green, PhD	Inflexxion/Integrated Behavioral Health (IBH)	NAVIPPRO Treatment Centers Study
Dan Beachler, PhD, MHS	HealthCore	Insured Populations Study
Janetta Iwanicki, MD	Rocky Mountain Poison and Drug Safety RADARS System	RADARS Program Thrombotic Microangiopathy
Richard Mannion, PhD	Mannion Consulting, LLC	Abuse deterrent formulations
Garth Whiteside, PhD	Purdue Pharma L.P.	Non-clinical/ Animal Studies
F. Michael Ferrante, MD	University of California, Los Angeles	Clinical perspective

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Sponsor Backup Slides Shown

Joint Meeting of the Drug Safety and Risk Management and Anesthetic and Analgesic Drug Products Advisory Committees

September 10-11, 2020

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Covariates Appropriately and Consistently Capture Risk of OD During Treatment Episodes

	HIRD	MarketScan	Medicaid
Characteristic	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
High added risk			
Prior overdose	29.3 (20.4, 42.0)	19.0 (14.8, 24.5)	14.6 (13.2, 16.2)
Modest added risk			
Stroke	1.5 (1.1, 2.2)	1.3 (1.0, 1.7)	1.3 (1.1, 1.5)
COPD	1.5 (1.3, 1.8)	1.3 (1.1, 1.5)	1.3 (1.3, 1.4)
Impaired respiratory function	1.4 (1.2, 1.8)	1.6 (1.4, 1.9)	1.5 (1.4, 1.6)
Chronic pain	1.5 (1.3, 1.7)	1.5 (1.3, 1.7)	1.4 (1.3, 1.4)
Diminished risk			
Malignancy	0.6 (0.4, 0.9)	0.7 (0.5, 0.8)	0.7 (0.7, 0.8)

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Age Ranges for PMR Studies 3051-1, -2 and -3

	NAVIPPRO Treatment Centers Study	RADARS Treatment Centers Study	RADARS Poison Centers Study
Abuse Cases	18 to 70 years	18 to >80 years	6 to >80 years

For primary analyses

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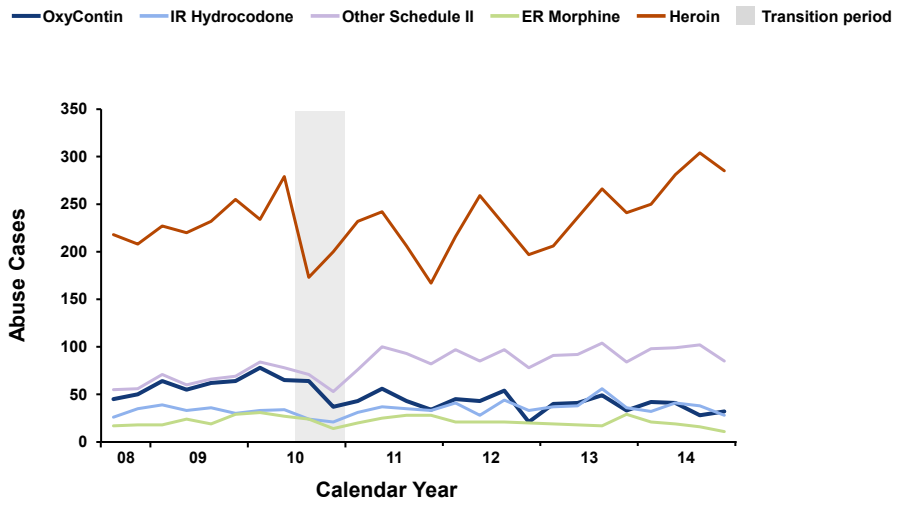
Non-oral Abuse Cases
NAVIPPRO Treatment Centers Study



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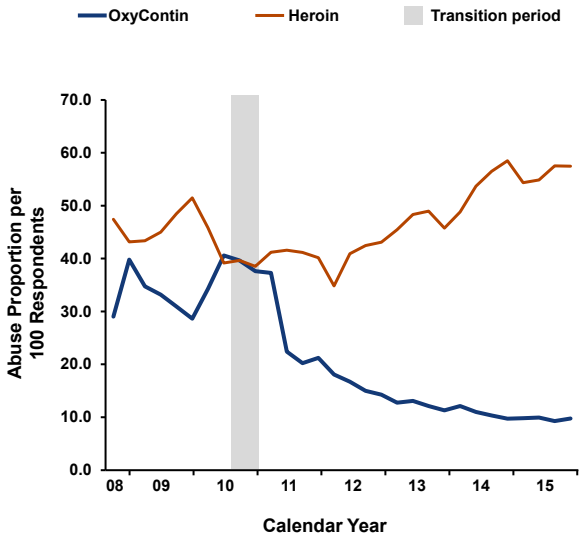
Heroin and OxyContin – Proportion
RADARS Treatment Centers Study



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Literature on Heroin Trends after Reformulation

Author, Year	Title	Main Findings	Major Limitations
Alpert, 2018	Supply-side drug policy in the presence of substitutes	• Heroin mortality increased most in states with high pre-reformulation OxyContin misuse	• No mortality data examined beyond 2013 • No comparators beyond heroin
Evans, 2019	How the reformulation of OxyContin ignited the heroin epidemic	• Heroin mortality increases larger in states with higher pre-reformulation oxycodone shipments	• Oxycodone shipments may not approximate OxyContin availability
Powell, 2020	The evolving consequences of OxyContin reformulation on drug overdoses	• Mortality from heroin, synthetic opioids, and cocaine increased more in states with higher pre-reformulation OxyContin NMU	• Does not account for pre-reformulation rates of cocaine, heroin, or synthetic mortality by state
Beheshti, 2019	Adverse health effects of abuse-deterrent opioids	• Hepatitis B and C increased most in states with high pre-reformulation OxyContin misuse	• No comparators • Limited adjustment for confounders
Powell, 2019	A transitioning epidemic: How the opioid crisis is driving the rise in hepatitis C	• Hepatitis C increased most in states with higher pre-reformulation OxyContin misuse	• No comparators • Limited adjustment for confounders

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The Impact of the Abuse-Deterrent Formulation of Extended-Release OxyContin on Prescription Pain Reliever Misuse and Heroin Initiation

- **Investigators from FDA, DHHS, AHRQ, CBO and academic institutions**
- **US National Survey of Drug Use and Health (NSDUH), 2005-2014**
- **Populations**
  - Exposed: Misused OxyContin prior to reformulation
  - Unexposed: Misused other prescription opioids prior to reformulation
- **Measures**
  - Past Year: Heroin Use, Use Disorder, and Initiation

Wolff C, et al. Addictive Behaviors 2019 https://doi.org/10.1016/j.addbeh.2019.106268

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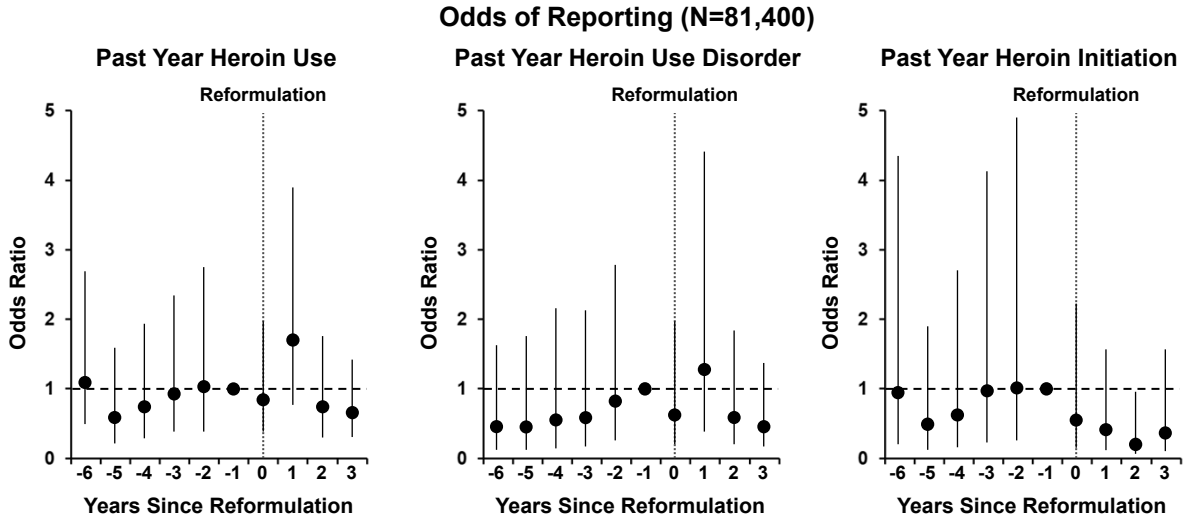
Heroin Use, Disorder and Initiation, Exposed vs. Unexposed Groups After OxyContin Reformulation



Wolff C, et al. Addictive Behaviors 2019 https://doi.org/10.1016/j.addbeh.2019.106268

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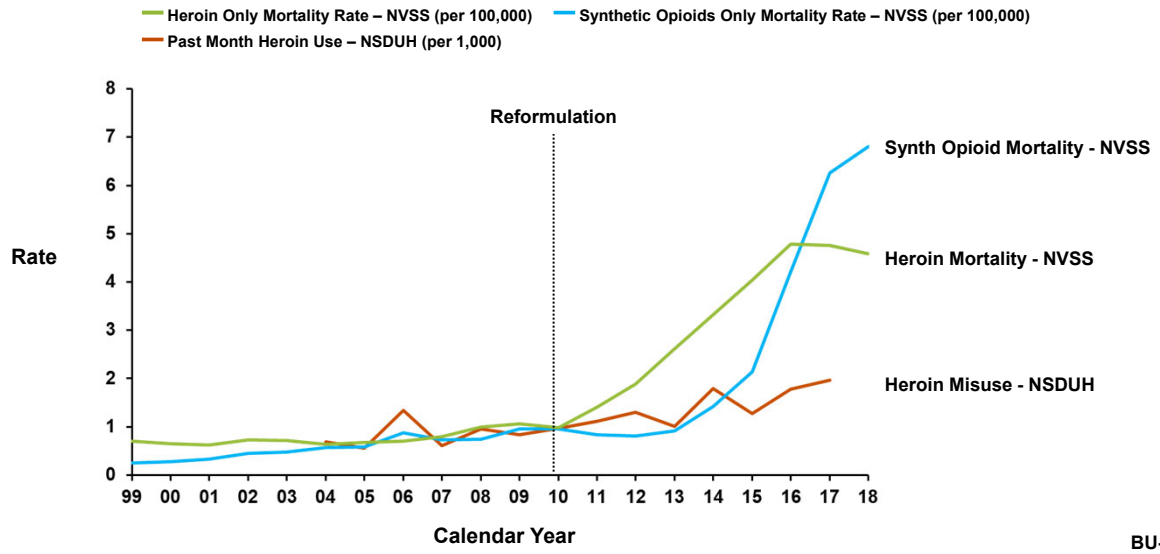
Heroin Use, Mortality and Synthetic Opioid Mortality



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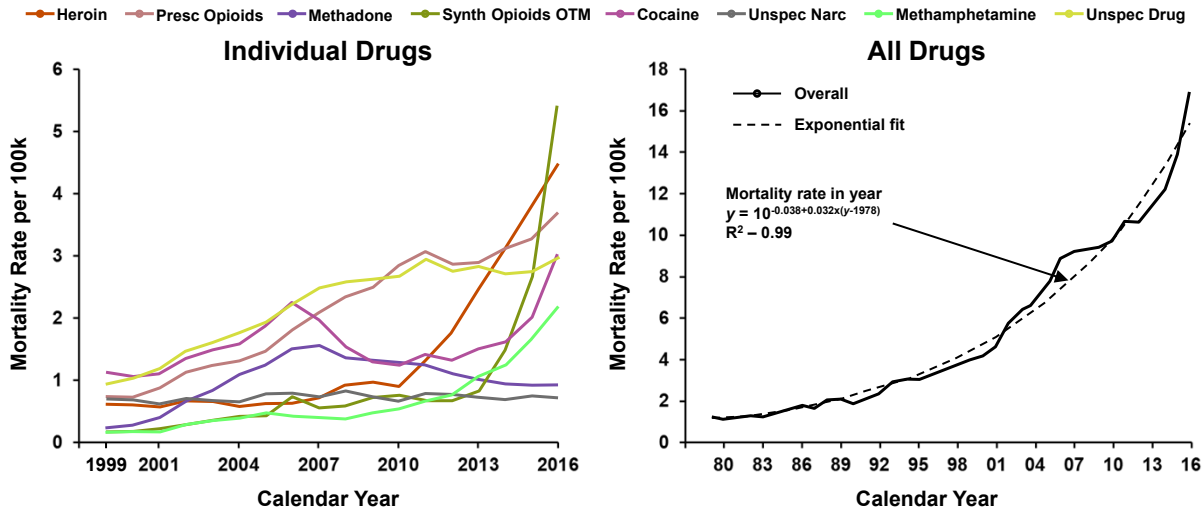
Drug-Induced Mortality in US



Jalal, et al. *Science* 21 Sep 2018: Vol. 361, eaau1184 DOI: 10.1126/science.aau1184

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