Literature Review: Impact of Reformulated OxyContin on Abuse and Opioid-related Morbidity and Mortality

DSaRM/AADPAC Joint Meeting
September 10 – 11, 2020

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Background

- PMR studies 3051-1 through 3051-4 designed to assess the impact of the OxyContin reformulation on OxyContin abuse and risk of opioid overdose
- Division of Epidemiology (DEPI) II evaluated studies from the peer-reviewed and selected grey literature examining the impact of reformulated OxyContin on its use, nonmedical use and opioid-related morbidity and mortality

Objectives

- To supplement and contextualize PMR studies
- Improve understanding of broader public health impact of OxyContin's reformulation

Outline

1. Methods
2. Results
   a. Dispensing
   b. Nonmedical Use and Other Measures of Abuse
   c. Non-oral Abuse and Opioid Addiction
   d. Substitution of Other Substances
   e. Opioid Overdose
   f. Other Abuse-related Harms
3. Summary and FDA Interpretation of the Literature

Methods

- PubMed search of original research articles
  - Focused on Abuse-Deterrent Formulation (ADF) OxyContin
  - Quantitative and qualitative studies
- Examined impact of **reformulation** on **opioid use, misuse, abuse, morbidity,** and **mortality**
- Original studies from peer-reviewed journals and selected grey literature (46 articles)
  - PMR-related studies (15)*
  - **Non-PMR related studies** (31)**
- Review articles and editorials reviewed for any additional data not included in the above (32)

*6 studies funded by Purdue or Purdue-affiliated pharmaceutical company
**15 studies funded by Purdue or Purdue-affiliated pharmaceutical company

DISPENSING

Impact on Dispensing

- Consistent with FDA Drug Utilization analyses
  - Prescription sales of OxyContin declined after reformulation
  - Contemporaneous exit of generic Extended Release (ER) oxycodone in U.S. led to sharp decline in ER oxycodone prescriptions[1]
  - Decrease in average milligrams dispensed for OxyContin prescriptions[2]

Sources: [1]Hwang (2015),[2] Nolan(2020)

Impact on Dispensing Among Patients Prescribed Original ER Oxycodone

Opioid utilization patterns following the introduction* of reformulated ER oxycodone in retrospective study of commercial claims, U.S., 2010-2011

A. Following the introduction of reformulated ER oxycodone

Primary drug post-reformulation of ER oxycodone	ER oxycodone patients (*N* = 15,162)	
	N	%
Reformulated ER oxycodone	10,520	69.4
Other ER/LA opioid without abuse-deterrent technology	3230	21.3
No ER/LA opioids	1412	9.3
IR/SA opioids	1073	7.1
No IR/SA or ER/LA opioids	339	2.2

***Note**: Pre-reformulation period: February-August 2010

Post-reformulation: November 2010- May 2011

Sources: Michna (2014)

Impact on Dispensing Among Patients Prescribed OxyContin

- Analysis of New York City Prescription Drug Monitoring Program (PDMP)

- After introduction of ADF OxyContin (2010):
  - 46% continued oxycodone ER 80mg
  - 40% switched opioid analgesic
  - 14% discontinued

- Before introduction of ADF OxyContin (2009):
  - 85% continued oxycodone ER 80mg
  - 5% switched opioid analgesic
  - 10% discontinued

- Over 70% of those who switched to another opioid analgesic received oxycodone IR 30mg
- Median daily Morphine Milligram Equivalents (MME) decreased after ADF in both those who continued oxycodone ER and who switched opioid analgesics

Sources: Nolan(2020)

Possible Reasons for Switching or Discontinuation

- Several studies noted reasons unrelated to abuse for switching or discontinuation of OxyContin following reformulation
  - Providers reported patient complaints of difficulty swallowing reformulated OxyContin[1]
    - Difficulty swallowing consistent with postmarketing reports that resulted in safety labeling change (OxyContin label 2015)
  - Physicians may be less likely to prescribe OxyContin after ADF[2]
    - Possibly due to emphasis on **abuse** in label
  - Concern about the cost and insurance coverage of ADFs[3,4,5]
    - Unable to assess changes in formulary coverage in U.S. due to changing private and public insurance coverage

Sources: [1]Argoff (2013), [2]Cicero (2015a), [3]Med Lett Drugs Ther (2017), [4]Twillman (2014), [5]Singer (2018)

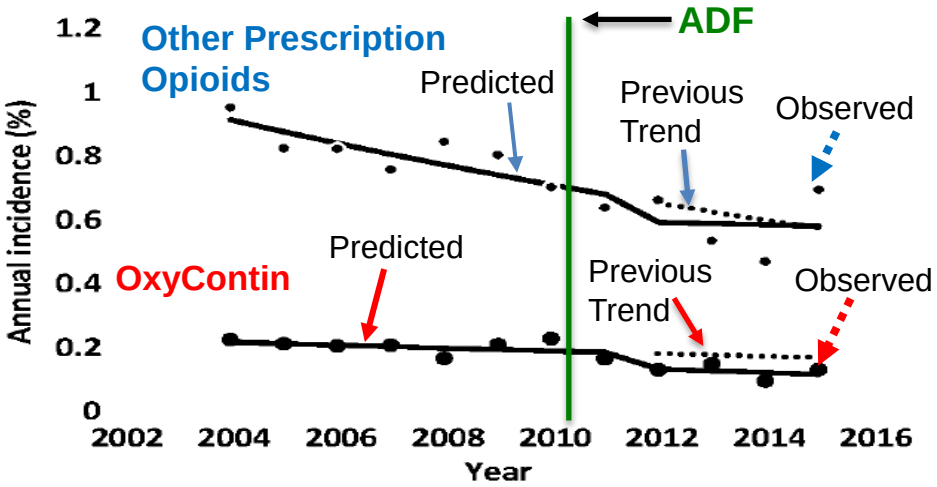
NONMEDICAL USE, STREET PRICE, DIVERSION, AND DOCTOR SHOPPING

Impact on Nonmedical Use (NMU) in the General Population

- Examined changes in OxyContin nonmedical use (NMU) in the general population using National Survey on Drug Use and Health (NSDUH)
- Cheng (2018) found modest decline in past year NMU of OxyContin after reformulation *(see figure)*
  - Post-reformulation OxyContin NMU rate lower than previous trend
  - Rate of NMU of other prescription opioids closer to levels predicted by previous trend, but wide variability in annual estimates

Source: Cheng (2018)

Past-year Initiation of OxyContin and other Prescription Opioid (PPR)* Nonmedical use based on Observed and Predicted Estimates, U.S., NSDUH, 2002-2016



*Other prescription opioid (PPR) include: Darvocet, Darvon, Tylenol with codeine, Demerol, Dilaudid, Fioricet, Fiorinal, Hydrocodone, Methodone, Morphine, Phenaphen, Propoxyphene, SK65, Stadol, Talacen, Talwin, Talwin-nX, Tramadol, Ultram

Source: Cheng (2018)

Impact on NMU in the General Population

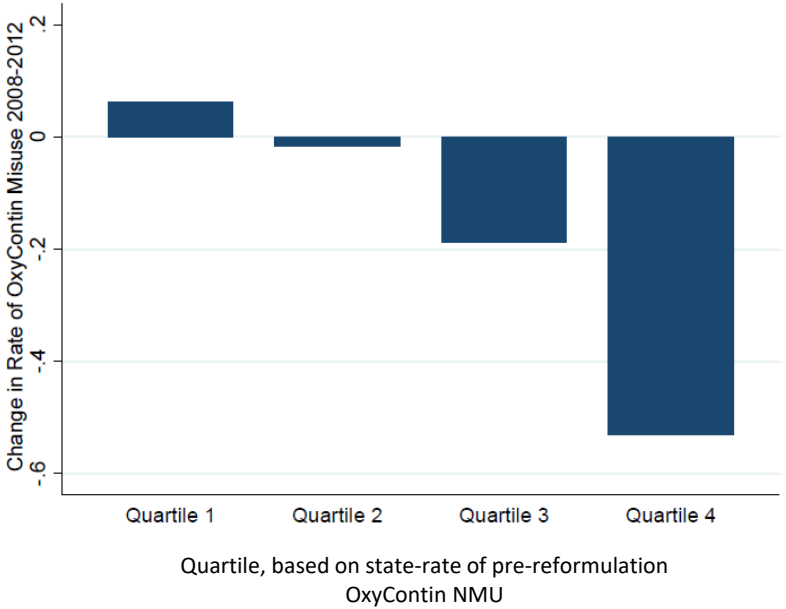
- Another study also examined impact of OxyContin ADF using NSDUH
- Jones (2017) found that reformulation was associated with declines in prevalence of OxyContin NMU[1]
  - Prevalence of NMU declined from 2010 (0.7%) to 2013 (0.5%; $p<0.05$)
    - Decline in annual OxyContin NMU not significant until 2013
  - Post-reformulation (2013) rates similar to 2006-2009 rates
- Neither Cheng (2018) nor Jones (2017) studies adjusted for reductions in prescription dispensing[1,2]

Sources:[1]Jones (2017), [2]Cheng (2018)

Impact on NMU in the General Population

- States with higher pre-reformulation rates of NMU of OxyContin experienced declines in post-reformulation nonmedical use
  - States with lower pre-existing rates experienced increases in nonmedical OxyContin use

Relationship between pre-reformulation prevalence of OxyContin NMU and change in OxyContin NMU after reformulation, U.S., NSDUH, 2008-2012



Source: Alpert (2018)

Source: Figure adapted from Alpert (2018)

Impact on Street Price

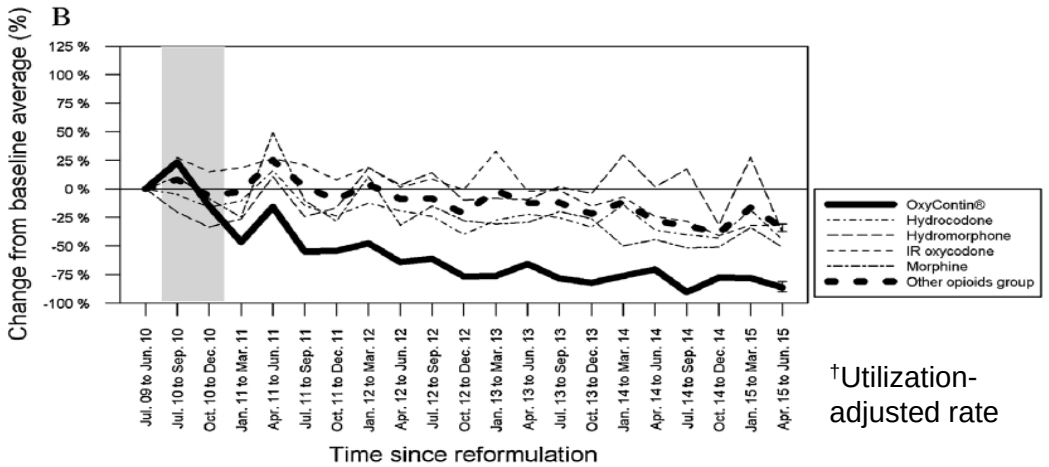
- Price per milligram of non-ADF oxycodone 19% higher than ADF oxycodone[1]
  - Prices compared for drugs reported between August 2014 - June 2016
- Difference in street price between original and ADF OxyContin decreased in first five years after reformulation[2]
  - Original OxyContin 36% higher in 2011, 13% higher in 2015
  - Prices not compared to OxyContin prior to August 2010
- Prices collected from anonymous crowdsourcing website, StreetRx
  - Reported street prices are not independently verified
- Participants in qualitative interviews reported that ADF OxyContin was cheaper because of difficulty manipulating product for abuse[3]

Sources: [1]Lebin (2019), [2]Severtson (2016),[3]Buer (2014)

Impact on Drug Diversion

- Severtson (2016) examined drug diversion based on recorded drugs in law enforcement cases
- OxyContin diversion cases declined more than other prescription opioids after reformulation*
  - Based on cases arising from arrests or street buys
  - Findings on drug diversion indicator of law enforcement activity

Relative Change in Rate† of Diversion Cases for OxyContin and Other Opioids, Drug Diversion Program, 2009-2015**



†Utilization-adjusted rate

**Other Opioid group is comprised of IR oxycodone, IR and ER hydrocodone, IR and ER morphine, IR and ER hydromorphone, IR and ER tramadol, IR and ER oxymorphone, and IR and ER tapentadol

* Based on utilization adjusted rates

Source: Severtson , 2016

Impact on Doctor Shopping

- Examined rates of “doctor shopping” using pharmacy claims
  - Overlapping prescriptions based on days supply from 2+ prescribers and 3+ pharmacies
- Rate of “doctor shopping” decreased 50% for OxyContin, but a similar decline was not observed for comparators*
- Not necessarily a measure of abuse
  - Unable to ascribe motive for seeking medications from multiple prescribers/pharmacies
  - “Doctor shopping” metric not well characterized as a measure of abuse

*IR hydromorphone, IR oxycodone APAP, IR hydrocodone APAP, benzodiazepines, ER Morphine, IR oxycodone SE, ER oxymorphone

Source: Chilcoat, 2016

NON-ORAL ABUSE AND OPIOID ADDICTION

Impact on Non-oral OxyContin Abuse

- Studies describe decreases in non-oral OxyContin abuse in two populations with high prevalence of non-oral opioid abuse[1,2]
- Both studies relied on retrospective report of past abuse behaviors[1,2]
  - Havens (2014): Serial cross-sectional interviews about recent abuse of oxycodone formulations in individuals who had abused original OxyContin[1]
    - Past-month snorting and injecting of OxyContin decreased after ADF
  - Cicero (2015): Survey of individuals entering treatment for OUD who reported abusing both original and ADF OxyContin[2]
    - 43% switched from non-oral (injecting/inhaling) to oral abuse of the product

Sources: [1]Havens (2014), [2]Cicero (2015b)

Impact on Non-oral OxyContin Abuse

- Larance (2018): Australian NOMAD study
  - Prospective cohort study examined impact of reformulation in individuals who tamper with prescription opioids
    - Three-months pre-reformulation 55% reported past-month non-ADF 80mg OxyContin injection
    - One-year after reformulation 2% reported past-month ADF 80mg OxyContin injection
    - Reported past-month injection of other drugs also declined to a lesser extent
  - Safe injection site data showed decline in number of visits to inject OxyContin after reformulation
- No information on reformulation deterring **initiation** of non-oral abuse of OxyContin

Source: Larance (2018)

Impact on Opioid Addiction

- Wolff (2020) used serial **cross-sectional** NSDUH data to compare multiple outcomes in individuals who misused OxyContin prior to the ADF to those who misused other pain relievers
  - Difference-in-differences design
  - Pre-reformulation OxyContin misuse was not associated with change in prescription pain reliever use disorder prevalence after ADF
- Methodological limitations
  - No longitudinal follow-up, different participants surveyed each year
  - Potential systematic bias
    - Variable interval between exposure (time of reformulation) and outcome measurement
    - Possible underrepresentation of individuals who used original OxyContin nonmedically and developed serious outcomes

Source: Wolff (2020)

Impact on Opioid Addiction

- Michna (2014) found higher rates of insurance claims coded as **opioid abuse** in patients who switched or discontinued treatment of reformulated ER oxycodone[1]
  - Highest rates of opioid abuse in those who switched to IR/SA opioids
  - Did not capture cash purchases or claims submitted to other insurers
- **Claims based algorithms do not accurately identify opioid abuse and addiction**[2]

Sources: [1]Michna(2014), [2]Carrell (2020)

SUBSTITUTION OF OTHER SUBSTANCES

Impact on Substitution of Other Prescription or Illicit Opioids

- Havens (2014): Reported prevalence of IR oxycodone abuse increased after OxyContin reformulation[1]
  - 64% increase in oxycodone IR injection
  - 50% increase in oxycodone IR insufflation
  - Note: Pre-reformulation use measured retrospectively
- Cicero (2015): One third of individuals with any lifetime abuse of original OxyContin entering treatment for OUD reported replacing OxyContin with other drugs after ADF[2]
  - 70% of these reported switching to heroin
- McNaughton (2014), Vosburg (2017): Analyses of internet postings
  - Individuals reported switching to heroin and other prescription opioids after OxyContin's reformulation[3,4]
  - Dynamic, undefined sample

Sources: [1]Havens (2014), [2]Cicero (2015b), [3]McNaughton (2014), [4]Vosburg (2017)

Impact on Heroin Use and Initiation

- Australian data mixed on shift to heroin after OxyContin's reformulation there in 2014[1,2]
  - Proportion of people injecting drugs who reported past six-month heroin injection remained stable[1]
  - Numeric increase (3-fold) in monthly visits to safe injection site to inject heroin, but pre- post-reformulation mean change not statistically significant[1]
  - Increases in heroin-related ambulance encounters and emergency department visits[2]

- Carlson 2016: Prospective cohort of young non-dependent individuals misusing prescription drugs in Ohio, examined heroin initiation from 2010-2013[3]
  - 100% of heroin initiators reported misuse of original OxyContin
  - Only 46% of non-initiators reported original OxyContin misuse
  - Non-oral use of prescription opioids strongly associated with heroin initiation
  - Unable to directly measure effect of OxyContin reformulation on heroin initiation

Sources: [1]Larance (2018), [2]Lam (2019), [3]Carlson (2016)

Impact on Heroin Use and Initiation

- Wolff (2020): Compared multiple outcomes in individuals who misused OxyContin prior to the ADF to those who misused other pain relievers (NSDUH)
  - Pre-reformulation OxyContin misuse not associated with change in prevalence of heroin use or heroin use disorder after ADF
  - Heroin *initiation* increased in both groups, yet increase smaller in those who previously misused OxyContin

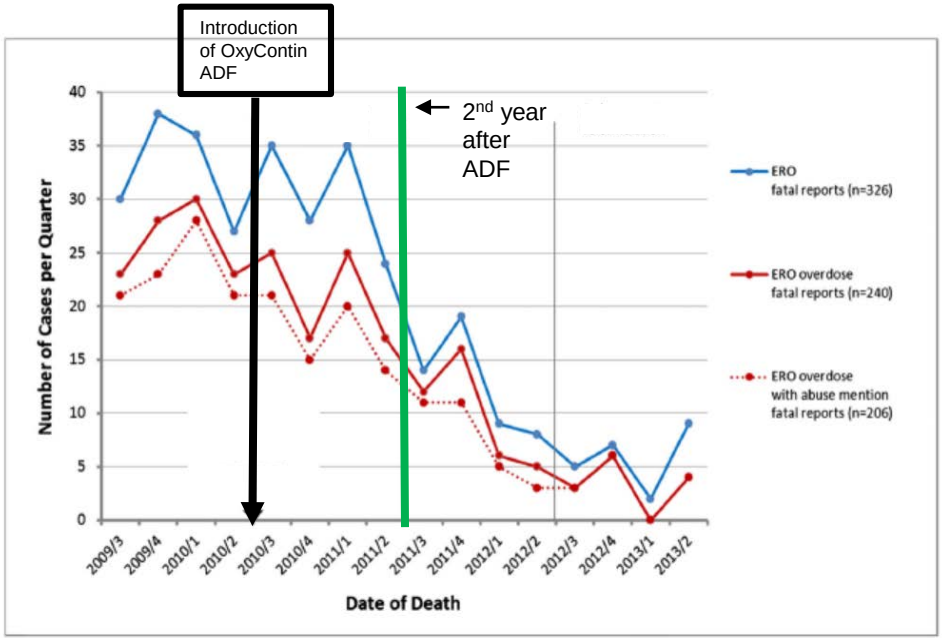
Sources: Wolff (2020)

OPIOID OVERDOSE

Spontaneous Reports: Fatal Overdose

- Sessler (2014) evaluated impact of OxyContin's reformulation on deaths using Purdue's spontaneous adverse event reporting system data
- 326 fatal cases* involving OxyContin® met selection criteria
- Decline in case reports appears around **2nd year** after reformulation
- Serious flaws:
  - **Spontaneous reporting of exposures and outcomes cannot be used to estimate incidence or make inferences about trends**
  - Reported cases do not represent totality of events
  - Many factors can influence reporting of adverse events
  - Case selection criteria could have biased results
  - No use of comparator to account for variability in reporting

Number of Extended Release oxycodone (ERO) fatality reports per quarter, Q3 2009: Q2 2013



Source: Figure adapted from Sessler (2014)

* Pre-reformulation (3Q2009-2Q2010):131 cases; Post-reformulation (3Q2010-2Q2013):195 cases

Impact on Prescription Opioid Overdose Deaths

- Mixed evidence on OxyContin reformulation's impact on prescription opioid-related overdose mortality
  - Evans (2018): Found a decline in prescription opioid mortality in areas with "high" exposure to oxycodone and "low" exposure to heroin[2]
    - Relied on oxycodone shipment data rather than OxyContin nonmedical use
  - Alpert (2018): Authors found small, non-significant decrease in prescription opioid-related mortality in states with higher pre-reformulation OxyContin NMU[1]
    - Did not account for effect of changing availability of prescription opioids

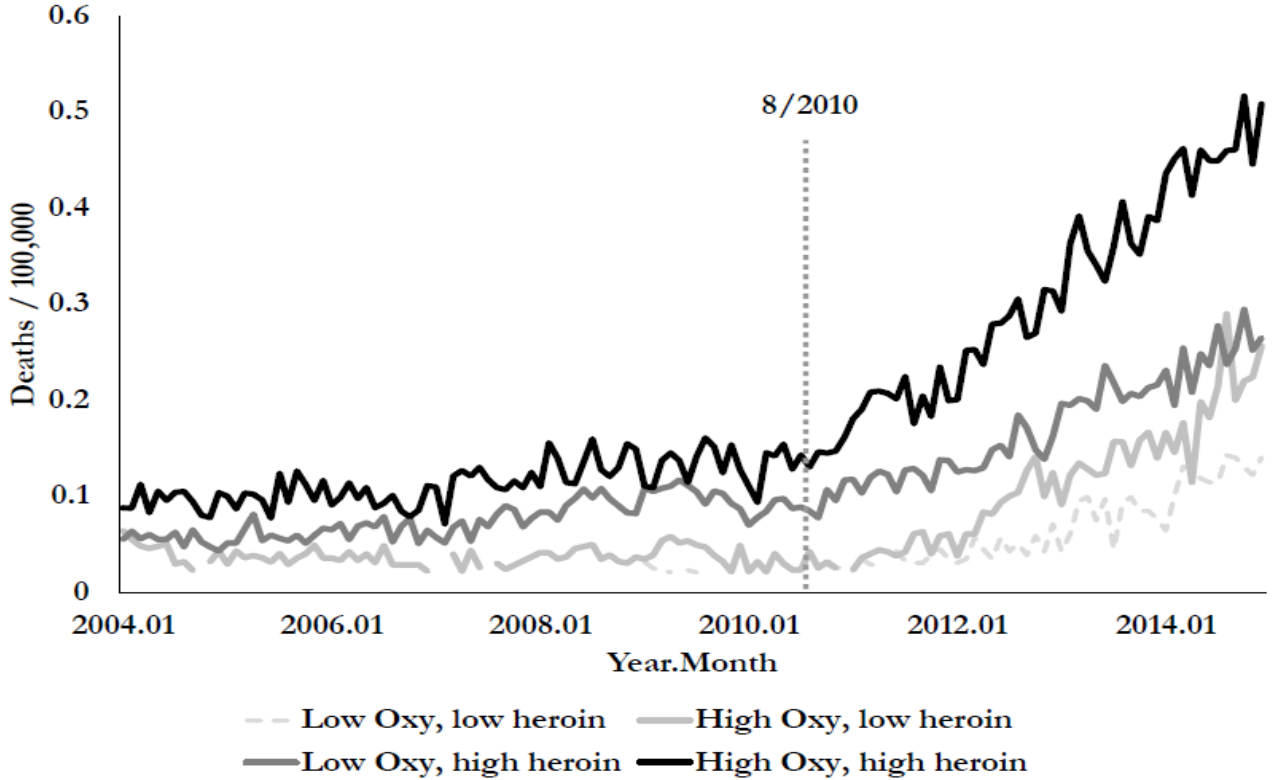
Sources: [1]Alpert (2018), [2]Evans (2018)

Impact on Heroin Overdose Deaths

- Several ecologic studies estimated the impact of OxyContin reformulation on heroin overdose deaths in the U.S.[1,2,3,4]
  - States with high pre-reformulation supply of oxycodone, nonmedical OxyContin use, and heroin deaths experienced larger increases in heroin-related deaths after the reformulation[1,2,3]
  - No association between level of other prescription opioid NMU and increase in heroin-related deaths[1,2]
  - Authors concluded that OxyContin's reformulation significantly contributed to the increase in heroin overdose deaths[1,2,3,4]

Sources: [1]Alpert (2018), [2]Evans (2018), [3]Powell(2020), [4]Tuazon (2019)

Monthly Heroin Death Rate by Oxycodone Shipments* and Heroin Availability, 2004-2014, U.S.



*based on volume shipped pre-reformulation

Source: Evans, 2018, Figure 3

Impact on Overall Opioid Overdose Deaths

- Alpert (2018): Concluded OxyContin's reformulation did not impact **overall** opioid overdose death rates through 2013[1]
- Powell (2020): Subsequent study estimated that the reformulation's contribution to increasing synthetic opioid mortality further offset any reduction in prescription opioid deaths attributable to OxyContin ADF[2]
  - Overdose deaths involving synthetic opioids increased more in states that had higher previous rates of OxyContin misuse
    - Association not seen for other prescription pain relievers

Sources: [1]Alpert (2018), [2]Powell (2020)

Considerations: Impact on Opioid Overdose

- Efforts addressing unregulated pain clinics (e.g. the "Florida pill mill crackdown") implemented around the same time
  - Evans (2018): Estimated that Florida pill mill crackdown explains at most 25% of the increase in heroin mortality[1]
- Complex mixture of data limitations of data, concurrent interventions, and secular trends make it difficult to determine the exact contribution of OxyContin's reformulation to U.S. opioid mortality trends
- Impact of reformulated OxyContin on overdose rate likely depends on environment
  - Availability and use of other opioids
  - Local policy interventions and treatment availability

Sources: [1]Evans (2018)

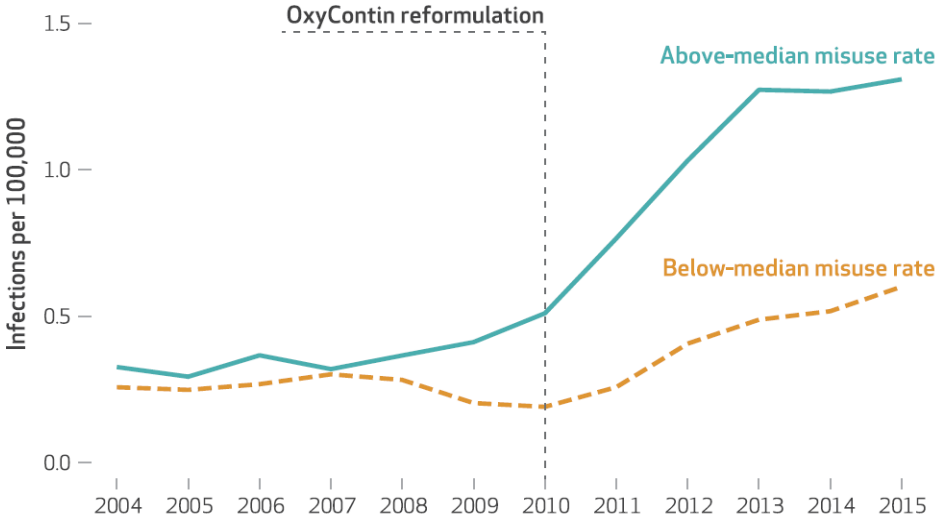
OTHER ABUSE-RELATED HARMS: HEPATITIS C TRANSMISSION

Other Abuse-related Harms: Hepatitis C Transmission

- Higher pre-reformulation OxyContin NMU rates were associated with post-reformulation increases in hepatitis C infection rates at the state level[1,2]
  - This association was not found for NMU of other prescription pain relievers[1]

Source: [1]Powell, 2019, [2]Behesti,2019

Rate of Acute Hepatitis C Infection per 100,000, by State Rate of Nonmedical OxyContin Use Pre-reformulation, 2004-2015, U.S.



Source: Powell, 2019

SUMMARY AND FDA INTERPRETATION OF THE LITERATURE

Overarching Study Limitations

- No U.S. studies had published pre-specified protocols
- Many studies provided limited detail on methods
  - Variability in exposure and outcome definition
- Non-representative samples, limited generalizability
- Multiple studies relied on participant recall of past abuse behaviors, potential for recall bias
- Unvalidated outcome algorithms
  - Claims-based abuse and addiction measures
- Ecologic study design
  - Individual-level inferences based on group-level associations

Summary Interpretation of the Literature

- Literature supports the hypothesis that OxyContin's reformulation reduced its attractiveness for abuse and diversion in populations who abuse prescription opioids non-orally
- Modest declines in OxyContin NMU in general population after reformulation
  - Unclear how much due to ADF
- Substitution of other prescription and illicit opioids after reformulation
  - Varied across populations, based on baseline substance abuse and drug availability
- No reliable evidence on the impact of OxyContin's reformulation on risk of addiction

Summary Interpretation of the Literature

- Ecologic studies suggest neutral or possibly adverse impact on opioid overdose
  - Any decreases in prescription opioid overdose due to ADF may have been offset, or more than offset, by increases in illicit opioid overdose due to substitution
- Similar analyses suggest OxyContin's reformulation contributed to increases in hepatitis C infection in the U.S.
- Remains difficult to determine causal role of OxyContin's reformulation in these trends
  - Data limitations
  - Concurrent interventions (e.g., pill mill crackdowns)
  - Changes and geographical heterogeneity in heroin availability/use
  - Complex drivers of drug abuse behaviors


FDA
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ADMINISTRATION

FDA Summary of Postmarketing Findings on OxyContin ADF Effectiveness and Public Health Impact

DSaRM/AADPAC Joint Meeting
September 10 – 11, 2020

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Summary of Meeting Thus Far

- Summary of experimental evidence (Category 1-3)
- Regulatory history; post-marketing required (PMR) studies (Category 4)
- FDA's public health systems approach
- Dr. Dasgupta — studying ADFs in the community
- Industry presentations
- FDA review findings
  - Drug utilization patterns
  - Methodologic considerations
  - Findings of PMR reviews
- Dr. Compton — the evolving opioid crisis
- FDA review of the published literature

FDA Review Team Scientific Approach to Interpreting Postmarket Data

- **Reasoned qualitative synthesis of the totality of evidence**
- Assess strength of the evidence

  ➡ Used principles of pharmacoepidemiology and causal inference, *e.g.,*

  - ❖ Temporal association — cause precedes effect
  - ❖ Range of possible effect sizes — multiple models, sensitivity analyses
  - ❖ Consistency of findings — within/across studies
  - ❖ Coherence with experimental data — category 1-3 studies
  - ❖ Alternative explanations — e.g., other interventions, secular trends, bias
  - ❖ Data quality — e.g., misclassification, missing data
  - ❖ Appropriate statistical methods — e.g., model adequacy

Considerations Using a Public Health Systems Approach

- Important to determine whether the ADF reduced abuse of OxyContin by specific routes—improved safety of the medication
- Also must consider broader public health impact
  - ❖ Multiple outcomes (e.g., misuse, abuse, addiction, overdose, death, injection-related harms)
  - ❖ Potential for varying impacts across populations
    - – Patients receiving prescription opioids
    - – Individuals abusing prescription opioids, but NOT regularly via non-oral routes
    - – Individuals abusing prescription opioids regularly via non-oral routes (more severe OUD)
  - ❖ Unintended adverse effects (e.g., excipient harms, substitution effects)
  - ❖ Complex system of inter-related clinical, sociocultural, economic factors

Summary of FDA Review Findings

Drug Utilization

- OxyContin represents a small fraction of opioid analgesic market
- Following OxyContin's reformulation
  - ❖ Steady decline in OxyContin dispensing
  - ❖ Initial declines were greatest for higher dosage strengths (e.g., 80 mg)
  - ❖ Many patients discontinued OxyContin, usually switching to another Rx opioid
  - ❖ Total mg oxycodone per OxyContin prescription decline
- Little empiric data on reasons for changes, but may include
  - ❖ Abuse-deterrent effect (reduced demand, patient self-selection)
  - ❖ Changes in insurance coverage with contemporaneous exit of generics
  - ❖ Increasing prescribing of immediate-release single entity oxycodone
  - ❖ Interventions to reduce unlawful prescribing (e.g., pill mill crackdowns)
  - ❖ Increased prescriber awareness of abuse risk (e.g., due to REMS)
  - ❖ Excipient-related gastrointestinal problems (e.g., dysphagia)

Main Finding #1

OxyContin's reformulation reduced its abuse by non-oral routes (snorting and injection), but we cannot quantify magnitude of effect

- The postmarketing (Category 4) findings qualitatively confirm Category 1-3 study results
  - PMR 1 (NAVIPPRO ASI-MV) provided strongest evidence
  - PMR 2 (RADARS Poison Center) and published literature provided corroborating evidence
- Effect size estimates varied widely
- Reductions mainly observed among those with more advanced substance use disorders (SUDs) and/or already tampering with prescription opioids

Main Finding #2 (1)

Evidence was not robust that the reformulation caused a reduction in overall OxyContin abuse

PMR Study	Findings
PMR 1: NAVIPPRO ASI-MV	• Range of effect estimates included both increased and decreased overall OxyContin abuse rates relative to comparators • Possible shift to oral abuse
PMR 2: RADARS Poison Center	• OxyContin abuse mostly oral • Large declines in abuse rates for comparators: Decreases in OxyContin abuse rates > comparators, but not after adjusting for utilization • Large declines in non-abuse related calls (even after utilization adjustment) • *Unclear if reductions largely due to ADF versus other factors*
PMR 3: RADARS Treatment Center	• Decreases in OxyContin abuse rates > comparators, but not after adjusting for utilization

Main Finding #2 (Continued)

Published literature

- National survey data* analyses suggest modest declines in nonmedical OxyContin use (any use other than as directed)
  - Mirrored declines in utilization
  - Unclear if declines greater than other prescription opioids
- Studies suggest the reformulation reduced OxyContin diversion and doctor-shopping
  - Not direct measures of abuse
  - Many other limitations

**National Survey on Drug use and Health*

Main Finding #3

Adjusted for differences in prescription volume, OxyContin abuse rates (overall and non-oral) remained relatively high among the opioids examined

- Observed in PMRs 1-3
  - *Direct comparisons across drugs must be interpreted cautiously due to non-representative samples, product misclassification, and missing data*
- Reminder that abuse of ADF OxyContin was evaluated relative to original formulation, not other currently marketed opioid analgesics
- No evidence that ADF OxyContin is less prone to abuse than other marketed opioid analgesics

Main Finding #4 (1)

Unclear if reformulation had an overall public health benefit

Systems approach: consider impacts in different populations

- Reduction in non-oral OxyContin abuse primarily seen in those with more advanced SUD, but overall benefit of ADF in this population somewhat unclear
  - Polysubstance abuse is common
  - Substitution of other opioids (prescription and/or illicit)
    - Published studies reported substitution, including heroin, after OxyContin reformulation
    - PMRs 2 and 3 showed increases in heroin abuse after reformulation

Main Finding #4 (Continued)

Systems approach: consider impacts in different populations

- ADF may reduce non-oral OxyContin abuse and associated harms among patients and others not regularly abusing non-orally, but little supporting data
- **No direct evidence** on whether ADF reduced
  - *Risk of abuse* among **patients** dispensed OxyContin
    - Can we infer from other populations?
  - *Initiation* of OxyContin snorting or injection, among **patients or others not regularly abusing non-orally**
  - *Progression* of opioid use disorder or *risk of addiction*, either among **patients or others**

Main Finding #4 (Continued)

Systems approach: consider impacts in different populations

- Among **insured patients dispensed OxyContin**, no reduction in risk of opioid *overdose*, overall
- Among **insured patients dispensed OxyContin *alone***, results more favorable, but interpretation not straightforward
  - Finding only significant in commercial claims cohorts, not Medicaid
  - OxyContin use without other opioids was relatively uncommon
  - May indicate a reduced risk of overdose in patients (including through abuse, misuse, medication errors) **BUT**
  - Patients receiving ADF may have been at lower risk of overdose (e.g., if lower prevalence of OUD and risky drug use behaviors, prescribed lower dose)
    - May be consistent with abuse-deterrent effect, but does lower overdose incidence in a lower-risk group mean ADF reduced risk of overdose?
    - What about overdose risk in those who migrated *away* from OxyContin due to ADF?

Main Finding #4 (Continued)

Systems approach: consider unintended adverse consequences

- Published ecologic studies suggest neutral or possibly adverse impact on opioid overdose
  - Any decreases in prescription opioid overdose due to ADF may have been offset, or more than offset, by increases in illicit opioid overdose due to substitution
- Similar analyses suggest OxyContin's reformulation contributed to increases in hepatitis C infection in the U.S.
- Despite methods to control for other factors, difficult to determine the causal role of OxyContin's reformulation in these trends
  - Data limitations
  - Concurrent interventions (e.g., pill mill crackdowns)
  - Changes and geographical heterogeneity in heroin availability/use
  - Complex drivers of drug abuse behaviors

Main Finding #4 (Continued)

Systems approach: consider unintended adverse consequences

- ADF excipient-related risks*
  - Gastrointestinal problems
    - Dysphagia, choking
    - Potential for bowel obstruction in patients with narrow lumen
  - Thrombotic microangiopathy (TMA) with intravenous abuse
    - Infrequently reported for OxyContin (6 reports in 10 years)
    - Higher frequency of reports for Opana ER—high molecular weight polyethylene oxide (PEO)
    - Work is ongoing to better understand
    - Risk of TMA may increase with molecular weight of PEO

**Risks described in OxyContin label (full prescribing information)*

Summary

- Many scientific challenges, data limitations
- Evidence fairly compelling that reformulation deterred OxyContin abuse by non-oral routes (snorting and injecting)
  - Qualitatively confirms Category 1-3 study findings
- Effect on overall OxyContin abuse and overdose risk is less clear
- Uncertainty remains about the overall public health impact of OxyContin's reformulation
  - Impacts likely varied in different populations
  - Deterrent effect seen primarily in populations with more advanced SUDs
  - Unintended consequences—substitution effects, including illicit opioids
  - Unknown impact on initiation of non-oral abuse or risk of addiction


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