The Clinical Journal of Pain Publish Ahead of Print
DOI:10.1097/AJP.0000000000001034

OPEN

An evaluation of the effect of the OxyContin® reformulation on unintentional fatal and non-fatal overdose

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Acknowledgments

We acknowledge Nianya Liu and Shiva Krishna Vojjala (HealthCore) for programming support, and Mark Paullin (HealthCore) for operational support of the validation study. Sulena Shrestha, Li Wang, and Lu Li formerly of STATinMED who were involved of the Medicaid database related analyses. Rachelle

Rodriguez and Stacy Baldridge of Purdue Pharma L.P., also provided advice on the research. We also acknowledge former Purdue Pharma L.P. researchers who had a role in the early study conceptualization and design aspects.

Role of Funding Source

This work was supported by Purdue Pharma L.P.; HealthCore Inc., STATinMED Research, IBM Watson Health, and World Health Information Science Consultants (WHISCON) received funding from Purdue Pharma L.P. to conduct this study and for the development of this manuscript. This underlying study was an FDA-mandated Post Market Requirement (PMR) study presented at the "Joint Meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)" on September 10th to 11th 2020.[1]

Abstract

Objectives: OxyContin® was reformulated with a polyethylene oxide matrix in August 2010 to reduce the potential for intravenous abuse and for abuse by insufflation. The objective of this study was to evaluate the impact of OxyContin's reformulation on overdose risk for individuals dispensed OxyContin in comparison to those dispensed other opioids under regular care.

Methods: Three national insurance databases with National Death Index linkage identified OD in individuals with any dispensing of OxyContin or a primary comparator opioid (ER morphine, transdermal fentanyl, or methadone) between July 2008 through September 2015. A difference-in-differences design was used to compare the pre-post reformulation changes in OD rates for OxyContin versus comparators.

Results: 297,836 individuals were dispensed OxyContin and 659,673 individuals were dispensed a primary comparator across the three databases. Overall, there was little or no difference in the temporal change in OD incidence in comparators versus OxyContin (Medicaid: adjusted ratio-of-rate-ratios (aRoRs) ranging from 0.90 to 1.05; MarketScan/HIRD: aRoR ranging from 1.10 to 1.22). However, restriction to person-time without concomitant opioid use revealed a modestly greater reduction in OD incidence over time during OxyContin use, as the aRoRs comparing the primary comparators to OxyContin ranged from 1.06 to 1.30 in Medicaid and from 1.64 to 1.85 in MarketScan/HIRD.

Discussion: This study did not detect an overall effect of the OxyContin reformulation on OD in insured patients under regular medical care. There is a suggestion of a modestly reduced OxyContin-associated OD risk following the reformulation but only in commercially-insured individuals receiving single-opioid regimens.

Keywords: Opioids; Abuse Deterrent; OxyContin; Reformulation; Overdose

1. Introduction

Misuse and abuse of prescription opioids are serious public health problems and place a significant burden on national health systems. OxyContin® is a commonly used extended-release (ER) oral tablet formulation of oxycodone hydrochloride. Although the original formulation of OxyContin was intended to be taken orally intact (i.e., swallowing the tablet whole), similar to other opioids, it was possible to manipulate the original formulation of OxyContin for misuse and abuse to engage in unapproved routes of administration (e.g., chewing, crushing/swallowing, insufflation [snorting], intravenous injection).[2-4]

In 2010, the United States (US) Food and Drug Administration (FDA) approved an abuse-deterrent formulation (ADF) of OxyContin tablets intended to reduce misuse and abuse of OxyContin and their consequences, including overdose and death. OxyContin was reformulated with a polyethylene oxide matrix which hardens tablets and resists syringe aspiration and subsequent injection. Reformulated OxyContin became commercially available on August 9, 2010, and, in consultation with FDA, shipments of the original formulation ceased that same month. There was no notification to the general public or prescribers, and no modification in price. By December 2010 and December 2011, 90% and 99%, respectively, of OxyContin prescriptions dispensed were for reformulated OxyContin.

In 2013, FDA approved new labeling of OxyContin describing abuse-deterrent properties (ADP), based on evidence generated from in-vitro studies and short-term clinical trials regarding abuse.[5-7] However, there have been no long-term randomized trials examining the effect of reformulated OxyContin on abuse of OxyContin and related outcomes. As a condition of approval,[8] FDA required a post-marketing epidemiology program for reformulated OxyContin, including this study.[1]

Several prior publications have assessed the impact of the OxyContin reformulation in the US [9-19] including studies that used claims data which suggested a decline in OxyContin utilization after the reformulation.[17, 18] One of the studies suggested a decline in the rate of overdose due to prescription opioids after the reformulated OxyContin entered the market,[18] but did not attempt to identify which

specific opioid product(s) had been dispensed prior to each overdose. It is possible that overall estimates could miss or misstate effects in patients specifically dispensed OxyContin. Overall changes in the incidence of overdose may have been impacted by co-varying temporal factors causally unrelated to the OxyContin reformulation.

To date, there had been no direct evaluation of the impact of OxyContin's reformulation on overdose risk for individuals dispensed OxyContin in comparison to those dispensed other opioids. In this study, we utilized three large administrative claims databases to evaluate and compare unintentional fatal and non-fatal overdose (OD) rates among patients dispensed OxyContin or comparator opioids.

2. Materials and Methods:

2.1 Study Population and Design

This study included the national Medicaid database and two national commercial claims databases (IBM MarketScan Commercial and Medicare Supplemental Claims and Encounters database (MarketScan) and the HealthCore Integrated Research Database (HIRD)). The Medicaid database, Medicaid Analytic eXtract (MAX), covers all 50 states and Washington DC through 2012. The Medicaid population was restricted to treatment episodes that were from fee-for-service (FFS) or comprehensive managed care (CMC) plans in which the combined state, year, and basis of eligibility (BOE) group demonstrated research usability (i.e., continuity and connectivity between data elements following criteria defined by Li et al.).[20] MarketScan collects data from employers and health plans. The HIRD includes health plan members insured through Anthem. Each database was restricted to populations that were linkable to the National Death Index (NDI), a central computerized index of death record information derived from state vital statistics data.[21, 22] For inclusion into this study, individuals were required to be aged 16-74 years (16-64 years in Medicaid) and have >3 months continuous health plan enrollment prior to eligible opioid dispensings.

The study design was a retrospective cohort study comparing rates of OD before and after the OxyContin reformulation in users of OxyContin and in contemporaneous users of comparator opioids. The study period ranged from July 1, 2008 to June 30, 2010 as the pre-reformulation period (pre-period), and January 1, 2011 to September 30, 2015 for the post-reformulation period for the commercial databases and through December 31, 2012 for Medicaid (post-period) (Supplemental Figure 1, Supplemental Digital Content 1, http://links.lww.com/CJP/A873). The main analyses excluded a transition period of July 1, 2010 to December 31, 2010 when both the original and reformulated versions of OxyContin were likely used. Analyses included all users (new and prevalent) and separately restricted to new users which allowed for the application of the new user design. We compared the five-year post-period to the two-year pre-period for the main analyses in the commercial insurance databases, and a two-year post-period and two-year pre-period in Medicaid due to the unavailability of more recent data (Supplemental Figure 1, Supplemental Digital Content 1, http://links.lww.com/CJP/A873).

2.2 Exposures

The primary exposure evaluated in this study was OxyContin. The primary comparator opioids were ER morphine, transdermal (TD) fentanyl, and methadone tablets/capsules, selected due to similarities with OxyContin in labeled indications, long marketing histories, and large, stable market shares throughout the study period. Secondary comparator opioids consisted of single-entity ER oxymorphone, IR oxycodone tablets, and IR hydromorphone tablets. Evidence showed that these products were the most preferred alternatives for abuse among prescription opioids during the time of decreasing popularity of OxyContin after it was reformulated.[12]

The analytic datasets were constructed using treatment episodes, with time-dependent covariates evaluated at the beginning of each treatment episode. Individuals were considered exposed to OxyContin and comparator opioids beginning on the day of dispensing and continuing through the days' supply of the drug plus an extension period of half of the days' supply. A treatment episode ended if there was one or more days of discontinuity between dispensings, and was censored if an individual discontinued any of

the opioids that defined the episode, initiated another study opioid, had an OD, died, terminated their health insurance coverage, or reached the end of the pre-period, transition period, or study period. Thus, if two study opioids were dispensed within days of each other, the treatment episode for the first study opioid was terminated on the day of the dispensing of the second study opioid, and a new treatment episode was created at the dispensing of the second study opioid. If an individual obtained a new dispensing of an opioid agent prior to exhausting the days' supply of a prior dispensing of that agent, we assumed that medication was taken starting on the day of the pharmacy dispensing.

Exposure for each treatment episode was classified in subcategories including "any use" of the drug (i.e., with or without concomitant opioid use) and "only use" of the drug (i.e., without concomitant opioid use). An example of treatment episode construction and exposure groups is provided in Supplemental Figure 2, Supplemental Digital Content 1, http://links.lww.com/CJP/A873. "Only use" treatment episodes represented approximately one third of the "any use" person-time. For comparative analyses with the primary comparators, we excluded treatment episodes with concomitant use of two or more primary comparators, or OxyContin with a primary comparator.

New (i.e., incident) use was assessed for each treatment episode and defined as having had no recorded dispensing of any opioid study drug in the three months prior to the start of the treatment episode. This new use treatment episode plus any adjacent, continuous treatment episodes for that study drug comprised an incident use episode. An individual could have multiple incident use treatment episodes in the study if more than one treatment episode met the incident use criteria.

2.3 Outcomes

The primary outcome was unintentional fatal or non-fatal unintentional OD. Opioid overdose was defined using a previously validated algorithm that uses the diagnostic codes associated with services in US health insurance data [23, 24] for events resulting in health services (both fatal and nonfatal). Further identification of fatal OD employed linkage to the US NDI. A patient was classified as having

experienced an overdose event if they had at least one overdose related ICD-9 and ICD-10 code (provided in Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CJP/A873) in any position or setting. Events were restricted to those not classified as intentional (defined via codes for suicide and other correlated factors) [23, 24] and those that occurred during a treatment episode.

Validation of non-fatal (insurance claims-based) OD was conducted through medical record review for 159 cases in the HIRD. Standardized data collection techniques were used to abstract information from the medical records including medical history and treatment of the possible overdose event. Results from this validation study were similar to the previous validation studies of Green et al. [23, 24]Among the 159 code-defined ODs, 135 (positive predictive value (PPV)=85%) were confirmed on chart review (47 intentional and 88 unintentional). The algorithm to detect intentionality had lower accuracy than the overall OD algorithm (PPV=69%), but a high sensitivity (98%). This suggests that a sizeable subset of intentional ODs were classified as unintentional with the unintentional OD algorithm. Additional methods and results for the validation study are further described in our prior publication. [25]

2.4 Covariates

Demographic characteristics, clinical characteristics, and other comorbidities and conditions noted in Supplemental Table 2, Supplemental Digital Content 1, http://links.lww.com/CJP/A873 were assessed in claims for each treatment episode during a three- or six- month lookback period prior to each treatment episode, except certain demographic characteristics which were assessed on the index date. Evaluation at each treatment episode allowed for the ability to account for potential time-varying confounding.

2.5 Statistical Analyses

Poisson regression models, which model log-linear relationships for rates, were used to calculate incidence rates (IRs) and all comparison measures for OxyContin and comparator opioid groups. Since only the numerator of a rate (the number of events) is random, the dependent variable for each treatment category was the logarithm of the number of events. The logarithm of the denominator (person-time) was

introduced into the model as an offset. The regression models were carried out using repeated-measures Generalized Estimating Equations (GEE) with sandwich variance estimators and with independent covariance matrices for repeated observations due to multiple treatment episodes per patient. Approximately 10% of patients with an OD had multiple, distinct ODs during follow-up of the study. A time-varying covariate term for "prior OD event" was introduced to account for the most substantial source of within-person correlation.

Incidence rate ratios (IRRs) compared IRs between OxyContin and comparator groups within the pre- and post- reformulation time periods. For pre-post comparisons, analyses were conducted in three ways in each database: (1) unadjusted for covariates, (2) adjusted for possibly time-varying covariates, and (3) adjusted for possibly time-varying covariates as well as other baseline characteristics via propensity score weighting in a new-user cohort.

Post- versus pre- reformulation rate ratios (RRs) were calculated for OxyContin and each of the comparator opioid groups. To compare pre-post reformulation changes in overdose rates (i.e., the RRs) for OxyContin and for comparator opioids, this study utilized a difference-in-differences design (implemented here as ratios-of-rate-ratios (RoRs)). Rate ratios and RoRs were also adjusted for baseline demographic and clinical covariates provided in Supplemental Table 2, Supplemental Digital Content 1, http://links.lww.com/CJP/A873 using the Poisson regression models with GEE.

Adjusted RRs and RoRs were determined in the new user cohort using propensity score weighting (via inverse probability of treatment weighting) to match the covariate distributions of the pre- and post-reformulation cohorts. The aim was to weight the post-reformulation group to match the covariate structure of the pre-reformulation group in regard to demographic and clinical characteristics, in addition to other comorbidities and conditions. For OxyContin and each of the comparator opioids propensity scores were derived using logistic regression to estimate the fitted probability that a given incident use treatment episode with a specified set of covariates was from the pre-reformulation period as opposed to

the post-reformulation period. Propensity scores outside the range of overlap between the two time periods (pre- and post-reformulation) were trimmed.

Sensitivity analyses included examination of the main results stratified by incident versus prevalent opioid use, fatal versus non-fatal overdose status, and intentional versus unintentional overdose status. We also examined results restricting the post-period to three years in the commercial databases, and stratifying results by CMC versus FFS status in the Medicaid database. Analyses were conducted by HealthCore, IBM, and STATinMED using SAS.

Results from the two commercial databases (HIRD and MarketScan) were additionally pooled using random-effects meta-analysis.[26-28] The Medicaid population was not included in the pooling given a priori differences in this population (e.g., lower social economic status).

2.6 Human Subjects

Institutional Review Board (IRB) approval was obtained for each site prior to NDI linkage and for conducting the validation of the algorithm for OD in the HIRD. No individual-level data were shared with the study sponsor.

3. Results:

3.1 Study Population

This study included 94,445 Medicaid patients, 122,254 MarketScan patients, and 81,137 HIRD patients who were dispensed OxyContin, and 367,814 Medicaid patients, 181,240 MarketScan patients, and 110,619 HIRD patients dispensed at least one of the primary comparator opioids. Exposed person-time per patient in each of the databases ranged from six to ten months (Table 1). The dose of the dispensed OxyContin was 40 mg or more in 54% of Medicaid patients, 20% of MarketScan patients, and 36% of HIRD patients. Much of the use of OxyContin and primary comparator was concomitant with other opioids such as IR oxycodone or other non-primary or secondary opioids (Table 1). Patient characteristics

were largely similar between OxyContin treatment episodes and primary comparator opioid treatment episodes, with a few notable differences including a higher proportion of females and patients with certain pain disorders (abdominal, chronic, and neuropathic) among primary comparator opioid treatment episodes compared to OxyContin treatment episodes. Each of these personal characteristics included in the analysis had modest or no association with subsequent overdose risk (all IRRs<2 and >0.5). By contrast, having experienced a prior overdose was strongly associated with a subsequent overdose (IRRs>14 in each database; results available upon request).

3.2 Incidence of OD during OxyContin use

The IR for OD during OxyContin treatment episodes varied by database between 0.8 (MarketScan) and 1.6 (Medicaid) per 1,000 person-months and was lower than the IR during comparator opioid use, which varied between 0.9 and 2.9 per 1,000 person-months (Table 2 and Figure 1). Over 80% of ODs were non-fatal for both OxyContin and comparator opioids. In each database, the IR for OD during any-use OxyContin exposure time declined from pre- to post-reformulation (Medicaid: post-period versus pre-period adjusted rate ratio [aRR]=0.93, 95% confidence interval [CI]=0.83-1.04; MarketScan/HIRD: aRR=0.86, 95%CI=0.75-1.00; Supplemental Table 3, Supplemental Digital Content 1, http://links.lww.com/CJP/A873). For the any-use analysis, these comparisons permitted concurrent dispensing of Schedule II opioids (other than the comparators). The decline in the IR for OD over time was more pronounced during use of OxyContin when it was dispensed with no other concurrent Schedule II opioid (Medicaid: aRR=0.80, 95% CI=0.63-1.01; MarketScan/HIRD: aRR=0.57, 95%CI=0.42-0.77; Figure 2 and Supplemental Table 3, Supplemental Digital Content 1, http://links.lww.com/CJP/A873).

3.3 OxyContin versus Primary Comparators

For “any use” exposures, the post- versus pre-reformulation RRs of OD were similar for OxyContin and each of the primary comparators (Figure 3). In Medicaid, the crude RoRs measuring the post- versus pre-reformulation RRs for comparator versus OxyContin ranged from 0.89 to 1.04, with the adjusted RoRs

(aRoRs) ranging from 0.90 to 1.05 (Figure 3; aRoR>1 means that the pre-post *decline* was greater during use of OxyContin than during use of the comparator). In the pooled MarketScan/HIRD results, the RoRs ranged from 1.13 and 1.26 comparing the pre-post trend in each comparator to OxyContin, with the aRoRs ranging from 1.10 to 1.22 (Figure 3). In the "only-use" comparisons, which were restricted to person-time exposed only to OxyContin or only to a single primary comparator, there was evidence of trends in OD incidence in the pre- to post-reformulation periods that were more favorable for OxyContin versus the primary comparators in the commercial databases (Medicaid: aRoRs ranged from 1.06 to 1.30 comparing primary comparators to OxyContin; MarketScan/HIRD: aRoRs ranged from 1.64 to 1.85 comparing the primary comparators to OxyContin; Figure 3).

3.4 OxyContin versus Secondary Comparators

Results were largely similar to the primary-comparator analysis for OxyContin versus the secondary comparators. There was a lack of an association when comparing any use, but there was evidence of lower risk of OD during OxyContin only use than comparator only use, particularly in the commercial databases (Table 3). There were differences between the two commercial databases. In the HIRD, there were relatively similar patterns in OD during any OxyContin use, while there was a stronger decline in the OD rate during OxyContin only use than during secondary comparator only use (Table 3). In MarketScan, there was evidence of a stronger decline for OxyContin in the OD rate over time than those observed in the HIRD for both analyses (any use and only use; Table 3). The pooled aRoR results for any use of each of the three secondary comparators relative to any use of OxyContin ranged from 1.42 to 1.74. The pooled aRoRs for only use of each of the three secondary comparators relative to OxyContin only ranged from 1.43 to 2.91 (data available upon request).

3.5 Sensitivity Analyses

Results were largely similar in sensitivity analyses. Results were similar when stratified by prevalent versus incident use, by fatal versus non-fatal OD, by intentional versus unintentional OD, and when restricting the post-period in commercial databases to three years (data available upon request). In the

Medicaid database, results appeared modestly different by FFS/CMC status. A decline in the overdose rate during any use of OxyContin in the pre- to post-period was observed in the FFS population (aRR=0.81, 95%CI=0.69-0.95), but no change was observed in the CMC population (aRR=1.10, 95%CI=0.92-1.31). The estimates for the aRoRs were also often slightly different by population, as the OD comparing any TD fentanyl to any OxyContin was 1.28 (95%CI=1.03-1.59) in the FFS population, and 0.84 (95%CI=0.66-1.07) in the CMC population.

4. Discussion:

The 2010 reformulation of OxyContin to a product with physicochemical barriers to deter injection or insufflation was not associated with a decline in the incidence of OD in OxyContin users beyond what might have been expected from secular trends seen in comparator opioids. However, when analyses were restricted to person-time during which there was no use of concomitant opioids, in the commercially-insured databases, the OxyContin reformulation was modestly associated with a decline in OD rates during OxyContin only use as compared to during the use of comparators. This decline was not seen among the Medicaid population in this study, generally, a higher risk population for opioid misuse and abuse.[29]

While this study noted a modest decline in the OD rate over time during any OxyContin use and a lower rate of OD during any OxyContin use than any comparator use, in most of the analyses, the reformulation appeared to have had minimal impact on the rate of OD among insured patients receiving medical care and dispensed OxyContin. The lack of an effect among individuals using multiple opioids concomitantly may be because the reformulated OxyContin was intended to deter abuse of OxyContin (i.e., not other opioids).

The analyses that focused on OxyContin use without concomitant opioids (i.e., “OxyContin only”), which represented approximately one-third of the person-time in the overall analyses, showed a decline in the incidence of OD in the post-reformulation period in comparison to the pre-reformulation period in the

commercially-insured databases. Comparisons to the primary and secondary comparator opioids without concomitant opioids supported the hypothesis of improvement among OxyContin recipients (i.e., greater reduction in OD rates over time). The decline may suggest that the reformulation could represent a barrier to injecting or snorting OxyContin (as suggested in other treatment and poison center studies), (FDA, 2020) but not a barrier to overdosing from poly-opioid use involving oral OxyContin. Thus, the reformulation may only have a measurable effect among OxyContin use without concomitant opioids in certain populations. Alternatively, persons using one opioid may tend to misuse or abuse only that drug. Thus, the direct effect of the OxyContin reformulation may be to drive people who misuse or abuse opioids to request another opioid in the place of OxyContin, or to request supplementary opioids given that the reformulation was not intended to treat opioid addiction. Either scenario would result in a decline in the OD rate during OxyContin usage after the reformulation.

In this study of insured, largely middle-aged patients in active medical treatment with opioids, the incidence of OD was between 1.0 and 2.0 non-fatal ODs per 1,000 person-months (i.e., 1,200 to 2,400 non-fatal ODs per 100,000 person-years), and between 0.1 and 0.4 fatal ODs per 1,000 person-months (i.e. 120 to 480 fatal ODs per 100,000 person-years). As expected, these OD IRs are considerably higher than the general US population (~5 fatal ODs from prescription opioids per 100,000 person-years) [30], but are likely significantly lower than the fatal OD rates seen among patients who misuse or abuse opioids and those with opioid use disorder.[31] Medical monitoring in this study's population may have limited or prevented the emergence of prescription opioid misuse or abuse, or resulted in early treatment of misuse or abuse if it occurred. This study was unable to identify opioids obtained outside of insurance claims (e.g. cash only payments).

There are a few limitations to this study. Misclassification of the exposure or outcome could bias results of this study. This study used a previously validated algorithm for OD, [23, 24] and results from the validation study in the HIRD suggest that this algorithm may be transportable to at least some of this study's populations, but somewhat limited in the accuracy of intentionality of the overdose. Given its

observational nature, this study is also prone to confounding and there was potential for channeling of individuals in either direction. While higher risk individuals may have initiated/switched to other opioids after the OxyContin reformulation, it is also possible that individuals at higher risk of OD may have been channeled to ADFs during the post-period, as doctors and other prescribers may have become aware of the presence and potential value of the ADF. However, the results for the unadjusted, covariate adjusted, and propensity-score weighted models were all relatively similar in this study, and this overall lack of impact of the covariate control is consistent with small or absent changes in the covariates within study drug use categories; at most, there was a modest effect of each of the covariates on the OD outcome (other than recent history of OD, which was strongly associated with the outcome). Although, it should be noted that not all potential important confounders could be directly measured in this study. For example, while we included opioid abuse/dependence from claims diagnoses in propensity score-weighted models, we were unable to directly measure opioid misuse or abuse or the predilection to misuse or abuse opioids or other substances. Given that the association between misuse or abuse and OD may be large, modest differences between exposure categories could have an impact of inferences even if misuse or abuse were relatively uncommon in these populations receiving active medical care.[29, 32] It should also be noted that this study was restricted to individuals dispensed opioids while in active medical care and may not fully capture those at greatest risk of OD from illicit use.[33] Finally, despite the size of the study and robustness of the sample, power was still limited for some sub-populations.

This study also had a number of strengths. It included three large administrative claims databases tracked longitudinally with a high degree of certainty for the opioid exposures and linkage to NDI to ascertain fatal outcomes. The opioid(s) dispensed to the individual overlapping with the OD is identified from prescription claims database records, rather than relying on respondents' self-report such as in-drug treatment center studies. Additionally, while there were likely other ongoing secular trends and policies during the study period that could have impacted opioid use and OD incidence, this study utilized contemporaneous opioid comparators, the difference-in-differences design, regression adjustment,

propensity score weighting, and numerous sensitivity analyses aiming to address confounding and other biases.

5. Conclusions:

The results of this study of individuals medically treated with opioids suggest that for any use of OxyContin or of comparator opioids there was little or no change in the rate of OD following the reformulation of OxyContin, although there was a suggestion in commercially-insured individuals receiving single-opioid regimens of a reduced OxyContin-associated OD risk following the reformulation in commercially-insured individuals. However, this was not seen among the Medicaid population captured in this study.

6. Acknowledgments:

Contributors

Study conception/design: DCB, KH, LB, GB, RG, HY, AW; Analysis: LL, RG, GB, HY; Interpretation of data: DCB, KH, LB, GB, RG, LL, HY, AW; Draft or revision of manuscript: DCB, KH, LB, GB, RG, LL, HY, AW; All authors have approved the final manuscript.

Conflict of interest

DCB and KH are employees of HealthCore Inc., RG, GB and LL were employees of HealthCore Inc. at the time of the study, LB is an employee of IBM Watson Health, HY is an employee of New York City College of Technology-CUNY and collaborated as an external consultant to STATinMED Research for this study, and AW is an employee of WHISCON. Purdue Pharma L.P. provided funding to HealthCore Inc., STATinMED Research, IBM Watson Health, and WHISCON to conduct this study and for the development of this manuscript.

References:

1. U.S. Food & Drug Administration. September 10-11, 2020 Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee Meeting Announcement [online]. Available at: https://www.fda.gov/advisory-committees/advisory-committee-calendar/september-10-11-2020-joint-meeting-drug-safety-and-risk-management-advisory-committee-and-anesthetic.
2. Butler SF, Black RA, Cassidy TA, Dailey TM, Budman SH. Abuse risks and routes of administration of different prescription opioid compounds and formulations. Harm Reduct J 2011;8:29.
3. Hays LR. A profile of OxyContin addiction. J Addict Dis 2004;23:1-9.
4. Katz N, Dart RC, Bailey E, Trudeau J, Osgood E, Paillard F. Tampering with prescription opioids: nature and extent of the problem, health consequences, and solutions. Am J Drug Alcohol Abuse 2011;37:205-217.
5. Cone EJ, Giordano J, Weingarten B. An iterative model for in vitro laboratory assessment of tamper deterrent formulations. Drug Alcohol Depend 2013;131:100-105.
6. Harris SC, Perrino PJ, Smith I, et al. Abuse potential, pharmacokinetics, pharmacodynamics, and safety of intranasally administered crushed oxycodone HCl abuse-deterrent controlled-release tablets in recreational opioid users. J Clin Pharmacol 2014;54:468-477.
7. OxyContin [package insert] [online]. Available at: http://app.purduepharma.com/xmlpublishing/pi.aspx?id=o. Accessed May 11, 2019.
8. FDA letter dated April 05, 2010, NDA 02272, NDA approval. Silver Springs, MD: Department of Health and Human Services, 2010.
9. Chilcoat HD, Coplan PM, Harikrishnan V, Alexander L. Decreased diversion by doctor-shopping for a reformulated extended release oxycodone product (OxyContin). Drug Alcohol Depend 2016;165:221-228.
10. Cicero TJ, Ellis MS, Surratt HL. Effect of abuse-deterrent formulation of OxyContin. N Engl J Med 2012;367:187-189.
11. Cicero TJ, Ellis MS, Kasper ZA. A tale of 2 ADFs: differences in the effectiveness of abuse-deterrent formulations of oxymorphone and oxycodone extended-release drugs. Pain 2016;157:1232-1238.
12. Cicero TJ, Ellis MS. Abuse-Deterrent Formulations and the Prescription Opioid Abuse Epidemic in the United States: Lessons Learned From OxyContin. JAMA Psychiatry 2015;72:424-430.
13. Coplan PM, Kale H, Sandstrom L, Landau C, Chilcoat HD. Changes in oxycodone and heroin exposures in the National Poison Data System after introduction of extended-release oxycodone with abuse-deterrent characteristics. Pharmacoepidemiol Drug Saf 2013;22:1274-1282.
14. Coplan PM, Chilcoat HD, Butler SF, et al. The effect of an abuse-deterrent opioid formulation (OxyContin) on opioid abuse-related outcomes in the postmarketing setting. Clin Pharmacol Ther 2016;100:275-286.
15. Dart RC, Severtson SG, Bucher-Bartelson B. Trends in opioid analgesic abuse and mortality in the United States. N Engl J Med 2015;372:1573-1574.
16. Havens JR, Leukefeld CG, DeVeaugh-Geiss AM, Coplan P, Chilcoat HD. The impact of a reformulation of extended-release oxycodone designed to deter abuse in a sample of prescription opioid abusers. Drug Alcohol Depend 2014;139:9-17.
17. Hwang CS, Chang HY, Alexander GC. Impact of abuse-deterrent OxyContin on prescription opioid utilization. Pharmacoepidemiol Drug Saf 2015;24:197-204.
18. Larochelle MR, Zhang F, Ross-Degnan D, Wharam JF. Rates of opioid dispensing and overdose after introduction of abuse-deterrent extended-release oxycodone and withdrawal of propoxyphene. JAMA Intern Med 2015;175:978-987.

19. Sessler NE, Downing JM, Kale H, Chilcoat HD, Baumgartner TF, Coplan PM. Reductions in reported deaths following the introduction of extended-release oxycodone (OxyContin) with an abuse-deterrent formulation. Pharmacoepidemiol Drug Saf 2014;23:1238-1246.
20. Li Y, Zhu Y, Chen C, et al. Internal validation of Medicaid Analytic eXtract (MAX) data capture for comprehensive managed care plan enrollees from 2007 to 2010. Pharmacoepidemiol Drug Saf 2017;27:1067-1076.
21. Skopp NA, Smolenski DJ, Schwesinger DA, Johnson CJ, Metzger-Abamukong MJ, Reger MA. Evaluation of a methodology to validate National Death Index retrieval results among a cohort of U.S. service members. Ann Epidemiol 2017;27:397-400.
22. Williams BC, Demitrack LB, Fries BE. The accuracy of the National Death Index when personal identifiers other than Social Security number are used. Am J Public Health 1992;82:1145-1147.
23. Green CA, Perrin NA, Janoff SL, Campbell CI, Chilcoat HD, Coplan PM. Assessing the accuracy of opioid overdose and poisoning codes in diagnostic information from electronic health records, claims data, and death records. Pharmacoepidemiol Drug Saf 2017;26:509-517.
24. Green CA, Perrin NA, Hazlehurst B, et al. Identifying and classifying opioid-related overdoses: A validation study. Pharmacoepidemiol Drug Saf 2019.
25. Beachler DC, Zhou, S.; Gangemi, K., Lanes, S., Walker, A.M., Rodrigues, R., Coplan, P.;. Validation of an Algorithm to Identify Opioid Overdose Among US Commerically Insured Individuals. International Conference on Pharmcoepidemiology and Therapeutic risk Mangement Meeting (ICPE 2018). Prague, Czech Republic 2018.
26. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010;1:97-111.
27. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-188.
28. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials 2015;45:139-145.
29. Roland CL, Lake J, Oderda GM. Prevalence of Prescription Opioid Misuse/Abuse as Determined by International Classification of Diseases Codes: A Systematic Review. J Pain Palliat Care Pharmacother 2016;30:258-268.
30. Compton WM, Jones CM, Baldwin GT. Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. N Engl J Med 2016;374:154-163.
31. Hser YI, Mooney LJ, Saxon AJ, et al. High Mortality Among Patients With Opioid Use Disorder in a Large Healthcare System. J Addict Med 2017;11:315-319.
32. Mojtabai R, Amin-Esmaeili M, Nejat E, Olfson M. Misuse of prescribed opioids in the United States. Pharmacoepidemiol Drug Saf 2019;28:345-353.
33. Hedegaard H, Minino AM, Warner M. Drug Overdose Deaths in the United States, 1999-2017. NCHS Data Brief 2018:1-8.

Figure 1: Incidence rates of unintentional fatal or non-fatal opioid overdose (OD) in the post and pre reformulation period during "any use" of OxyContin and the primary comparators

Abbreviations: OD=opioid overdose; ER= extended-release; TD=transdermal; HIRD=HealthCore Integrated Research Database.

Any Use – Concurrent use of opioids other than the study drugs was permitted.

Figure 2: Incidence rates of unintentional fatal or non-fatal opioid overdose (OD) in the post and pre reformulation period during "only use" of OxyContin and the primary comparators

Abbreviations: OD=opioid overdose; ER= extended-release; TD=transdermal; HIRD=HealthCore Integrated Research Database.

Only Use – No concurrent use of any opioid.

Figure 3: Adjusted ratio of rate ratios (aRoRs) comparing the rate ratio of unintentional opioid overdose (OD) in the post versus (versus) pre reformulation period for primary comparators to the rate ratio of unintentional OD in the post versus pre-reformulation period for OxyContin

Abbreviations: ER=extended-release; TD=transdermal; OD=opioid overdose.

Any Use – Concurrent use of opioids other than the study drugs was permitted.

Only Use – No concurrent use of any opioid.

Table 1: Demographic and clinical characteristics summary of OxyContin and primary comparator opioid use in the Medicaid, MarketScan and HIRD databases

Variable	Value	Any OxyContin Use*			Any Primary Comparator Opioid Use^		
		Medicaid	MarketScan	HIRD	Medicaid	MarketScan	HIRD
Patients		94,445	122,254	81,137	367,814	181,240	110,619
Total person-time per patient in months	Mean (SD)	7.8 (10.0)	6.0 (10.3)	6.1 (11.4)	8.1 (10.3)	8.0 (11.9)	9.5 (13.9)
Treatment Episodes		522,775	561,703	378,441	2,039,232	975,389	654,462
Gender	Female	295,875 (56.6%)	285,366 (50.8%)	189,986 (50.2%)	1,241,520 (60.9%)	560,051 (57.4%)	382,769 (58.5%)
	Male	226,900 (43.4%)	276,337 (49.2%)	188,455 (49.8%)	797,712 (39.1%)	415,338 (42.6%)	271,693 (41.5%)
Age (years)	Mean (SD)	46.7 (10.5)	53.1 (12.0)	51.4 (12.2)	46.9 (10.6)	54.6 (11.6)	53.4 (11.9)
DCI	Mean (SD)	2.0 (2.8)	2.0 (3.1)	1.7 (2.8)	2.0 (2.8)	2.4 (3.3)	2.0 (3.0)
Comparator use, any, n (%)	ER Morphine	0 (0%)	0 (0%)	0 (0%)	964, 343 (47.3%)	383,442 (39.3%)	252, 960 (38.7%)
	TD Fentanyl	0 (0%)	0 (0%)	0 (0%)	564,161 (27.7%)	441,383 (45.3%)	272,898 (41.7%)
	Methadone	0 (0%)	0 (0%)	0 (0%)	510,728 (25.1%)	150,564 (15.4%)	128,604 (19.7%)

Variable	Value	Any OxyContin Use*			Any Primary Comparator Opioid Use^		
		Medicaid	MarketScan	HIRD	Medicaid	MarketScan	HIRD
	IR oxycodone	133,497 (25.5%)	148, 267 (26.4%)	96,452 (25.5%)	290,641 (14.3%)	122,702 (12.6%)	89,639 (13.7%)
	IR hydromorphone	29, 378 (5.6%)	24,217 (4.3%)	17,397 (4.6%)	137,657 (6.8%)	67,264 (6.9%)	46,086 (7.0%)
	ER oxymorphone	4,937 (0.9%)	5,769 (1.0%)	3,602 (1.0%)	14,035 (0.7%)	10,630 (1.1%)	6,200 (0.9%)
Other Opioid use (non primary/secondary comparators		210,501 (40.3%)	229,127 (40.8%)	153,387 (40.5%)	924,121 (45.3%)	451,161 (46.3%)	290,985 (44.5%)
Clinical and co-morbidity characteristics°	Abdominal Pain	99,797 (19.1%)	80,535 (14.3%)	55,554 (14.7%)	436,472 (21.4%)	179,919 (18.4%)	120,612 (18.4%)
	Chronic pain	104,311 (20.0%)	65,463 (11.7%)	63,456 (16.8%)	427,644 (21.0%)	143,661 (14.7%)	138,170 (21.1%)
	Neuropathic pain	16,857 (3.2%)	14,164 (2.5%)	10,627 (2.8%)	70,734 (3.5%)	32,678 (3.4%)	26,043 (4.0%)
	COPD	102,942 (19.7%)	64,556 (11.5%)	49,926 (13.2%)	401,863 (19.7%)	129,161 (13.2%)	104,775 (16.0%)
	Major depression disorder	88,372 (16.9%)	62,556 (11.1%)	58,692 (15.5%)	378,331 (18.6%)	128,661 (13.2%)	119,470 (18.3%)
	History of overdose	2,657 (0.5%)	1,428 (0.3%)	1,110 (0.3%)	15,485 (0.8%)	3,801 (0.4%)	3,160 (0.5%)
	Opioid type dependence	30,472 (5.8%)	9,560 (1.7%)	11,343 (3.0%)	119,537 (5.9%)	18,777 (1.9%)	23,706 (3.6%)

Variable	Value	Any OxyContin Use*			Any Primary Comparator Opioid Use^		
		Medicaid	MarketScan	HIRD	Medicaid	MarketScan	HIRD
	Non-opioid drug dependence	32,589 (6.2%)	7,963 (1.4%)	8,840 (2.3%)	119,625 (5.9%)	15,083 (1.5%)	19,215 (2.9%)
	Benzodiazepines°	97,110 (18.6%)	86,631 (15.4%)	60,818 (16.1%)	368,051 (18.1%)	154,579 (15.8%)	109,074 (16.7%)

Abbreviations: COPD=Chronic Obstructive Pulmonary Disease DCI=Deyo-Charlson Index; ER=extended release; HIRD=HealthCore Integrated Research Database; IR=immediate release; SD=standard deviation; TD=transdermal.
Frequency (percent) presented unless otherwise specified
*Any use of OxyContin excluding concomitant primary comparator opioid use.
^Any use of any of the primary comparators (ER morphine, TD fentanyl, or methadone) excluding concomitant OxyContin or other primary comparator use.
°Each of the clinical and co-morbidity characteristics listed used a three-month lookback period prior to each treatment episode for their calculation, except for the comparator use, other opioid use and benzodiazepines which were measured during the treatment episodes.

Table 2. Incidence rates (IRs) of unintentional fatal or non-fatal opioid overdose (OD) among any OxyContin and any primary comparator opioid (non-overlapping)^ use two years before and five years after the reformulation by database

Unintentional Fatal or Non-Fatal Opioid Overdose	Period	Patients	Overdoses	Person-months	IR per 1,000 person-months	IRR (Comp / OxyContin)
Medicaid*						
OxyContin	Pre	54,855	630	384,417	1.64	-
ER morphine	Pre	98,795	1,352	581,045	2.33	1.42
TD fentanyl	Pre	59,597	780	337,179	2.31	1.41
Methadone	Pre	55,930	1,201	421,755	2.85	1.74
OxyContin	Post*	53,161	569	349,899	1.63	-
ER morphine	Post*	132,902	1,794	803,822	2.23	1.37
TD fentanyl	Post*	62,377	860	359,083	2.40	1.47

Methadone	Post*	60,932	1,205	477,538	2.52	1.55
MarketScan						
OxyContin	Pre	51,027	212	268,476	0.79	--
ER morphine	Pre	34,180	185	190,891	0.97	1.23
TD fentanyl	Pre	37,991	194	216,440	0.90	1.14
Methadone	Pre	13,262	100	102,965	0.97	1.23
OxyContin	Post	82,797	344	459,907	0.75	--
ER morphine	Post	60,206	407	378,948	1.07	1.44
TD fentanyl	Post	57,861	404	373,612	1.08	1.45
Methadone	Post	18,396	209	177,857	1.18	1.57
HIRD						
OxyContin	Pre	34,740	156	176,145	0.89	--
ER morphine	Pre	19,523	128	121,089	1.06	1.19
TD fentanyl	Pre	21,992	151	132,254	1.14	1.29

Methadone	Pre	10,859	95	86,429	1.10	1.24
OxyContin	Post	53,217	256	314,899	0.81	--
ER morphine	Post	37,153	302	293,756	1.03	1.26
TD fentanyl	Post	31,662	277	250,060	1.11	1.36
Methadone	Post	14,943	209	169,022	1.24	1.52

Abbreviations: HIRD=HealthCore Integrated Research Database®; IR=incidence rate; IRR=incidence rate ratio; ER=extended-release; OD=overdose; TD=transdermal.

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

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

Table 3: Rate ratios of unintentional fatal or non-fatal overdose (OD) among OxyContin and secondary comparator opioid use before and after the reformulation, by database

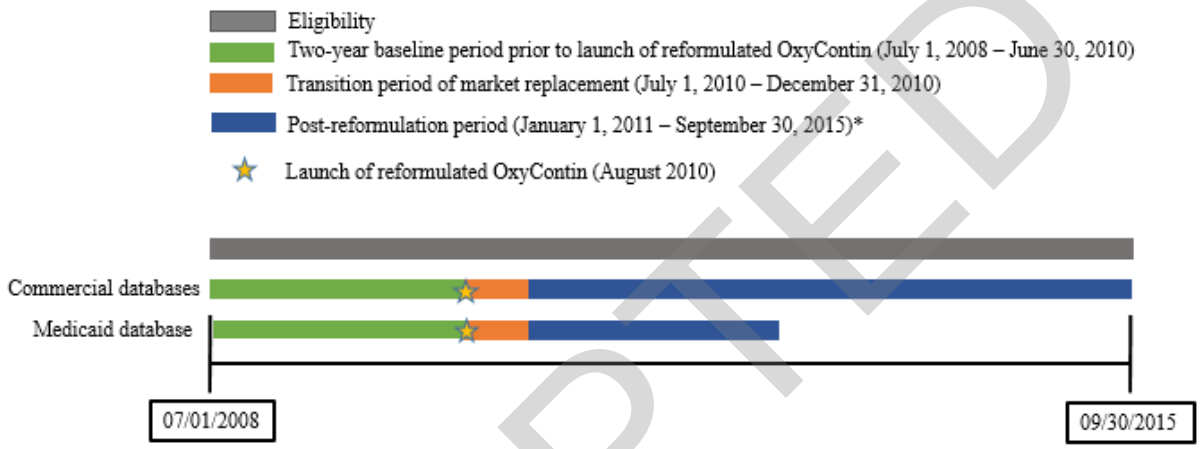
	Rate Ratio for Post- versus Pre-Reformulation Periods			Ratio of Rate Ratios for Comparator Opioids versus OxyContin		
	Adjusted Rate Ratio	**95% LCL**	**95% UCL**	**Adjusted Ratio of Rate Ratios**	**95% LCL**	**95% UCL**
Medicaid						
Any non-overlapping use^						
OxyContin	0.85	0.73	0.98	Ref	-	-
ER Oxymorphone	1.06	0.81	1.38	1.25	0.92	1.69
IR oxycodone SE	0.92	0.83	1.01	1.08	0.9	1.29
IR hydromorphone	0.90	0.76	1.07	1.06	0.85	1.33
Use without concomitant opioids ("Only use")						
OxyContin	0.80	0.63	1.01	Ref	-	-
ER oxymorphone	1.01	0.66	1.54	1.27	0.79	2.06
IR oxycodone SE	0.94	0.83	1.05	1.18	0.90	1.53
IR Hydromorphone	1.00	0.80	1.25	1.26	0.91	1.74
MarketScan						
Any non-overlapping use^						
OxyContin	0.69	0.55	0.86	Ref	-	-
ER oxymorphone	1.74	0.94	3.24	2.54	1.31	4.92
IR oxycodone SE	1.20	0.94	1.54	1.75	1.26	2.44
IR hydromorphone	1.03	0.72	1.47	1.50	0.99	2.29

Use without concomitant opioids ("Only use")						
OxyContin	0.64	0.44	0.94	Ref	-	-
ER oxymorphone	2.76	0.84	9.08	4.30	1.23	15.04
IR oxycodone SE	1.29	0.96	1.73	2.01	1.24	3.25
IR hydromorphone	0.83	0.54	1.25	1.29	0.73	2.26
HIRD						
Any non-overlapping use^						
OxyContin	0.59	0.44	0.80	Ref	-	-
ER oxymorphone	0.72	0.41	1.26	1.21	0.64	2.28
IR oxycodone SE	0.98	0.71	1.35	1.65	1.07	2.53
IR hydromorphone	0.78	0.53	1.16	1.32	0.81	2.14
Use without concomitant opioids ("Only use")						
OxyContin	0.48	0.30	0.78	Ref	-	-
ER oxymorphone	1.00	0.35	2.87	2.08	0.65	6.66
IR oxycodone SE	1.00	0.68	1.48	2.09	1.13	3.84
IR hydromorphone	0.80	0.49	1.28	1.66	0.86	3.19

Abbreviations: ER=extended release; HIRD=HealthCore Integrated Research Database; IR=immediate release; LCL=lower confidence limit; SE=single entity; UCL=upper confidence limit.

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

Supplemental Figure 1. Timeline of reformulated OxyContin launch and eligibility



*The primary post-reformulation period extends from January 1, 2011 to December 31, 2012 for the Medicaid data.

Supplemental Table 1: ICD-9 and ICD-10 codes used in the algorithm to find opioid overdoses^

	ICD-9 Code	ICD-10 Code
Poisoning by opium (alkaloids) unspecified	965.00	
Poisoning by heroin	965.01	
Poisoning by methadone	965.02	
Poisoning by other opiates and related narcotics	965.09	
Accidental poisoning by heroin	E850.0	
Accidental poisoning by methadone	E850.1	
Accidental poisoning by other opiates and related narcotics	E850.2	
COD: Poisoning by opiates and related narcotics	9650	
COD: Poisoning by opium		T40.0*
COD: Poisoning by heroin		T40.1
COD: Poisoning by other opioids		T40.2*
COD: Poisoning by methadone		T40.3*
COD: Poisoning by other synthetic narcotic		T40.4*
COD: Accidental poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified		X42
COD: Intentional self-poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified*		X62
COD: Undetermined poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified		Y12

^Of note, in 2010 categories X40 to X49, X60 to X69, and Y10 to Y19 in the ICD-10-CM codes were deactivated with notation to see T36 to T65 with the fifth or sixth character for replacement . Thus, the codes in categories T36-T65 are combination codes that include the substance that was taken as well as the intent. No additional external cause code is required for poisoning, toxic effects, adverse effects, and underdosing codes.
*All codes are included within these categories except for four following "underdosing" codes: T40.0X6 (Underdosing of opium), T40.2X6 (Underdosing of other opioid), T40.3X6 (Underdosing of methadone), or T40.4X6 (Underdosing of other synthetic narcotics)

Supplemental Table 2. Covariates included in this study

Group	Definition
Demographic characteristics	• Age* • Gender* • Geographic region (commercial databases)* • United States (US) state (Medicaid database)* • Calendar year of index date • Plan type (Health Maintenance Organization [HMO], preferred provider organization [PPO], consumer driver health insurance [CDHP]/high deductible health plan [HDHP])* • Medicaid coverage type (fee-for-service [FFS], managed care [CMC])* • Medicaid basis of eligibility (basis of eligibility [BOE]) group (disabled, adult)*
Clinical characteristics	• Abdominal pain* • Amputation* • Arthritis, arthropathies, osteoarthritis, and musculoskeletal pain* • Back pain* • Chronic pain* • Fibromyalgia* • Headache* • Malignancy* • Multiple sclerosis*

	• Neuropathic pain* • Peripheral vascular disease* • Stroke* • Liver disease* • Renal disease* • Chronic Obstructive Pulmonary Disease (COPD*) • Impaired respiratory function*
Co-morbidities	• Deyo-Charlson-comorbidity index* • History of overdose/poisoning* • Alcoholism^ • Generalized anxiety disorder^ • Attention deficit hyperactive disorder (ADHD)^ • Bipolar disorder^ • Major depressive disorder^ • History of attempted suicide^ • Post-traumatic stress disorder^ • Sleep disorder^ • Somatoform disorder^ • Opioid type dependence^ • Non-opioid type dependence^ • Borderline personality disorder^ • All-cause office visits in last six months^ • All cause emergency department visits in last six months^ • All cause hospitalizations in last six months^

	• Distinct medication classes in last six months^
Opioid use and other characteristics	• Prior use of opioid analgesic (none, extended-release [ER] opioid only, immediate-release [IR] opioid only, ER + IR opioids)* • Prior use of Tramadol (ER or IR)^ • Time since last opioid analgesic • Type of ER opioid analgesic used during episode • Use of Buprenorphine delivery system • Duration of opioid analgesic(s) use during treatment episode • Number of different opioid study drugs • Concurrent use of opioid maintenance therapy medications (Suboxone, Subutex, solutions of methadone) • Concurrent use of benzodiazepines • Concurrent use of barbiturates • Concurrent use of sleep medications • Concurrent use of amphetamines • Concurrent use of methylphenidate • Concurrent use of dextromethorphan • Concurrent use of muscle relaxants • Number of prescribers of IR or ER opioid analgesics • Number of pharmacies where IR or ER opioid was obtained • Prescribing physician specialty

*Variable included in regression adjusted and propensity score adjusted models

^Variable included only in propensity score adjusted models.

Supplemental Figure 2: Patient A's opioid treatment episodes from January 2009 until May 2010. Health plan coverage started 01 January 2009

<table>
<tr><td>Study Drug Type</td><td colspan="3">January 2009</td><td>February 2009</td><td>March 2009</td><td>April 2009</td><td>May 2009</td></tr>
<tr><td>OxyContin</td><td colspan="6">OxyContin 1/9-1/31</td></tr>
<tr><td>Primary Comparator</td><td colspan="6">ER Morphine 1/20-1/31</td></tr>
<tr><td>Secondary Comparator</td><td colspan="6">IR Oxycodone 1/27-2/7
92 Day Gap</td></tr>
<tr><td>Treatment Episode</td><td>1</td><td>2</td><td>3</td><td>4</td><td colspan="3"></td></tr>
</table>

Treatment Episode 1 (1/9-1/19): Any Oxy use; Oxy w/o CO; Any Oxy; No new use.

Treatment Episode 2[a] (1/20-1/26): Any Oxy use; Oxy w/ CO; No new use.

Treatment Episode 3[a] (1/27-1/31): Any Oxy use; Oxy w/ CO; No new use.

Treatment Episode 4 (2/1-2/7): Any SC; SC w/o CO; No new use.

<table>
<tr><td>May 2009</td><td>June 2009</td><td>July 2009</td><td>August 2009</td><td>September 2009</td></tr>
<tr><td colspan="5">ER Morphine 5/27-7/17</td></tr>
</table>

		OxyContin 6/19-8/2				OxyContin 8/15-9/6
		TD Fentanyl 7/4-8/10				
						ER Morphine 8/15-9/6
5	6	7	8	9		10

Treatment Episode 5[b] (5/27-6/18): Any PC; PC w/o CO; New use ER Morphine.

Treatment Episode 6[a] (6/19-7/3): Any Oxy use; Oxy w/ CO; New use ER morphine.

Treatment Episode 7[a] (7/4-7/17): Any Oxy use; Oxy w/ CO; New use ER morphine.

Treatment Episode 8[a] (7/18-8/2): Any Oxy use; Oxy w/ CO; No new use.

Treatment Episode 9 (8/3-8/10): Any PC; PC w/o CO; No new use.

Treatment Episode 10[a,c] (8/15-9/6): Any Oxy use; Oxy w/ CO; New use ER morphine.

September 2009	October 2009	November 2009	December 2009	January 2010
ER Morphine 9/7-11/3				
	OxyContin 10/7-11/20			
		Other opioids 10/28/2009-1/1/2010		

11	12	13	14	15

Treatment Episode 11 (9/7-10/6): Any PC; PC w/o CO; New use ER Morphine.

Treatment Episode 12[a] (10/7-10/27): Any Oxy use; Oxy w/ CO; New use ER morphine.

Treatment Episode 13[a] (10/28-11/3): Any Oxy use; Oxy w/ CO; New use ER morphine.

Treatment Episode 14 (11/4-11/20): Any Oxy use; Any Oxy; Oxy w/o CO; No new use.

January 2010	February 2010	March 2010	April 2010	May 2010

Other Opioids 1/1/2010-2/15/2010		ER Oxymorphone 3/1-6/30
15		16

Treatment Episode 15[d] (11/21/2009-2/15/2010): N/A

Treatment Episode 16 (3/1-6/30): Any SC; SC w/o CO; New use ER oxymorphone.

Abbreviations: ER=extended release; IR=immediate release; oxy= OxyContin; CO=comparator opioid; PO=primary objective; PC=primary comparator; SC=secondary comparator; N/A= not applicable

a. Treatment episode not included in PO's 2 and 3 because of concomitant OxyContin and primary comparator use.

b. Treatment episode is new use for ER morphine because patient A did not have any dispensings for OxyContin, primary, or secondary comparator opioids in the 92 days prior.

c. Treatment episode remains a new use episode for ER morphine because the gap between previous treatment episode with new use ER morphine and this treatment episode is <30 days (also known as the 30 days extension period).

d. Treatment episode is an "other ER or IR opioid". It is not OxyContin, a primary comparator, or secondary comparator.

Supplemental Table 3: Changes in the rates of unintentional fatal or non-fatal overdose (OD) among OxyContin users from 2008-2015

	Pre-Period				Post-Period				Pre-Period [REF] vs. Post Period		
	N Patients	N Cases	Person-months	Rate per 1000 person-months°	N Patients	N Cases	Person-months	Rate per 1000 person-months°	Adjusted* Rate Ratio°	95% LCL	95% UCL
Medicaid: Incident and Prevalent (Two years before compared to Two years after reformulation)											
Any use of OxyContin (used alone or with other opioids concomitantly)	57,156	733	4147937	1.77	55,242	642	3737662	1.72	0.93	0.83	1.04
Use of only OxyContin (without the use of other opioids)	37,609	213	1431156	1.49	32,464	111	907909	1.21	0.80	0.63	1.01

MarketScan: Incident and Prevalent (Two years before compared to Five years after reformulation)											
Any use of OxyContin (used alone or with other opioids concomitantly)	52,558	253	2855	0.89	85,028	406	4805	0.84	0.88	0.74	1.05
Use of only OxyContin (without the use of other opioids)	34,457	56	9745	0.57	52,617	56	1408	0.40	0.64	0.43	0.94
HIRD: Incident and Prevalent (Two years before compared to Five years after reformulation)											
Any use of OxyContin (used alone or with other opioids concomitantly)	35,758	196	1882	1.04	54,411	306	3318	0.92	0.83	0.64	1.08
Use of only OxyContin (without the use of other opioids)	23,635	57	6395	0.89	34,728	41	9014	0.45	0.48	0.30	0.78
Pooled Commercial Results: Incident and Prevalent (Two years before compared to Five years after reformulation)											
Any use of OxyContin (used alone or with other opioids concomitantly)									0.86	0.75	1.00
Use of only OxyContin (without the use of									0.55	0.	0.

other opioids)			7	4 2	7 7

Abbreviations: N=number; p=person; LCL=lower confidence interval; UCL=upper confidence interval.

*Models adjusted for demographics and clinical characteristics.

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