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THE EVOLVING CONSEQUENCES OF OXYCONTIN REFORMULATION ON DRUG OVERDOSES

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ABSTRACT

Recent evidence suggests that the short-term transition of the opioid crisis from prescription opioids to heroin can be attributed to the reformulation of OxyContin, which substantially reduced access to abusable prescription opioids. In this paper, we find that over a longer time horizon, reformulation stimulated illicit drug markets to grow and evolve. We compare overdose trajectories in areas more exposed to reformulation, defined as states with high rates of non-medical OxyContin use before reformulation, to less exposed areas. More exposed areas experienced disproportionate increases in fatal overdoses involving synthetic opioids (fentanyl) and non-opioid substances like cocaine, suggesting that these new epidemics are related to the same factors driving the rise in heroin deaths. Instead of just short-term substitution from prescription opioid to heroin overdoses, the transition to illicit markets spurred by reformulation led to growth in the overall overdose rate to unprecedented levels.

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1. Introduction

The opioid crisis is a national emergency, and policymakers are struggling to implement policies to curb rising overdose rates. Exacerbating the difficulties in finding effective policy options, the crisis has rapidly transitioned from prescription to illicit opioids, altering the epidemic's landscape. Prior to this transition, there was some evidence that overdose death rates had plateaued – the national overdose rate had increased by less than 0.9 overdoses per 100,000 people in the previous five years combined. However, the shift to illicit markets has subsequently pushed overdose rates to unprecedented levels.

This recent growth has been startlingly disparate across the country. The 10 states with the slowest growth in overdose rates experienced, on average, less than 1 additional overdose per 100,000 residents in 2017 compared to their 2009 rates. On the other end of the spectrum, the 10 states with the fastest growing overdose rates experienced a staggering *27* additional overdoses per 100,000 residents. It would have been difficult to predict separation of this magnitude in 2009 – both sets of states had 11 overdoses per 100,000 people in that year. In fact, the states which would experience the slowest overdose growth rates initially had 16% *higher* rates of nonmedical pain reliever use. What explains why the opioid crisis stabilized in some states while devastating others? Notably, the 10 states which would experience the fastest growth in overdose rates between 2009 and 2017 initially had nonmedical use rates of OxyContin over 60% higher than the bottom 10 states, despite the lower rates of pain reliever misuse overall.

The reformulation of OxyContin, the "drug of choice" for many misusing opioids (Cicero et al., 2005), made the drug harder to abuse. Recent work shows that states with higher rates of nonmedical OxyContin use before reformulation experienced a disproportionate rise in heroin overdoses after reformulation and the removal of the original formulation in August 2010 (Alpert et al., 2018). This research suggests that the reformulation led to the heroin epidemic, explaining the

vast majority – if not all – of the increase in heroin overdoses between 2010 and 2013. As access to abusable prescription opioids decreased, people switched to illicit drug markets (Cicero et al, 2012; Coplan et al., 2013), increasing heroin overdoses and infectious diseases (Beheshti, 2019; Powell et al., 2019).[1] This line of research strongly suggests that the reformulation of OxyContin initiated the transformation of the opioid crisis from prescription to illicit opioids.

However, previous work found little evidence that reformulation affected overdose rates beyond just a shift in the types of opioids involved in overdoses. Since 2013, the opioid crisis has further evolved and illicit markets have grown (O'Donnell et al, 2017a; O'Donnell et al, 2017b; Ciccarone, 2017), suggesting that the longer-term consequences may be very different. Did reformulation lead to just shifting in types of overdoses or has it spurred the subsequent rise in overdose rates? This longer-term relationship is unknown but understanding the causes of the changing landscape of the opioid crisis is key for combatting this public health emergency. This paper addresses this gap.

The evolution of the opioid crisis can be observed in Figure 1A, which shows overdose trends for 1999-2017. Prior to 2011, natural and semisynthetic opioids were the driving force behind the opioid crisis. However, heroin overdose rates began to escalate near the end of 2010. Beginning in 2013, the growth of overdoses involving synthetic opioids overshadowed even heroin's rapid escalation. In addition, the third wave has included overdoses involving substances other than opioids, typically mixed with fentanyl (Jones et al., 2017; Pardo et al., 2019). Since 2010, the number of overdoses involving cocaine has more than tripled as shown in Figure 1B; over 70% of cocaine overdoses in 2017 involved some type of opioid.[2]

[1] Other work has found some evidence of similar types of responses to supply-side interventions such as prescription drug monitoring programs (see Mallatt, 2018 and Meinhofer, 2018).
[2] Authors' calculations.

The changes to illicit drug markets in just the past few years have been wide-reaching and striking. Illicitly-manufactured fentanyl is now the primary driver of overdoses. We analyze its ties to the reformulation of OxyContin to better understand its increasing dominance in illicit drug markets as well as its broader effects on overdose rates. We adopt and extend the approach of Alpert et al. (2018) to study the longer-term evolution of the opioid crisis since the reformulation of OxyContin in August 2010.

Our analysis has three primary motivations. First, we seek to understand the net impact of OxyContin's reformulation on opioid-related mortality as the opioid crisis continues to evolve. If reformulation reduced initiation of misuse, then short-run shifts of the existing OxyContin-misusing population to heroin would eventually drop off, and in the long-run we would see a decline in both natural/semi-synthetic opioid mortality and heroin mortality tied to reformulation. Alternatively, reformulation may have induced illicit markets to grow and innovate to meet demand, resulting in long-term growth of overdoses. The longer-term consequences of reformulation may be very different from the short-term ramifications.

Second, it is critical to evaluate the extent to which opioid users entering selective illicit markets in search of a substitute for the reformulated OxyContin drove the supply of fentanyl (supply responding to demand). Considerable attention has been given to the dynamics of the supply of fentanyl and how it has permeated the opioid market (e.g., Abouk et al., 2019; Pardo et al., 2019); however, less attention has been given to the underlying demand-driven factors and the role they might have had in driving the introduction of fentanyl (and its derivatives) into the supply of opioids and then subsequently into other illicit market substances, such as cocaine. While illicitly-manufactured fentanyl is primarily produced in an international market (Pardo et al., 2019), we explore whether the rise in deaths involving synthetic opioids and cocaine can be partially explained by the same demand factors that drove the earlier rise in heroin overdoses. Earlier work found an

immediate relationship with heroin. However, the short-term connection may miss an even more dramatic association with synthetic opioids, which are currently driving the opioid crisis to distressing new heights.

Our third motivation is the importance of understanding the longer-term consequences of expanding participation in the illicit opioid market. The degree to which markets for different illicit substances integrate is important for evaluating policy approaches for tackling this opioid problem. For example, if supply-side interventions are paired with substance abuse treatment expansions targeting opioid use disorder, but the move to the black market expands use of other illicit drugs for which medication-assisted therapy for opioids is not effective, then we cannot fully address the long-term consequences of this shift in demand. Broadly, there are few opportunities to study the ramifications of exogenous growth in illicit drug markets (see Jacobson, 2004) and how these markets evolve and innovate over time.

This paper examines whether pre-reformulation OxyContin misuse rates, reflecting exposure to reformulation, predict differential rises in fatal overdoses involving heroin, synthetic opioids, cocaine, and psychostimulants over a longer time horizon. Our analysis provides evidence that the OxyContin reformulation triggered a pivotal and enduring transformation in the opioid crisis.

We find that the substitution of heroin overdoses for prescription opioid overdoses has persisted and grown. In addition, the extraordinary rise of synthetic opioid overdoses that now drives the opioid crisis can be traced to the same demand factors as the rise in heroin overdoses. We also find that those same forces explain the rise in cocaine overdoses. Finally, and departing from prior conclusions regarding short-term impacts, we find that reformulation substantially increased overall overdose rates.

By 2013, there was limited evidence that reformulation was responsible for a small increase in overdoses, suggesting that reformulation was mainly leading to substitution (in terms of

overdoses) across opioid types. There are potentially negative consequences of switching from legal to illicit markets even if the overall overdose rate is unchanged, such as an increase in infectious diseases. However, the welfare calculus of any supply-side intervention changes when, over a longer time horizon, it drastically increases fatal overdose rates. By extending prior analyses just a few years, we uncover evidence that reformulation increased overdose rates to unprecedented levels through the expansion of illicit drug markets.

We provide additional background about the reformulation of OxyContin in the next section. In section 3, we describe the data. We discuss our empirical strategy in Section 4 and provide results in Section 5. We conclude in Section 6.

2. Background

OxyContin was introduced in 1996 by Purdue Pharma. It is a brand-name drug for the extended-release formulation of oxycodone, a semi-synthetic opioid, used for the management of acute and chronic pain. The key innovation of OxyContin was its long-acting formula, which provided 12 hours of continuous pain relief, significantly improving the quality and ease of pain management compared to previous drugs. However, crushing or dissolving the pill caused the complete dose of oxycodone to be delivered immediately, making OxyContin especially easy to abuse and there were concerns about widespread abuse of OxyContin by 2000, if not earlier (Cicero et al., 2005).

OxyContin had more than $3 billion in sale in 2010, making it one of the highest selling drugs in the United States (Bartholow, 2011). The drug's wide market presence occasioned extensive diversion to non-medical use, making it one of the leading drugs of abuse (Cicero et al., 2005). Many experts have implicated OxyContin as a key driver of the opioid epidemic (e.g., Kolodny et al., 2015) and recent work concludes that its introduction explains a significant share of

the growth in overdoses since 1996 (Alpert et al., 2019), suggesting that its removal or reformulation could also have large effects.

In April 2010, Purdue Pharma introduced a reformulated version of OxyContin designed to make the drug more difficult to abuse. The abuse-deterrent version uses physicochemical barriers to make the pill hard to break, crush, or dissolve. The change increased the costs of misusing OxyContin while maintaining the medical benefits of the drug. The reformulated version can still be abused orally (i.e., taking higher doses than prescribed) and some users have counteracted the abuse-deterrent properties of the new version.[3] In August 2010, Purdue Pharma stopped distributing the original formulation of OxyContin to pharmacies. The removal of the original formulation represents one of the largest reductions in the supply of abusable prescription opioids to date.

Prior work has provided quasi-experimental evidence that this reduction initiated widespread substitution to heroin, leading to a sharp rise in heroin overdoses (Alpert et al., 2018; Evans et al., 2019). The opioid crisis has evolved considerably since the end of the sample periods previously analyzed in this literature. There is little existing evidence that reformulation induced a meaningful change in the overall overdose rate. However, our understanding of the effectiveness of supply-side interventions requires studying longer-term outcomes, permitting time for illicit markets to expand and innovate.

3. Data

3.1 Mortality

We use the National Vital Statistics System (NVSS) Multiple Cause of Death mortality files—the census of deaths in the United States— to study annual overdose deaths from 1999 to

[3] Highly sophisticated methods were shared on websites for how to counteract the abuse-deterrent properties of the drug involving baking, freezing, or soaking the pill in solvents (Goodnough and Zezima, 2011; Becker and Fiellin, 2017). Cicero and Ellis (2015) noted that the significant time effort required should deter use of these methods.

2017. We use restricted data to access state identifiers. We code deaths as drug poisonings, which we refer to as "overdoses" throughout this paper, by using ICD-10 external cause of injury codes X40-X44, X60-64, X85, or Y10-Y14. We use drug identification codes for information about the substances found in the body at death. T40.1 indicates poisoning by heroin. T40.2 designates natural and semisynthetic opioids (e.g., oxycodone), and T40.4 refers to synthetic opioids excluding methadone (e.g., fentanyl). To study opioid overdoses, we will aggregate T40.0-T40.4 plus T40.6, which include opium, methadone, and unspecified narcotics in addition to the categories previously mentioned. In addition, we will study overdoses involving cocaine (T40.5) and psychostimulants (T43.6).

There are significant concerns about missing opioid-related overdoses overall or by type, such as those coded as unspecified narcotics (T40.6) or unspecified drugs (T50.9) (Ruhm, 2018). Imputation methods are potentially valuable but rely on assumptions that unspecified drugs can be predicted by the same model as observations with specified opioids. We study T40.6 and T50.9 overdoses specifically and test whether these unspecified overdoses are related to OxyContin misuse. In addition, we perform sensitivity analyses limited to states meeting the standard of "very good to excellent reporting."

3.2 Nonmedical OxyContin Use and OxyContin Supply

To measure nonmedical use of OxyContin and pain relievers, we use aggregated, state-level data from the National Survey on Drug Use and Health (NSDUH). The NSDUH, a nationally-representative household survey of individuals ages 12 and older, is the country's largest survey collecting information on substance use and mental health issues. The survey provides information on self-reported "nonmedical OxyContin use" as well as "nonmedical pain reliever use" within the past year. The NSDUH began asking about nonmedical OxyContin use in 2004. These data were

publicly available as two-year waves and aggregated further to 2004-2009 to reduce measurement errors concerns. Results are similar if we construct our measures of nonmedical use with only one wave of data.

The NSDUH has two important advantages. First, it specifies OxyContin in the survey question, which is the exact drug product affected by the reformulation. Second, it specifies nonmedical use, the relevant dimension since reformulation did not affect the medical capabilities of OxyContin. Nonmedical use or misuse captures use by individuals who were not the ones for whom the medication was prescribed or who use it in a manner inconsistent with the physician's prescription instructions. Alternative data sources on OxyContin use through legal channels, such as pharmacy claims data or reports of legal distribution, do not capture the differential effects of the reformulation—which we would expect to affect nonmedical users more than medical users—across states. Alpert et al. (2018) find that, in practice, nonmedical use is highly correlated with oxycodone supply and OxyContin prescriptions. Evans et al. (2019) pursue a similar strategy as Alpert et al. (2018) but use oxycodone supply as the measure of exposure to reformulation. This metric results in similar conclusions given the correlations shown in Alpert et al. (2018), but we rely on the NSDUH measure as our primary metric of exposure to reformulation here for the reasons supplied above.

The NSDUH measures are self-reported and possibly prone to some reporting error. NSDUH uses techniques designed to elicit accurate and honest answers from respondents. These methods – such as showing pictures of OxyContin – reduce concerns that the "OxyContin misuse" measure reflects misuse of other types of oxycodone. NSDUH provides respondents with a highly private and confidential method for responding to questions in an effort to increase honest reporting. Under-reporting due to missing values is rare. To the extent that there is misreporting in the OxyContin misuse variable, our estimates should be attenuated. Moreover, if people were

reporting nonmedical pain reliever use but not nonmedical OxyContin use, even though they misused OxyContin specifically, then we should find that the nonmedical pain reliever misuse variable is also associated with differential growth in overdoses. We do not.

To further consider concerns about measure error, we adopt an alternative measure of cross-state variation in exposure to OxyContin reformulation -- per capita OxyContin supply, measured in morphine equivalent doses (MEDs, defined as 60 morphine milligram equivalents). These data are collected as part of the Drug Enforcement Administration's (DEA's) Automation of Reports and Consolidated Orders System (ARCOS), which tracks the distribution of controlled substances to each state (and sub-state geographies). Data are available by ingredient but due to our interest in OxyContin specifically, we filed a Freedom of Information Act request to the DEA for OxyContin specifically. The data included the census of OxyContin supplied throughout the country. We aggregate the years 2004 to 2009 to remain consistent with our NSDUH measures.

We present summary statistics in Table 1 for 2004-2009. Before reformulation, OxyContin misuse rates had almost no correlation with heroin and cocaine overdose rates. We show the geographic variation in OxyContin misuse in Figure A1.

4. Empirical Strategy

We conduct our analysis at the state level primarily due to data availability. State boundaries are likely not appropriate boundaries for medical or illicit drug markets, but there is little loss for our purposes of performing the analysis at this level. If it were possible, using more granular data would provide additional variation in exposure to reformulation to exploit, potentially providing more power. However, there is no bias caused by aggregating to a higher level in a linear model. Our analysis does not suffer from inadequate power so we do not consider this a meaningful limitation.

We adopt an event study design, which estimates the relationship between initial OxyContin misuse and overdose outcomes in each year, normalized to 0 in 2010. This approach permits us to flexibly trace the relationship between exposure to the reformulation of OxyContin and overdose rates. The specification is

$$(1) \qquad Y_{st} = \alpha_s + \gamma_t + \delta_t \times OxyRate_s^{Pre} + \theta_t \times PainRelieverRate_s^{Pre} + \varepsilon_{st},$$

where Y_{st} is fatal overdoses per 100,000 in state s and year t; $OxyRate_s^{Pre}$ represents the fixed OxyContin misuse rate in state s in the pre-reformulation period (2004-2009). $PainRelieverRate_s^{Pre}$ represents the pain reliever misuse rate in state s in the pre-reformulation period (2004-2009).

The specification includes state (α_s) and time fixed effects (γ_t) to account for fixed differences across states and national trends in overdoses. This model permits us to test for pre-existing trends while studying the timing of any effect given the expectation of lagged effects in this context. We plot the δ_t estimates with 95% confidence intervals, adjusted for state-level clustering. We graphically mark 2011 as the first full year of reformulation, though partial effects in 2010 are consistent with causal impacts associated with reformulation. The timing of effects is expected to vary by substance. All regressions are population-weighted using population data from the Surveillance, Epidemiology, and End Results Program (SEER).

Including time-varying demographics and state policy variables has little effect on our estimates so we present results from a simplified model without additional covariates. The pain reliever misuse variable (interacted with time indicators) addresses many concerns about secular changes across states. Most policies targeting opioid misuse and most predictors correlated with overdoses typically relate to all opioids, not OxyContin specifically. The inclusion of these pain reliever misuse variables helps to isolate effects unique to OxyContin while accounting for

characteristics that influence overdoses more broadly.[4] In principle, this variable is not perfect because there may still be some variation within the more general measure of pain reliever use that should be captured. However, we find that other time-varying covariates and policy variables provide little additional information once these pain reliever misuse variables are included in the specification. We show this in sensitivity tests. This insensitivity suggests that these variables adequately soak up many of the concerns that we may have about other confounding policies or shocks. We also note that our results for heroin overdoses, synthetic overdoses, cocaine overdoses, and all overdoses are generally *strengthened* by the inclusion of the pain reliever misuse variables, suggesting that any residual unobserved confounders are also likely attenuating the estimates.

5. Results

5.1 Opioid Overdoses

We begin by estimating the relationship between pre-reformulation OxyContin misuse and opioid-related overdoses – both overall and by opioid type. Figure 2A presents event study estimates for heroin overdoses. We observe no evidence of a pre-existing trend, followed by an increase beginning in 2011. This sharp rate of growth continues through 2016 before we see the first decrease in 2017. The finding that the trend continues through 2016 casts doubts on the hypothesis that reformulation of OxyContin would lead to reductions in initiation and subsequent longer-term declines in misuse. Instead, the results suggest that reformulation continues to play a meaningful role in explaining the rise in heroin overdoses.

[4] Alpert et al. (2018) found evidence of relative *reductions* in heroin overdoses associated with the more general pain reliever misuse variable, consistent with systematic adoption of policies to reduce opioid-related harms in high misuse states.

We estimate a similar, though delayed, pattern for synthetic opioids in Figure 2B. Again, the estimates are flat prior to reformulation, suggesting the absence of confounding trends. We observe a rise in the estimates for synthetic opioid overdoses beginning in 2013, and these effects then escalate precipitously until the end of the sample. The 2017 estimate is 19.9, implying that a state with a one standard deviation higher rate of OxyContin misuse experienced 4.6 additional synthetic opioid overdoses per 100,000 due to additional exposure to reformulation.

This result suggests that the entry of fentanyl was not independent of demand but, instead, strongly followed demand for illicit opioids. As the supply of abusable prescription opioids was reduced in the medical market, users switched to illicit markets. The fact that heroin overdoses increased immediately after reformulation indicates an expansion in the illicit market in terms of the number of users, followed by an evolution in the substances. These results, which show a systematic relationship between exposure to OxyContin reformulation and mortality involving synthetic opioids, suggest that fentanyl was part of this evolution. The delay in effect was likely due to the time it took for illicit suppliers to innovate in order to meet the rising demand for heroin, with that innovation initially being the use of fentanyl and its analogs as cheap fillers in bags sold as heroin (Pardo et al., 2019).

In Panel 2C, we explore the effect of exposure to OxyContin reformulation on natural and semi-synthetic opioids, the category that includes OxyContin. A pre-existing upward trend is observed here but flattens around the time of reformulation, and there is little evidence of a return to this prior trend. The pre-existing trend is expected due to our identification strategy. States with high rates of OxyContin misuse prior to reformulation would be more likely to experience increasing rates of misuse in the pre-period in order to be identified as "high misuse" states, and hence these states have higher (and growing) rates of natural and semi-synthetic opioid mortality.

In Panel 2D, we study the aggregated measure of opioid overdoses (T40.0-T40.4, T40.6), thereby incorporating opioid overdoses not specified as a particular type of opioid. The results for this outcome represent one of the key differences from prior work. We estimate large increases in opioid overdoses. Initially, reformulation may have had only small effects on overall overdose mortality, but it is clear that the increase in heroin and fentanyl overdoses is dominating any reduction in overdoses involving natural and semi-synthetic opioids in states most exposed to OxyContin reformulation. This finding is consistent with large spillover effects, which are explored further below.

One interpretation of this finding is that the OxyContin reformulation led some individuals to move from prescription opioids to illicitly-produced and -sold opioids, expanding demand in the illicit market. As demand expanded and given the lack of information regarding actual product quality and contents in black markets (Galenianos et al., 2012; Miron 2003), there were spillovers throughout the illicit drug market. Specifically, suppliers mixed fentanyl with other drugs. Given the additional potency of illicit fentanyl, overdose rates grew even faster. Because of this market growth, we no longer observe a simple substitution of overdoses from natural/semisynthetic opioids to illicit opioids, but overall growth of opioid-related overdoses.

To explore these dynamics further, we study overdoses involving only a single reported opioid type in Figure 3. When we examine overdoses involving only heroin, we estimate a similar relationship in the first years after reformulation, but that relationship eventually deteriorates, as shown in Panel A. By 2017, there is almost no relationship between pre-reformulation OxyContin misuse and heroin-only overdose rates. When we examine overdoses involving natural and semisynthetic opioids that do not involve heroin or synthetic opioids, we also see larger reductions.

The large reductions may partially represent a decline in overdoses involving only one reported[5] opioid due to growth in overdoses involving substances contaminated with fentanyl.

5.2 Spillovers

We next consider whether OxyContin reformulation affected cocaine overdoses. Cocaine overdoses might increase if individuals who were using OxyContin for nonmedical purposes switched to cocaine post reformulation, in which case mortality should rise immediately (similar to that observed for heroin). Alternatively, suppliers in geographic areas where fentanyl was being used to extend heroin supplies might start mixing it with cocaine too, in which case we could see a delayed increase in cocaine mortality.

In Figure 4A, we observe a pattern for cocaine overdoses similar to the one estimated for synthetic opioids (Figure 2B). The results suggest a strong relationship between prior OxyContin misuse and the rise in cocaine overdoses after reformulation, but the effect is delayed. The 2017 estimate is 5.6, implying that a state with a one standard deviation higher rate of OxyContin misuse experienced 1.3 additional cocaine opioid overdoses per 100,000 due to additional exposure to reformulation.

In Figure 4B, we study cocaine overdoses that do not also involve opioids. Here the trend is generally flat. There is some evidence of a small differential increase in 2013; however, the imperfect coding of synthetic opioids at this time would imply that we should observe some rise in cocaine overdoses not involving *reported* opioids. The relative magnitudes of the Panel A estimates compared to the Panel B estimates strongly suggest that the relationship with cocaine is not due to

[5] See Section 5.3 for tests about appropriate coding in the mortality data. We generally find that the data concerns bias our results towards zero. In this context, findings related to a decline in single-opioid overdoses would also be consistent with systematic differences in coding quality changing over time. We cannot rule out this possibility here.

some confounding secular trend specific to cocaine. Instead, reformulation had a delayed effect on cocaine overdoses involving opioids, which could be due to either sellers spiking the cocaine supply[6] or users deciding to use cocaine in combination with their opioids.

In recent years, the United States has also experienced a surge in overdoses involving psychostimulants, such as methamphetamine and dextroamphetamine (Kariisa et al., 2019). We find less evidence of a relationship with reformulation in the case of these substances. Results are shown in Figure 5. The analyses showed a relative decline in states with high rates of pre-reformulation OxyContin misuse. This reduction may suggest that psychostimulants are more likely to be used as complements with prescription opioids than with heroin. However, after fentanyl's entry, this trend reverses, suggesting again that the connection might be driven either by contaminated supply or consumer preferences to use multiple substance with synthetic opioids. When we consider overdoses involving psychostimulants without any opioid present (Panel B), we observe stronger evidence of a differential and persistent decline, consistent with substitution in the absence of fentanyl.

5.3 Changes in Overdoses Versus Changes in Coding of Overdoses

There are concerns about the appropriate coding of opioid overdose deaths and how such coding has changed over time. Inappropriate coding will likely attenuate our results, assuming that they are not systematically related to nonmedical OxyContin use since we are "missing" some of the overdoses (overall or for specific opioid types) caused by reformulation.[7] To test the magnitude and direction of this problem, we study overdoses involving unspecified narcotics/drugs. We exclude

[6] This mixing could be intentional, or it could be accidental if suppliers unintentionally mix substances while in preparation for distribution.

[7] Our event study framework makes a systematic relationship with miscoding less likely since the miscoding rate would have to systematically change in high OxyContin misuse states at the time of reformulation given the timing of many of the results.

overdoses also specifying another substance. The concern is that the differential rise in synthetic opioid overdoses related to our misuse variable is a data artifact, and we will observe a corresponding decrease in overdoses involving unspecified narcotics/drugs.

We find weak evidence of a systematic increase post reformulation for unspecified narcotics (Figure A2A). There is stronger evidence that OxyContin misuse predicts growth in the category of unspecified drugs (Figure A2B), suggesting that our main estimates are undercounts since some of these unspecified drug overdoses likely involve opioids. Since we do not observe differential *reductions* in overdoses involving unspecified narcotics or other drugs, we are more confident that we are observing actual changes, though muted, in overdoses and not systematic improvements in the coding of synthetic opioids.

In addition, we replicate Figure 2 for the 27 states that Scholl et al. (2019) classify as "states with very good to excellent reporting" in 2016. The results, presented in Figure A3, are noisier given the smaller sample sizes (the post-reformulation estimates are jointly statistically significant at the 5% level for both heroin and synthetic opioids), but the point estimates are consistent with our main results.

5.4 Time-Varying Factors

Our main estimates reflect the effects of pre-reformulation non-medical OxyContin use, holding constant the broader effects and trends related to pain reliever misuse. While not shown, we do not estimate similar increases (for heroin, synthetic opioids, cocaine, and overall overdoses) associated with pain reliever misuse, suggesting that the effects are unique to OxyContin misuse.

For reasons discussed above, including additional time-varying factors does not affect our results. Figure A4 replicates Figure 2 while conditioning on a set of time-varying covariates and policy variables including fraction of population ages 25+ with a college degree (from Current

Population Study, CPS), fraction white (SEER), fraction in three age groups (25-44, 45-64, 65+, SEER), fraction of 25+ population married (CPS), and fraction foreign-born (CPS). The policy variables include whether the state has a "must access" prescription drug monitoring program (Prescription Drug Abuse Policy Surveillance), active and legally-protected medical marijuana dispensaries (RAND Marijuana Policy database; see Powell et al., 2018; Williams et al., 2019), and laws regulating pain clinics (National Alliance of Model State Drug Laws). The results are similar. The insensitivity of the results to these additional covariates is evidence that the nonmedical pain reliever use variable, interacted with year indicators, is addressing many of the potential confounding factors.

5.5 Exponential Model

We focus on a linear model for our main analyses. In this section, we replicate Figure 2 but use an exponential model, estimated using Poisson regression. Poisson regression only requires that the conditional mean is correctly-specified (Santos-Silva and Tenreyro, 2006) and is appropriate for difference-in-differences analyses (Ciani and Fisher, 2018). While it is commonly thought that Poisson regression imposes additional assumptions about the variance, these assumptions are not enforced when generating the estimates and robust standard errors circumvent the imposition of the assumptions when estimating the standard errors. Other related approaches, such as negative binomial regression, do impose assumptions on the relationship between the mean and variance and are, therefore, often considered less robust than Poisson regression.

The outcome is total number of overdoses and population is treated as an exposure variable. The results in Figure A5 have the same pattern as those observed in Figure 2. The point estimates imply similar level effects.

5.6 Measure of Exposure to Reformulation

Due to some concerns about measurement error in the NSDUH, we replicate Figure 2 using administrative ARCOS data on OxyContin supply in the state, obtained through a Freedom of Information Act request, to construct our pre-reformulation measure of "exposure." We present the results in Figure A.6. The pattern of results is generally similar. There is some evidence that the estimates using OxyContin supply are, in fact, noisier than when using nonmedical use. This additional noise would reflect that this variable conflates medical use and nonmedical use. However, we find that the general conclusions of this paper do not rely on use of the NSDUH or ARCOS measure.

5.7 Broader Effects

Alpert et al. (2018) found only limited evidence that reformulation led to a short-term increase in overdoses (the estimated increase was not statistically different). However, as the opioid crisis has escalated and transitioned, there is much stronger evidence that reformulation induced a sharp rise in overdoses. This relationship is shown in Panel A of Figure 6, which examines the relationship between reformulation and all (opioid and non-opioid) fatal drug poisonings.

The states most exposed to reformulation have experienced much sharper growth in overall overdoses, suggesting that the reformulation of OxyContin led to growth in illicit markets and increased the overall overdose rate. This growth is partially due to the shift of demand from the medical market to the illicit market, but it is also due to the additional potency of new, cheap synthetic opioids that were mixed with all sorts of illicit drugs available through illicit markets, which lack quality controls. Our evidence suggests that spillovers of fentanyl to other illicit substances have played an important role, but this opportunity was initiated by new users entering these markets given reduced access to abusable prescription opioids.

To quantify the overall effect of reformulation, we consider the overdose trajectory for a hypothetical "country" unexposed to OxyContin reformulation. After estimating the event study in Figure 6A, we subtract off the exposure metric multiplied by the estimate for each year. This eliminates the effect of exposure to reformulation (i.e., setting exposure to zero). This counterfactual is an extrapolation with the usual caveats about the implicit assumptions required for such out-of-sample extrapolations. We graph the national overdose rate compared to this counterfactual in Panel B. The lines intersect in 2010 since the event study estimates are normalized to zero in this year. We do not use the event study estimates prior to reformulation to plot a pre-reformulation "counterfactual" trend, though these points are close to the observed overdose rates prior to 2010 (as should be clear from the estimates in Panel A). After reformulation, we see slow divergence at first. By 2013, this separation is modest, consistent with the conclusions of Alpert et al. (2018). We estimate that reformulation increased the 2013 overdose rate by 1.7 overdoses per 100,000 people, a 14% increase relative to the counterfactual.

However, by 2017, our estimates imply that reformulation increased overdose rates by over 8.7 overdoses per 100,000 people, more than a two-thirds increase relative to our counterfactual. Interestingly, Figure 6B suggests that the overdose rate would have gradually decreased in the absence of reformulation (holding everything else constant[8]). This counterfactual decrease may simply be the result of extrapolating too far out of sample. Note, however, that even if we evaluate the counterfactual in-sample, we still estimate large differences between the observed and counterfactual overdose rates. The estimated decrease would be consistent with policy-driven improvements and changes in prescribing patterns beginning to reverse the course of the opioid crisis in the absence of growth in illicit opioid markets. These policy-driven and culture-driven

[8] For example, the rise in overdoses since 2010 may have induced policy adoption that independently reduced overdoses. The above exercise assumes that these policies would have still been adopted.

overdose reductions, which have been found in the literature for a variety of implemented policies,[9] could be masked by national trends driven by the transformation of the opioid crisis.

6. Conclusion

Prior evidence identifies a short-term shift from prescription to illicit opioids in the years immediately after the reformulation of OxyContin. Understanding this short-term effect helps explain substitution patterns in overdoses between prescription and illicit opioids and provides core evidence about the initiating forces behind the second wave of the opioid crisis. However, by expanding the time frame for our analysis, we identify large causal increases in overall overdoses, not just substitution between different types of opioids.

There are many reasons that switching people from legal to illicit markets may have harmful consequences, even if fatal overdose rates themselves do not change (e.g., exposure to infectious diseases[10]). However, our analysis strongly suggests that the switch eventually increased overdose rates to unprecedented levels. As we evaluate the consequences of large supply-side opioid interventions, such as the reformulation of OxyContin, such effects are first-order concerns.

The shift to illicit opioids can be observed by a sudden and persistent rise in heroin overdoses. As the market evolved, we observe a delayed but even more dramatic rise in synthetic opioid deaths in states more exposed to reformulation. This link to reformulation suggests that the rise in illicit fentanyl was driven by demand considerations existing years prior to the entry of

[9] For example, PDMPs have been widely-adopted and strengthened with evidence that these more robust and modern PDMPs reduce misuse (Buchmueller and Carey, 2018) and overdose rates (e.g., Pardo, 2017; Dowell et al., 2016; Patrick et al., 2016). Popovici et al. (2018) find evidence that both pain management and doctor shopping laws reduce opioid-related overdoses. Substance use treatment access has also been shown to decrease drug overdose rates (Swensen, 2015) while policies such as the Affordable Care Act (ACA) Medicaid expansions have improved access to substance use disorder medications (Maclean and Saloner, 2019) and opioid use disorder treatment availability (Meinhofer and Witman, 2018). The ACA also improved treatment access through the dependent care provision (Saloner et al., 2017).

[10] As found in Beheshti (2019) and Powell et al. (2019).

fentanyl. Synthetic opioids disproportionately affected states that had higher rates of OxyContin misuse, even conditional on pain reliever misuse more generally.

In addition, we find evidence of spillovers to non-opioid drug markets – specifically, cocaine. We can attribute the rise in cocaine overdose rates to reformulation, suggesting possible complementarities or accidental mixing in production. The increase in cocaine overdoses is not an independent phenomenon but linked to the supply response to increased demand for opioids in illicit drug markets.

There is limited work in the broader substance use literature on the ramifications of exogenous shocks to the size of illicit markets. As illicit markets have grown and evolved, overdose rates have skyrocketed. The effect of reformulation did not disappear after a few years, instead it grew over time as markets developed and innovated, leading to a public health emergency. We find that the large shift in demand for illicit opioids spurred by reformulation had large and enduring effects on illicit drug markets more broadly.

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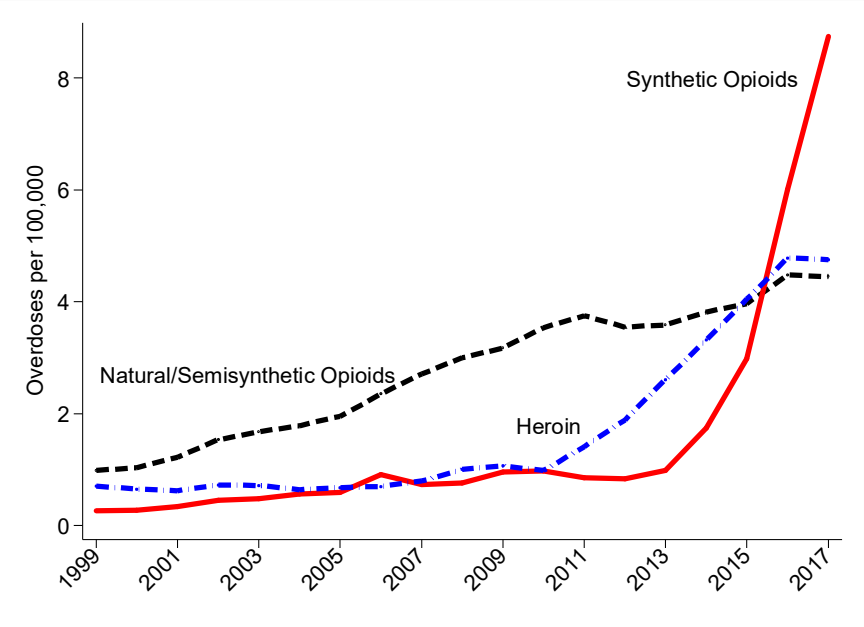
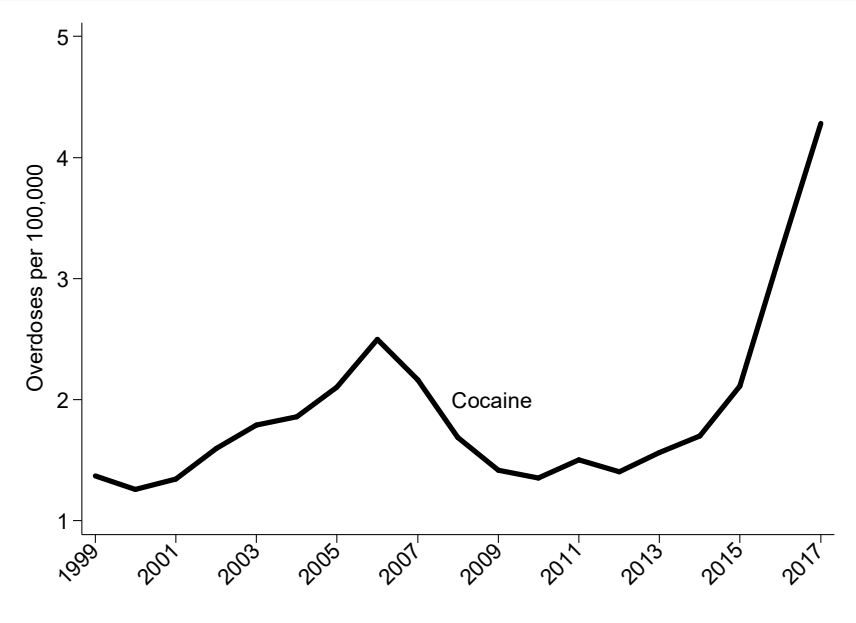
Figures



A: Annual Overdose Rates by Opioid Type



B: Annual Cocaine Overdose Rate

Figure 1: National Fatal Overdose Rate Trends

Notes: Figure A plots national annual fatal overdose trends in natural and semi-synthetic opioids, heroin, and synthetic opioids per 100,000. These categories are not mutually exclusive and sum to rates higher than the overall opioid overdose rate. Figure B plots national trends in fatal cocaine overdoses per 100,000.

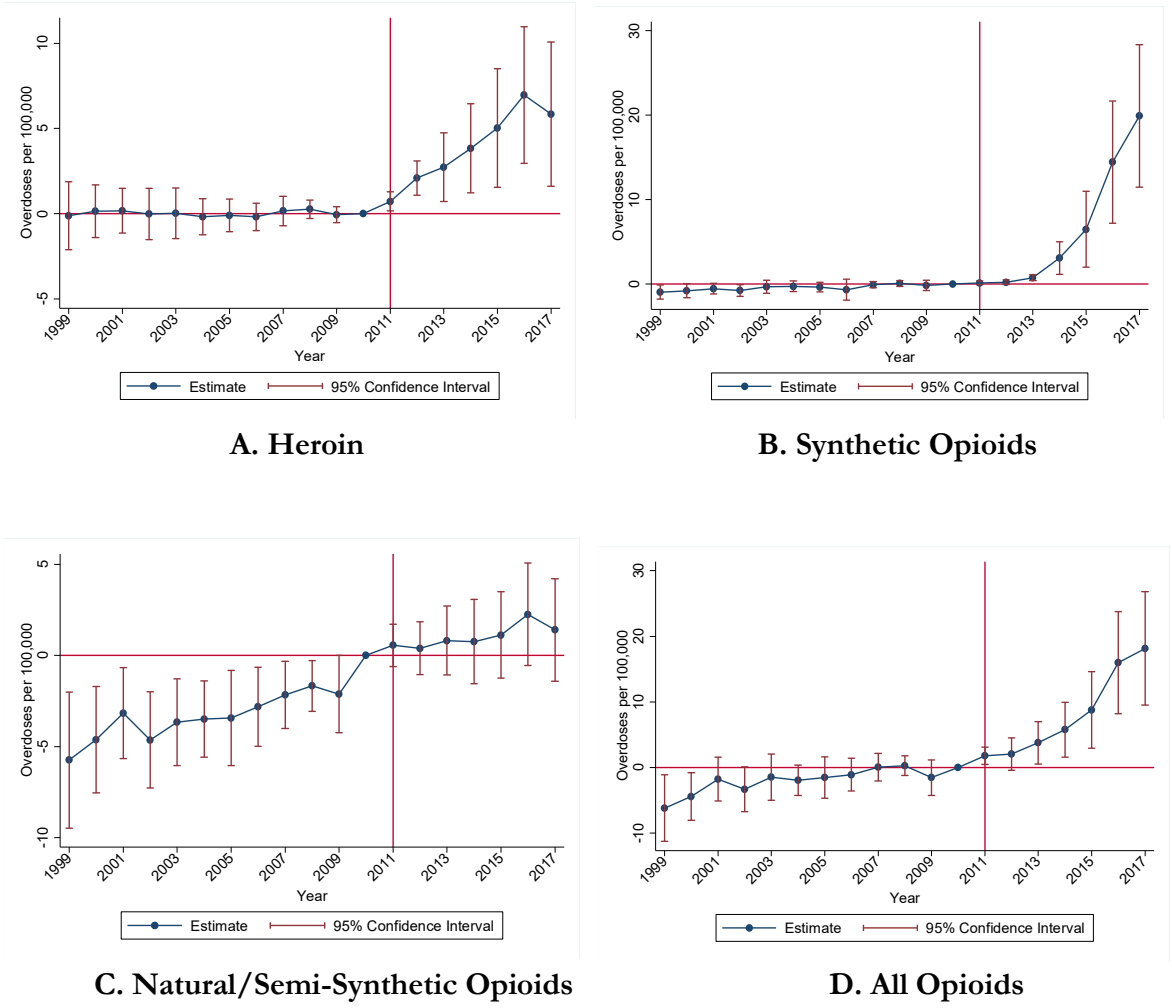
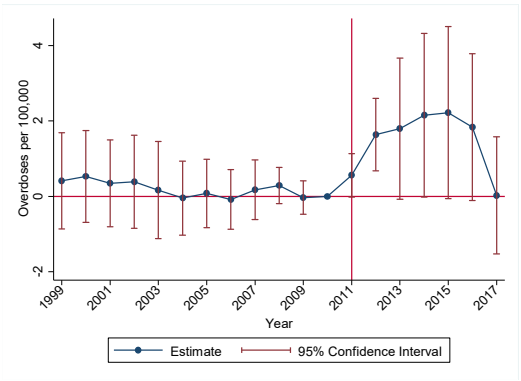
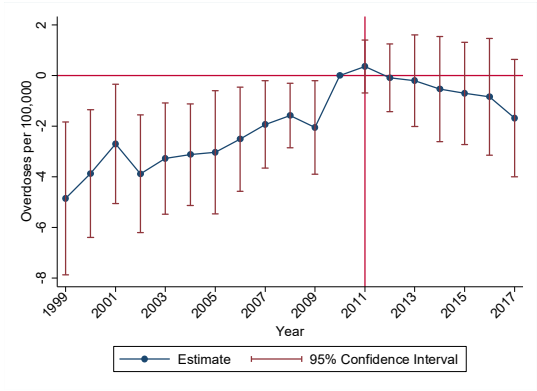


Figure 2: Non-Medical OxyContin Misuse Event Study Estimates for Opioid Overdoses

Notes: 95% confidence intervals adjusted for state-level clustering. Outcome is overdoses per 100,000 for the specified category. The estimates reported in the figures are the coefficients on the pre-reformulation non-medical OxyContin use rate interacted with year indicators. The 2010 interaction is excluded and the corresponding estimate is normalized to 0. The specification includes state and time fixed effects. We also jointly estimate effects for pain reliever misuse interacted with year indicators.



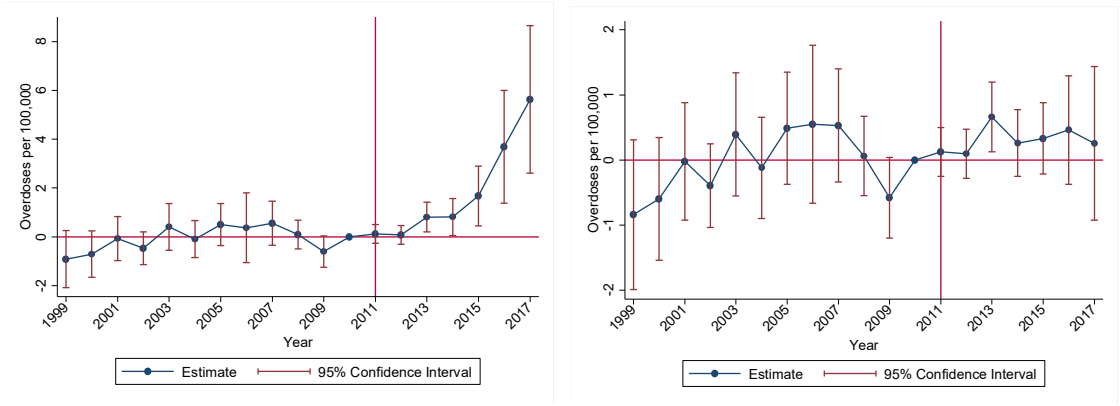
A. Heroin Only



B. Natural/Semisynthetic Opioids Only

Figure 3: Non-Medical OxyContin Misuse Event Study Estimates for Single Opioid-Type Overdoses

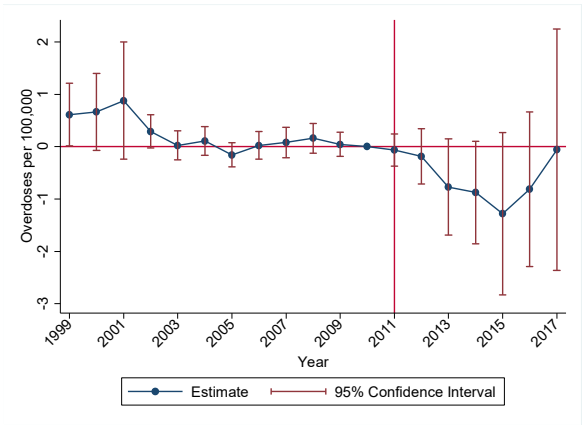
Notes: 95% confidence intervals adjusted for state-level clustering. Outcome is overdoses per 100,000 for the specified category. The estimates reported in the figures are the coefficients on the pre-reformulation non-medical OxyContin misuse rate interacted with year indicators. The 2010 interaction is excluded and the corresponding estimate is normalized to 0. The estimated specification is represented by equation (1). The specification includes state and time fixed effects. We also jointly estimate effects for pain reliever misuse interacted with year indicators.



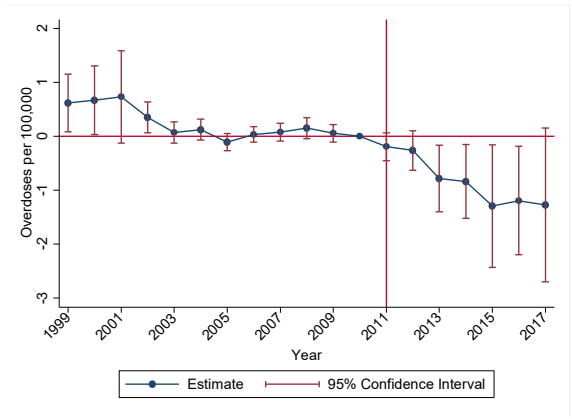
A. All Cocaine **B. Cocaine, Excluding Opioids**

Figure 4: Non-Medical OxyContin Misuse Event Study Estimates for Cocaine Overdoses

Notes: 95% confidence intervals adjusted for state-level clustering. Outcome is overdoses per 100,000 for the specified category. The estimates reported in the figures are the coefficients on the pre-reformulation non-medical OxyContin use rate interacted with year indicators. The 2010 interaction is excluded and the corresponding estimate is normalized to 0. The specification includes state and time fixed effects. We also jointly estimate effects for pain reliever misuse interacted with year indicators.



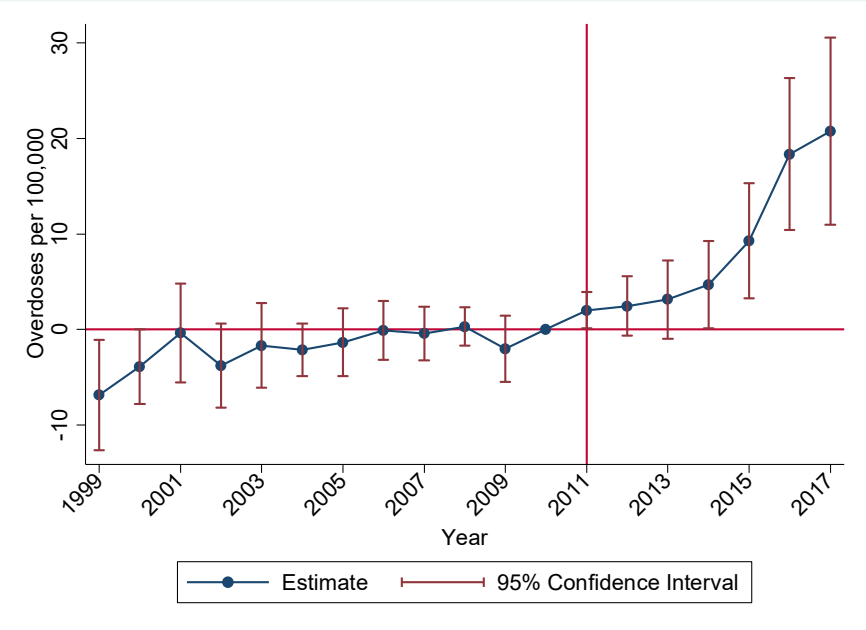
A. Psychostimulants



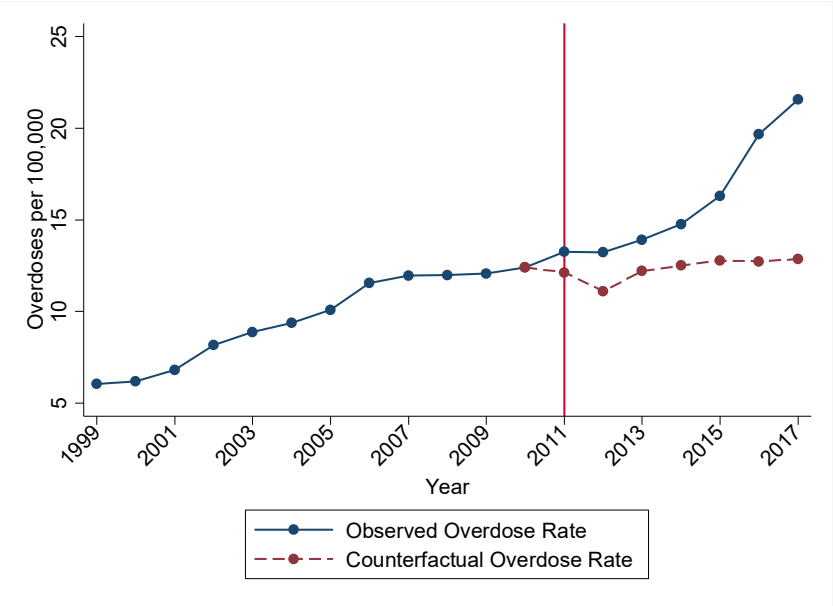
B. Psychostimulants, No Opioids

Figure 5: Non-Medical OxyContin Misuse Event Study Estimates for Overdoses Involving Psychostimulants

Notes: 95% confidence intervals adjusted for state-level clustering. Outcome is overdoses per 100,000 for the specified category. The estimates reported in the figures are the coefficients on the pre-reformulation non-medical OxyContin use rate interacted with year indicators. The 2010 interaction is excluded and the corresponding estimate is normalized to 0. The specification includes state and time fixed effects. We also jointly estimate effects for pain reliever misuse interacted with year indicators.



A. Event Study Estimates



B. Actual and Counterfactual Overdose Rates in Absence of Reformulation

Figure 6: Total Overdose Rate

Notes: In Panel A, outcome is fatal overdoses per 100,000. See Figure 4 for additional information about model. In Panel B, we plot the actual overdose rate over time. In addition, we estimate the event study shown in Panel A and then calculate the overdose rate if OxyContin misuse were equal to zero to predict the overdose trajectory starting in 2010 in the absence of exposure to reformulation. We plot the population-weighted averages by year of the counterfactual overdose rate. The lines intersect in 2010 since the event study estimates are normalized to zero in this year. We could also plot the counterfactual rates prior to 2010 using the event study estimates -- they are close to the observed rates (as should be clear from Panel A).

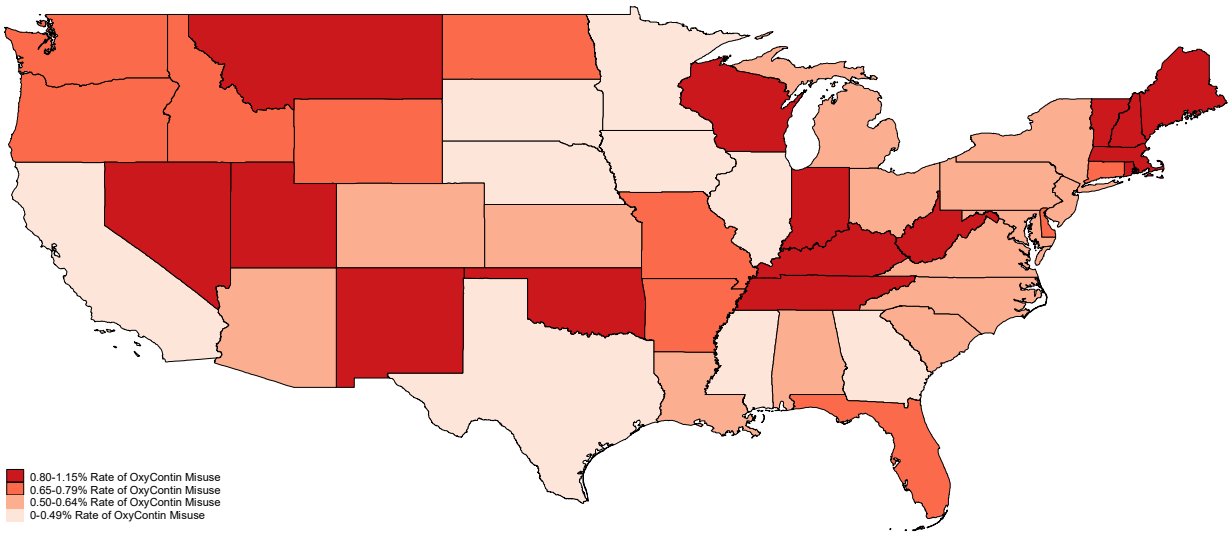
Table 1: Summary Statistics

Variable (Mean)	All States	States with Low OxyContin Misuse Rate	States with High OxyContin Misuse Rate	Source
Outcomes				
OxyContin Misuse Rate (%)	0.567	0.447	0.842	NSDUH, 2004-2009
Deaths per 100,000:				
All Opioids	5.824	4.891	7.957	Vital Statistics, 2004-2009
Heroin	0.817	0.820	0.811	Vital Statistics, 2004-2009
Natural/Semisynthetic Opioids	2.504	2.000	3.656	Vital Statistics, 2004-2009
Synthetic Opioids	0.755	0.639	1.019	Vital Statistics, 2004-2009
Cocaine	1.951	1.855	2.171	Vital Statistics, 2004-2009
Demographics Characteristics				
Population	5,877,760	8,444,077	3,545,669	SEER, 2004-2009
Age (%):				
25-44	27.55	27.89	26.78	SEER, 2004-2009
45-64	25.31	25.03	25.96	SEER, 2004-2009
65+	12.58	12.11	13.64	SEER, 2004-2009
Race (%):				
White	80.22	77.82	85.71	SEER, 2004-2009
Black	13.39	15.02	9.67	SEER, 2004-2009
College Degree (% of ages 25+)	28.49	28.97	27.38	CPS, 2004-2009
Foreign-Born (%)	13.26	14.53	10.35	CPS, 2004-2009
Married (% of ages 25+)	60.53	60.12	61.45	CPS, 2004-2009
Number of States	51	25	26	

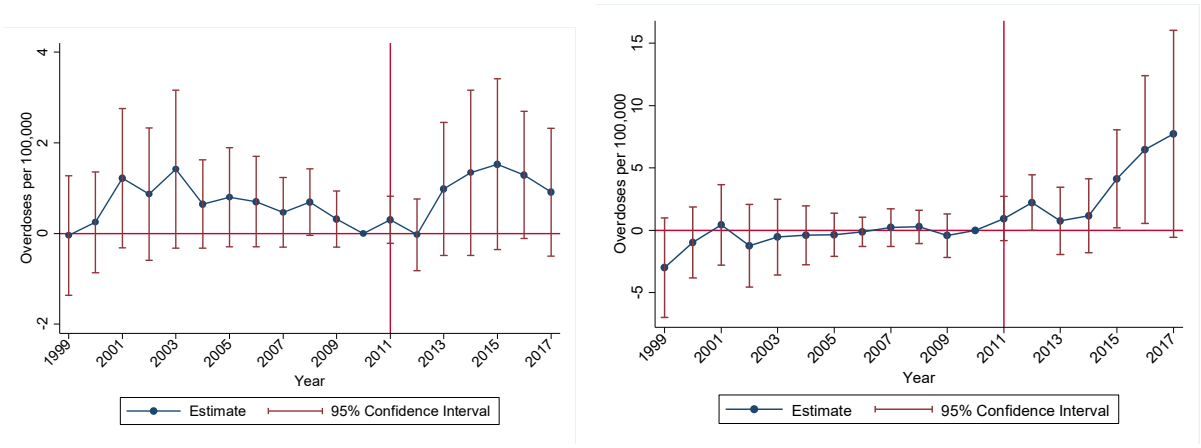
Notes: All statistics are for 2004-2009. Except for the population figures, they are all population-weighted.
SEER = Surveillance, Epidemiology, and End Results Program.
CPS = Current Population Study.

Appendix

Figure A1 – Geographic Variation in nonmedical OxyContin use (2004-2009)



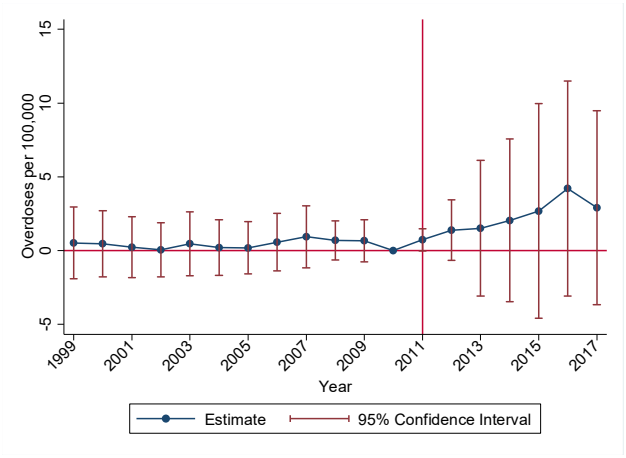
Source: Authors' calculations using National Survey of Drug Use and Health.



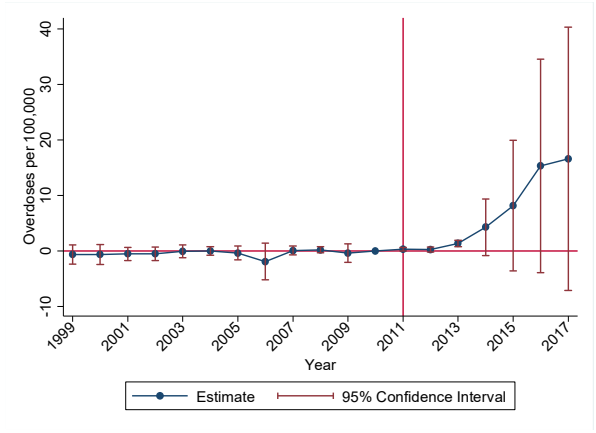
A. Unspecified Narcotics (T40.6) **B. Unspecified Drugs (T50.9)**

Figure A.2: Non-Medical OxyContin Misuse Event Study Estimates for Unspecified Overdoses

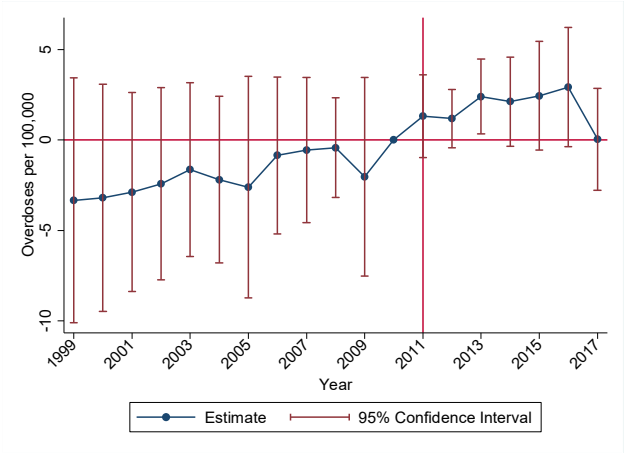
Notes: 95% confidence intervals adjusted for state-level clustering. Outcome is overdoses per 100,000 for the specified category. We exclude overdoses that also specify another substance. The estimates reported in the figures are the coefficients on the pre-reformulation non-medical OxyContin use rate interacted with year indicators. The 2010 interaction is excluded and the corresponding estimate is normalized to 0. The estimated specification is represented by equation (1). The specification includes state and time fixed effects. We also jointly estimate effects for pain reliever misuse interacted with year indicators.



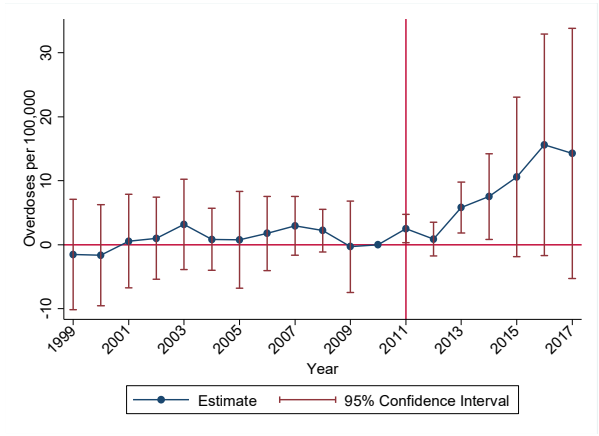
A. Heroin



B. Synthetic Opioids



C. Natural/Semi-Synthetic Opioids



D. All Opioids

Figure A.3: Non-Medical OxyContin Misuse Event Study Estimates for Opioid Overdoses, Selecting on 27 States with "very good to excellent reporting"

Notes: 95% confidence intervals adjusted for state-level clustering. Outcome is overdoses per 100,000 for the specified category. The estimates reported in the figures are the coefficients on the pre-reformulation non-medical OxyContin use rate interacted with year indicators. The 2010 interaction is excluded and the corresponding estimate is normalized to 0. The estimated specification is represented by equation (1). The specification includes state and time fixed effects. We also jointly estimate effects for pain reliever misuse interacted with year indicators. The sample is selected based on quality of reporting of specific drugs involved in overdoses in 2016 as categorized in Scholl et al. (2019).

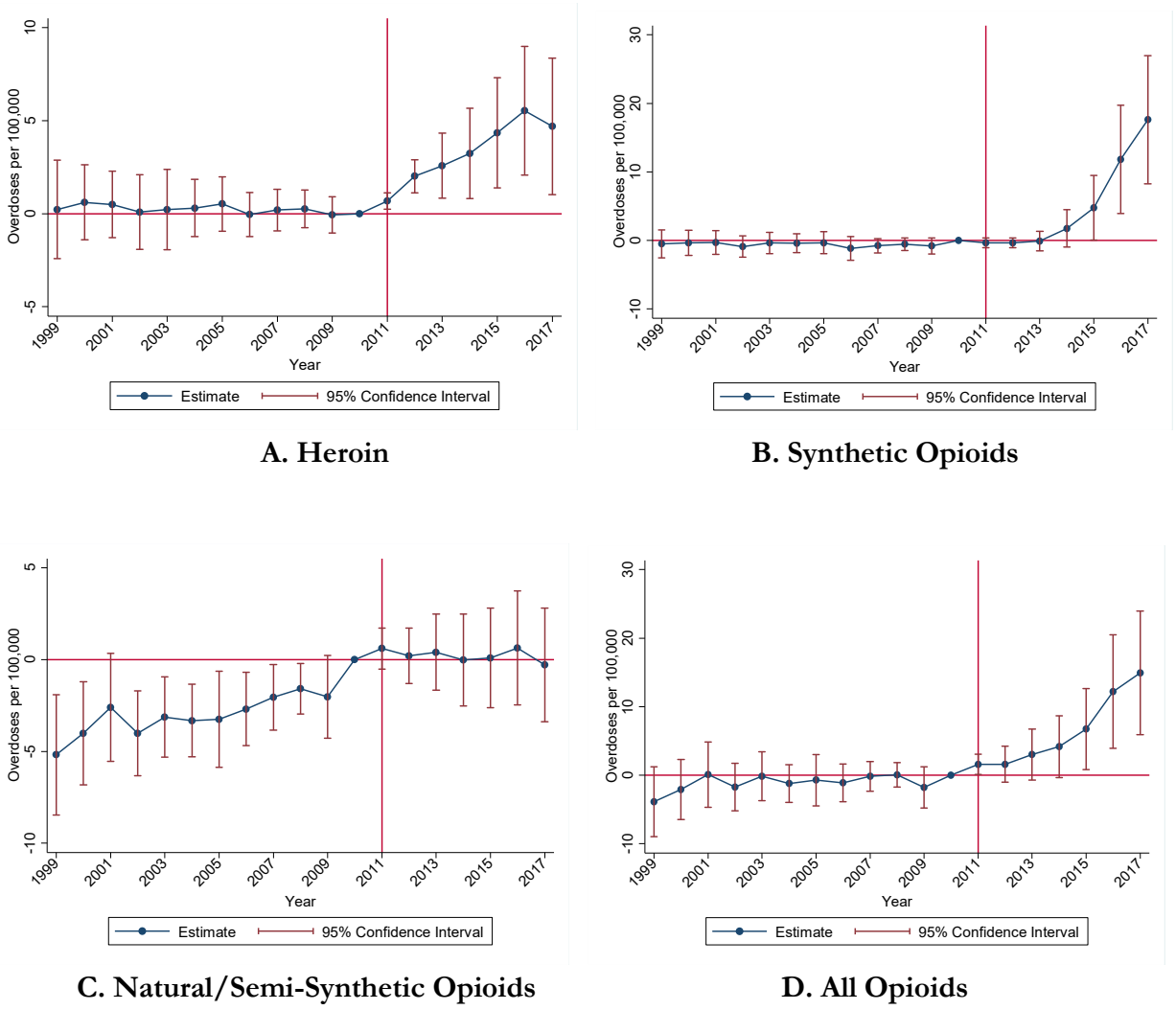
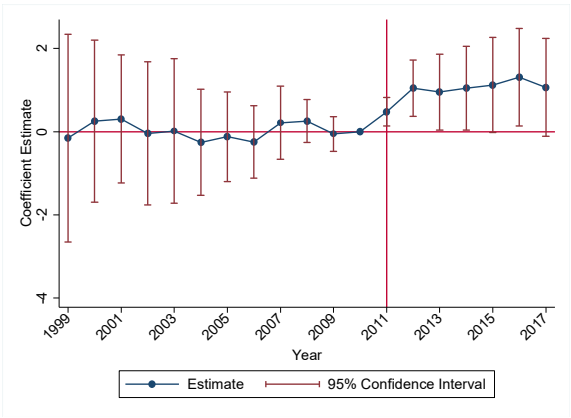
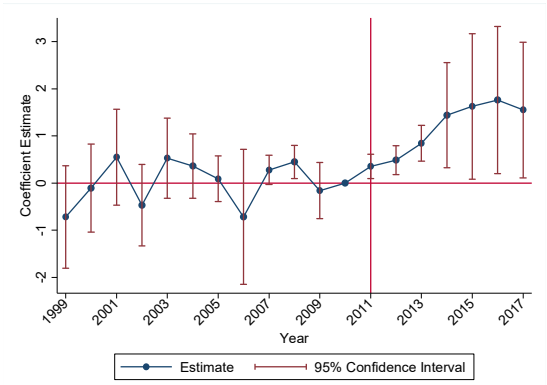


Figure A.4: Non-Medical OxyContin Misuse Event Study Estimates for Opioid Overdoses, Controlling for Time-Varying Variables

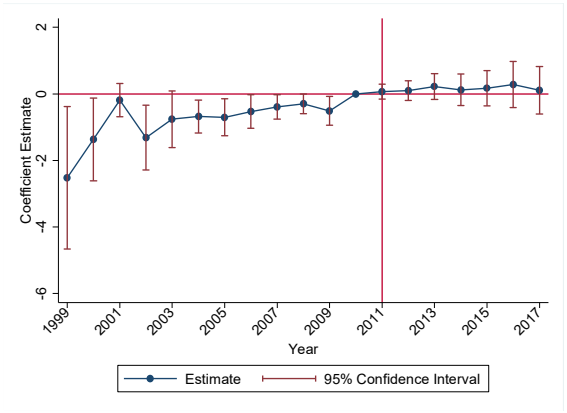
Notes: 95% confidence intervals adjusted for state-level clustering. Outcome is overdoses per 100,000 for the specified category. The estimates reported in the figures are the coefficients on the pre-reformulation non-medical OxyContin use rate interacted with year indicators. The 2010 interaction is excluded and the corresponding estimate is normalized to 0. The estimated specification is represented by equation (1). The specification includes state and time fixed effects. We also jointly estimate effects for pain reliever misuse interacted with year indicators. Covariates include fraction of population ages 25+ with a college degree, fraction white, three ages shares (25-44, 45-64, 65+), fraction of 25+ population married, fraction foreign-born, whether the state has a "must access" prescription drug monitoring program, active and legally-protected medical marijuana dispensaries, and laws regulating pain clinics.



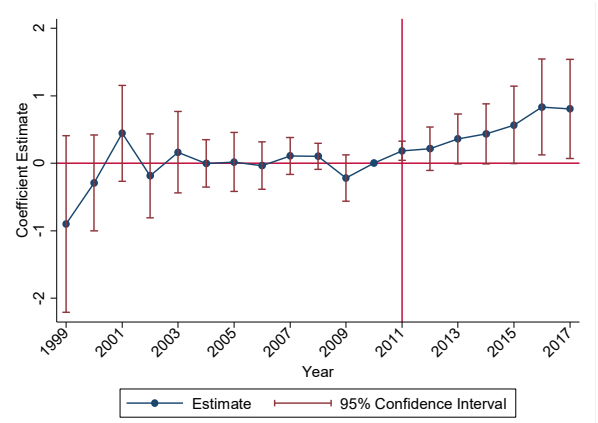
A. Heroin



B. Synthetic Opioids



C. Natural/Semi-Synthetic Opioids



D. All Opioids

Figure A.5: Non-Medical OxyContin Misuse Event Study Estimates for Opioid Overdoses, Poisson Estimation

Notes: 95% confidence intervals adjusted for state-level clustering. Outcome is overdoses for the specified category and population is the exposure variable. The estimates reported in the figures are the coefficients on the pre-reformulation non-medical OxyContin use rate interacted with year indicators. These are proportional effects. The 2010 interaction is excluded and the corresponding estimate is normalized to 0. The specification includes state and time fixed effects. We also jointly estimate effects for pain reliever misuse interacted with year indicators.

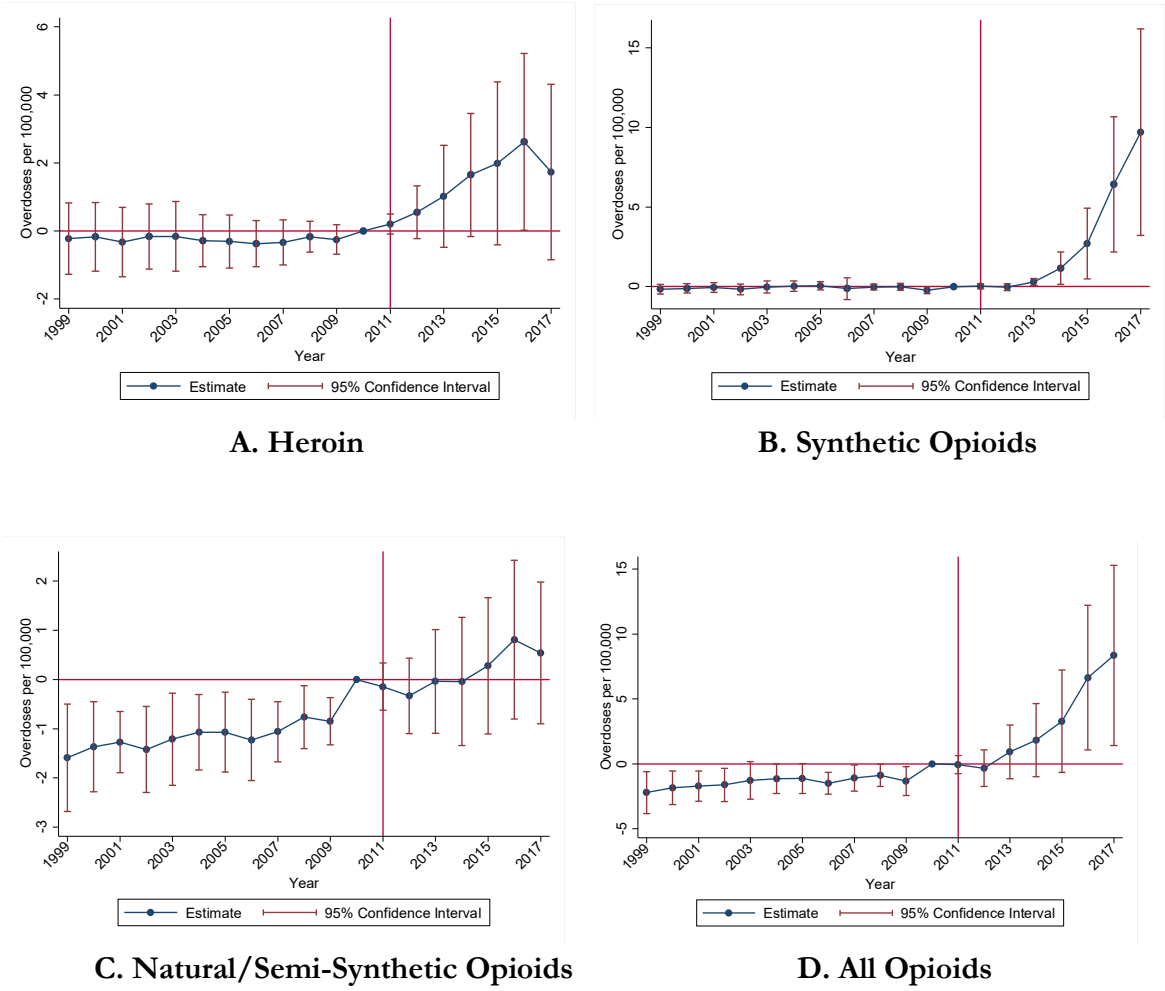


Figure A.6: OxyContin Supply Event Study Estimates for Opioid Overdoses

Notes: 95% confidence intervals adjusted for state-level clustering. Outcome is overdoses per 100,000 for the specified category. The estimates reported in the figures are the coefficients on the pre-reformulation OxyContin MED rate interacted with year indicators. The 2010 interaction is excluded and the corresponding estimate is normalized to 0. The estimated specification is represented by equation (1). The specification includes state and time fixed effects. We also jointly estimate effects for pain reliever misuse interacted with year indicators.