HHS Public Access

Author manuscript

Am J Health Econ. Author manuscript; available in PMC 2021 September 23.

Published in final edited form as:

Am J Health Econ. 2021 ; 7(1): 41–67. doi:10.1086/711723.

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 higher rates of nonmedical OxyContin use before reformulation, to less exposed areas. More exposed areas experienced disproportionate increases in fatal overdoses involving synthetic opioids (fentanyl) and nonopioid 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.

Keywords

opioid crisis; overdose rates; fentanyl; cocaine; illicit drug markets

JEL CLASSIFICATION:

I12; I18

I. Introduction

The opioid crisis is a national emergency, and policy makers are struggling to implement policies to curb rising overdose rates that are now being driven primarily by illicit opioids. The evolution of the opioid crisis can be observed in Figure 1A, which shows trends by category of opioid overdose for the period 1999–2017. Prior to 2011, natural and semisynthetic prescription opioids were the driving force behind opioid mortality. However, heroin overdose rates began to escalate near the end of 2010. Beginning in 2013, the growth

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of overdoses involving synthetic opioids, primarily illicitly manufactured fentanyl (Pardo et al. 2019), outpaced even heroin's rapid escalation. The shift to illicit opioids and the growth of illicit opioid markets have pushed drug overdose rates overall to unprecedented levels. In recent years, we have observed increases in overdoses involving nonopioid drugs (Ruhm 2019), often mixed with fentanyl (Jones, Baldwin, and Compton 2017; Ciccarone 2017; Pardo et al. 2019). The number of overdoses involving cocaine, for example, has almost tripled since 2013 (see Figure 1B); the vast majority of these (over 70 percent in 2017) involve some type of synthetic opioid.

Recent work shows that states with higher rates of nonmedical OxyContin use before reformulation experienced a disproportionate rise in heroin overdoses after reformulation (Alpert, Powell, and Pacula 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, the current stock of individuals misusing opioids switched to illicit drug markets (Cicero, Ellis, and Surratt 2012; Coplan et al. 2013; Tuazon et al. 2019), increasing heroin overdoses and infectious diseases (Beheshti 2019; Powell, Alpert, and Pacula 2019).[1] Previous quasi-experimental work, however, found little short-term evidence that reformulation affected overdose rates beyond just a shift in the types of opioids involved in overdoses (Alpert, Powell, and Pacula 2018; Evans, Lieber, and Power 2019).

Longer-term consequences of supply-side interventions may differ from short-term effects, and the expectation was that the reformulation of OxyContin would reduce the number of new people who misused and then became dependent on OxyContin, with possible downstream consequences on overdose deaths. However, drug overdoses have continued to rise since 2013, suggesting that the longer-term consequences may be very different than expected. While there are potentially negative consequences of switching from legal to illicit opioid markets even if the overall overdose rate is unchanged (e.g., spread of hepatitis C), the welfare calculus of any supply-side intervention becomes more negative if, over the longer-term horizon, it also led to drastically higher fatal overdose rates.

In this paper we seek to understand the longer-term impacts of the 2010 OxyContin reformulation and whether it may have contributed to the recent rise in fatal overdoses. Understanding the causes of the changing drug mortality landscape is important if we want to understand how to properly combat the ongoing public health emergency, as well as properly assess the overall welfare implications of OxyContin reformulation. We adopt and extend the approach of Alpert, Powell, and Pacula (2018) to study the evolution of the opioid crisis since the reformulation of OxyContin in August 2010. This approach studies how differential exposure to reformulation, defined in terms of pre-reformulation levels of OxyContin misuse, predicts changes in overdose deaths and other outcomes after reformulation. We use these relationships to infer the national-level implications of reformulation.

[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]).

We begin by studying heroin overdoses over a longer time period than previous work, permitting us to test whether their relationship with OxyContin reformulation weakened over time, as we would predict if reformulation led to decreases in initiation. We then examine whether exposure to reformulation also predicts geographic variation in the rise in synthetic opioid deaths. This analysis helps us understand whether reformulation is responsible for deaths involving illicitly manufactured fentanyl, a primary driver of the recent escalation of the opioid crisis. Next, we consider potential spillovers in other drug markets, specifically cocaine and psychostimulants. To summarize the effect on overdose death rates, we consider the net effects of reformulation on total fatal drug overdose rates.

In addition, we also examine new substance use treatment admissions related to heroin and other opioids to ascertain whether there is evidence of a reduction in the number of newly dependent users. A relationship between reformulation and reductions in initiation into dependence would potentially signal future decreases in overdose death rates.

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 takes advantage of one of these opportunities and extends existing evidence to more carefully consider the longer-term impacts of the massive shift to the black market caused by OxyContin reformulation. By extending prior analyses just a few years, we uncover evidence that reformulation led to the increase in total drug fatal overdoses, driving them to unprecedented levels, through the expansion of illicit drug markets.

The rest of the paper is organized as follows. We provide a brief background about the reformulation of OxyContin in the next section. In Section III, we describe the data. We discuss our empirical strategy in Section IV. We provide results in Section V and consider the implications of our results in terms of illicit drug market responses to reformulation. We conclude in Section VI.

II. Background

OxyContin was introduced in 1996 by Purdue Pharma. It is a brand-name drug for the extended-release formulation of oxycodone, a semisynthetic 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 with previous drugs. However, crushing or dissolving the pill caused the complete dose of oxycodone to be delivered immediately, making OxyContin especially easy to abuse. By 2010, OxyContin had more than $3 billion in sales, making it one of the highest-selling drugs in the United States (Bartholow 2011). The drug’s wide market presence and its abuse potential stimulated extensive diversion to nonmedical use, and there were concerns about widespread abuse of OxyContin as early as 2000 (Cicero, Inciardi, and Muñoz 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.[2] 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, Powell, and Pacula 2018; Evans, Lieber, and Power 2019). There is little existing evidence that reformulation induced a meaningful change in the overall overdose rate. However, the opioid crisis has evolved considerably since the end of the sample periods previously analyzed in this literature. Our understanding of the effectiveness of supply-side interventions requires studying longer-term outcomes, permitting time for illicit markets to expand and innovate.

III. Data

A. 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 2017. We use restricted data to access state identifiers and categorize overdoses based on the state of residence of the deceased. 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–X64, 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 excluding heroin (e.g., oxycodone), and T40.4 refers to synthetic opioids excluding methadone (e.g., fentanyl). To study opioid overdoses, we 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 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). We study T40.6 and T50.9 overdoses directly and test whether these unspecified overdoses are related to OxyContin misuse to infer possible biases affecting our main results.

B. SUBSTANCE ABUSE TREATMENT ADMISSIONS

As a complementary measure to help capture escalation to dependence, we study substance abuse treatment admissions in the Treatment Episode Data Set (TEDS) for 1999–2017. The TEDS, which is maintained by the Substance Abuse and Mental Health Services Administration (SAMHSA), includes admissions data from all treatment facilities receiving public funding, whether through federal block grants, Medicaid or Medicare insurance, or

[2]The reformulated version can still be abused orally (i.e., taking higher doses than prescribed), and some users have counteracted the abuse-deterrent properties. Cicero and Ellis (2015) noted that the significant time effort required should deter use of these methods.

other state funding sources. These data comprise a significant portion of all admissions to substance abuse treatment facilities and represent the best available national source on treatment admissions available.

Each admission record reports up to three substances of abuse at the time of treatment. We consider any admission in which heroin is listed as either the first, second, or third substance as a heroin substance abuse treatment admission. We also examine admissions including at least one opioid, whether heroin, nonprescription methadone, or "other opiates and synthetics," as any of the three substances of abuse, and refer to these as "opioid treatment admissions." Admissions refer to ages 12+, which we scale by the population size for the same ages.

As part of the admissions record, TEDS records the number of prior substance use treatment episodes reported by the client at the time of intake, allowing us to study heroin and opioid admissions for people with no prior substance use treatment episodes. While not a perfect measure of initiation into dependence, a relative decline in these types of admissions would be consistent with a decline in opioid misuse initiation. However, a rise in these new cases would cast further doubts on the possible scope for reduced initiation to later impact overdose rates.

There are concerns regarding consistent reporting of admissions data across states in the TEDS, as differences in state licensure and accreditation practices can influence which facilities are reporting into the system over time (SAMHSA 2014).[3] Our assumption will be that any state-level changes in reporting of opioid admissions are not correlated with pre-reformulation level of OxyContin misuse beginning in 2011. We will consider the possible effects of misreporting when discussing the TEDS results below.

C. 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), a nationally representative household survey of individuals ages 12 and older. NSDUH, also maintained by SAMHSA, is the country's largest survey collecting information on substance use and mental health issues, including information on self-reported "nonmedical OxyContin use" and "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 2004–09 to reduce measurement errors concerns.

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. The interaction of these two properties is essential for this analysis.

[3]During our time period, 42 states report admissions every year and all states report admissions for at least 15 of the 19 years. Results are similar if we select on a balanced panel. In total, we have 969 observations in the TEDS for 1999–2017.

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, Powell, and Pacula (2018) find that, in practice, nonmedical use is highly correlated with oxycodone supply and OxyContin prescriptions. Evans, Lieber, and Power (2019) pursue a similar strategy as Alpert, Powell, and Pacula (2018) but use oxycodone supply as the measure of exposure to reformulation. This metric results in similar conclusions given the correlations shown in Alpert, Powell, and Pacula (2018), but we rely on the NSDUH measure of OxyContin nonmedical use as our primary metric of exposure to reformulation to avoid conflating medical use with nonmedical use and to focus on OxyContin.

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. Underreporting 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.

As a complementary though imperfect measure, 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 substate geographies). Public data are available by ingredient but because of our interest in OxyContin, we filed a Freedom of Information Act request to the DEA for OxyContin specifically. The data include 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 2004–09, separated into "low" and "high" misuse states based on 2004–09 OxyContin misuse rates. The difference in OxyContin misuse rates between low and high misuse states is large, with high misuse states having nearly twice the rate of low misuse states. In the pre-reformulation period, we see no difference in rates of heroin mortality. Heroin treatment admissions are actually lower in high OxyContin misuse states than in low states. We do observe higher rates of deaths caused by natural/semisynthetic opioids (prescription analgesics, including OxyContin), synthetic opioids, and cocaine in the high misusing states. Table 2 shows the correlations between different drug overdose rates for 2004–09. Before reformulation, there is a

strong positive correlation between natural/semisynthetic and synthetic opioids as well as psychostimulants.

We show the geographic variation in OxyContin misuse in Figure A1 in the Online Appendix. There is substantial variation even among neighboring states. As one metric of this variation, we calculate the average nonmedical OxyContin use rate for each state's neighbors. We then regress (excluding Hawaii and Alaska, N=49) each state's rate on this average neighbor rate. The estimate is *negative* and statistically different from zero (using heteroskedastic-robust standard errors), implying considerable amounts of variation even among neighboring states.

IV. Empirical Strategy

We conduct our analysis at the state level because of data availability. State borders are likely not appropriate boundaries for medical or illicit drug markets. However, this level of aggregation should not be problematic, and the main cost is that we do not observe additional substate variation in nonmedical OxyContin use to exploit.

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

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

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 (2004–09). $PainReliever Rate_s^{Pre}$ represents the pain reliever misuse rate in state s in the pre-reformulation period (2004–09).

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 preexisting 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 percent confidence intervals, adjusted for state-level clustering. The δ_t terms represent how overdose rates would have been different in year t for a state had its pre-reformulation nonmedical OxyContin use rate been 1 percentage point higher. A 1 percentage point increase in nonmedical OxyContin use is very large; its (weighted) standard deviation is only 0.23. We will often report the change in the overdose rate implied by the estimates for a one standard deviation increase in exposure to OxyContin (i.e., how overdose rates in a state would have evolved if it had been one standard deviation more exposed to reformulation).

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 (SEER) Program.

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, 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 is consistent with these variables adequately soaking 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.

The assumption of equation 1 is that, in the absence of reformulation, state overdose rate growth would have been unrelated to pre-reformulation rates of nonmedical OxyContin use (conditional on nonmedical pain reliever use). This "parallel trends" assumption cannot be tested, though we can evaluate the appropriateness of this assumption in the pre-period, which may suggest its appropriateness in the post-period.

Finally, it will be useful to summarize our findings. In the spirit of Alpert, Powell, and Pacula (2018), we estimate a trend break specification:

$$\begin{aligned} Y_{st} = {} & \alpha_s + \gamma_t \\ & + \delta_1 \times OxyRate_s^{Pre} \times t + \delta_2 \times OxyRate_s^{Pre} \times (t \geq 2011) \\ & + \delta_3 \times OxyRate_s^{Pre} \times (t \geq 2011) \times (t - 2011) \\ & + \theta_1 \times PainRate_s^{Pre} \times t + \theta_2 \times PainRate_s^{Pre} \times (t \geq 2011) \\ & + \theta_3 \times PainRate_s^{Pre} \times (t \geq 2011) \times (t - 2011) + \varepsilon_{st}\,. \end{aligned} \tag{2}$$

We use only 2006–09, 2011–17 for this estimation, and we report $\delta_2 + 6\delta_3$, which is the implied relationship between pre-reformulation OxyContin misuse and the outcome in 2017 in this parameterized model. The OxyContin misuse variable is permitted to have an overall linear trend relationship with the outcome as well as a separate shift and linear trend break in the post-period. The more general pain reliever variable is parameterized in the same manner. We exclude 2010 from this analysis since it is partially treated.

Our models assume that overdose rates are affected by a state's own rate of exposure to reformulation. In practice, there could be spillovers across states. Illicit markets may expand in states experiencing large increases in demand for illicit opioids, and these growing markets may affect substance use and markets in other states. These spillovers will likely attenuate our estimates since some "low misuse states" would experience larger increases than expected in overdose deaths because of their proximity to "high misuse states."

[4]Alpert, Powell, and Pacula (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.

V. Results

A. 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 overdose deaths. We observe no evidence of a preexisting 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.

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 19.7, implying that a one standard deviation higher rate of exposure to reformulation caused 4.5 additional synthetic opioid overdoses per 100,000.

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 Figure 2C, we explore the effect of exposure to OxyContin reformulation on natural and semisynthetic opioids, the category that includes OxyContin. A preexisting 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 preexisting trend is expected because of 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[5] (and growing) rates of natural and semisynthetic opioid mortality.

In Figure 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 total opioid overdoses due to exposure to reformulation.

[5]This was shown in Table 1.

Initially, reformulation may have had only small effects on overall overdose mortality, but the increase in heroin and fentanyl overdoses eventually dominates any reduction in overdoses involving natural and semisynthetic opioids in states most exposed to OxyContin reformulation. This finding is also consistent with large spillover effects to nonopioid drugs, 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 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, Pacula, and Persico 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.

We parameterize these results using estimates from equation 2 in Table 3, panel A. We estimate that states more exposed to reformulation experienced large and statistically significant growth in overdoses by 2017 for heroin, synthetic opioids, and all opioids.

B. SPILLOVERS TO NONOPIOID DRUG OVERDOSES

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 might start mixing it with cocaine too, in which case we could see a delayed increase in cocaine mortality.

In Figure 3A, 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 5.5, implying that a one standard deviation increase in exposure to reformulation increased cocaine overdoses by 1.3 per 100,000. Table 3 includes the equivalent result from the parametric model, suggesting even larger effects.

In Figure 3B, we study cocaine overdoses that do not also involve synthetic 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 with the panel B estimates strongly suggest that the relationship with cocaine is not due to 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 provided in Figure 3C. The analyses show a relative immediate 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 by either contaminated supply or consumer preferences to use multiple substance with synthetic opioids. When we consider overdoses involving psychostimulants without any synthetic opioid present (Figure 3D), we observe stronger evidence of a differential and persistent decline, consistent with substitution in the absence of fentanyl. In panel A of Table 3, we estimate a negative (but not statistically different) relationship between pre-reformulation OxyContin misuse and growth in overdoses involving psychostimulants.

C. 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 (Ruhm 2018, 2019). 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 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.

In the Online Appendix, we show 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.

D. TOTAL EFFECTS ON OVERDOSE DEATH RATES

Alpert, Powell, and Pacula (2018) found only limited evidence that reformulation led to a short-term increase in total (opioid and nonopioid) fatal drug overdoses (the estimated increase was not statistically different from zero). However, as the opioid crisis has escalated and transitioned, there is much stronger evidence that reformulation induced a sharp rise in total overdose deaths. This relationship is shown in Figure 4, which examines the relationship between reformulation and all fatal drug poisonings.

[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.

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 through medical markets.

The parameterized estimate for 2017 is included in the last column of Table 3. The event study estimate is 20.4 while the parameterized estimate is larger. An estimate of 20.4 implies that a one standard deviation increase in exposure to reformulation increased overdoses by 4.7 per 100,000 people in 2017. We revisit the implications of this finding in Section V.G.

E. SENSITIVITY ANALYSES

Table 3 includes results from several sensitivity analyses, which we explain in this section. Our main estimates reflect the effects of pre-reformulation nonmedical 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—the effects are unique to OxyContin misuse.

For reasons discussed above, including additional time-varying factors should not affect our results given the inclusion of the nonmedical pain reliever use variables. We test this assumption here. In the spirit of Jaeger, Joyce, and Kaestner (2020), we include a set of covariates, defined as averages for 2004–09, and parameterize their impact in the same manner as the misuse variables in equation 2 (i.e., we interact them with a linear trend while also permitting them to have a level and trend shift beginning in 2011). Our covariates are the log of population, percentage foreign born, percentage white, and percentage 25–44 (see Table 1 for data sources). These variables were selected because they are often associated with overdose trends but also because we observe notable differences based on initial pre-reformulation OxyContin misuse rates in these variables.[8]

We include these results in panel B of Table 3. The estimates are generally similar. The insensitivity of the results to these additional covariates is evidence that the nonmedical pain reliever use variable is addressing many of the potential confounding factors.

Next, we estimate equation 2 but use an alternative (though flawed) measure of exposure to reformulation using administrative ARCOS data on OxyContin supply in the state. We present the results in panel C of Table 3. The standard deviation of OxyContin supply is 0.45, about twice as large as the standard deviation for the misuse variable, so the equivalent exercise of thinking about the effects of a one standard deviation increase in exposure to reformulation requires doubling the implied effects (relative to before).

[8]We selected only a limited set of covariates because of concerns of overfitting since each covariate is interacted with three terms.

The pattern of results is similar and the one standard deviation effects are generally, with some exceptions, comparable to those observed before. However, there is also evidence that some of the results are attenuated and noisier. The additional noise when using the ARCOS measure reflects the conflation of medical use and nonmedical use of OxyContin, as ARCOS cannot distinguish between appropriate use and diverted supply.

In our main analysis, we aggregated 2004–09 data to construct our measures of pre-reformulation misuse. There may be concerns that a transitory shock to substance use in a state immediately prior to reformulation is captured in this metric and that transitory shock itself may also predict future (post-reformulation) changes in overdose rates. To test the possible importance of this concern, we replicate our analyses while using only 2004–05 to construct the nonmedical use measures. The advantage of these years is that we can measure misuse rates prior to the sample period used for estimation of equation 2, reducing concerns about the variable itself predicting growth or mean reversion. These results are presented in Table 3, panel D. They too are generally similar to the main estimates.

Finally, our standard error and confidence interval estimates are adjusted for within-state clustering. With only 51 units, there may be concerns about finite sample bias. As one approach to test for this, we randomly (without replacement) and jointly assign our misuse rates to different states and then reestimate equation 2. We compare the absolute value of the t-statistics from the true sample with those generated in 999 placebo samples. The final row (panel E) of Table 3 includes the implied *p*-values from this method in brackets. We still reject the null hypothesis of no effect at conventional levels for heroin, synthetic opioid, all opioid, cocaine, and all overdoses.

F. CHANGES IN INITIATION RATES

It may be surprising that the relationship between reformulation and overdose deaths has continued to strengthen. One hypothesis was that reformulation may reduce initiation rates, leading to longer-term benefits including decreases in overdose death rates. People prescribed OxyContin could potentially be less likely to develop dependency issues when the drug is harder to abuse. We do not see convincing evidence of a downturn in the relationship between exposure to reformulation and overdoses, suggesting that the benefits —at least in terms of overdose deaths by 2017—of reduced initiation rates are small.

As complementary evidence, we study heroin substance treatment admissions in the TEDS. The event study estimates are presented graphically in Figure 5. In panel A, the outcome is all heroin substance abuse treatment admissions per 100,000 (people ages 12+). The estimates generally increase throughout the post-reformulation period (a joint test of the post-reformulation estimates produces *p*-value = 0:054), expressing a similar pattern as the heroin overdose death results. In panel B, we study heroin substance abuse treatment admissions without a prior treatment episode per 100,000. These estimates also increase throughout most of the post-period (joint *p*-value = 0:003).

Selecting on admissions for those without any prior treatment episodes is potentially problematic given that having a prior treatment is endogenous to exposure to reformulation. We find evidence that reformulation increased treatment admissions, suggesting that the

population eligible for categorization as not having any prior episodes is endogenously declining more in areas more exposed to reformulation. This selection mechanism would bias the estimates *downward*, but we find relative *increases* in these new substance treatment episodes, suggesting that dependence initiation rates are not declining due to reformulation.

In panels C and D, we repeat the above analysis but include all opioid treatment admissions, which includes those who are in treatment for heroin, methadone, or any other prescription opioids. As before, there is no evidence of a relative *decline* in admissions due to reformulation even among those who had no prior treatment admissions (panel D).[9]

These results suggest that we are not observing a decline in the incidence of dependence that might predict future reductions in overdose rates associated with reformulation. This conclusion is consistent with descriptive evidence from the NSDUH that shows that the share of the household population suffering from opioid analgesic dependence, using DSM criteria, has not been declining since reformulation (Mintz et al. 2019; Saloner and Karthikeyan 2015).

As noted in the Section III, there are concerns about data comparability in the TEDS. Our assumption is that there are not shifts in reporting correlated with pre-reformulation OxyContin misuse. We observe some evidence of a differential decline in the estimates between 2005 and 2006, but the general consistency of the pre-reformulation estimates suggests that there are not systematic shifts in reporting affecting interpretation of the estimates.

G. DISCUSSION

What does the evidence in this paper tell us about reformulation's long-term effects on illicit drug markets? The relationship between overdose deaths and exposure to reformulation has only grown over time. The duration of this increase through 2017—and the fact that its growth does not appear to be slowing—is suggestive that we are not simply observing those misusing OxyContin prior to 2010 gradually but increasingly dying from overdoses up to seven years later. Instead, we have suggestive evidence of market growth and new consumers entering into illicit drug markets.

Part of the strengthening relationship between reformulation and overdose death rates appears to be explained by the delayed introduction of new and more deadly opioids into illicit markets. We observe especially large overdose rate growth tied to reformulation beginning when fentanyl began to permeate illicit drug markets. Similarly, we find strong evidence that synthetic opioid death rates rose disproportionately in areas more exposed to reformulation.

In addition, we observe spillovers into nonopioid drug markets potentially among people with little prior medical or illicit opioid exposure. This result suggests that market expansion has played a critical role. Finally, we find evidence of increases in heroin (and all opioid) dependence as measured by treatment admissions, among those with no prior history of

[9]We can reject that the post-reformulation estimates are jointly equal to zero in both panel C ($p = 0{:}014$) and panel D ($p = 0{:}002$).

substance use treatment, tied to reformulation. This relationship is also increasing through 2017, which is consistent with new entrants into the market, though alternative explanations are also possible. The lack of evidence of declines on this dimension strongly suggests that we will not observe declines in overdose rates tied to reformulation in the near future.

Overall, the evidence in this paper suggests that reformulation led markets to sell deadlier substances and contaminate nonopioid drugs, expanding illicit opioid drug use. The evidence is also consistent with an increasing flow of new consumers into these markets, though we are unable to observe this relationship directly.

To quantify the overall national effect of reformulation on overdose rates, we consider the overdose trajectory for a hypothetical "country" unexposed to OxyContin reformulation. After estimating the event study in Figure 4, 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 with this counterfactual in Figure 6. 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 Figure 4). After reformulation, we see slow divergence at first. By 2013, this separation is modest, consistent with the conclusions of Alpert, Powell, and Pacula (2018). We estimate that reformulation increased the 2013 overdose rate by 1.7 overdoses per 100,000 people, a 14 percent increase relative to the counterfactual.

However, by 2017, our estimates imply that reformulation increased overdose rates by over 11.6 overdoses per 100,000 people, more than a 100 percent increase relative to our counterfactual. Interestingly, Figure 6 suggests that the overdose rate would have gradually decreased in the absence of reformulation (holding everything else constant).[10] This counterfactual decrease may simply be the result of extrapolating too far out of sample. However, 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 overdose reductions, which have been found in the literature for a variety of implemented policies,[11] could be masked by national trends driven by the transformation of the opioid crisis.

[10]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.

[11]For example, prescription drug monitoring programs have been widely adopted and strengthened with evidence that these more robust and modern prescription drug monitoring programs reduce misuse (Buchmueller and Carey 2018; Kaestner and Ziedan 2020) 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. 2018).

VI. 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 why 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). However, our analysis strongly suggests that the transition eventually increased overdose rates to unprecedented levels as the large increase in demand within the black market associated with reformulation generated a supply innovation (fentanyl) that impacted more than just the illicit opioid market. As we evaluate the consequences of large supply-side opioid interventions, such as the reformulation of OxyContin, such effects are first-order concerns.

The potential benefits of reformulation include reductions in the propensity of beginning to misuse opioids. However, there is little empirical evidence that such reductions are having a meaningful impact on overdose rates. The relationship between exposure to reformulation and overdose rates has strengthened over time. In addition, initial substance use treatment admissions are also increasing faster in states more exposed to reformulation, suggesting that initiation rates are still not declining in response.

The shift to illicit opioids due to reformulation can be observed by a sudden and persistent rise in heroin overdoses in states more exposed to reformulation. 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 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 nonopioid drug markets—specifically, cocaine. We can attribute the rise in cocaine overdose rates to reformulation, suggesting possible complementarities but more likely mixing in production given the large number of cocaine overdoses involving fentanyl (Pardo et al. 2019). The increase in cocaine overdoses is not an independent phenomenon but is linked to the supply response to increased demand for opioids in illicit drug markets.

There is limited work on the ramifications of exogenous shocks to the size of illicit markets. This study represents an important contribution showing the impact of a large exogenous shift in demand on the black market caused by the reformulation of OxyContin. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

We thank Abby Alpert and Mary Vaiana for helpful comments.

FUNDING INFORMATION

Powell and Pacula gratefully acknowledge financial support from NIDA (grant numbers 1R21DA041653 and P50DA046351) and CDC (R01CE02999).

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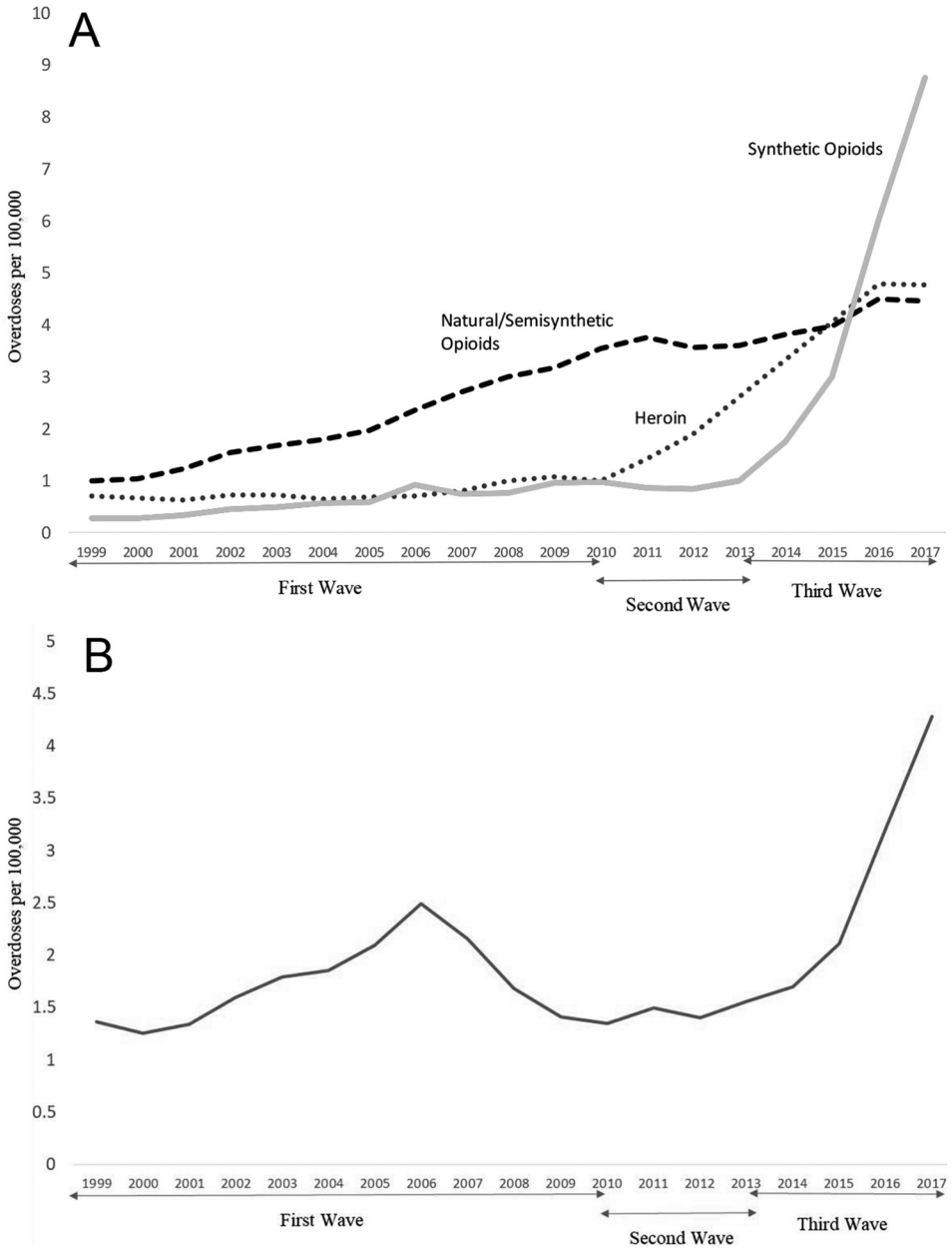

FIGURE 1.

National fatal overdose rate trends. A: National annual fatal overdose trends in natural and semisynthetic 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. B: National trends in fatal cocaine overdoses per 100,000.

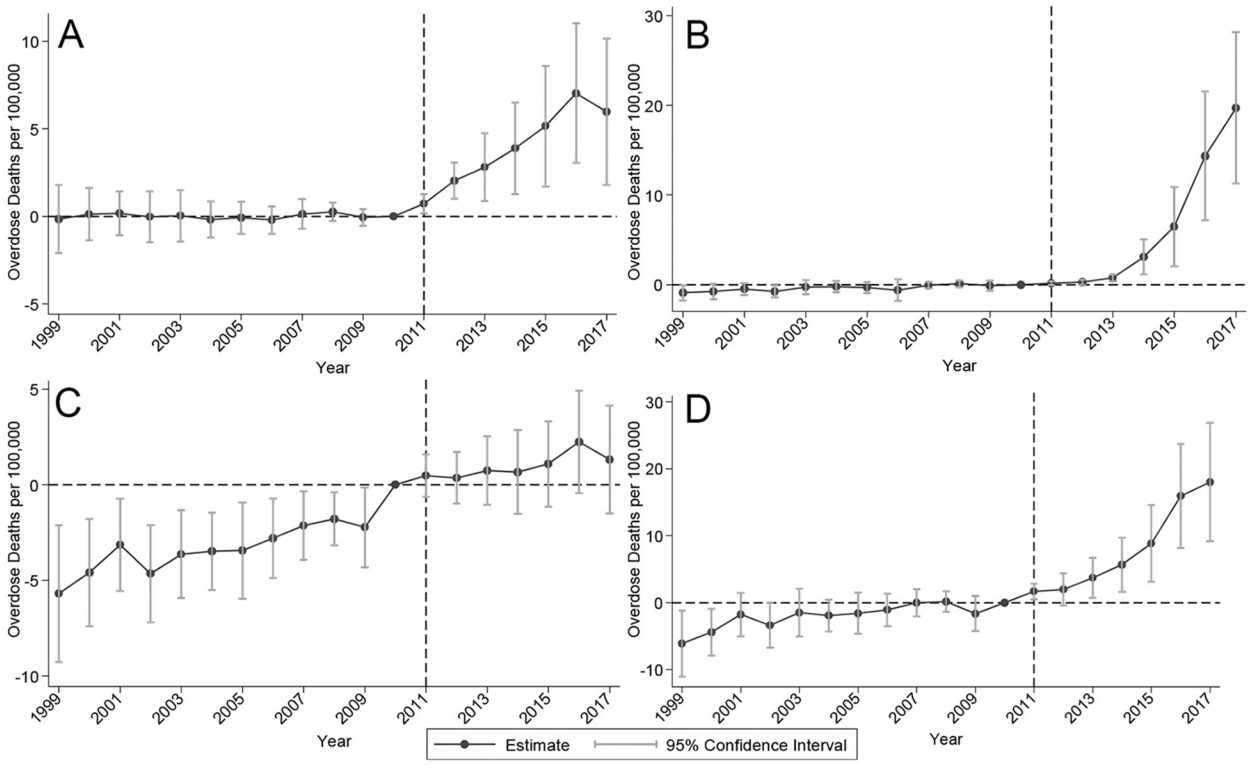

FIGURE 2.

Nonmedical OxyContin misuse event study estimates for fatal opioid overdoses. Ninety-five percent 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 nonmedical OxyContin use rate interacted with year indicators. The 2010 interaction is excluded and the corresponding estimate is normalized to zero. 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/semisynthetic opioids. D: All opioids.

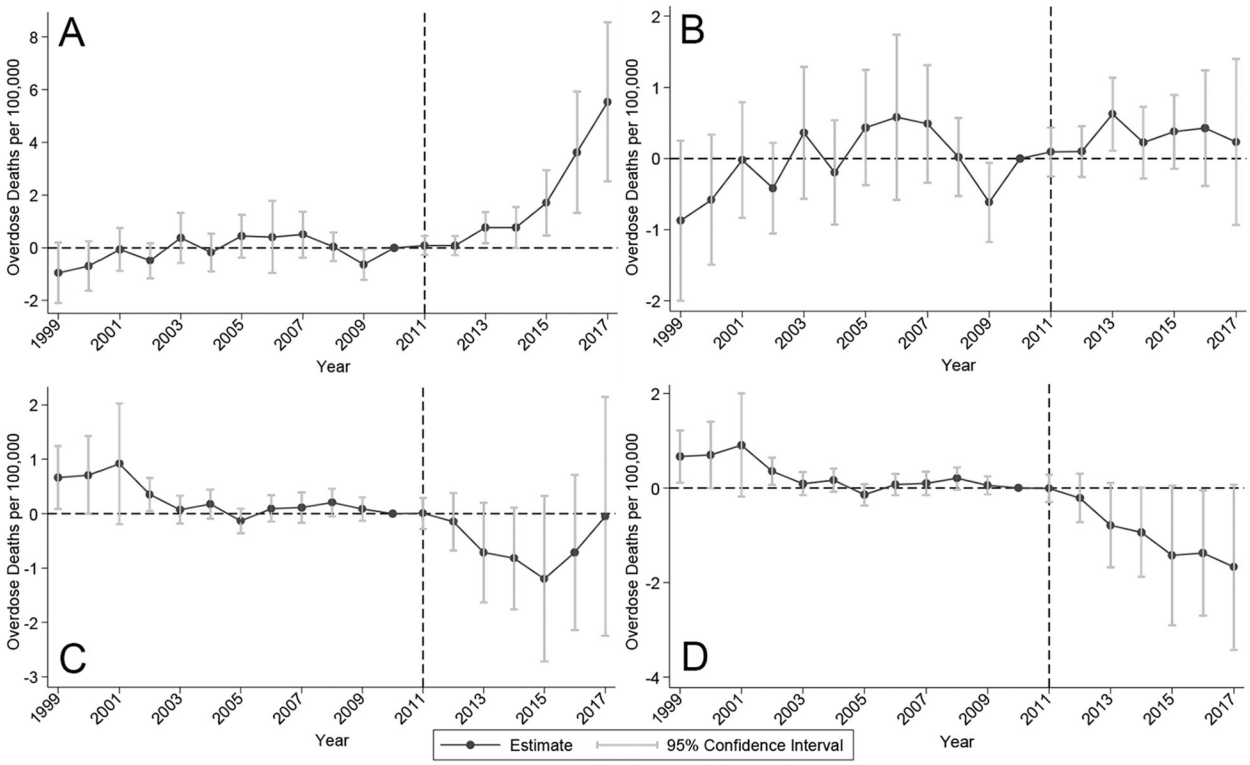

FIGURE 3.

Nonmedical OxyContin misuse event study estimates for cocaine and psychostimulant fatal overdoses. Ninety-five percent 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 nonmedical OxyContin use rate interacted with year indicators. The 2010 interaction is excluded and the corresponding estimate is normalized to zero. The specification includes state and time fixed effects. We also jointly estimate effects for pain reliever misuse interacted with year indicators. A: Cocaine. B: Cocaine, excluding synthetic opioids. C: Psychostimulants. D: Psychostimulants, no synthetic opioids.

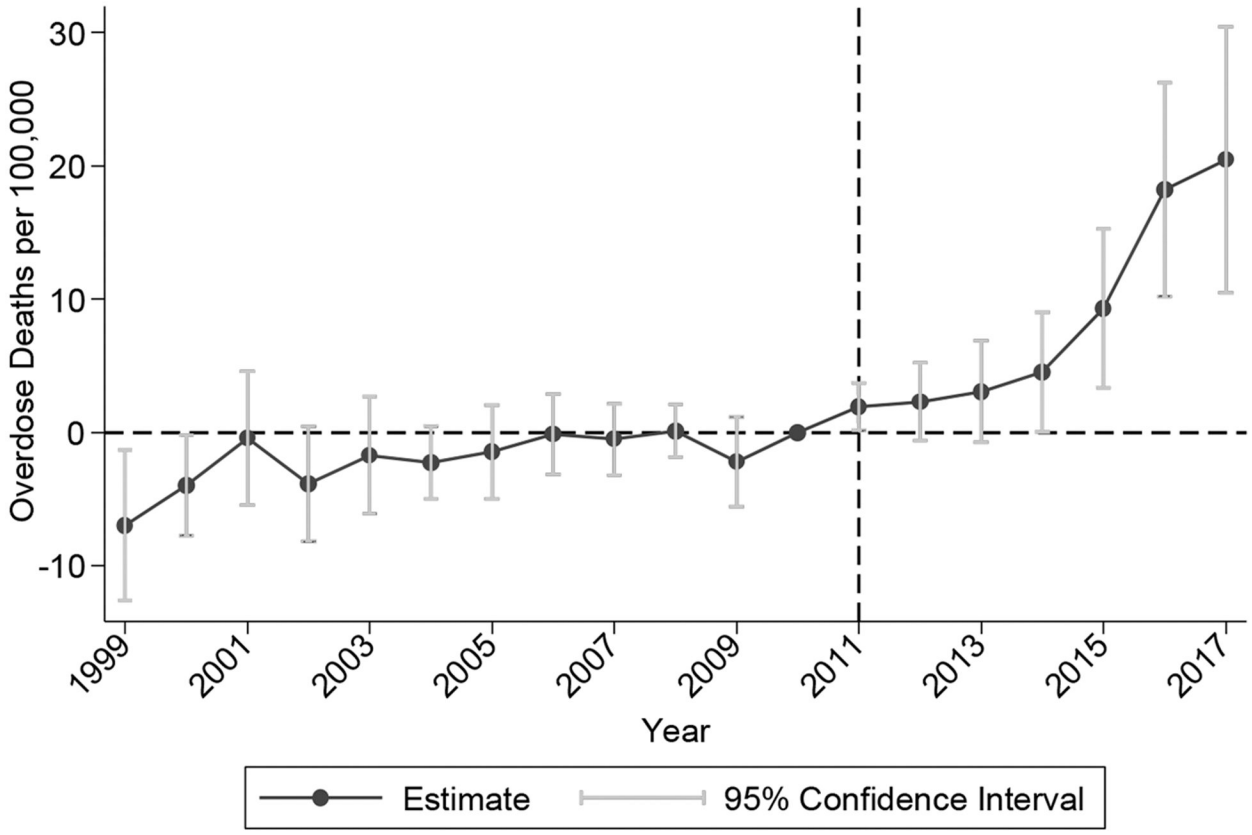

FIGURE 4.

Event study estimates for the total drug overdose rate. Ninety-five percent confidence intervals adjusted for state-level clustering. Outcome is total overdoses per 100,000. The estimates reported in the figures are the coefficients on the pre-reformulation nonmedical OxyContin use rate interacted with year indicators. The 2010 interaction is excluded and the corresponding estimate is normalized to zero. The specification includes state and time fixed effects. We also jointly estimate effects for pain reliever misuse interacted with year indicators.

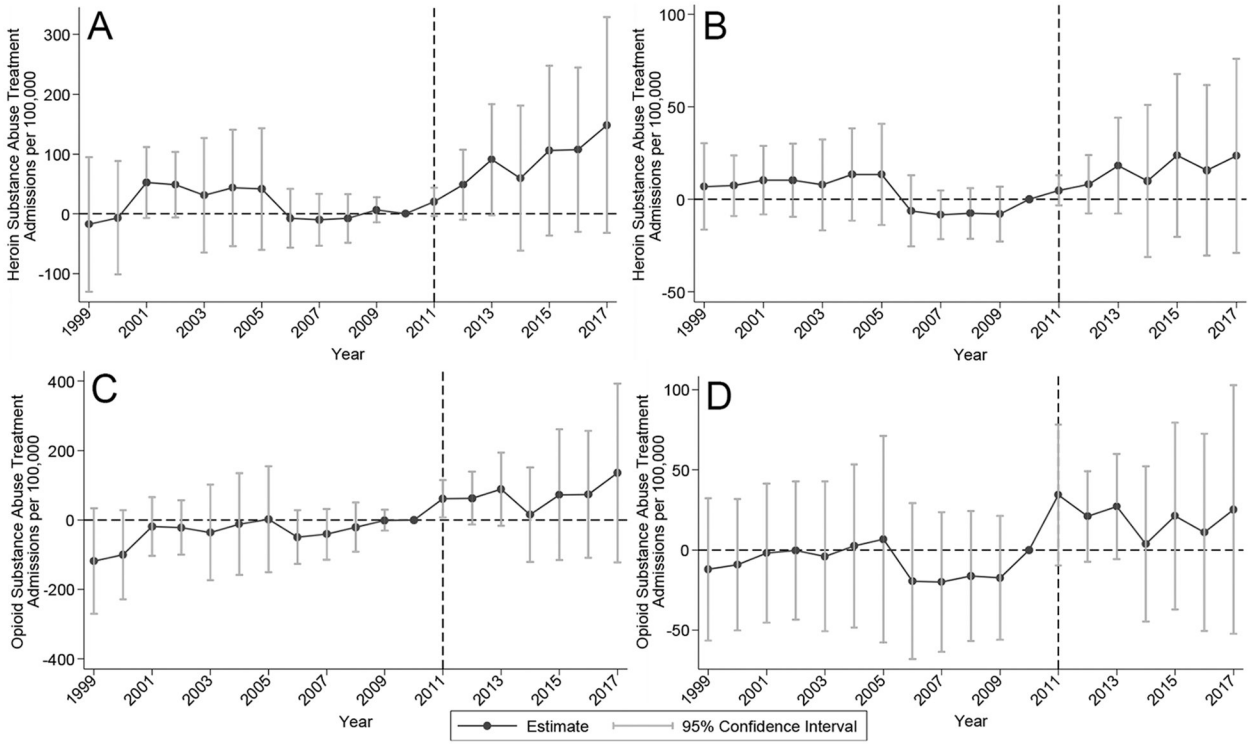

FIGURE 5.

Nonmedical OxyContin misuse event study estimates for substance abuse treatment admissions. *N* =949. Ninety-five percent confidence intervals adjusted for state-level clustering. Outcome is substance abuse treatment admissions per 100,000 for the specified category for ages 12+. Data are from the TEDS. The estimates reported in the figures are the coefficients on the pre-reformulation nonmedical OxyContin use rate interacted with year indicators. The 2010 interaction is excluded and the corresponding estimate is normalized to zero. The specification includes state and time fixed effects. We also jointly estimate effects for pain reliever misuse interacted with year indicators. See main text for joint significance tests of post-reformulation estimates. A: All heroin. B: Heroin, no prior treatment admissions. C: All opioid. D: Opioid, no prior treatment admissions.

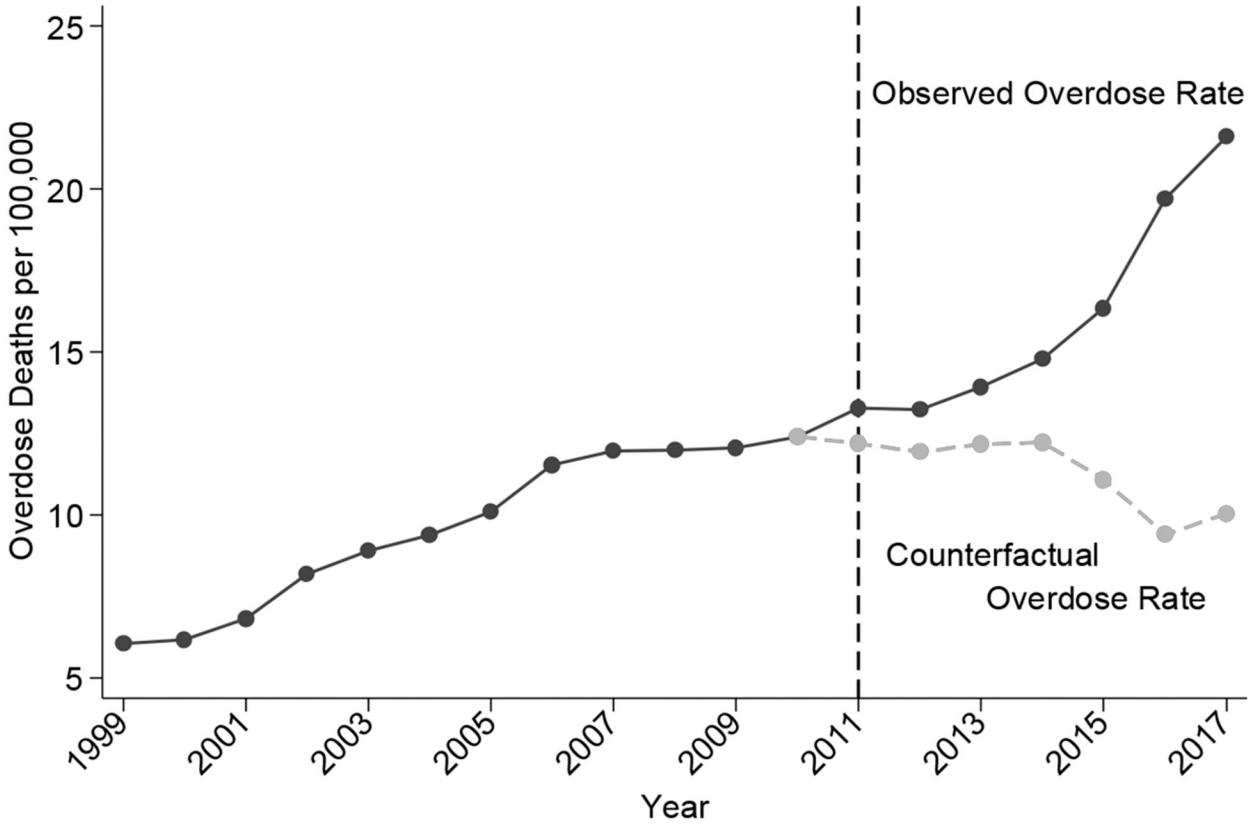

FIGURE 6.

Actual and counterfactual overdose rates in absence of reformulation. We plot the actual overdose rate over time. In addition, we estimate the event study shown in Figure 4 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 Figure 4).

TABLE 1.

Summary statistics: Means by initial OxyContin misuse rates (2004–09)

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, 2004–09
Deaths per 100,000				
All opioids	5.824	4.903	7.928	Vital Statistics, 2004–09
Heroin	0.817	0.820	0.809	Vital Statistics, 2004–09
Natural/semisynthetic opioids	2.504	2.012	3.630	Vital Statistics, 2004–09
Synthetic opioids	0.755	0.642	1.104	Vital Statistics, 2004–09
Cocaine	1.951	1.860	2.159	Vital Statistics, 2004–09
Substance abuse treatment admissions per 100,000				
Heroin	115.53	124.96	96.67	TEDS, 2004–09
Heroin + methadone + opiates	194.82	199.63	187.07	TEDS, 2004–09
Demographic characteristics				
Population	5,877,760	8,444,077	3,545,669	SEER, 2004–09
Age (%)				
25–44	27.55	27.89	26.78	SEER, 2004–09
45–65	25.31	25.03	25.96	SEER, 2004–09
65+	12.58	12.11	13.64	SEER, 2004–09
Race (%)				
White	80.22	77.82	85.71	SEER, 2004–09
Black	13.39	15.02	9.67	SEER, 2004–09
CPS statistics				
College degree (% of ages 25+)	28.49	28.97	27.38	CPS, 2004–09
Foreign born (%)	13.26	14.53	10.35	CPS, 2004–09
Married (% of ages 25+)	60.53	60.12	61.45	CPS, 2004–09
Number of states	51	25	26	

Note: All statistics are for 2004–09. Except for the population means, they are all population-weighted. SEER = Surveillance, Epidemiology, and End Results Program. CPS = Current Population Survey. TEDS =Treatment Episode Data Set. The TEDS outcomes refer to ages 12+.

TABLE 2.

Correlations between overdose rates (2004–09)

Overdoses per 100,000	Heroin	Synthetic opioids	Natural/semisynthetic opioids	Cocaine	Psychostimulant
Heroin	1.0000				
Synthetic opioids	−0.0500	1.0000			
Natural/semisynthetic opioids	0.0653	0.5989	1.0000		
Cocaine	0.2298	0.2854	0.2243	1.0000	
Psychostimulant	0.0433	−0.0896	0.5113	−0.2285	1.0000

TABLE 3.

Relationship between OxyContin misuse and 2017 overdose death rates from parametric model

Types of overdoses	Heroin	Synthetic	Natural/semisynthetic	All opioids	Cocaine	Psychostimulants	All overdoses
	A. Main effects						
OxyContin effect	8.803[a] (3.101)	20.018[a] (5.355)	4.430 (3.709)	28.319[a] (7.349)	11.041[a] (2.563)	−0.751 (1.138)	31.462[a] (9.574)
	B. Add covariates						
OxyContin effect	11.676[a] (3.653)	26.604[a] (8.704)	3.914 (4.683)	36.510[a] (9.946)	16.545[a] (3.665)	−1.761 (1.575)	41.088[a] (13.314)
	C. Using OxyContin supply as measure of exposure						
OxyContin effect	2.613 (2.431)	10.159[a] (3.370)	0.821 (1.612)	10.956[c] (5.703)	4.160[b] (2.038)	0.329 (0.355)	15.115* (7.768)
	D. Using 2004–05 nonmedical OxyContin use						
OxyContin effect	8.155[a] (2.813)	19.340[a] (4.996)	6.757[b] (2.834)	25.414[a] (6.874)	8.260[a] (3.066)	−1.898[c] (1.056)	25.793[a] (8.087)
	E. Main effects (repeated) with *p*-values from permutation-style test						
OxyContin effect [*p*-value]	8.803[a] [0.016]	20.018[a] [0.001]	4.43 [0.464]	28.319[a] [0.003]	11.041[a] [0.008]	−0.751 [0.707]	31.462[a] [0.009]

Note: $N = 510$. Standard errors in parentheses are adjusted for state-level clustering for panels A–D. Outcomes are overdose deaths per 100,000. All regressions in clude state and year fixed effects. Pre-reformulation OxyContin misuse rates (2004–09) are interacted with a linear trend and permitted to have a level and slope shift in 2011. We also control for nonmedical pain reliever use interacted in the same manner. The sample includes years 2006–09, 2011–17. We report the implied estimated effect for 2017. Covariates in panel B are defined as averages for 2004–09 and include log of population size, fraction white, fraction foreign born, and fraction ages 25–44. The covariates are also interacted in the same manner as the misuse variables are. Panel E replicates panel A but reports *p*-values from a permutation test. *P*-values are reported in brackets. We randomly, without replacement, assigned misuse rate pairs (jointly) to different states and then estimated the t-statistic associated with the OxyContin misuse rate. The t-statistic for the true sample was then compared with this distribution of 999 placebo t-statistics.

[a]1%,

[b]5%,

[c]10% statistical significance.