The Review of Economics and Statistics

VOL. CI  MARCH 2019  NUMBER 1

HOW THE REFORMULATION OF OXYCONTIN IGNITED THE HEROIN EPIDEMIC

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Abstract—We attribute the recent quadrupling of heroin death rates to the August 2010 reformulation of an oft-abused prescription opioid, OxyContin. The new abuse-deterrent formulation led many consumers to substitute an inexpensive alternative, heroin. Using structural break techniques and variation in substitution risk, we find that opioid consumption stops rising in August 2010, heroin deaths begin climbing the following month, and growth in heroin deaths was greater in areas with greater prereformulation access to heroin and opioids. The reformulation did not generate a reduction in combined heroin and opioid mortality: each prevented opioid death was replaced with a heroin death.

I. Introduction

Deaths from drug overdoses have steadily increased over the past fifteen years and are now at epidemic levels. Figure 1 shows that the national death rate (deaths per 100,000) for drug poisonings doubled from 1999 to 2014.1 Case and Deaton (2015) argued that this increase was an important contributor to the unprecedented rise in all-cause mortality for middle-aged non-Hispanic whites. As seen in the figure, the rise in deaths involving heroin or opioids accounts for 75% of the overall increase in deaths from drug poisonings.2

Received for publication July 31, 2017. Revision accepted for publication February 16, 2018. Editor: Amitabh Chandra.

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Opioids are narcotic pain relievers and are available, legally, only by prescription. When used as directed, they are an important element of fighting acute and chronic pain. Starting in the mid-1990s, medical groups argued there was an epidemic of untreated pain and urged greater use of opioid pain medicines, especially for those with chronic conditions. The efforts changed prescribing practices considerably. Between 1991 and 2013, opioid prescriptions increased threefold.3 Opioids are addictive, and as their everyday use increased, so did abuse rates. The National Survey on Drug Use and Health (NSDUH) estimates that in 2014, 4.3 million people aged 12 and over used pain medicines recreationally (Center for Behavioral Health Statistics and Quality, 2015).

When taken in large quantities, opioids shut down the respiratory system and can lead to death. In the bottom two lines of figure 1, we report separate time series for heroin and opioid death rates. Between 1999 and 2009, opioid death rates were rising rapidly, but heroin death rates were much lower and increasing slowly. In 2010, this changed: over the next four years, heroin death rates increased by a factor of four while opioid death rates remained fairly flat.

In this paper, we argue that the rapid rise in the heroin death rate since 2010 is largely due to the reformulation of OxyContin, an opioid introduced in 1996. OxyContin became popular for recreational use and abuse because the drug offered much more of the active ingredient oxycodone than other prescription opioids and the pills could easily be manipulated to access the entire store of the active ingredient. In early August 2010, the makers of OxyContin, Purdue Pharma, pulled the existing drug from the market and replaced it with an abuse-deterrent formulation (ADF) that made it difficult to abuse the drug in this fashion. This made the drug far less appealing to opioid abusers and led many to shift to a readily available and cheaper substitute: heroin.

A large literature in the medical and public health fields has demonstrated that opioid abuse rates in general, and OxyContin abuse rates in particular, have declined since reformulation (Severtson et al., 2012; Butler et al., 2013; Sessler et al., 2014; Havens et al., 2014; Dart et al., 2015;...
Larochelle et al., 2015; Coplan et al., 2016; Chilcoat et al., 2016). Most of this work uses interrupted time-series analysis with annual or quarterly data and suggests that outcomes such as OxyContin prescriptions, deaths from opioids, fatalities reported to the makers of OxyContin, calls to poison control centers for opioids, and entrance into opioid treatment programs all have fallen since the third quarter of 2010. At the same time, an equally large literature suggests a shift to heroin toward the end of 2010 (Coplan et al., 2013; Cicero, Ellis, & Surratt, 2012; Cicero et al., 2014; Cicero, Ellis, & Harvey, 2015; Compton, Jones, & Baldwin, 2016). These papers point to evidence like in our figure 1 or analyze data from surveys of opioid users who have entered substance abuse treatment facilities.

Our work begins with these findings and, using techniques from the well-established literature on estimating structural breaks in time-series models, pinpoints the timing of the changes to the reformulation of OxyContin. The results of these analyses are illustrated in figure 2a where the solid black line displays the national monthly heroin death rate. The vertical dotted line shows the month that the analysis chose as the most likely one in which a trend break occurred. For the heroin death rate, this is the month immediately following the OxyContin reformulation. A number of national time series, including shipments of oxycodone (a proxy for consumption), prescriptions for oxycodone, the fraction of people who use pain medicine recreationally, and health care encounters for heroin poisonings, all show a trend break in August 2010 or immediately after.

Although we date the changes to the month following the reformulation of OxyContin, it is possible that some other event in August 2010 led to the observed changes in the heroin and opioid markets. First, we use our structural break analysis to show that none of the seven other opioids that the Drug Enforcement Administration (DEA) tracks have a negative trend break in the third quarter of 2010. This suggests that there was not a different shock at that time reducing the use of opioids more broadly. Second, we provide additional evidence in favor of the reformulation causing the increase in heroin deaths that takes advantage of differences in the degree to which the reformulation would have affected abusers’ home markets. In particular, we note that markets with greater access to heroin and markets with higher rates of prereformulation opioid abuse are likely to show more substitution away from opioids and toward heroin than markets with less access to heroin or lower opioid abuse rates. We proxy for the former with whether a state is above or below the median prereformulation per capita heroin death rate and the latter with whether a state is above or below the median prereformulation per capita oxycodone consumption. Breaking states into four groups based on these measures, we estimate prereformulation trends and postreformulation trends and test whether there are trend breaks after August 2010 for each of the groups. We find that the heroin death rates increased substantially in all groups. In addition, we find that the trend breaks are largest in states that appear ex ante to be at the highest risk of substitution. These results are previewed graphically in figure 2b, where we display the monthly heroin death rate from 2004 through 2014 for the four groups of states. While trends in heroin death rates are similar across the groups before the reformulation, afterward the groups diverge, and the states likely to be at the highest risk of substitution, those above the median in both pre-reformulation measures, diverge the most.

We also estimate the models outlined in the previous paragraph using opioid death rates, as well as the combined heroin or opioid death rate as the outcomes of interest. The results from these models suggest that across all groups, opioid death rates were increasing rapidly before reformulation but were flat afterward. When we combine heroin and opioid deaths together, we find no evidence that total heroin and opioid deaths fell at all after the reformulation; there appears to have been one-for-one substitution of heroin deaths for opioid deaths. Thus, it appears that the intent behind the abuse-deterrent reformulation of OxyContin was completely undone by changes in consumer behavior, reminiscent of the unintended consequences phenomenon pointed out in Peltzman (1975).

Our results indicate the potential limitation of this type of supply response to the opioid epidemic. As the abuse rates of pharmaceutical opioids have increased, governments at all levels have looked for technological, medical, and legal solutions to this problem. One of the more popular innovations has been the design of ADFs of drugs. Currently, there are seven drugs on the market with ADFs, five of them opioids (FDA, 2016). As of September 2014, there were 129 pharmaceutical products with an abuse-deterrent formulation in

5 The dotted line is the $F$-test on the null that there is no break. We discuss this in more detail later.
6 There are gaps in the series because months with fewer than ten heroin deaths have been suppressed per CDC reporting requirements.
some stage of development. The Food and Drug Administration (FDA) has promoted the development of abuse-deterrent opioids to pharmaceutical companies (FDA, 2015) and worked with manufacturers to bring these products to market as quickly as possible (FDA, 2016). Recently, the FDA listed the development of ADFs a national policy priority, five states have adopted laws requiring insurance companies to cover ADFs, and similar laws have been proposed in fifteen other states. Despite the enthusiasm for ADFs, our results suggest that the benefits of the reformulation are easily undone when there are readily available substitutes.

We also present evidence that a number of alternative explanations do not appear capable of generating the patterns found in the data. The adoption of prescription drug monitoring programs and the rise of the potent synthetic opioid fentanyl likely have important effects on the markets for opioids and heroin, but they do not seem to be the driving force behind the abrupt growth in heroin death rates starting in 2010. We also explore the impacts of the crackdown on pill mills in Florida.

Our work is most closely related to the concurrent work of Alpert, Powell, and Pacula (2018), who also examined the increase in heroin deaths. Using a panel of annual state-level data, they hypothesized that the switch to other narcotics after the reformulation of OxyContin should be larger in states with higher prereformulation abuse rates of OxyContin. They constructed a prereformulation measure of OxyContin abuse rates at the state level and interact that with a dummy variable for the postreformulation period. They found that outcomes such as heroin death rates increased more after reformulation in states that had higher prereformulation OxyContin abuse rates. Our work diverges from theirs in two important ways. First, our time-series evidence is able to date the changes in the heroin and opioid markets to the month in which the reformulation occurred. Second, we incorporate information about how developed an area’s heroin market is, an important determinant of how much substitution will occur from opioids to heroin, and show that the increase in heroin deaths entirely offsets reductions in opioid deaths in the short run.

In the next section, we provide background on OxyContin and its reformulation and heroin markets in the United States. In section III, we use time-series techniques from macroeconomics to date regime changes and identify August and September 2010 as the turning points for five national time series measuring heroin and oxycodone use and abuse. In section IV, we use a panel of monthly state-level mortality rates to demonstrate that the increase in the heroin death rate was much higher in states where the market for heroin was thicker or where there were higher levels of prereformulation use of oxycodone. In section V, we consider alternative explanations for the rise in heroin death rates, and in section VI we make some concluding remarks.

II. Background on OxyContin and the Reformulation

A. The Rise of OxyContin

OxyContin is a name-brand painkiller marketed by Purdue Pharma containing the ingredient oxycodone, an opioid that has been in clinical use since 1917 (Kalso, 2005). OxyContin is an extended-release formulation that allows for up to twelve hours of pain relief; hence, there is typically a high milligram (mg) content of oxycodone in the pills.  

We refer to OxyContin ER as OxyContin. According to the Physicians’ Desk Reference online, Percocet (oxycodone with acetaminophen) contains anywhere from 2.5 to 10 mg of oxycodone per pill, while OxyContin contains 10 to 80 mg of active ingredient. http://www.pdr.net/full-prescribing-information/OxyContin-oxycodone-hydrochloride-492#section-standard-2.
Since its release in 1996, OxyContin has been one of the most successful pharmaceuticals of all time, with worldwide sales totaling $35 billion.11

OxyContin was introduced at a time when the medical profession was reevaluating its use of opioid-based painkillers. Historically, opioids were reserved for those with acute pain, such as postsurgical and cancer patients, but not for those with chronic pain conditions. This was viewed by many as a failure of the medical profession. In the mid-1990s, a number of physicians began to argue for much greater use of opioids for patients with chronic pain. In the 1995 presidential address of the American Pain Society, James Campbell (1995) introduced the notion that pain is the “5th vital sign.” In 1996, the American Pain Society and the American Academy of Pain released a consensus statement outlining the need for greater opioid use, especially for chronic pain (Consensus Statement, 1997). In 2001, the Joint Commission on Accreditation of Healthcare Organizations introduced standards for pain assessment and management in a variety of patient settings (Berry & Dahl, 2000) that focused on patients’ rights to appropriate pain care, encouraged hospitals to make pain evaluation a priority, and introduced the use of pain scales. In 2006, the Centers for Medicare and Medicaid began fielding a 32-question postdischarge survey for Medicare inpatients that contained three questions asking if the patient’s pain was adequately controlled during their hospital stay. A number of observers, most notably the Physicians for Responsible Opioid Prescribing, have argued that the Joint Committee standards and the Medicare survey have encouraged “dangerous pain control practices, the endpoint of which is often the inappropriate provision of opioids.”12

During this time, state medical boards and state laws started to relax regulations about prescribing opioids to noncancer patients (Alexander, Frattaroli, and Gielen, 2015). It is not clear how each of these changes affected prescribing practices, but prescribing opioids for those in chronic pain was becoming acceptable, if not encouraged.

With the heightened concern about patient pain, pharmaceutical manufacturers started to market opioids directly to physicians. A key message in many presentations was that the risks of addiction were small when opioids were used appropriately. Purdue Pharma was particularly aggressive at promoting this line of argument for OxyContin. Quinones (2015) and Van Zee (2009) note that an important study that Purdue Pharma used in its advertising materials, Porter and Jack (1980), reported that of “11,882 patients who received at least one narcotic preparation [opioid], there were only four cases of reasonably well documented addiction in patients who had no history of addiction.” This “study” was in actuality a 100-word letter to the editor in the New England Journal of Medicine, the entire substance of which is contained in the quote above. When OxyContin was first marketed in 1996, the FDA allowed Purdue Pharma to claim that addiction was rare if opioids were legitimately used in the treatment of pain. By 2001, the FDA required that the label be modified to reflect that data were not available to establish the true incidence rate of addiction (Van Zee, 2009).13

The effect of this panoply of changes was a massive increase in opioid use. Between 1996, when OxyContin was released, and 2003, sales of OxyContin increased from $44.8 million to $1.5 billion per year (U.S. General Accounting Office, 2003). Between 1991 and 2011, opioid prescriptions tripled from 76 million to 211 million with oxycodone-based products representing a quarter of these prescriptions in later years.14

B. The Reformulation of OxyContin and the Shift to Heroin

Given its extended-release nature, OxyContin had a large amount of the active ingredient oxycodone. When taken properly, OxyContin slowly releases oxycodone over the course of twelve hours. However, the extended-release properties could be circumvented by crushing the pill into a fine powder that could then be snorted, smoked, or liquefied and injected. In this way, a person could gain access to the full milligram content of oxycodone all at once and rapidly achieve an intense high.

To help combat this abuse, Purdue Pharma developed an ADF of the drug. When the new pills were crushed, they did not turn into a fine powder, but instead a gummy substance that was much more difficult to snort or inject.15 The ADF was approved by the FDA in April 2010. It became the first drug that was allowed to claim on its label that it had abuse-deterrent properties. Without any public notice, Purdue Pharma ceased shipping the old OxyContin formulation on August 5, 2010. On August 9, 2010, it began shipping exclusively its reformulated version (Butler et al., 2013).

Coplan et al. (2016) note that although the formulation for OxyContin changed, its price did not. We find evidence consistent with this claim in the Truven Marketscan Research Database (Marketscan). This is a database of individual-level claims for inpatient, outpatient, and prescription drug use that by the end of our sample period provided information for over 37 million covered clients per month from 350 self-insured plans.16 Appendix figure C1 shows

13 In 2007, Purdue Pharma paid $600 million in fines, acknowledging that “with the intent to defraud and mislead” it marketed and promoted OxyContin as a drug that was less addictive, less subject to abuse, and less likely to cause other narcotic side effects than other pain medications. http://www.nytimes.com/2007/05/10/business/11drug-web.html.
16 Information about Marketscan data can be found at http://truvenhealth.com/your-healthcare-focus/analytic-research/Marketscan-research-databases.
the monthly time series of the total price and the price that patients paid out-of-pocket for oxycodone from 2006 through 2013. There is no large change in either price series at the time of the reformulation, and so it is unlikely that changes in the legal price for oxycodone are driving substitution to heroin.\footnote{17}

Unfortunately, at the time of the reformulation, there was a readily available and inexpensive substitute for OxyContin: heroin. Historically, heroin markets were supplied by two groups. East of the Mississippi, users consumed white powder heroin that was usually distributed through networks out of New York. West of the Mississippi, much of the supply was “black tar” heroin from Mexico (Drug Enforcement Administration, 2016). Over the past thirty years, there has been an increasing supply of heroin from Mexican gangs. Of confiscated heroin, 79% is now from Mexico (DEA, 2016). Many of the Mexican suppliers compete for market share by offering higher-quality heroin (Quinones, 2015). When price is calculated per pure gram, this high quality has pushed the price down to very low levels (see appendix figure C2). The price fell from more than $3,000 per pure gram in 1981 to less than $500 in 2012.\footnote{18} In appendix figure C3, we display a time series of the number of heroin deaths per 1,000 heroin uses; this series combines quarterly estimates of the number heroin uses and the number of heroin deaths per 1,000 heroin uses; this series combines quarterly estimates of the number heroin uses and the number of heroin deaths per 1,000 heroin uses starting in 2013 that the DEA suggests is due to suppliers mixing the drug with fentanyl (DEA, 2016), but this was not a problem in the prereformulation period (we discuss this trend later in the paper).

Mexican gang suppliers are not only gaining an increasing share of well-established markets for heroin such as Baltimore, New York, Boston, and Washington, DC, but they have moved operations into suburban and rural areas as well (DEA, 2016). Groups like the Xalisco Boys have transformed the supply of heroin to suburban and rural U.S. markets. Independent cells within a city are operated by cell managers, and each cell is supplied with high-quality Mexican heroin by the cell’s owner. The cell manager employs a telephone operator, who receives orders and then relays those orders to the drivers. A driver meets the client at a designated spot or delivers the drugs directly to the customer’s location. Each cell operates almost completely independently and constantly cycles through lower-level employees to help prevent detection by authorities. As this organizational form spread throughout the United States, the cost to the consumer of obtaining heroin was greatly reduced (Díaz-Briseno, 2010; Quinones, 2015). The DEA (2016) notes that thirty years ago, the typical heroin user was an urban resident. Heroin use in the 1990s and 2000s has now “spread to users in suburban and rural areas, more affluent users, younger users, and users of a wider range of ages. There is no longer a typical heroin user.” Entry into heroin use is now much easier than it was in the 1970s when it was mostly an injected drug. Because of increased purity, the drug can now be smoked or inhaled, decreasing the cost of drug initiation (Mars et al., 2014).

The available literature suggests that because of the easy availability of heroin, many OxyContin abusers switched to heroin after the product’s reformulation. Interrupted time-series data indicate that outcomes such as deaths, poisonings, emergency room visits, and enrollments in treatment programs from heroin abuse have all increased since August 2010 (Coplan et al., 2013, Cicero et al., 2012, 2014; Cicero, Ellis, Harvey, 2015; Compton et al., 2016). The movement to heroin from opioids is borne out in survey data as well. In a survey of 244 people who entered drug treatment programs for OxyContin abuse in the postreformulation period, respondents were asked how they dealt with reformulation (Cicero & Ellis, 2015). About one-third of respondents said they reacted by switching to other drugs, and about 70% of this group said the drug they switched to was heroin. In the population of people who use pain medicine recreationally, few eventually moved to heroin. According to data from the third quarter of 2010 through the end of 2014 in the annual NSDUH, among respondents who used pain medicine recreationally over the past year, less than 1 percent said they ever used heroin. However, over the same period, 79% of people who used heroin in the past thirty days reported a younger age of initiation for recreational pain medicine use than their initiation age for heroin.\footnote{20}

III. Dating the Timing of the Shift from Oxycodone to Heroin

We draw on the macro–time series literature on structural breaks to estimate when the changes in the oxycodone and heroin markets occurred. For time period $t$ and break period $c$, we estimate the quadratic spline,

$$Y_t = \gamma + t_c (1 - A_c') \beta_1 + t_c (1 - A_c') \beta_2 + t_c A_c' \alpha_1 + t_c A_c' \alpha_2 + \epsilon_t,$$  \hspace{0.5cm} (1)

where $A_c' = 1$ if $t \geq c$, $A_c' = 0$ if $t < c$, and $Y_t$ is the outcome of interest. As Quandt (1960), originally suggested, we find the period that is most likely to have had a trend break by varying $c$ and choosing the $c$ that maximizes the $F$-statistic

\footnote{17} The sawtooth pattern in the out-of-pocket series is due to patient cost sharing.

\footnote{18} Although there was a slight decrease in the price between 2010 and 2012, the elasticity of demand would have to be greater in magnitude than 15 to generate the observed rise in heroin death rates.

\footnote{19} Heroin use is known to be significantly underreported in self-report survey data (Harrell, 1997). As long as this underreporting is constant over time, it will not affect the implication of appendix figure C3 that the purity of heroin did not significantly change at the time OxyContin was reformulated.

\footnote{20} Author’s calculation from the NSDUH.
on the test of a break in trend ($\beta_1 = \alpha_1$ and $\beta_2 = \alpha_2$). In most series, the break visually occurs between 2009 and 2011, so we allow $c$ to vary between the start of 2009 to the end of 2011. Each of the figures that follows plots the time series, the quadratic spline fit to the time series, the time period that is most likely to have had a trend break, and the $F$-statistics for potential break dates near the maximum.

Figure 3a shows quarterly data on milligrams of oxycodone per 1,000 individuals from the DEA’s Automation of Reports and Consolidated Orders System (ARCOS). Within this system, drug manufacturers and distributors report to the DEA controlled substance transactions from manufacture to points of sale or distribution. Many of the drugs tracked in ARCOS are opioids, and we use data from Report 2, which lists quarterly drug distributions for oxycodone in milligrams of the active ingredient. We divide this by quarterly state population ($\frac{C}{1,000}$) and include data from the start of 2004 through the end of 2014 in the regressions. As seen in the figure, oxycodone per person was rising steadily until 2010. At that time, it stopped increasing and even fell somewhat over the next four years. In table 1, we present information about the sample and the results from estimating equation (1). The data suggest that the third quarter of 2010 is the most likely date for a trend break in oxycodone shipments. The $F$-test of equality for the pre- and posttrends is presented and is larger than the critical value needed to reject the null hypothesis (Andrews, 1993). As seen in figure 3a, the $F$-statistics for nearby dates are considerably lower than the most likely break date.

Figure 3b presents monthly data on milligrams of oxycodone prescribed per 1,000 subscribers in the Marketscan data. Prescribed oxycodone per 1,000 subscribers shows a similar pattern to that observed in the ARCOS data: it rises until 2010 and then levels off partway through the year. As seen in the second row of table 1, the most likely date for a
The substitution of heroin for opioids is not likely to be the same in all areas. Areas where heroin is more easily available or where there is pervasive abuse of oxycodone will probably see larger shifts from opioids to heroin. We use two proxies for these types of conditions and assess whether there was in fact a greater shift to heroin in places that appear to be at a greater risk for substitution. This is similar in spirit to the work of Alpert et al. (2018) who use annual state-level data on drug poisonings to demonstrate that the shift to heroin after the reformulation of OxyContin was larger in states that had higher prereformulation recreational use of OxyContin. In what follows, we first outline whether there was in fact a greater shift to heroin in the areas where we would expect greater substitution. This is similar in spirit to the work of Alpert et al. (2018) who use annual state-level data on drug poisonings to demonstrate that the shift to heroin after the reformulation of OxyContin was larger in states that had higher prereformulation recreational use of OxyContin. In what follows, we first outline whether there was in fact a greater shift to heroin in the areas where we would expect greater substitution.

### IV. Heterogeneity in the Impacts of the Reformulation

The substitution of heroin for opioids is not likely to be the same in all areas. Areas where heroin is more easily available or where there is pervasive abuse of oxycodone will probably see larger shifts from opioids to heroin. We use two proxies for these types of conditions and assess whether there was in fact a greater shift to heroin in places that appear to be at a greater risk for substitution. This is similar in spirit to the work of Alpert et al. (2018) who use annual state-level data on drug poisonings to demonstrate that the shift to heroin after the reformulation of OxyContin was larger in states that had higher prereformulation recreational use of OxyContin. In what follows, we first outline whether there was in fact a greater shift to heroin in the areas where we would expect greater substitution.
Our first measure is intended to capture the extent of oxycodone abuse in the period immediately preceding the reformulation. Areas with greater abuse are more likely to have individuals who substitute heroin than areas where there is less oxycodone abuse. We use milligrams of oxycodone per 1,000 people shipped to states in 2008 and 2009, the two years preceding the reformulation. This measure relies on areas where there is high oxycodone use and high abuse. The correlation coefficient between the state-level opioid mortality rate for the 2008–2009 period and the state-level milligrams of oxycodone shipped to the state per 1,000 people in 2008 and 2009 is 0.45.

Based on the distribution of states’ oxycodone shipments per 1,000 people, we divide states into two groups: those above and those below the median. As seen in figure 4a, areas with greater prereformulation oxycodone shipments per person also had higher rates of heroin deaths. This level difference supports the validity of our proxy since some opioid users transitioned to heroin even before the reformulation. The two groups’ heroin death rates track each other extremely well right up to the reformulation. However, as soon as the reformulation occurs, the two groups immediately begin to diverge. States with above-median per capita oxycodone shipments saw their heroin death rates rise from just under 0.1 to more than 0.4; the other states started at a slightly lower level but increased far less and did not surpass 0.25.

Our second proxy is intended to measure the availability of heroin. In areas where it is costly to find and purchase heroin (e.g., where the market for heroin is thin), the reformulation is not likely to lead many people to substitute to heroin; in areas where there is an active, thick heroin market, it is more likely that a person could find a dealer and begin to use or increase heroin use. We measure the availability of heroin using a state’s heroin death rate in the two years preceding the reformulation, 2008 and 2009. We assume that high heroin death rates indicate greater availability of the drug.

We divide states into two categories according to their prereformulation heroin death rates. The “low” risk group contains the states that were below the median of the distribution; the “high” risk group contains states that were above the median of the distribution. Figure 4b plots the heroin death rates from 2004 through 2014 for these groups. Prior to the reformulation, the groups’ heroin death rates were different in levels but followed similar trends. Both groups had flat heroin death rates from 2004 through 2007; from there, both groups increased slightly before leveling off. After the reformulation, the death rates increased, but at quite different rates. The high-risk group experienced much greater increases in the death rate than the low-risk group.

Although the raw figures suggest that places that are more likely to have been affected by the reformulation saw larger increases in heroin death rates, the areas that are most likely to have been affected are those that had both high prereformulation heroin death rates and high prereformulation oxycodone use. At the same time, those least likely to be affected are those with low prereformulation heroin death rates and low prereformulation oxycodone use. We pursue this by putting states into one of the four groups created by the interaction of our two risk factors. To ease exposition, we will refer to whether a state is above or below the median with “high” and “low,” respectively, and the prereformulation oxycodone shipments rate as “Oxy.” The heroin death rates for these four groups were shown in figure 2b. Once reformulation occurs, every group experi-

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23 Even in the prereformulation period, the majority of heroin users started as recreational pain medicine users. Using data from 2004 through the second quarter of 2010 in the NSDUH, we calculate that 67% of heroin users who started in the past two years had recreational pain medicine use that predates their heroin use.
enced a noticeable increase in its heroin death rate, with the greatest change occurring in the states that had both high oxycodone shipments and high heroin death rates before the reformulation.

To formalize the analysis, we estimate trends and trend breaks for each of the groups based on our proxies. For the heroin death rate in state \( i \) in month \( t \), we estimate

\[
y_{it} = \sum_{j=1}^{4} \left( (1 - A_j^t) T(j) t_i, B_{ij} + A_j^t T(j) t_i, B_{ij}^* + x_{it} \gamma \right) + \lambda_i + \epsilon_{it},
\]

where \( A_j^t \) and \( t_i \) are defined as before, \( T(j) \) is a dummy variable indicating which group the state is in, \( \lambda_i \) are basic demographics including the fractions of individuals in a set of age bins (under 20, 20–34, 35–49, 50+), in race bins, local economic conditions via the unemployment rate, a set of month fixed effects, and a set of state fixed effects, \( \lambda_i \). In these specifications, we impose August 2010 as the month of the break in trend. Standard errors are clustered at the state level. In the previous models, where we allowed for a quadratic trend, we use a linear model to simplify the statistical tests and interpretations of the coefficients. The key hypotheses to test are whether there is a break in trend for each state type, \( H_0: B_{ij}^* = B_{ij} \), and whether there is a difference in the trend breaks between the low Oxy/low heroin death rate group (which we refer to as group 1) and the other three groups, \( H_0: (B_{ij}^* - B_{ij}) = (B_{ij}^* - B_{ij}^k) \) where \( j = 2, 3, \text{ and } 4 \).

Data for this exercise come from the CDC Multiple Cause of Death database and range from January 2004 through December 2014 for all states and the District of Columbia. The CDC normally suppresses data when there are fewer than ten deaths in a cell, a frequent occurrence for monthly heroin deaths in small states. However, we obtained the restricted-use microdata and so have accurate counts for all states and months. We combine these data with the population counts referenced above to calculate heroin deaths per 100,000 people in the state and month.

For our initial analysis, we restrict the sample to the years before 2013 because individuals began increasing their use of fentanyl, a deadly synthetic opioid, at that time. The regression results for heroin death rates are shown in panel A of table 3. The first row presents the estimated trends for each of the four groups (each group gets its own column) prior to the reformulation. In all cases, the point estimates are positive but suggest relatively slow rates of growth. The second row suggests that the trends before the reformulation are much larger. The third row of the table shows the estimated trend breaks (the difference in trends, after minus before reformulation) and their standard errors. In each case, the trend breaks are positive; in states with high exposure to oxycodone, we can reject the null of no increase in growth at conventional levels of statistical significance. The point estimate for the high Oxy/high heroin death rate trend break is 0.0049. It would have taken these states only one and a half years to double the prereformulation heroin death rate of 0.083. In the final row of panel A, we present the difference between the column’s trend break and the trend break for the low Oxy/low heroin group. Although our estimates suggest both the high Oxy/low heroin group and the low Oxy/high heroin group saw larger trend breaks than the low Oxy/low heroin group, we lack the statistical power to differentiate the impacts. The heroin death rate for the high Oxy/high heroin group does show a statistically significantly larger trend break than the low Oxy/low heroin group.

Even if the reformulation of OxyContin increased heroin deaths, it could still have reduced the total death rate for heroin and opioids together if the reformulation encouraged some to quit opioid use altogether. Panels B and C of table 3

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Low Oxy/low Heroin</th>
<th>High Oxy/low Heroin</th>
<th>Low Oxy/High Heroin</th>
<th>High Oxy/High Heroin</th>
</tr>
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<tbody>
<tr>
<td>Trend before</td>
<td>0.0016 (0.0007)</td>
<td>0.0019 (0.0008)</td>
<td>0.0029 (0.0008)</td>
<td>0.0025 (0.0008)</td>
</tr>
<tr>
<td>Trend after</td>
<td>0.0024 (0.0006)</td>
<td>0.0044 (0.0012)</td>
<td>0.0039 (0.0009)</td>
<td>0.0075 (0.0013)</td>
</tr>
<tr>
<td>Difference after</td>
<td>0.0008 (0.0005)</td>
<td>0.0024 (0.0011)</td>
<td>0.0010 (0.0007)</td>
<td>0.0049 (0.0013)</td>
</tr>
</tbody>
</table>
| Difference group | 0.0017 (0.0011) | 0.0003 (0.0008) | 0.0042 (0.0013) | }

The \( R^2 \) is in braces and the mean of the dependent variable in the twelve months prior to August 2010 is in brackets. Standard errors are in parentheses and are clustered by state. Each regression has monthly data for fifty states and the District of Columbia from 2004 through 2012 for a total of 5,508 observations. Other control variables are state fixed effects, month effects, the fraction of the population that is 19 years old or younger, 20 to 34 years of age, 35 to 50 years of age, 50 or more years of age, the fraction black, the fraction some other race, the fraction Hispanic, and the monthly unemployment rate.

### Table 3.—Impact of Reformulation on the Trends in Heroin and Opioid Death Rates, 2004–2012

<table>
<thead>
<tr>
<th>Covariates</th>
<th>A. Heroin Death Rates [0.66] [0.083]</th>
<th>B. Opioid Death Rates [0.75] [0.464]</th>
<th>C. Combined Heroin/Opioid Death Rate [0.74] [0.532]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trend before</td>
<td>0.0074 (0.0023)</td>
<td>0.1040 (0.0026)</td>
<td>0.0091 (0.0026)</td>
</tr>
<tr>
<td>Trend after</td>
<td>0.0029 (0.0022)</td>
<td>0.0029 (0.0034)</td>
<td>0.0047 (0.0026)</td>
</tr>
<tr>
<td>Difference after</td>
<td>0.0045 (0.0019)</td>
<td>0.0075 (0.0028)</td>
<td>0.0044 (0.0014)</td>
</tr>
<tr>
<td>Difference group</td>
<td>0.0030 (0.0028)</td>
<td>0.0001 (0.0018)</td>
<td>0.0055 (0.0026)</td>
</tr>
</tbody>
</table>
present the same analysis as in panel A, but for opioid death rates and deaths that involved opioids, heroin, or either of the two. The point estimates in the third row of panel B suggest that all of the groups experienced a reduction in the opioid death rate and that the reduction was largest in the states with high oxycodone exposure and low heroin exposure. Panel C presents the results for opioid and heroin rates together. For three of the four groups, the combined heroin and opioid death rates grew more slowly after the reformulation. In these areas, the reformulation may have been successful at reducing opioid and heroin deaths in the short run. However, states with high exposure to both oxycodone and heroin did not experience a reduction in combined mortality. If anything, they saw their combined death rates increase slightly. We can reject the hypothesis that the null hypothesis of no break because the F-statistic is only 1.21. This implies that in the aggregate, we cannot reject one-for-one substitution of heroin deaths for opioid deaths in the short run.

The results from panel C of table 3 suggest that the reformulation had impacts on combined heroin and opioid death rates, but only in some states. To estimate the overall impact, we perform a trend break analysis on combined heroin and opioid death rates. Appendix figure C5 shows the national time series for combined heroin and opioid death rates from 2004 to 2012. Although the most likely date for a break is estimated to be August 2010, we cannot reject the null hypothesis of no break because the F-statistic is only 1.21. This implies that in the aggregate, we cannot reject one-for-one substitution of heroin deaths for opioid deaths in the short run.

Ruhm (2016) points out that 20% to 25% of drug poisoning deaths do not specify a particular drug and that these “unspecified” deaths lead to noisy measurement of drug-specific death rates. He suggests an adjustment procedure that assumes the distribution of unspecified deaths is similar to the distribution among specified drug deaths. We use this procedure and reestimate the basic models reported in table 3. The results for these new models are included in online appendix A and in table A1. Once we make these adjustments, the difference in post-versus prereformulation trends is actually larger in magnitude. The results also suggest that in the high Oxy/high heroin states, there is still no change in the trend in combined heroin and opioid deaths as a result of reformulation.

V. Other Influences on the Heroin Epidemic

There are a number of potential alternative explanations for the observed increase in heroin deaths. As discussed previously, changes in the price of oxycodone or changes in the price or lethality of heroin are unable to explain the changes in the oxycodone and heroin markets. In this section, we discuss how the passage of prescription drug monitoring programs (PDMPs) and the rise of fentanyl are unable to explain the observed changes in the oxycodone and heroin markets. We also provide evidence on the role that changes in the legal environment in Florida, one of the largest oxycodone markets in the country, might have played.

A potentially important change in recent years has been the adoption of state-level PDMPs, which are databases of prescriptions that doctors have written for patients. By giving doctors, pharmacists, and in some cases law enforcement officials access to this information, patients might have greater difficulty obtaining large amounts of prescription drugs that can be abused and doctors might be more conscious of their prescribing. A large body of research has studied the impacts of PDMPs on prescribing and come to mixed results. While some find that PDMPs reduce opioid overdose deaths (Kilby, 2015), others find no effects on prescribing patterns or effects for a very limited subset of PDMPs (Buchmueller & Carey, 2018). Figure 5 shows the heroin death rate separately for states that had passed PDMPs prior to 2010 and those that passed a PDMP in 2010 or later.24 Death rates for states with a PDMP before 2010 and states with a PDMP in 2010 or later have extremely similar heroin death rates over time. This suggests that PDMPs are unlikely to be causing the abrupt rise in heroin death rates at the end of 2010. In addition, states began passing PDMPs in 2004 and have continued fairly steadily since then (National Alliance for Model State Drug Laws, 2014). One was created in 2004; two in 2005; two in 2006; four in each of 2007, 2008, and 2009; two in 2010; four in 2011; and so on. Although the timing does not rule out the possibility that the PDMPs had an impact on opioid prescribing and heroin deaths, it does strongly suggest that the PDMPs are not responsible for the sharp, nationwide increase in heroin deaths that began at the end of 2010.

24 Washington, DC, and Missouri did not have PDMPs by 2013 and are thus excluded.
A second important change to the opioid and heroin markets is the rise of fentanyl, a synthetic opioid fifty times stronger than heroin. It has been included in counterfeit oxycodone pills and used to increase heroin’s potency in recent years. Beginning in 2013, the DEA noted an increase in fentanyl-related deaths and has suggestive, but not definitive, evidence that fentanyl-laced heroin is distributed by the Mexican gangs selling heroin (DEA, 2016). Anecdotal evidence in the documentary *Death by Fentanyl* is consistent with the DEA’s suggestions. In the documentary, an individual who exports heroin to the United States from Sinaloa, Mexico, claims that all of the heroin exported to the United States is now laced with fentanyl. The solid black line in the middle of figure 6 (left axis) shows a stark increase in synthetic opioid deaths, including fentanyl, starting toward the end of 2013. The bottom line in figure 6 shows that of deaths that include a synthetic opioid, the fraction that also include heroin (right axis) increases precipitously beginning in 2013, and the top line shows a declining mix of synthetic opioids with other opioids (right axis). Because of this, we did not use data from 2013 or later in the previous section.

To assess whether the rise of fentanyl would alter our findings, we reestimate our previous specifications and include data from 2013 forward. This approach is preferable to including all years but excluding synthetic opioid deaths because heroin laced with fentanyl might not be uniformly distributed across the country. To the extent that it is correlated with increased demand for heroin—states where demand has grown the fastest could be more likely to have fentanyl-laced heroin because dealers might need to stretch their supply or increase its potency—comparisons of trend breaks would be biased toward zero. The results are in appendix table C1. The estimated impacts of the reformulation on death rates are very similar to those presented in table 3 with two exceptions. When the later years are included, the trend breaks for opioid death rates and combined heroin and opioid death rates are slightly smaller in magnitude; it is less clear that the reformulation would have reduced combined heroin and opioid death rates in the absence of well-developed heroin markets.

Another important change to the markets for opioids and heroin was the crackdown on Florida’s “pill mills.” During the 2000s, Florida medical laws allowed physicians to prescribe and dispense pharmaceuticals from their offices. Given the changes in prescribing patterns outlined in section II, this institutional structure allowed the proliferation of pain clinics throughout the state where patients could meet with a physician, receive an opioid prescription, and leave the clinic with the drug. By 2010, there were over 900 pain clinics across the state. These clinics could dispense any opioid, but Oxycodone was a popular drug of choice. The ARCOS data discussed previously indicate that in 2009, 25% of shipments of oxycodone were sent to Florida. Johnson et al. (2014) report that in 2010, 98 of the 100 doctors in the country who dispensed the highest quantities of oxycodone from their offices were located in Florida.

The Florida pill mills were a popular destination for out-of-state residents. Interstate 75 runs from the Canadian border in Michigan through Ohio, Kentucky, Tennessee, Georgia, and all the way through Florida to Miami. This interstate came to be known as the “Oxy Express.” The use of pill mills by out-of-state residents is shown in the award-winning documentary *The Oxycodone Express.* was a plot line in various TV shows such as *Justified,* and was described in John Temple’s 2015 book, *American Pain,* which details the rise and fall of the largest pill mill in Florida.

Beginning in 2009, a series of federal and state programs were started that were designed to reduce the impact of Florida’s pill mills. A number of authors have documented using a variety of methods that the negative outcomes associated with opioids in Florida began to decline after the introduction of these efforts (Johnson et al., 2014; Delcher et al., 2015; Rutkow et al., 2015; Chang et al., 2016; Kennedy-Hendricks et al., 2016; Meinhofer, 2016). If the Florida pill mills were a significant component of Oxycodone supply throughout the country, then the crackdown could also be responsible for the shift to heroin in a way similar to the reformulation of Oxycodone.

We investigate the pill mill hypothesis and find mixed evidence. Two analyses suggest the crackdown in Florida had little impact on the national increase in heroin deaths and two suggest it might have. The analyses are in appendix B.

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25 http://interactive.fusion.net/death-by-fentanyl/.


28 https://www.youtube.com/watch?v=GZeWNeq DAMAGE=epidemic.
First, in appendix table B1, we provide a time line of the significant events in the pill mill crackdown in Florida. As the dates in the table suggest, the majority and potentially most effective components of the pill mill crackdown did not go into effect until the second half of 2011, well after the shift to heroin occurred. Second, we graph the time series of oxycodone and the seven other opioids available in the ARCOS data for Florida and all other states. There does not appear to have been a reduction in any opioid in Florida starting in the third quarter of 2010 except for oxycodone (see appendix figures B1a to B1h). In fact, there appear to have been slight increases in the use of other opioids in Florida starting at that time. If the pill mill crackdown had been effective, there should likely have been reductions in all opioids that were being abused, not just oxycodone.

We do, however, find some evidence that states that were more exposed to the Florida pill mills, and thus are more likely to be affected by the crackdown, see differential changes in the growth of their heroin death rates. Our primary approach is based on anecdotal evidence from The OxyContin Express, which suggests that individuals who traveled to Florida to obtain opioids for distribution in their home states were also using opioids. Using the universe of emergency department and hospital admissions in Florida from 2007 through the second quarter of 2010, for each state of residence, we calculate the admissions per capita for people aged 18 to 64 in Florida due to opioids (labeled as OPCs), the nonopioid per capita admissions for the same group (NOPCs), and generate the ratio, OPCs/NOPCs. We then designate states in the highest third of the distribution as being more exposed to Florida’s pill mills. Our procedure identifies all states served by Interstate 75, five states contiguous to these states (Alabama, Indiana, North Carolina, West Virginia, Pennsylvania), and six other states (Rhode Island, Maine, New Jersey, Maryland, Mississippi, and New York) as likely affected by Florida’s pill mills. It is worth noting that the procedure suggests that no states west of the Mississippi are being served by Florida’s pill mills.

In figure 7, we graph the monthly heroin mortality for the states that are likely users of Florida pill mills (black line) and all other states (gray line). The time trend for both series is very similar prior to reformulation, and both show a large change in slope starting near the August 2010 period. The increase in slope in the non–pill mill using states must be generated by some other factor—a factor common to both sets of states. Fitting our quadratic spline through the monthly data for the states unlikely to be pill mill users, the data suggest that the trend break occurs in August 2010. There is a noticeable break in trend for the pill mill states at the same period, but the trend break analysis suggests that the break occurs in October 2011, when all components of the Florida pill mill crackdown law went into effect. This graph suggests that the Florida reforms did not generate the initial shift to heroin but provides some evidence that the pill mill crackdown in Florida also encouraged a shift to heroin.

Because states without significant opioid use are less likely to have had large increases in heroin death rates after an intervention that raises the price of opioid use, we turn our focus to states with high levels of prereformulation oxycodone use.20 We divide these states into four groups depending on whether they had high prereformulation access to heroin and whether they were exposed to Florida’s pill mills. We estimate equation (2) with these groups and present the results in table 4. Among states with high heroin availability, those exposed to Florida are estimated to have had a greater increase in the heroin death rate following August 2010, though this difference is not statistically significant ($p = 0.156$).

In appendix B, we also run regressions measuring exposure to the pill mills with physical distance to Florida. In these models, we do not find that states closer to Florida see larger increases in their heroin death rates, though our point estimates are not precise enough to rule out moderately sized effects associated with distance.

Overall, our results suggest that the precipitating event for the explosion of heroin deaths is the reformulation of OxyContin. There is suggestive but not statistically significant evidence that the pill mill crackdown in Florida appears to encourage more of a shift to heroin but only after October 2011, when the full set of reforms in Florida was in effect. That said, even in states that appear to have little access to Florida pill mills, heroin mortality increased by a factor of 3.5 between August 2010 and the end of 2014, compared to a factor of 4.5 in pill mill access states. This indicates that at most, the pill mill crackdown can explain 25% of the increase in heroin death rates in pill mill access states between reformulation and the end of 2014.

20 The same analysis using all states is presented in appendix table B4..
VI. Conclusion

Although past work has suggested that the abuse-deterrent formulation of Oxycodone has reduced opioid poisonings and mortality, our results suggest that some of these benefits may have simply become costs related to heroin abuse. We provide quantitative evidence that the switch to the ADF of Oxycodone in August 2010 led to the increase in the heroin death rate, and we find that in states that were at a high risk of substitution from opioids to heroin, the reformulation did not reduce the combined heroin and opioid death rate at all. This provides an important counterpoint to the push for the development of ADFs of commonly abused pharmaceuticals. There is a general acknowledgment by the FDA (2016) that ADFs do not necessarily erase all abuse of the drug being reformulated but much less recognition of equilibrium effects of individuals switching to other readily available drugs. Our results call into question whether the promotion of ADFs is an effective policy to reduce drug abuse and poisonings in the presence of close substitutes.

An important caveat is that we are able to examine only short-run impacts of the reformulation. If the stock of opioid abusers is significantly reduced in the long run because of the introduction of ADFs, then it is likely that the stock of heroin users will also be reduced in the long run. As a consequence, although there does not appear to be a reduction in total opioid and heroin deaths due to the reformulation of Oxycodone in the first five years after reform, there could be a reduction in these death rates in the long run. However, a back-of-the-envelope calculation suggests that in the long run, the reformulation might prevent only a combined 120 opioid and heroin overdose deaths per year. In addition, if fentanyl continues to be mixed into heroin and the resulting increase in lethality is maintained over the long run, the mortality benefits from the reformulation will be even smaller. Furthermore, the short run in this context could last many years. While some individuals die from heroin overdoses shortly after initiation, deaths among heroin addicts on average, occur between five and ten years after initiation of use (Ochoa et al., 2001; Darke & Hall, 2003). The transition from the old to the new steady state induced by the reformulation may play out over a decade or more. Another important caveat to our work is that it is based on a single reformulation and does not imply that all ADFs will be unsuccessful. Although we cannot reject one-for-one substitution of heroin deaths for opioid deaths in the aggregate, combined heroin or opioid death rates did fall after the reformulation in states that had high levels of prereformulation oxycodone use and relatively little heroin availability. This suggests that the ease with which individuals may substitute to similar other drugs plays a key role in whether any given ADF will reduce overall drug abuse and mortality in the short run.

REFERENCES


30 Based on data from the NSDUH and CDC, we estimate that recreational use of pain medications fell by 17% from 2010 to 2014, that 0.15% of those using pain medications recreationally die from an opioid overdose in a given year, and that the fraction of recreational pain medication users who transition to heroin in a given year is no more than 10% (an upper bound based).

