

How the Reformulation of OxyContin Ignited the Heroin Epidemic

William N. Evans
Department of Economics
University of Notre Dame
Notre Dame, IN 46530
wevans1@nd.edu
and NBER

Ethan Lieber
Department of Economics
University of Notre Dame
Notre Dame, IN 46530
elieber@nd.edu

Patrick Power
Department of Economics
Boston University
Boston, MA 02215
ppower1@bu.edu

February 14, 2018

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 to 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 pre-reformulation 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.

JEL: I12, I18, K42

We gratefully acknowledge helpful comments from seminar participants at the University of Colorado – Denver, University of Notre Dame, University of Southern California, University of Melbourne, NBER, Kellogg School of Management, and Southern Methodist University. We are especially grateful for Tom Dailey of Breaking Point Recovery whose guidance and suggestions directed much of our research. Although Tom helped hundreds through the recovery process, he recently lost his life to addiction. He will be missed.

I. Introduction

Deaths from drug overdoses have steadily increased over the past 15 years and are now at epidemic levels. Figure 1 shows the national death rate (deaths/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 can account for 75 percent of the overall increase in deaths from drug poisonings.²

Opioids are narcotic pain relievers and are available, legally, only by prescription. When used as directed, they are an important component of fighting acute and chronic pain. As we outline below, starting in the mid-1990s, a number of medical groups argued there was an epidemic of untreated pain and urged for greater use of opioid pain medicines, especially for those with chronic conditions. The efforts changed prescribing practices considerably and between 1991 and 2013, there was a three-fold increase in opioid prescriptions.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 (Centers 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.⁴ Between 1999 and 2009, opioid death rates were rising rapidly but heroin death rates were much lower and increasing slowly.

¹ Data is taken from the CDC Wonder web page for multiple causes of death which is available here <https://wonder.cdc.gov/controller/datarequest/D77>. To identify drug poisonings, we use ICD10 codes suggested by the CDC https://www.cdc.gov/drugoverdose/pdf/pdo_guide_to_icd-9-cm_and_icd-10_codes-a.pdf which include: Unintentional drugs poisonings (X40-X44) Self-harm and suicide drug poisonings (Xh60-X64), Assault/homicide drug poisonings (X85), drug poisonings with an undetermined intent (Y10-Y14), drug poisonings that were contributing causes of death (T36-T50). To ensure consistency across outcomes, we use SEER population data to convert counts into rates.

² Heroin deaths are identified by the ICD10 code T40.1 while opioid deaths are T40.2, T40.3 and T40.4. Throughout the rest of the paper we will use opioid (heroin) poisoning mortality and the opioid (heroin) death rate synonymously. Heroin is technically an opioid. However, we will use the term opioid to refer to all opioids except heroin.

³ <https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse>

⁴ As Ruhm (2016) points out, an interesting feature of the opioid epidemic is that there is an increasing incidence of multiple drugs in the system at the time of death. Therefore, the heroin or opioid death rate is less than the sum of the two individual series.

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; Severtson et al., 2013; Butler et al., 2013; Sessler et al., 2014; Havens et al., 2014; Dart et al., 2015; Laroche 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, there is an equally large literature that suggests there has been a shift to heroin towards the end of 2010 (Coplan et al., 2013; Cicero et al., 2012; Cicero et al., 2014; Cicero et al., 2015; and Compton et al., 2016). These papers either point to evidence like 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,⁵ pinpoints the timing of the changes to the reformulation of OxyContin. The results of these analyses are illustrated in Figure 2 where the solid line displays the national, monthly heroin death rate. The vertical, grey dotted line shows the month that the structural break analysis

⁵ See Hansen (2001) for an overview, Jayachandran et al. (2010) for an application in health economics

chose as the month in which the trend break occurred.⁶ For the heroin death rate, this is the month immediately following the OxyContin reformulation. A number of national time series including shipments of oxycodone (an imperfect measure of consumption), prescriptions for oxycodone, the fraction of people that use pain medicine recreationally, and health care encounters for heroin poisonings all show a trend break in August, 2010 or immediately thereafter.

Although we date the changes to the month following the reformulation of OxyContin, it is possible that there was some other event in August, 2010 that 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 pre-reformulation opioid abuse are likely to show more substitution away from opioids and towards 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 pre-reformulation per-capita heroin death rate and the latter with whether a state is above or below the median pre-reformulation per-capita oxycodone consumption. Breaking states into four groups based on these measures, we estimate pre-reformulation trends, post-reformulation 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 3 where we display the monthly heroin mortality rate from 2004 through 2014 for the four groups of states.⁷ Note that pre-reform trends in heroin death rates are similar across the groups of states but in the years after

⁶ The dotted line is the F-test on the null that there is no break. We will discuss this in more detail later in the paper.

⁷ There are gaps in the series because months in which there were fewer than 10 heroin deaths have been suppressed per Centers for Disease Control reporting requirements.

reformulation, 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 state groups, opioid death rates were increasing rapidly before reformulation but were flat afterwards. 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 some stage of development.⁸ 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.⁹ Currently, five states have adopted laws requiring insurance companies to cover ADFs and similar laws have been proposed in 15 other states.¹⁰ Despite the enthusiasm for ADFs, our results suggest that the benefits of the reformulation are easily undone when there are readily-available substitutes.

⁸ <http://drug-dev.com/Main/Back-Issues/ABUSEDETERRENT-MARKET-Whats-in-the-Pipeline-AbuseD-800.aspx>

⁹ https://www.whitehouse.gov/sites/default/files/ondcp/policy-and-research/ndcs_2013.pdf

¹⁰ <https://www.multistate.com/insider/2016/05/states-address-opioid-epidemic-with-abuse-deterrent-formulation-legislation/>

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 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 (2017) who also examined the increase in heroin deaths. Using a panel of annual, state-level data, the authors hypothesized that the switch to other narcotics after the reformulation of OxyContin should be larger in states with higher pre-reformulation abuse rates of OxyContin. The authors constructed a pre-reformulation measure of OxyContin abuse rates at the state level and interact that with a dummy variable for the post-reformulation period. The authors found that outcomes such as heroin death rates increased more after reformulation in states that had higher pre-reformulation 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 US. In Section III, we use time series techniques from macroeconomics to date regime changes and identify August and September of 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 pre-reformulation 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 opioid pain killer 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 12 hours of pain relief and hence there is typically a high milligram (mg) content of oxycodone in the pills.¹¹ Since its release in 1996, OxyContin has been one of the most successful pharmaceuticals of all time with worldwide sales totaling \$35 billion.¹²

OxyContin was introduced at a time when the medical profession was beginning to re-evaluate its use of opioid-based pain killers. Historically, opioids were reserved for those with acute pain, such as post-surgical 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 middle 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 Organization introduced standards for pain assessment and management in a variety of patient settings (Berry and Dahl, 2000) that focused on the patient’s 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 post-discharge 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.”^{13,14} During this time, state medical boards

¹¹ We will refer to OxyContin ER simply as OxyContin for the duration of the paper. 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 mgs of active ingredient. <http://www.pdr.net/full-prescribing-information/OxyContin-oxycodone-hydrochloride-492#section-standard-2>

¹² <http://www.latimes.com/projects/la-me-oxycontin-part3/>

¹³ <http://www.supportprop.org/wp-content/uploads/2014/12/TJC-Letter-Final-04-11-16.pdf>

¹⁴ In November of 2016, the CMS agreed to remove the pain questions from the HCAHPS survey. <https://www.federalregister.gov/documents/2016/11/14/2016-26515/medicare-program-hospital-outpatient-prospective-payment-and-ambulatory-surgical-center-payment>

and state laws started to relax regulations about prescribing opioids to non-cancer patients (Alexander, Frattaroli, and Gielen, 2015). It is not clear how each of these changes impacted 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 used by Purdue Pharma in their advertising materials, Porter and Jick (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 was not available to establish the true incidence rate of addiction (Van Zee, 2009).¹⁵

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 (United States General Accounting Office, 2003). Between 1991 and 2011, opioid prescriptions tripled from 76 to 211 million with oxycodone-based products representing a quarter of these prescriptions in later years.¹⁶

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 would slowly release oxycodone over the course of twelve hours. However,

¹⁵ In 2007, Purdue Pharma agreed to pay \$600 million in fines in Federal civil and criminal cases. It acknowledged 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 <https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse>

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.¹⁷ Purdue Pharma received FDA approval for their ADF 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 their old OxyContin formulation on August 5th, 2010. On August 9th, 2010, they began shipping exclusively their 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.¹⁸ Figure 4 reports the monthly time series of the total price and the price that patients pay out-of-pocket for oxycodone for 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.¹⁹

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 different 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 (DEA, 2016). Over the past 30 years, there has been an increasing supply of heroin from Mexican gangs. Of confiscated heroin, 79 percent is now from Mexico (DEA, 2016). Many of the Mexican suppliers compete for market share by

¹⁷ <http://www.nytimes.com/2011/06/16/health/16oxy.html>

¹⁸ Information about MarketScan data can be found at <http://truvenhealth.com/your-healthcare-focus/analytic-research/MarketScan-research-databases>

¹⁹ The saw-tooth pattern in the out-of-pocket series is due to patient cost-sharing.

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. Figure 5 shows the price of heroin from 1981 to 2012 in real 2012 dollars.²⁰ The price has fallen from more than \$3,000 per pure gram in 1981 to less than \$500 in 2012.²¹ In Figure 6, we combine quarterly estimates of the number of times heroin was used in the past thirty days from the NSDUH and the CDC's estimates of heroin deaths to construct a time series of the number of heroin deaths per 1,000 heroin uses at the national level.²² This measure of drug quality shows that deaths per use of heroin was volatile, but without trend in the pre-reformulation period. There is an uptick in heroin deaths per use 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 pre-reformulation period; we will 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 US markets. Within their distribution network, 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. This organizational form's spread throughout the United States has greatly reduced the costs to the consumer of obtaining heroin (Diaz-Briseno, 2010; Quinones, 2015). The DEA (2016) notes that 30 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 because of the purity

²⁰ This figure is based on data from DEA (2016).

²¹ Although there is a slight decrease in the price between 2010 and 2012, the elasticity of demand would have to be greater in magnitude than 15 in order to generate the observed increase in heroin death rates.

²² Heroin use is known to be significantly under-reported in self-report survey data (Harrell, 1997). Thus it is likely that the true number of heroin deaths per 1,000 uses is higher. However, as long as this under-reporting is constant over time, it will not affect the implication of Figure 8b that the purity of heroin did not significantly change when OxyContin was reformulated.

level. In the 1970s, heroin 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 reformulation. Interrupted time series data indicates that outcomes such as deaths, poisonings, emergency room visits, and enrollments in treatment programs from heroin abuse have all increased since August of 2010 (Coplan et al., 2013; Cicero et al., 2012; Cicero et al., 2014; Cicero et al., 2015; and Compton et al., 2016). The movement to heroin from opioids is born out in survey data as well. In a survey of 244 people that entered drug treatment programs for OxyContin abuse in the post-reformulation period, respondents were asked how they dealt with reformulation (Cicero and Ellis, 2015). About one-third of respondents said they reacted by switching to other drugs and about 70 percent of this group said the drug they switched to was heroin. In the population of people that use pain medicine recreationally, few eventually moved to heroin. Looking at data from the 3rd quarter of 2010 through the end of 2014 in the annual NSDUH, among respondents that have used pain medicine recreationally over the past year, less than 1 percent said they ever used heroin. However, over the same period, 79 percent of people that used heroin in the past 30 days report a younger age of initiation for recreational pain medicine use than their initiation age for heroin.

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

We draw on the 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

$$(1) \quad Y_t = \gamma + t_c(1 - A_t^c)\beta_1 + t_c^2(1 - A_t^c)\beta_2 + t_c A_t^c\alpha_1 + t_c^2 A_t^c\alpha_2 + \varepsilon_t$$

where $A_t^c=1$ if $t \geq c$, $A_t^c=0$ if $t < c$, and Y_t is the outcome of interest. As originally suggested in Quandt (1960), 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 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 7a 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 manufactures to points of sale or distribution.²³ Many of the drugs tracked in the ARCOS system are opioids and we use data from Report 3 that reports quarterly drug distributions for oxycodone in milligrams of the active ingredient. We divide this by quarterly state population (x1,000) and include data from the start of 2004 through the end of 2014 in the regressions.²⁴ 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 post trends is presented and is larger than the critical value needed to reject the null hypothesis.²⁵ As seen in Figure 7a, the F-statistics for nearby dates are considerably lower than the most likely break date.

Figure 7b presents monthly data on milligrams of oxycodone prescribed per 1,000 subscribers in the Marketscan which allows us to examine prescribed oxycodone at the monthly level. 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 part way through the year. As seen in the second row of Table 1, the most likely date for a break in trend was August, 2010 and we can reject the null hypothesis of no break.

Although the data are considerably noisier, we also test whether there was a trend break in the percentage of individuals in the NSDUH who reported using pain medications recreationally in the past thirty days. Figure 7c shows that this fraction was relatively flat between 2004 and 2010 with 1.5 to 2.5 percent of individuals reporting recreational use. The data suggest that in the second quarter of 2010, recreational use of pain medications began to fall. However, as seen in the third row of Table 1, we lack the statistical power to

²³ More information about the ARCOS data can be found at https://www.deadiversion.usdoj.gov/arcos/retail_drug_summary/2015/index.html

²⁴ The ARCOS data reports population by state, but an inspection of the data reveals errors for many observations. Instead of using these data, we obtained annual state population estimates from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (<https://seer.cancer.gov/popdata/>). These data are only available at the annual level. We assume population levels are recorded in the first period (e.g., quarter or month) of the year and change linearly over time until the next period.

²⁵ The relevant critical values for the F-test are provided in Andrews (1993).

reject the null. Taken together, the analyses indicate that oxycodone use and abuse broke sharply from their previous trends right as the reformulated version of OxyContin was injected into the market.

Figure 7d shows evidence from the Marketscan data that encounters for heroin poisonings per 1,000 subscribers were relatively flat until September, 2010. At that time, they began to increase sharply and continued their climb through the end of the sample. Table 1 reports the corresponding regression results. The data suggest that the break occurred in September of 2010, but there is not enough statistical power to formally reject the null.

Finally, Figure 2 that we discussed in the introduction shows that monthly heroin deaths per 100,000 people were flat or increasing slightly from 2004 through 2010, but began to rise dramatically in September of 2010 and continued to do so through the end of the sample in 2014. While a number of other studies have shown that heroin deaths began increasing quickly in 2010, we are unaware of any other studies that date the start of the rise so precisely. The final row of Table 1 shows strong evidence of a break in trend and that it is most likely to have occurred in September of 2010.

Thus far, the results indicate that the oxycodone and heroin markets were hit by shocks in August and September of 2010. A natural falsification test is to check for changes in the use of other opioids in August, 2010. If changes in prescribing practices, or some other event, were reducing opioid use instead of the reformulation of OxyContin, then we should expect these changes to be reflected in the seven other opioids in the DEA's ARCOS data. Past research suggests this was not the case, finding that the use of some other opioids rose when OxyContin was reformulated (e.g. Cicero et al., 2012; Cassidy et al., 2014). Figures 8a and 8b show the time series for hydrocodone, morphine, codeine, fentanyl, oxymorphone, meperidine, and hydromorphone. For each drug, we repeat our trend break analysis and include the most likely date for a break in the figures. None of the other opioids show a statistically significant, negative break in trend in the third quarter of 2010. Table 2 reports the F-statistics and critical values used to determine the significance of the most likely break dates. These results for other drugs suggest that there was not a change to the opioid market more generally, but that the shock was specific to oxycodone and heroin.

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 this type of substitution. This is similar in spirit to the work of Alpert, Powell, and Pacula (2017) 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 pre-reformulation recreational use of OxyContin. In what follows, we first outline each measure individually and proceed to demonstrate that there appears to be greater shifts to heroin after the reformulation in 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 will be more likely to have individuals who substitute to heroin than areas where there is less oxycodone abuse. We use milligrams of oxycodone/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 also having high abuse. The correlation coefficient between the state-level opioid mortality rate for the 2008 and 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 upon the distribution of states' oxycodone shipments per 1,000 people, we divide states into two groups: those above and below the median. As seen in Figure 9, areas with greater pre-reformulation 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.²⁶ 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

²⁶ Even in the pre-reformulation 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 percent of heroin users that started in the past two years had recreational pain medicine use that pre-dates their heroin use.

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 towards 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 pre-reformulation 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 10 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 pre-reformulation heroin death rates *and* high pre-reformulation oxycodone use. At the same time, those least likely to be affected are those with low pre-reformulation heroin death rates and low pre-reformulation oxycodone use. We pursue this by putting states into one of the four groups that are 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 pre-reformulation oxycodone shipments rate as “Oxy.” The heroin death rates for these four groups were shown earlier in Figure 3. Once reformulation occurs, every group experienced a noticeable increase in its heroin death rate with the greatest change occurring in the states that had both high oxycodone shipments as well as high heroin death rates before the reformulation.

To formalize the analysis, we estimate trends and trend breaks for each of the groups based upon our proxies. For the heroin death rate in state i in month t , y_{it} , we estimate

$$(2) \quad y_{it} = \sum_{j=1}^4 \left((1 - A_t^c) T(j) t_c \beta_b^j + A_t^c T(j) t_c \beta_a^j \right) + x_{it} \gamma + \lambda_i + \varepsilon_{it}$$

where A_t^c and t_c are defined as before, $T(j)$ is a dummy variable indicating which group the state is in, x_{it} are basic demographics including the fractions of individuals in a set of age bins (less than 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, λ_i . In these specifications, we impose that August, 2010 is 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, $H_o : \beta_a^j = \beta_b^j$, 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, $H_o : (\beta_a^j - \beta_a^1) = (\beta_b^j - \beta_b^1)$ where $j=2, 3$, and 4.

Data for this exercise come from the CDC Multiple Cause of Death database and range from January, 2004 through December of 2014 for all states and the District of Columbia. The CDC normally suppresses data when there are fewer than 10 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 heroin death data with population data from the SEER data referenced above to calculate the heroin death rate or heroin deaths per 100,000 people, in the state and month.

For our initial analysis, we restrict the sample to years before 2013 because individuals began increasing their use of fentanyl, a deadly synthetic opioid, at that time. The regression results with heroin death rates as the outcome of interest are shown in Panel A of Table 3.²⁷ 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

²⁷ Recent work argues that “unspecified” causes of death on death certificates leads to important measurement error in death rates from certain causes (Ruhm, 2016). In Appendix A, we implement a procedure to adjust for the measurement error and rerun our analysis on the adjusted death rates. The results are very similar to those presented in Table 3.

estimates are positive, but suggest relatively slow rates of growth. The second row suggests that the trends after 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 pre-reformulation 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 present the same analysis seen in Panel A, but for opioid death rates and for deaths that involved opioids, heroin, or either of the two. As seen in the third row of Panel B, the point estimates 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 deaths rate 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 actually saw their combined death rates increase slightly. We can reject the hypothesis that the break for the high Oxy/high heroin group is equal to the trend break for the high Oxy/low heroin group ($p=0.014$). This suggests that the availability of heroin might play an important role in the effectiveness of the reformulation 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. 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 20-25 percent of drug poisoning deaths do not include any specific drug mentioned 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 those reported and adjusts the unspecified drug deaths accordingly. We use this procedure and re-estimate 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 and pre-reformulation 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 we saw earlier in Figures 4-6, 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 and Carey, 2018). Figure 11 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.²⁸ 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 impacted 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.

A second important change to the opioid and heroin markets is the rise of fentanyl, a synthetic opioid 50 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;²⁹ 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 12 (left axis), shows that there was a stark increase in synthetic opioid deaths, including fentanyl, starting towards the end of 2013.³⁰ The bottom line of Figure 12 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.

²⁸ The District of Columbia and Missouri had not passed a PDMP by the end of 2013. Consequently, they are excluded from the figure.

²⁹ <http://interactive.fusion.net/death-by-fentanyl/>

³⁰ This graph is produced from the CDC wonder data and reports deaths with a T40.4 code, the code for synthetic opioid poisonings.

To assess whether the rise of fentanyl would alter our findings, we re-estimate our previous specifications and include the data from 2013 forward. This approach is preferable to including all years, but excluding deaths with a T40.4 designation 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 towards zero. The results are in Table 4. Qualitatively, 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 for the proliferation of pain clinics throughout the state where patients could meet with a physician, receive an opioid prescription, and depart the clinic with the drug. By 2010, there were over 900 pain clinics across the state.³¹ These clinics could dispense any opioid, but OxyContin was a popular drug of choice. The ARCOS data discussed previously indicate that in 2009, 25 percent of shipments of oxycodone were sent to the state of 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.³² 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.”³³ The use of pill mills by out-of-state

³¹ <http://myfloridalegal.com/pages.nsf/Main/AA7AAE5CAA22638D8525791B006A30C8>

³² We are not aware of any data that quantify the amount of oxycodone prescribed and dispensed in Florida but consumed in the other states.

³³ <http://www.npr.org/2011/03/02/134143813/the-oxy-express-floridas-drug-abuse-epidemic>

residents is shown in the award-winning documentary *The OxyContin Express*,³⁴ was a plot line in various TV shows such as *Justified*, and was described in detail in John Temple's 2015 book *American Pain* which tells the story of 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 with 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; and Meinhofer, 2016). If the Florida pill mills were a significant component of OxyContin supply throughout the country, then the crackdown could also be responsible for the shift to heroin in a way similar to the reformulation of OxyContin.

We investigate the pill mill hypothesis and find mixed evidence. We briefly summarize two analyses that suggest the crackdown in Florida had little impact on the national increase in heroin deaths and two that suggest it might have; the analyses can be found in Appendix B.

First, in Appendix Table B1, we provide a timeline 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, using the ARCOS data, we graph the time series of oxycodone and the seven other opioids used in Figure 8 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 – B1h). In fact, there appears 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, then 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

³⁴ <https://www.youtube.com/watch?v=wGZEvXNqzkM>

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 18-64 in Florida due to opioids (labeled as OPCs), the non-opioid per capita admissions for the same group (NOPCs), and generate the ratio, $OPC_s/NOPC_s$. 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 The OxyContin Express, 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 13, we graph the monthly heroin mortality for the states that are likely users of Florida pill mills (black line) and all other states (grey 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 suggests that the trend break occurs in August of 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 trend break occurs in October of 2011 – the month that all components of the Florida pill mill crackdown law go 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 pre-reformulation oxycodone use. We divide these states up into four groups depending on whether they had high pre-reformulation access to heroin and whether or not they were exposed to Florida's pill mills. We estimate equation (2) with these groups and present the results in Table 5. 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 where we measure 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 are 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 percent of the increase in heroin death rates in pill mill access states between reformulation and the end of 2014.

VI. Conclusion

Although past work has suggested that the abuse-deterrent formulation of OxyContin 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 OxyContin in August of 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 acknowledgement by the FDA that ADFs do not necessarily erase all abuse of the drug being reformulated (FDA, 2016), 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 only able to examine 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, even though there does not appear to be a reduction in total opioid and heroin deaths due to the reformulation of OxyContin 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 only prevent a combined 120 opioid and heroin overdose deaths per year.³⁵ In addition, if fentanyl continues to be mixed into heroin and the resulting increase in lethality is maintained over the long run, then 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, on average, deaths among heroin addicts occur between 5 and 10 years after initiation of use (Ochoa et al., 2001; Darke and 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 so it 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 pre-reformulation oxycodone use and relatively little heroin availability. This suggests that the ease with which individuals may substitute to other, similar drugs plays a key role in whether any given ADF will reduce overall drug abuse and mortality in the short run.

³⁵ Based upon data from the NSDUH and CDC, we estimate that recreational use of pain medications fell by 17 percent from 2010 to 2014, that 0.15 percent of those using pain medications recreationally die from an opioid overdose in a given year, that 0.5 percent of those using heroin die from an 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 ten percent (an upper bound based on NSDUH data).

References

- Alexander, G. Caleb, Shannon Frattaroli and Andrea C. Gielen. 2015. "The Prescription Opioid Epidemic: An Evidence-Based Approach." <http://www.jhsph.edu/research/centers-and-institutes/center-for-drug-safety-and-effectiveness/opioid-epidemic-town-hall-2015/2015-prescription-opioid-epidemic-report.pdf>.
- Alpert, Abby, David Powell and Rosalie Liccardo Pacula. 2017. "Supply-Side Policy in the Presence of Substitutes: Evidence from the Introduction to Abuse-Deterrent Opioids." NBER Working Paper No. 23031.
- Andrews, Donald W.K. 1993. "Tests for Parameter Instability and Structural Change with Unknown Change Point." *Econometrica* 61 (4): 821-856.
- Berry, Patricia H., and June L. Dahl. 2000. "The New JCAHO Pain Standards: Implications for Pain Management Nurses." *Pain Management Nursing* 1(1): 3-12.
- Buchmueller, Thomas C. and Colleen Carey. 2016. "The Effect of Prescription Drug Monitoring Programs on Opioid Utilization in Medicare." *American Economic Journal: Economic Policy* 10(1): 77-112.
- Butler, Stephen F., Theresa A. Cassidy, Howard Chilcoat, Ryan A. Black, Craig Landau, Simon Budman, and Paul M. Coplan. 2013. "Abuse Rates and Routes of Administration of Reformulated Extended-Release oxycodone: Initial Findings from a Sentinel Surveillance Sample of Individuals Assessed for Substance Abuse Treatment." *The Journal of Pain* 14 (4): 351-358.
- Campbell, James N. 1995. "APS Presidential Address." *Pain Forum* 5 (1): 85-88.
- Case, Anne, and Angus Deaton. 2015. "Rising Morbidity and Mortality in Midlife Among White Non-Hispanic Americans in the 21st Century." *Proceedings of the National Academy of Sciences of the United States of America* 112 (49): 15078-15083.
- Cassidy, Theresa A., Pronabesh DasMahapatra, Ryan A. Black, Matthew S. Wieman, and Stephen F. Butler. 2014. "Changes in Prevalence of Prescription Opioid Abuse after Introduction of an Abuse-Deterrent Opioid Formulation." *Pain Medicine* 15(3): 440-451.
- Center for Behavioral Health Statistics and Quality. 2015. "Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health (HHS Publication, no. SMA 15-4927, NSDUH Series H-50).
- Chang, Hsien-Yen, Tatyana Lyapustina, Lainie Rutkow, Matthew Daubresse, Matt Richey, Mark Faul, Elizabeth A. Stuart and G. Caleb Alexander. 2016. "Impact of Prescription Drug Monitoring Programs and Pill Mill Laws on High-Risk Opioid Prescribers: A Comparative Interrupted Time Series Analysis." *Drug and Alcohol Dependence* 165: 1-8.
- Chilcoat, Howard D., Paul M. Coplan, Venkatesh Harikrishnan and Louis Alexander. 2016. "Decreased Diversion by Doctor-Shopping for a Reformulated Extended Release oxycodone Product (OxyContin)." *Drug and Alcohol Dependence* 165: 221-228.
- Cicero, Theodore J., Matthew S. Ellis. 2015. "Abuse-Deterrent Formulations and the Prescription Opioid Abuse Epidemic in the United States: Lessons Learned from OxyContin." *JAMA Psychiatry* 72 (5): 424-429.
- Cicero, Theodore J., Matthew S. Ellis, and Jessie Harvey. 2015. "Shifting Patterns of Prescription Opioid and Heroin Abuse in the United States." *New England Journal of Medicine* 373 (18): 1789-1790.
- Cicero, Theodore J., Matthew S. Ellis, and Hilary L. Surratt. 2012. "Effect of Abuse-Deterrent Formulation of OxyContin." *New England Journal of Medicine* 367 (2): 187-189.
- Cicero, Theodore J., Matthew S. Ellis, Hilary Surratt, and Steven P. Kurtz. 2014. "The Changing Face of Heroin Use in the United States: a Retrospective Analysis of the Past 50 years." *JAMA Psychiatry* 71 (7): 821-826.
- Compton, Wilson M., Christopher M. Jones, and Grant T. Baldwin. 2016. "Relationship between Nonmedical Prescription-Opioid Use and Heroin Use." *New England Journal of Medicine* 374 (2): 154-163.
- Consensus Statement from the American Academy of Pain Medicine and the American Pain Society. 1997. "The Use of Opioids for the Treatment of Chronic Pain." *Clinical Journal of Pain* 13(1): 6-8.

- Coplan, Paul M., Howard D. Chilcoat, Stephen F. Butler, Edward M. Sellers, Aditi Kadakia, Venkatesh Harikrishnan, J. David Haddox and Richard C. Dart. 2016. "The Effect of Abuse Deterrent Opioid Formulation (OxyContin) on Opioid Abuse-Related Outcomes in the Postmarketing Setting." *Clinical Pharmacology & Therapeutics* 100: 275-286.
- Coplan, Paul M., Hrishikesh Kale, Lauren Sandstrom, Craig Landau, and Howard D. Chilcoat. 2013. "Changes in oxycodone and Heroin Exposures in the National Poison Data System after Introduction of Extended-Release oxycodone with Abuse-Deterrent Characteristics." *Pharmacoepidemiology and Drug Safety* 22 (12): 1274-1282.
- Darke, Shane and Wayne Hall. 2003. "Heroin Overdose: Research and Evidence-Based Intervention." *Journal of Urban Health* 80(2): 189-200.
- Dart, Richard C., Hilary L. Surratt, Theodore J. Cicero, Mark Parrino, Geoff Severtson, Becki B. Bartleson, and Jody L. Green. 2015. "Trends in Opioid Analgesic Abuse and Mortality in the United States." *The New England Journal of Medicine* 372 (3): 241-248.
- Delcher, Chris, Alexander C. Wagenaar, B.A. Goldberger, Robert L. Cook and Mildred M. Maldonado-Molina. 2015. "Abrupt decline in oxycodone-caused mortality after implementation of Florida's Prescription Drug Monitoring Program." *Drug and Alcohol Dependence* 150 (1): 63-68.
- Díaz-Briseño, Jose. 2010. "Crossing the Mississippi: how Mexican black tar heroin moved into the Eastern United States." In *Shared Responsibility*, edited by Eric L. Olson, Andrew Selee, and David Shirk, 95-120. Washington, DC: Woodrow Wilson Center for International Scholars.
- Drug Enforcement Administration. 2016. "National Heroin Threat Assessment Summary – Updated." https://www.dea.gov/divisions/hq/2016/hq062716_attach.pdf
- Food and Drug Administration. 2015. "Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry." <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>
- Food and Drug Administration. 2016. "FDA Facts: Abuse-Deterrent Opioid Medications." <https://www.fda.gov/newsevents/newsroom/factsheets/ucm514939.htm>
- Harrell, Adele V. 1997. "The Validity of Self-Reported Drug Use Data: The Accuracy of Responses on Confidential Self-Administered Answered Sheets." In *The Validity of Self-Reported Drug Use: Improving the Accuracy of Survey Estimates*, edited by Lana Harrison and Arthur Hughes, 37-58. Rockville, MD: National Institute on Drug Abuse.
- Havens, Jennifer R., Carl G. Leukefeld, Angela M. DeVeaugh-Geiss, Paul Coplan, and Howard D. Chilcoat. 2014. "The Impact of Reformulation on Extended-Release oxycodone Designed to Deter Abuse in a Sample of Prescription Opioid Abusers." *Drug and Alcohol Dependence* 139: 9-17.
- Hansen, Bruce E. 2001. "The New Econometrics of Structural Change: Dating Breaks in U.S. Labor Productivity." *Journal of Economic Perspectives* 15 (4): 117-128.
- Inocencio, Timothy J., Norman V. Carroll, Edward J. Read, and David A. Holford. 2013. "The Economic Burden of Opioid Poisonings in the United States." *Pain Medicine* 14(10): 1534-1547.
- Jayachandran, Seema, Adriana Lleras-Muney and Kimberly V. Smith. 2010. "Modern Medicine and the Twentieth Century Decline in Mortality: Evidence on the Impact of Sulfa Drugs." *American Economic Journal: Applied Economics* 2(2): 46-71.
- Johnson, Hal, Leonard Paulozzi, Christina Porucznik, Karin Mach and Blake Herter. "Decline in Drug Overdose Deaths After State Policy Changes – Florida, 2010-2012." <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6326a3.htm>
- Kalso, Elija. 2005. "oxycodone." *Journal of Pain Symptom Management* 29 (5): 47-56.
- Kennedy-Hendricks, Alene, Matthew Richey, Emma E. McGinty, Elizabeth A. Stuart, Colleen L. Barry and Daniel W. Webster. 2016. "Opioid Overdose Deaths and Florida's Crackdown on Pill Mills." *American Journal of Public Health* 106 (2): 291-29.
- Kilby, Angela E., 2015. "Opioids for the masses: Welfare tradeoffs in the regulation of narcotic pain medications." Unpublished.
- Larochelle, Marc R., Fang Zhang, Dennis Ross-Degnan and Frank Wharam. 2015. "Rates of Opioid Dispensing and Overdose After Introduction of Abuse-Deterrent Extended-Release oxycodone and Withdrawal of Propoxyphene." *JAMA Internal Medicine* 175 (6): 978-987.

- Mars, Sarah G., Philippe Bourgois, George Karandinos, Fernando Montero, and Daniel Ciccarone. 2014. "‘Every ‘Never’ I Ever Said Came True’: Transitions from Opioid Pills to Heroin Injecting." *International Journal of Drug Policy* 25 (2): 257-266.
- Meinhofer, Angélica. 2016. "The War on Drugs: Estimating the Effect of Prescription Drug Supply-Side Interventions." Unpublished.
- Miller, Emily. 2015. "Eight charged in pill mill probe" *Sun Sentinel*, May 27.
- National Alliance for Model State Drug Laws. 2014. "PDMP Dates of Operation."
- Norton, Erika. 2016. "How to recognize a pill mill in your community." *The Warwick Advertiser*, August 6.
- Ochoa, Kristen C., Judith A. Hahn, Karen H. Seal, and Andrew R. Moss. 2001. "Overdosing Among Young Injection Drug Users in San Francisco." *Addictive Behavior* 26: 453-460.
- Peltzman, Sam. 1975. "The Effects of Automobile Safety Regulation." *Journal of Political Economy* 83 (4): 677-726.
- Porter, Jane and Herschel Jick. 1980. "Addiction Rate in Patients Treated with Narcotics." *New England Journal of Medicine* 302 (2): 123.
- Quandt, Richard. 1960. "Tests of the Hypothesis that a Linear Regression Obeys Two Separate Regimes." *Journal of the American Statistical Association* 55 (290): 324-330.
- Quinones, Sam. 2015. *Dreamland: The True Tale of America's Opiate Epidemic*. New York: Bloomsbury Press.
- Ruhm, Christopher J., 2016. "Drug Poisoning Deaths in the United States, 1999-2012: A Statistical Adjustment Analysis" *Population Health Metrics* 14 (2).
- Rutkow, Lainie, Hsien-Yen Change, Matthew Daubresse, Daniel W. Webster, Elizabeth A. Stuart and G. Caleb Alexander. 2015. "Effect of Florida's Prescription Drug Monitoring Program and Pill Mill Laws on Opioid Prescribing and Use." *JAMA Intern Med* 175 (10): 1642-1649.
- Sessler, Nelson E., Jerod M. Downing, Hrishikesh Kale, Howard D. Chilcoat, Todd F. Baumgartner, and Paul Coplan. 2014. "Reductions in Reported Deaths Following the Introduction of Extended-Release oxycodone (OxyContin) with and Abuse-Deterrent Formulation." *Pharmacoepidemiology and Drug Safety* 23 (12): 1238-1246.
- Severtson Stevan G, Becki B. Bartelson, Jonathan M. Davis, Alvaro Munoz, Michael F. Scheider, Paul M. Coplan. 2012. "92 Difference in Rates of Abuse Following Reformulation of Extended Release (ER) oxycodone Using Data from Radars System Poison Center Program." *Annals of Emergency Medicine* 60 (4): S34-S35.
- Severtson, Stevan G., Becki B. Bartelson, Jonathan M. Davis, Alvaro Munoz, Michael F. Schneider, Howard Chilcoat, Paul M. Coplan, Hilary Surratt, and Richard Dart. 2013. "Reduced Abuse, Therapeutic Errors, and Diversion Following Reformulation of Extended-Release oxycodone in 2010." *The Journal of Pain* 14 (10): 1122-1130.
- Temple, John. 2015. *American Pain: How a Young Felon and his Ring of Doctors Unleashed America's Deadliest Drug Epidemic*. Guilford, CT: Lyons Press.
- United States General Accounting Office. 2003. *Prescription Drugs: OxyContin Abuse and Diversion and Efforts to Address the Problem*. Washington, DC: US GAO.
- Van Zee, Art. 2009. "The Promotion and marketing of OxyContin: Commercial Triumph, Public Health Tragedy." *American Journal of Public health* 99 (2): 221-227.

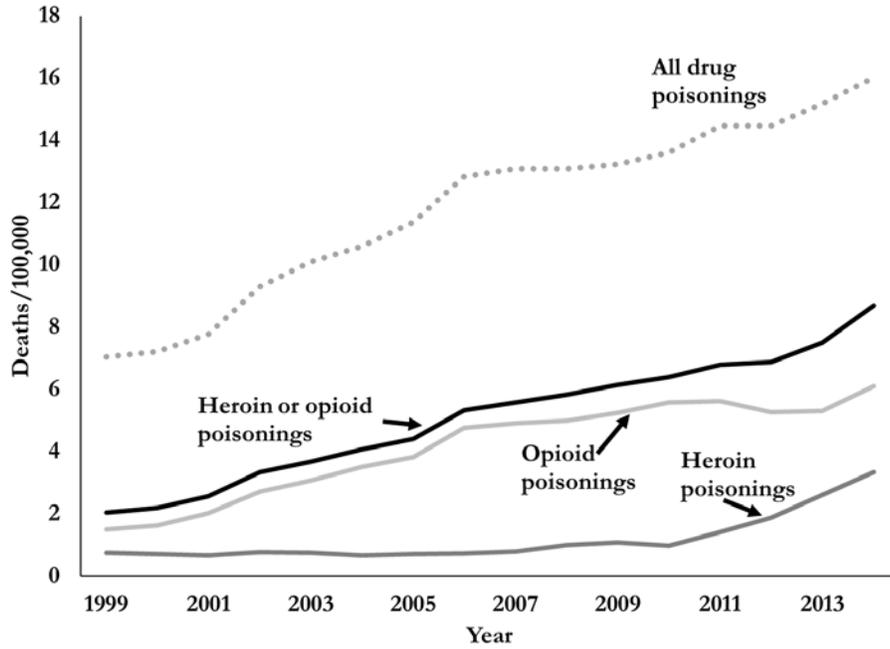


Figure 1: Drug Poisoning Death Rate, 1999-2014, CDC Multiple Cause of Death Data

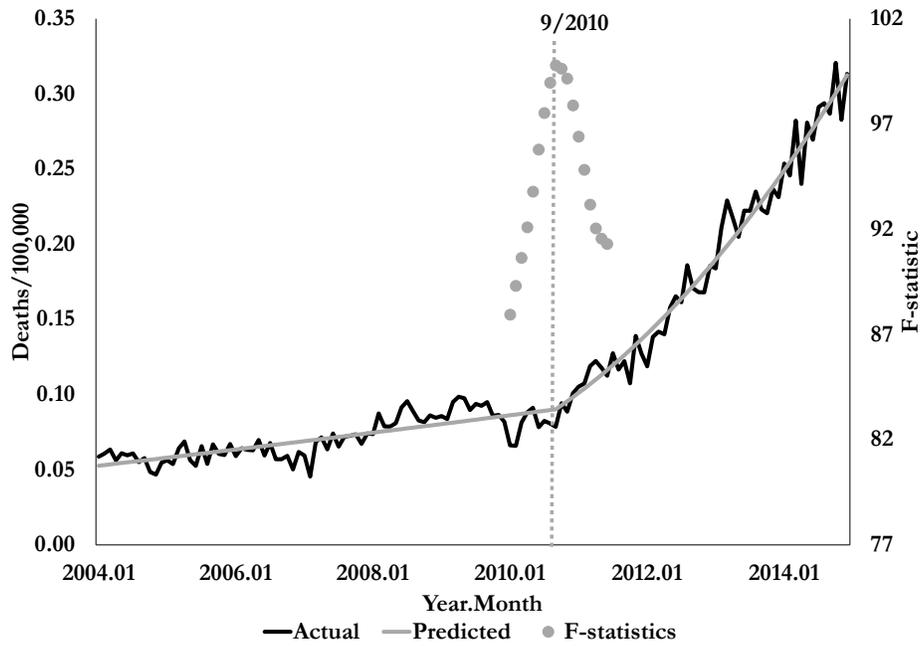


Figure 2: Monthly Heroin Death Rate, 2004.01 – 2014.12, CDC Multiple Cause of Death Data

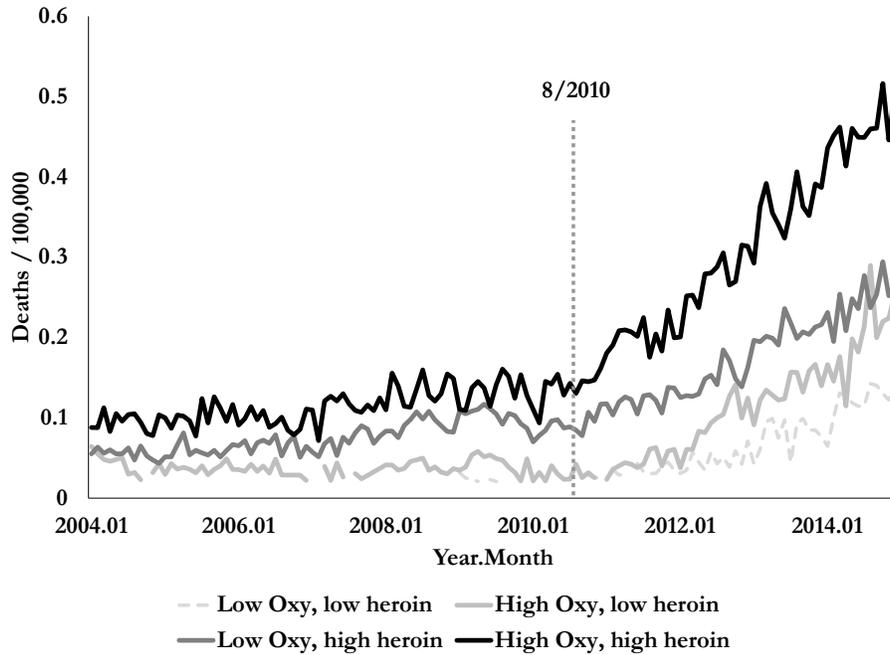


Figure 3: Monthly Heroin Death Rate, 2004.01 – 2014.12, by State Substitution Risk, CDC Multiple Cause of Death Data

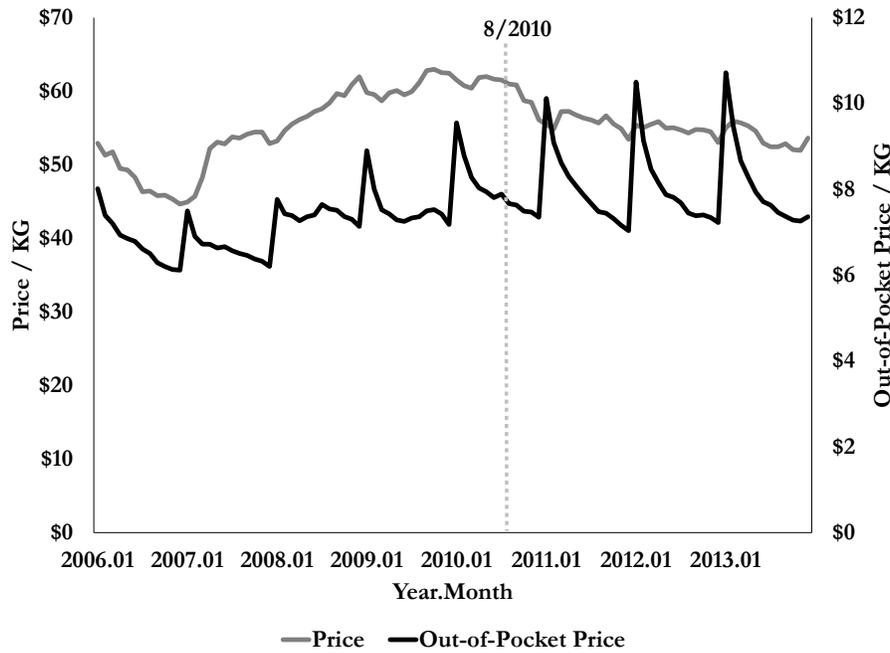


Figure 4: Average Monthly Price per KG of oxycodone, 2006.01 – 2013.12, Marketscan Data

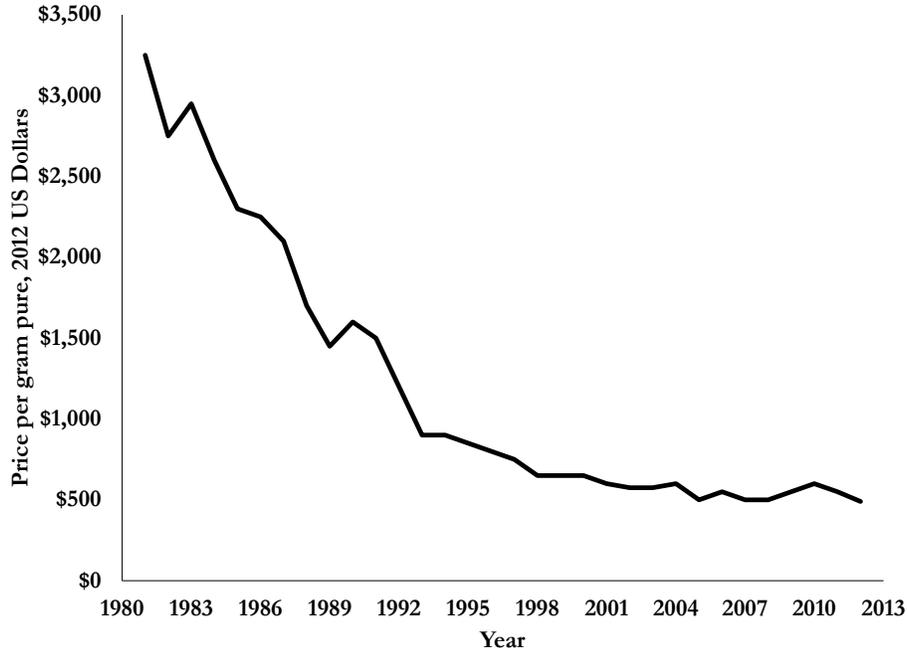


Figure 5: Average Price per Pure Gram, DEA Intelligence Report

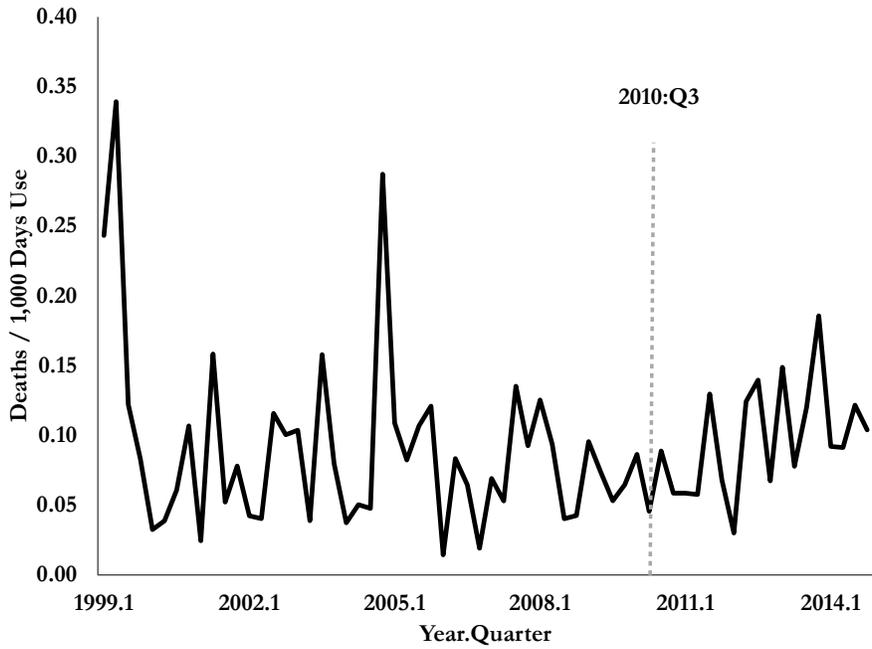


Figure 6: Heroin Deaths per 1,000 Days of Heroin Use, Quarterly, 1999.1 – 2014.4, National Survey on Drug Use and Health and CDC Multiple Cause of Death Data

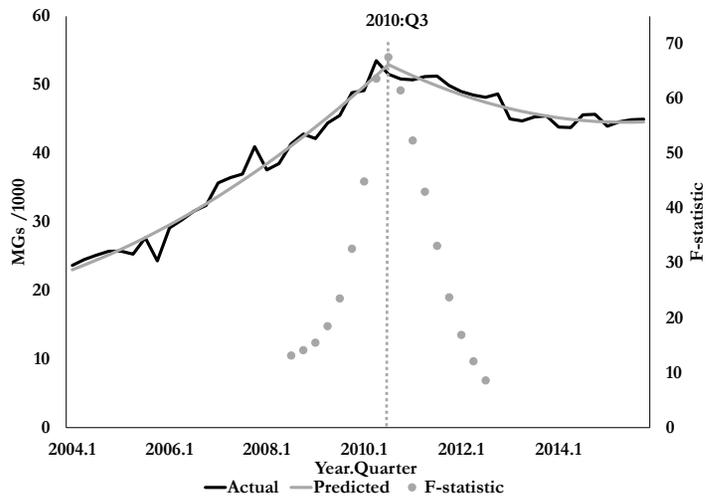


Figure 7a: Quarterly Shipments of Oxycodone, 2004.1 – 2014.4, ARCOS Data

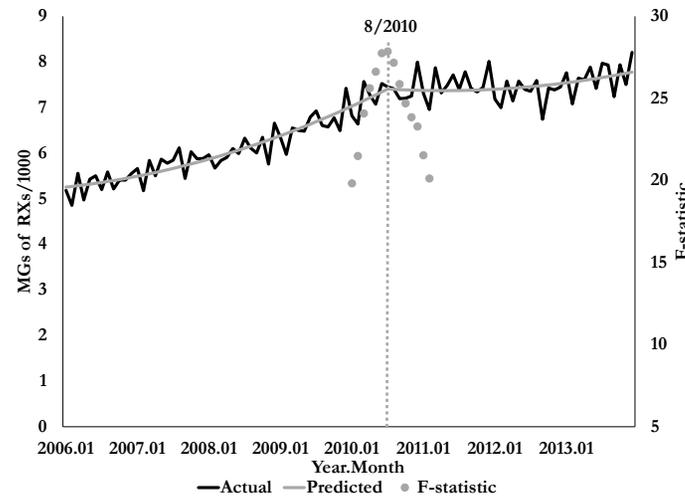


Figure 7b: Monthly Milligrams of Oxycodone Prescribed per 1,000 Subscribers, 2006.01 – 2013.12, Marketscan Data

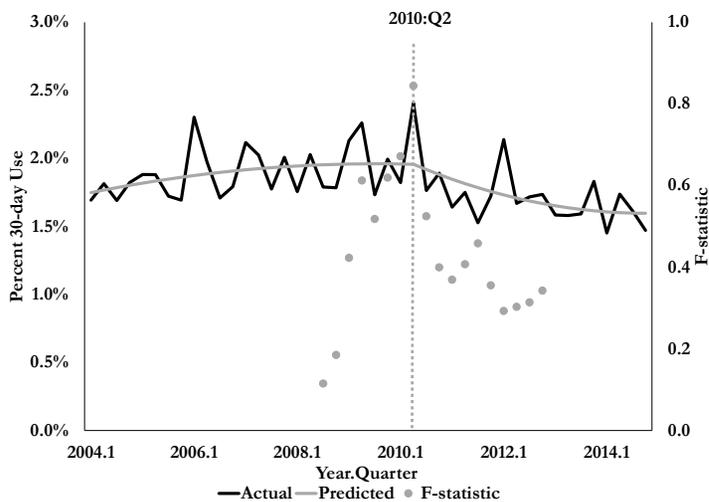


Figure 7c: Percent that use Pain Medicine Recreationally, by Quarter, 2004.1 – 2014.4, National Survey on Drug Use and Health

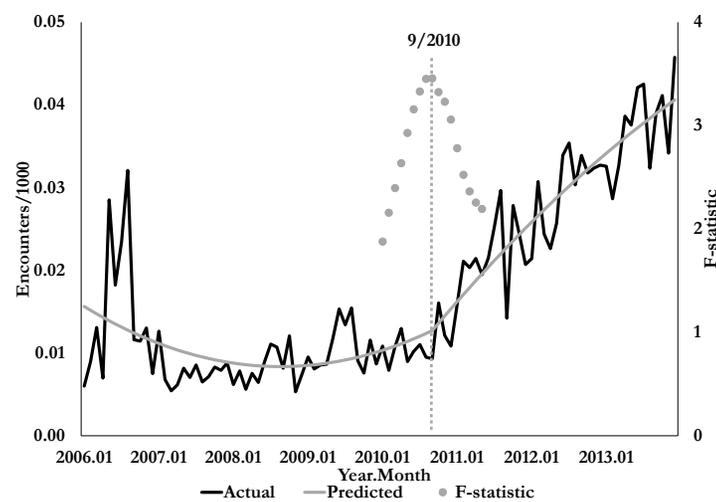
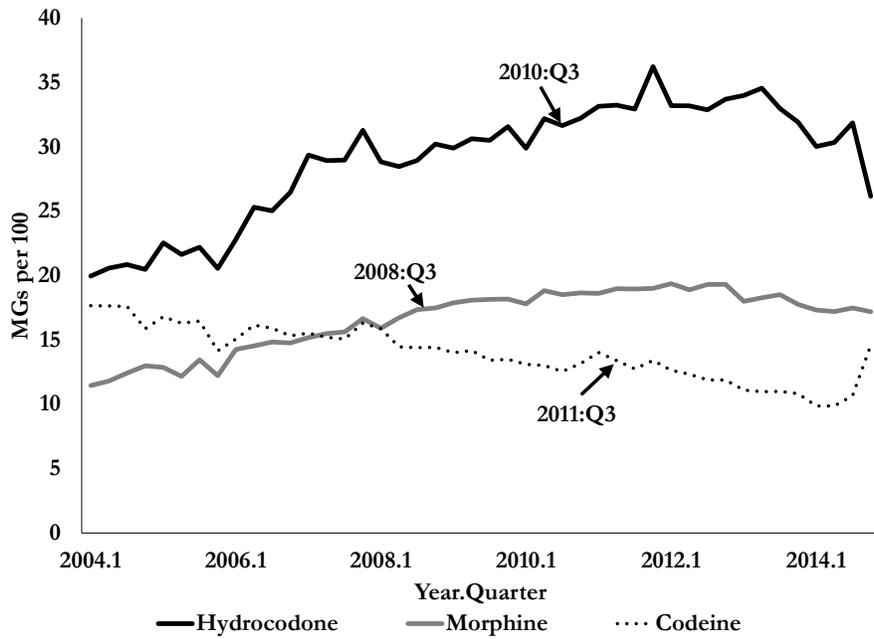
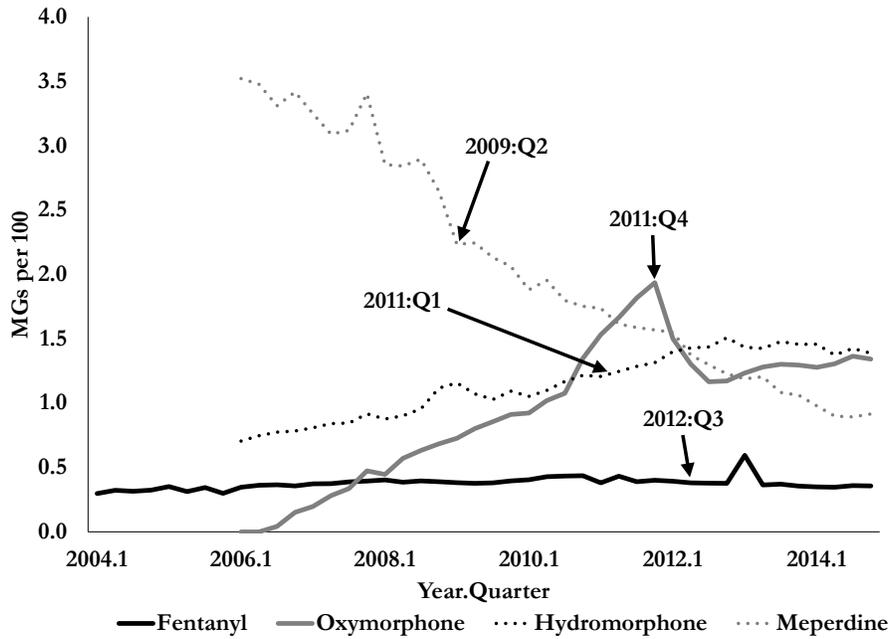


Figure 7d: Monthly Medical Encounters for Heroin Poisonings per 1,000 Subscribers, 2006.01 – 2013.12, Marketscan Data



a: Hydrocodone, Morphine, and Codeine



b: Fentanyl, Oxymorphone, Hydromorphone, and Meperidine

Figure 8: Quarterly Shipments of Pharmaceuticals in MGs per 1,000 Residents, 2004.1 – 2015.4, ARCOS Data

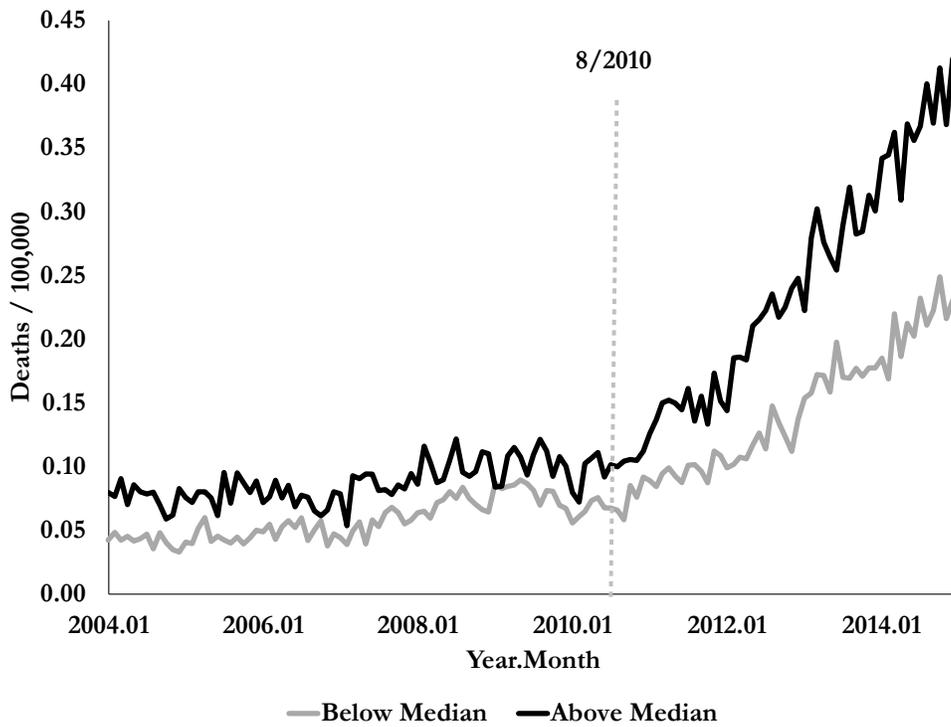


Figure 9: Heroin Death Rate by 2008-2009 Oxycodone Shipments per 1,000 Population, CDC Multiple Cause of Death Data and ARCOS Data

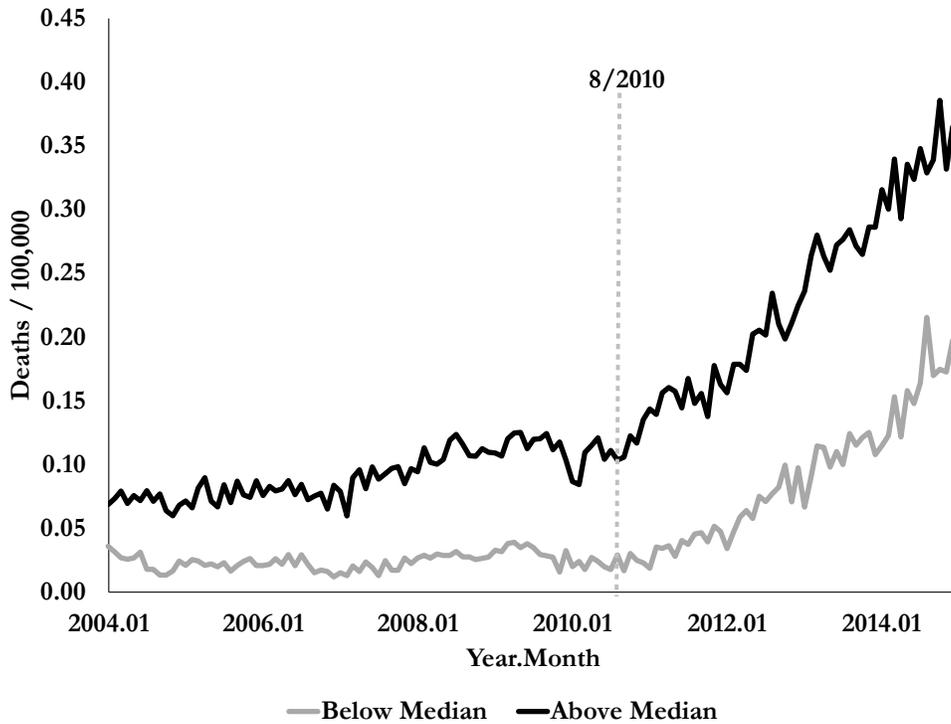


Figure 10: Heroin Death Rate by 2008-2009 Heroin Death Rate, CDC Multiple Cause of Death Data

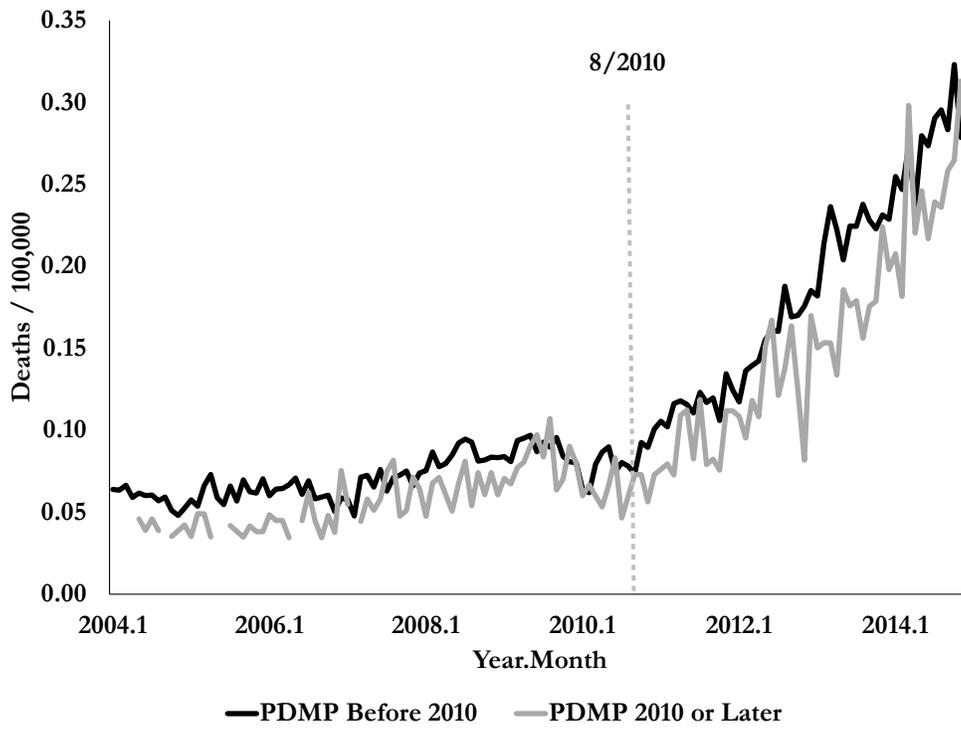


Figure 11: Heroin Death Rates by When State Had a PDMP, CDC Multiple Cause of Death Data

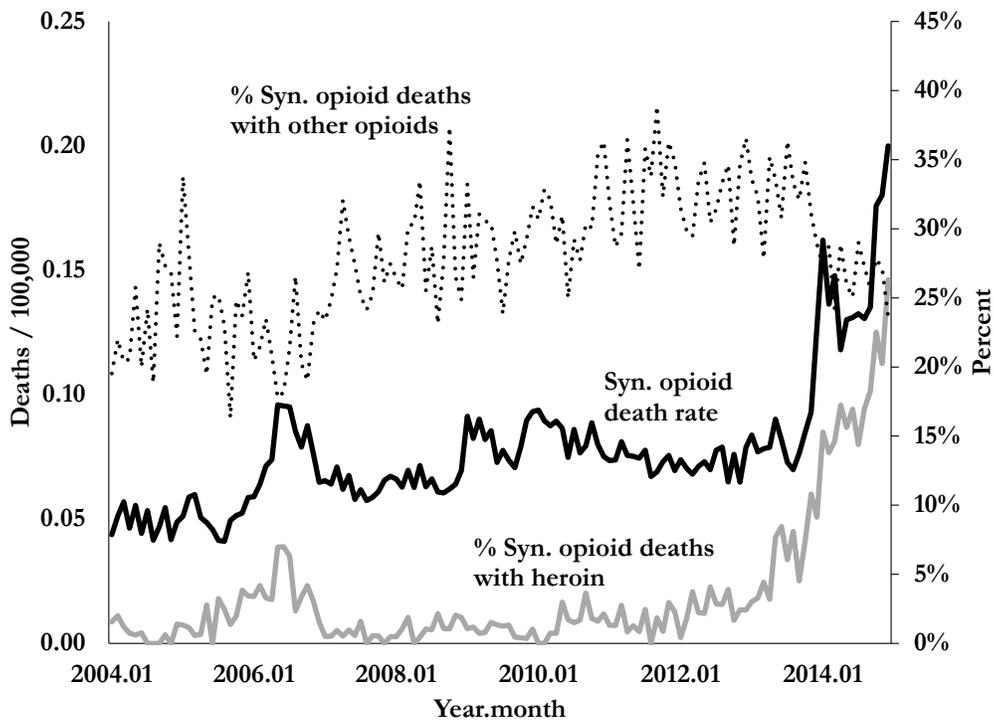


Figure 12: Monthly Synthetic Opioid Death Rate and Use with Other Drugs, 2004.01 – 2014.12, CDC Multiple Cause of Death Data

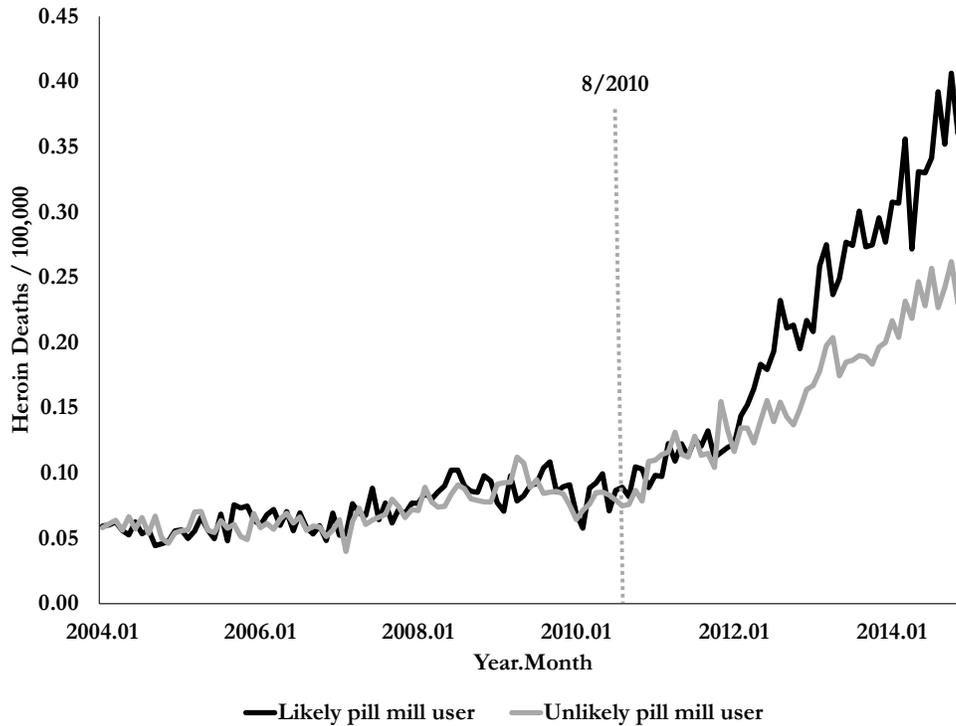


Figure 13: Monthly Heroin Death Rate, 2004.01 – 2014.12, by Likely Pill Mill Access, CDC Multiple Cause of Death Data

Table 1: Estimated Structural Break Points in National Time Series

Outcome	Freq.	Years in Sample	Obs.	Break point	R ²	F-test: trends are the same	λ	Critical Value of F
MGs of oxycodone/1,000	Q	2004-14	44	2010/Q3	0.980	67.5	4.9	7.39
MGs of oxycodone RXs/1000	M	2006-13	96	2010/M8	0.911	27.9	11.2	8.09
30-day recreational pain med use	Q	2004-14	44	2010/Q2	0.340	0.84	4.93	7.39
Heroin poisoning encounters/1,000	M	2006-13	96	2010/M9	0.847	3.46	11.2	8.09
Heroin deaths/100,000	M	2004-14	108	2010/M9	0.947	99.8	11.5	8.12

Each row presents results from a different regression. Frequency indicates whether the time dimension of the data is in months (M) or quarters (Q). Break point indicates the date at which there was a break in trend. F test/trends the same provides the F-statistic for the test of whether there was a trend break at break point. λ is related to the fraction of the sample in which we are testing for a trend break and is used to determine the relevant critical value taken from Andrews (1993), presented in the final row.

Table 2: Estimated Structural Break Points in National Time Series for Other Opioids

Outcome (MGs per 1,000 people)	Years in Sample	Break point	R ²	F-test:		Critical Value of F
				trends are the same	λ	
Hydrocodone	2004-14	2010/Q3	0.926	5.86	4.91	7.39
Morphine	2004-14	2008/Q3	0.973	23.8	4.91	7.39
Codeine	2004-14	2012/Q3	0.890	5.55	4.91	7.39
Fentanyl	2004-14	2012/Q3	0.511	0.68	4.91	7.39
Oxymorphone	2006-14	2011/Q4	0.967	27.0	6.76	7.67
Meperidine	2006-14	2009/Q2	0.989	7.20	6.76	7.67
Hydromorphone	2006-14	2011/Q1	0.975	28.7	6.76	7.67

Each row presents results from a different regression. All sample are quarterly from the ARCOS data. Break point indicates the date at which there was a break in trend. F test/trends the same provides the F-statistic for the test of whether there was a trend break at break point. λ is related to the fraction of the sample in which we are testing for a trend break and is used to determine the relevant critical value taken from Andrews (1993), presented in the final row.

Table 3: OLS Estimates of Impact of Reformulation on the Trends in Heroin and Opioid Death Rates, 2004-2012

Covariates	Low Oxy/ Low heroin	High Oxy/ Low heroin	Low Oxy/ High heroin	High Oxy/ High heroin
A: Heroin death rates {0.66} [0.083]				
Trend before	0.0016 (0.0007)	0.0019 (0.0008)	0.0029 (0.0008)	0.0025 (0.0008)
Trend after	0.0024 (0.0006)	0.0044 (0.0012)	0.0039 (0.0009)	0.0075 (0.0013)
Diff: after-before	0.0008 (0.0005)	0.0024 (0.0011)	0.0010 (0.0007)	0.0049 (0.0013)
Diff: group-Low Oxy/Low heroin		0.0017 (0.0011)	0.0003 (0.0008)	0.0042 (0.0013)
B: Opioid death rates {0.75} [0.464]				
Trend before	0.0066 (0.0021)	0.0094 (0.0024)	0.0073 (0.0024)	0.0074 (0.0024)
Trend after	0.0013 (0.0020)	-0.0002 (0.0030)	0.0016 (0.0023)	0.0040 (0.0028)
Diff: after-before	-0.0054 (0.0016)	-0.0096(0.0023)	-0.0056 (0.0012)	-0.0035 (0.0017)
Diff: group-Low Oxy/Low heroin		-0.0043 (0.0023)	-0.0003 (0.0014)	0.0019 (0.0018)
C: Combined Heroin/opioid death rate {0.74} [0.532]				
Trend before	0.0074 (0.0023)	0.0104 (0.0026)	0.0091 (0.0026)	0.0088 (0.0027)
Trend after	0.0029 (0.0022)	0.0029 (0.0034)	0.0047 (0.0026)	0.0098 (0.0032)
Diff: after-before	-0.0045 (0.0019)	-0.0075 (0.0028)	-0.0044 (0.0014)	0.0010 (0.0024)
Diff: group-Low Oxy/Low heroin		-0.0030 (0.0028)	0.0001 (0.0018)	0.0055 (0.0026)

The numbers in curly brackets is the R² for the regression and the numbers in square brackets is the mean of the dependent variable for the 12 months prior to August of 2010. Standard errors are in parentheses and values are calculated assuming regression errors are correlated at the state level. Each regression has monthly data for 50 states and DC 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 of age, 20-34 years of age, 35-50 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 4: OLS Estimates of Impact of Reformulation on the Trends in Heroin and Opioid Death Rates, 2004-2014

Covariates	Low Oxy/ Low heroin	High Oxy/ Low heroin	Low Oxy/ High heroin	High Oxy/ High heroin
		A: Heroin death rates {0.73} [0.083]		
Trend before	0.0000 (0.0010)	0.0004 (0.0012)	0.0014 (0.0012)	0.0009 (0.0011)
Trend after	0.0024 (0.0008)	0.0042 (0.0013)	0.0044 (0.0014)	0.0076 (0.0017)
Diff: after-before	0.0024 (0.0007)	0.0038 (0.0011)	0.0029 (0.0013)	0.0067 (0.0011)
Diff: group-Low Oxy/Low heroin		0.0013 (0.0009)	0.0005 (0.0011)	0.0043 (0.0013)
		B: Opioid death rates {0.74} [0.464]		
Trend before	0.0030 (0.0017)	0.0057 (0.0021)	0.0038 (0.0020)	0.0037 (0.0020)
Trend after	0.0012 (0.0014)	-0.0007 (0.0022)	0.0012 (0.0017)	0.0036 (0.0018)
Diff: after-before	-0.0017 (0.0014)	-0.0063 (0.0021)	-0.0026 (0.0013)	-0.0001 (0.0014)
Diff: group-Low Oxy/Low heroin		-0.0046 (0.0021)	-0.0009 (0.0011)	0.0016 (0.0016)
		C: Combined Heroin/opioid death rate {0.74} [0.532]		
Trend before	0.0025 (0.0021)	0.0055 (0.0026)	0.0044 (0.0026)	0.0040 (0.0025)
Trend after	0.0028 (0.0017)	0.0019 (0.0026)	0.0045 (0.0024)	0.0088 (0.0026)
Diff: after-before	0.0003 (0.0017)	-0.0036 (0.0026)	0.0001 (0.0019)	0.0048 (0.0018)
Diff: group-LowOxy/Low heroin		-0.0039 (0.0026)	-0.0002 (0.0017)	0.0046 (0.0022)

The numbers in curly brackets is the R^2 for the regression and the numbers in square brackets is the mean of the dependent variable for the 12 months prior to August of 2010. Standard errors are in parentheses and values are calculated assuming regression errors are correlated at the state level. Each regression has monthly data for 50 states and DC from 2004 through 2014 for a total of 6,732 observations. Other control variables are state fixed-effects, month effects, the fraction of the population that is ≤ 19 years of age, 20-34 years of age, 35-50 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 5: OLS Estimates of Impact of Reformulation on the Trends in Heroin Death Rates in States with Above Median Opioid Exposure, 2004-2012

Covariates	Low heroin/ Not exposed to pill mills	Low heroin/ Exposed to pill mills	High heroin/ Not exposed to pill mills	High heroin/ Exposed to pill mills
Trend before	0.0015 (0.0015)	0.0017 (0.0016)	0.0025 (0.0017)	0.0022 (0.0017)
Trend after	0.0030 (0.0009)	0.0046 (0.0014)	0.0066 (0.0009)	0.0101 (0.0024)
Diff: after-before	0.0015 (0.0011)	0.0029 (0.0015)	0.0041 (0.0017)	0.0078 (0.0024)
Diff: exposed-not exposed		0.0014 (0.0014)		0.0037 (0.0025)

Dependent variable is the heroin death rate. Standard errors are in parentheses and values are calculated assuming regression errors are correlated at the state level. The sample is limited to states that had above median pre-reformulation shipments of oxycodone per person. The regression has monthly data for 26 states from 2004 through 2012 for a total of 2,808 observations. Other control variables are state fixed-effects, month effects, the fraction of the population that is ≤ 19 years of age, 20-34 years of age, 35-50 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.

For Online Publication

Appendix A: Correcting for “Unspecified” deaths

Ruhm (2016) points out that 20-25 percent of drug poisoning deaths do not include any specific drug mentioned and that these “unspecified” deaths lead to noisy measurement of drug-specific death rates. In this appendix, we implement the adjustment procedure suggested in Ruhm (2016), re-estimate our main regression results for the adjusted measures of death rates, and report the results.

The adjustment procedure is as follows.³⁶ For each county-year combination, calculate the fraction of drug poisoning deaths which do not have any specific drugs mentioned; denote this fraction as *unspecified*. Let *heroin death_{ict}* be an indicator for whether or not individual death record *i*, in county *c*, in month *t*, mentioned heroin among the causes of death. Estimate the probit model

$$(B1) \quad \Pr(\textit{heroin death}_{ict} = 1) = \Phi(\textit{unspecified}_{ct}\theta + x_{ict}\gamma + \lambda_t)$$

where x_{ict} includes controls for gender, race, marital status, education level, age, day of the week, and census division. Given the parameter estimates, create predicted probabilities in which sample values are used for all variables except *unspecified_{ct}*, which is set equal to one. To get an adjusted heroin death rate, add up the individual probabilities for each state and month-year and divide by the population. We implement this process for heroin deaths, opioid deaths, and heroin or opioid deaths.

We estimate equation (2) with these adjusted versions of the dependent variable and report the results in Table B1. The magnitudes of the trend breaks are qualitatively similar to what we found for the unadjusted death rates, though the magnitudes appear to be slightly larger. We now estimate that growth in heroin death rates increased for each of our groups; opioid death rates fell for three of the four groups (not the high Oxy/high heroin group); and combined heroin and opioid death rates fell for all groups except for the high Oxy/high heroin group.

³⁶ See Ruhm (2016) for more details.

Table A1: OLS Estimates of Impact of Reformulation on the Trends in Heroin and Opioid Death Rates Using Measures of Drug Deaths Corrected for “Unspecified”

Covariates	Low Oxy/ Low heroin	High Oxy/ Low heroin	Low Oxy/ High heroin	High Oxy/ High heroin
A: Heroin death rates {0.76} [0.115]				
Trend before	0.0007 (0.0006)	0.0009 (0.0007)	0.0018 (0.0007)	0.0014 (0.0007)
Trend after	0.0030 (0.0006)	0.0044 (0.0012)	0.0054 (0.0012)	0.0079 (0.0012)
Diff: after-before	0.0024 (0.0005)	0.0035 (0.0013)	0.0035 (0.0010)	0.0065 (0.0012)
Diff: group-Low Oxy/Low heroin		0.0011 (0.0012)	0.0012 (0.0008)	0.0042 (0.0012)
B: Opioid death rates {0.77} [0.662]				
Trend before	0.0078 (0.0021)	0.0103 (0.0025)	0.0078 (0.0023)	0.0087 (0.0023)
Trend after	0.0007 (0.0019)	-0.0014 (0.0033)	0.0014 (0.0021)	0.0050 (0.0026)
Diff: after-before	-0.0071 (0.0017)	-0.0117 (0.0033)	-0.0063 (0.0013)	-0.0036 (0.0021)
Diff: group-Low Oxy/Low heroin		-0.0046 (0.0033)	0.0007 (0.0017)	0.0035 (0.0021)
C: Combined Heroin/opioid death rate {0.76} [0.749]				
Trend before	0.0079 (0.0022)	0.0106 (0.0027)	0.0087 (0.0026)	0.0092 (0.0025)
Trend after	0.0028 (0.0020)	0.0016 (0.0039)	0.0057 (0.0026)	0.0112 (0.0031)
Diff: after-before	-0.0051 (0.0018)	-0.0091 (0.0040)	-0.0030 (0.0016)	0.0020 (0.0027)
Diff: group-Low Oxy/Low heroin		-0.0040 (0.0040)	0.0021 (0.0019)	0.0071 (0.0026)

The numbers in curly brackets is the R^2 for the regression and the numbers in square brackets is the mean of the dependent variable for the 12 months prior to August of 2010. Standard errors are in parentheses and values are calculated assuming regression errors are correlated at the state level. Each regression has monthly data for 50 states and DC 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 of age, 20-34 years of age, 35-50 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.

Appendix B: Assessing the Impacts of the Florida pill mill Crackdown

It is easy to generate suggestive evidence that the pill mill crackdown worked. Most work (e.g. Johnson et al., 2014; Delcher et al., 2015; Rutkow et al., 2015; Kennedy-Hendricks et al., 2016; Chang et al., 2016) on the topic is some version of an interrupted time series analysis showing that opioid poisoning deaths in Florida started to fall after 2010. In Figure B1a, we report quarterly shipments of oxycodone in milligrams per 1,000 people for Florida and the rest of the US. By the middle of 2010, per capita shipments to Florida were more than four times what they were in the rest of the US. The time series in this graph shows a sharp decline in oxycodone shipments starting in the third quarter of 2010.³⁷ Although the break in trend is greater

³⁷ To test for trend breaks in the third quarter of 2010, we fit linear splines separately for Florida and for the rest of the United States.

for Florida than the rest of the United States, both groups have highly statistically significant negative breaks (t-statistics greater than 10).

We investigate the pill mill hypothesis and find mixed support for its ability to explain the national shift to heroin. First, 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. A comprehensive list of events related to the pill mill crackdown is presented in Table B1. The crackdown was phased in over an extended period of time. In June of 2009, the Governor signed legislation establishing a statewide Prescription Drug Monitoring Program (PDMP), a networked database designed to give doctors and pharmacists the ability to see if patients had multiple prescriptions for the same drug. The law was scheduled to go into effect in December of 2010.³⁸ The original PMDP plan is criticized by some because it gives doctors and pharmacists 15 days to enter a patient's prescriptions in the database, proving little deterrent for patients willing to visit multiple physicians in a short period for many prescriptions.³⁹ The PMDP however does not go into effect when scheduled for a variety of reasons. First, there were insufficient funds for the project.⁴⁰ Second, in December of 2010, incoming governor Rick Scott fires all of the full-time employees of the governor's Office of Drug Control, the agency that was responsible for the PDMP.⁴¹ In January of 2011, the governor-elect shuts down the Office of Drug Control and using administrative orders, freezes "all new regulations" which shelves the new standards for pain clinics.⁴²

In March of 2010, the Federal Drug Enforcement Agency (DEA) executes raids on the largest pain clinics in Florida.^{43,44} In October of 2010, various components of the law passed in 2009 that established the

³⁸ <http://www.tampabay.com/news/politics/stateroundup/new-law-may-crack-down-on-florida-illegal-prescription-drug-market/1011527>

³⁹ <http://www.tampabay.com/news/health/prescription-pain-pill-monitoring-limited-by-delay-in-reporting/1110710>. Buchmueller and Carey (2018) find that this phenomenon of doctor shopping is only prevented by PDMPs that require physicians to access the information before prescribing opioids to the patient.

⁴⁰ <http://www.tampabay.com/features/humaninterest/pill-mills-demise-brings-relief-to-neighbors/1098705>

⁴¹ <http://www.tampabay.com/news/politics/gubernatorial/rick-scott-moves-to-eliminate-floridas-office-of-drug-control/1141510>

⁴² Temple (2015).

⁴³ <http://abcnews.go.com/Business/PersonalFinance/feds-raid-alleged-pill-mills-florida/story?id=10022791>

⁴⁴ <http://www.mcclatchydc.com/news/crime/article24575644.html#!>

state PMDP went into effect: pain management clinics must register with the state, they can only provide a three-day supply of drugs, they can no longer advertise, and they must open their doors to inspection.^{45, 46}

In July of 2011, Governor Scott signed into law HB 7095.⁴⁷ The law prohibits most physicians from prescribing and dispensing prescriptions such as OxyContin from their office and fully funds the PDMP for the first time. Florida's PDMP becomes operational in September⁴⁸ and on October 17th, physicians can register on the PMDP for the first time.⁴⁹

It is difficult to see what part of these legislative actions would be responsible for the abrupt shift in shipments of oxycodone in the same quarter that the drug was reformulated. The most aggressive components of the laws, those that barred doctors from dispensing opioids and funding for the PDMP, did not go into effect until the third quarter of 2011. When discussing HB7095, Florida's then current Attorney General, Pam Biondi, a supporter of both the 2009 and 2011 legislation noted, "We had no tough laws in place; now we do."⁵⁰

Because customers of pill mills could get prescriptions for many different drugs, not just OxyContin, we would expect that if the crackdown on pill mills had been effective, the use of many different drugs would have declined. In Figures B1b through B1h, we report the milligrams of shipments per 1,000 people for Florida and for the rest of the US for seven other pain killers: hydrocodone, morphine, codeine, pentobarbital, hydromorphone, oxymorphone, and fentanyl. Note that for these seven drugs, before the reformulation, Florida tends to have much higher per capita use than the rest of the US. This suggests that pill mills were facilitating access to other drugs as well and could well be the reason that Florida is actually below the median in pre-reformulation heroin death rates. However, there is no sharp decrease in drug use

⁴⁵ http://www.gray-robinson.com/Elerts/03_05_12_Health_Elert_Florida_Legislation_Regarding_Pain_Management_Clinics.pdf

⁴⁶ <http://www.palmbeachpost.com/news/news/crime-law/32-new-florida-laws-take-effect-today/nMBP2/>

⁴⁷ <http://www.flgov.com/governor-rick-scott-signs-pill-mill-bill-that-will-be-a-model-for-the-nation/>

⁴⁸ http://www.huffingtonpost.com/entry/florida-legislation-opioid-prescriptions_us_55d244a3e4b055a6dab11c23

⁴⁹ <http://www.palmbeachpost.com/news/news/state-regional/law-requiring-florida-pharmacists-to-send-drug-inf/nLxZy/>

⁵⁰ <http://www.nytimes.com/2011/09/01/us/01drugs.html>

for *any* of these seven drugs. More telling, however, is that the time series patterns of shipments for these other drugs look very similar to what is happening in the rest of the US.

Although we have stressed the substitution from oxycodone to heroin, past research suggests that the reformulation led some to substitute to other prescription opioids (e.g. Cicero et al., 2012; Cassidy et al., 2014). Both the introduction of an abuse-deterrent version of oxymorphone (brand name Opana) and the rescheduling of hydrocodone from a class III drug to a class II drug (leading to restrictions on the amount of the drug that could be prescribed in a single visit) appear to have led to substitution to other opioids. As seen in Figure B2, there is an initial increase in oxymorphone shipments to Florida after the third quarter of 2010. When oxymorphone was reformulated to an ADF midway through the first quarter of 2012, oxymorphone shipments to Florida dropped precipitously. When hydrocodone was rescheduled in the first quarter of 2014, and likely less easy to obtain, codeine shipments increased. Because these other events appear to have had important effects on the use of opioids in Florida in 2012 or later, it is less clear that the crackdown on pill mills had much traction.

Using the quarterly ARCOS data, we fit separate linear splines for Florida and the rest of the US where we impose that the break occurs in the 3rd quarter of 2010. We report the results from these regressions in Table B2. Each row contains regression results for a different drug and for each drug we report the average of the dependent variable in the four-quarters prior to the third quarter of 2010, the regression results for the splines pre and post reformulation for Florida and the rest of the US, the R^2 , the p -values on the test of the hypotheses that the pre-reform trends are the same between Florida and the rest of the US, the post-trends are the same, and finally the joint test.

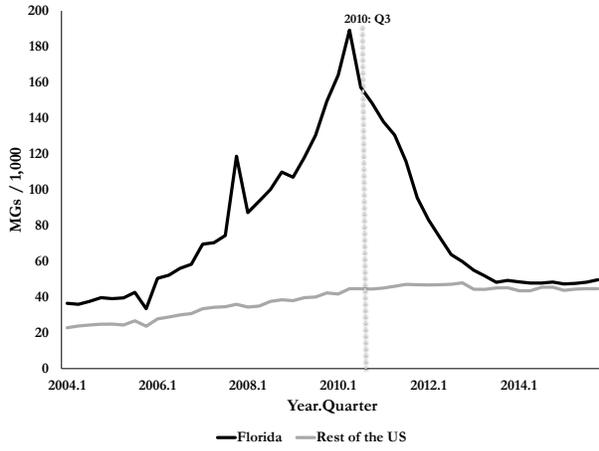
The results for oxycodone suggest there is a clear difference in trends after reformulation with Florida having a massive decline in use. For the other seven drugs, we cannot reject the null that Florida's post-reform trend is the same as the rest of the US in five of seven cases. In the two cases where we do reject, morphine and hydromorphone, use in Florida is a) substantially higher pre-reformulation, and b) the post-reformulation trends in the rest of the US show much sharper declines than in Florida, the opposite of what we'd expect if the pill mill crackdown were having dramatic effects.

Lastly, we test whether states that were more exposed to Florida’s pill mills experienced greater increases in heroin death rates than states that were less exposed. We take two approaches to estimating how exposed a state was to Florida’s pill mills. The first is described in the main text. Second, we use distance from Florida as a proxy for whether or not a state was affected by Florida’s pill mills; Hawaii is excluded from this analysis. For state s and month t , we estimate equations of the form

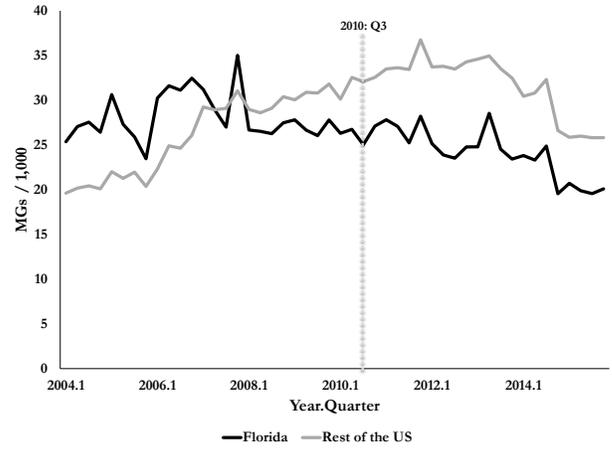
$$(B1) \quad y_{st} = trend_t \alpha_1 + trend_t * distance_s \beta_1 + treat_t \alpha_2 + treat_t * distance_s \beta_2 + x_{st} \gamma + \lambda_s + \varepsilon_{st}$$

where $trend_t$ is a linear time trend, $treat_t$ measures the break in trend starting in August, 2010, $distance_s$ is a measure of how far away state s is from Florida, x_{st} are basic demographics including the fractions of individuals in a set of age bins (less than 20, 20-34, 35-49, 50+), in race bins, local economic conditions via the unemployment rate, a set of month fixed effects, and λ_s is a set of state fixed effects. The main coefficient of interest in this analysis is β_2 because it indicates whether states that were closer to Florida’s pill mills had differentially larger or smaller breaks in their heroin growth rates. Table B3 presents the estimates of the pre-reformulation trend, the break in trend, and each of those terms interacted with a distance measure. The point estimates on the interaction terms are consistent with the hypothesis that states further from Florida had smaller increases in heroin death rates, though we lack the statistical power to reject the null of no effect. The largest (in magnitude) estimate would imply that the rise in heroin death rates was approximately 20 percent lower in states 1,000 miles from Florida (average distance from Florida in the sample is 1.7 thousand miles). Our findings are similar regardless of whether we measure distance between states as the miles between the centroids of the states or the time it takes to drive from one state’s capital to Florida’s capital as well as whether we interact the spline with a nonlinear (one over the distance) or linear measure of distance.

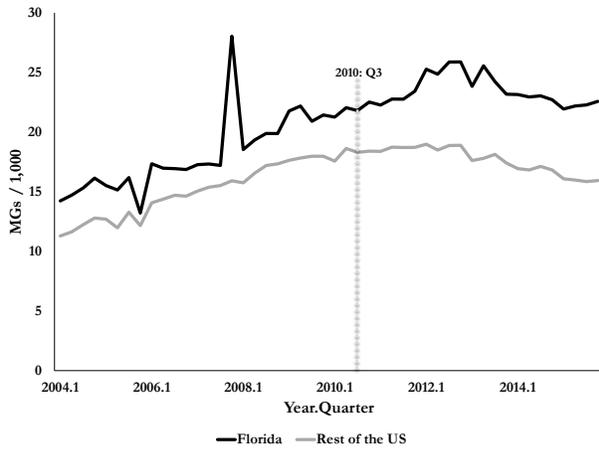
Taken together, our analyses of the crackdown on Florida’s pill mills in the main text and in this appendix does not provide strong evidence that it was primarily responsible for the national increase in the heroin death rate that began in 2010.



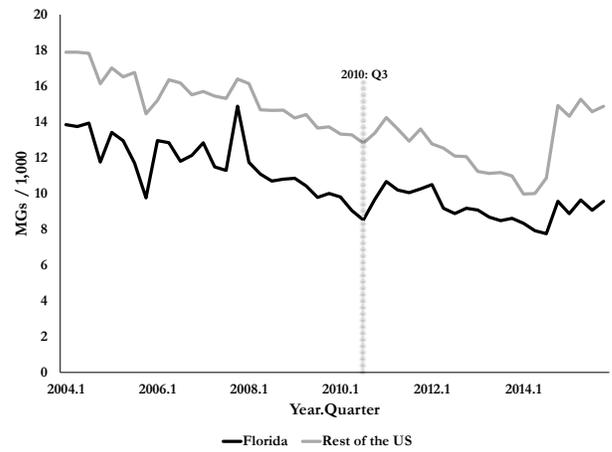
a: oxycodone



b: Hydrocodone

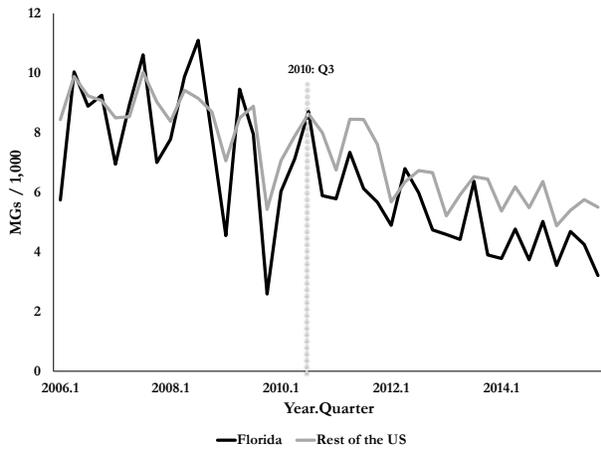


c: Morphine

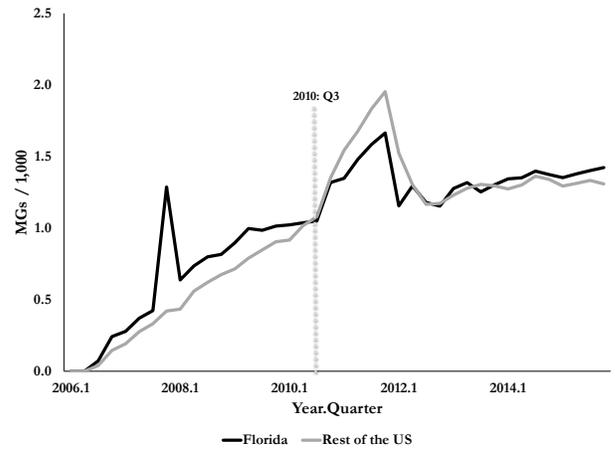


d: Codeine

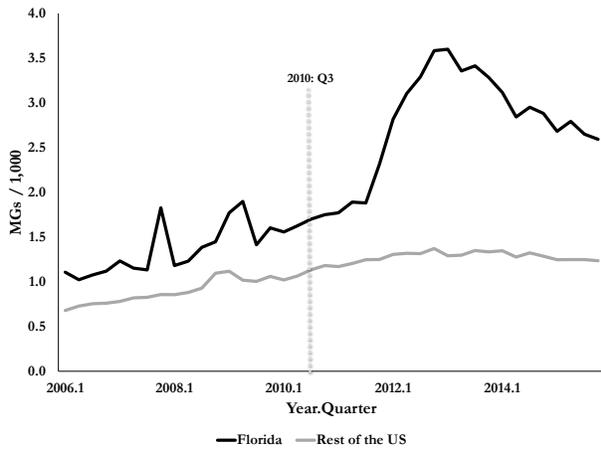
Figure B1: Quarterly Shipments of Pharmaceuticals in MGs per 1,000 Residents, Florida and the Rest of the United States, 2004.1 – 2015.4, ARCOS Data



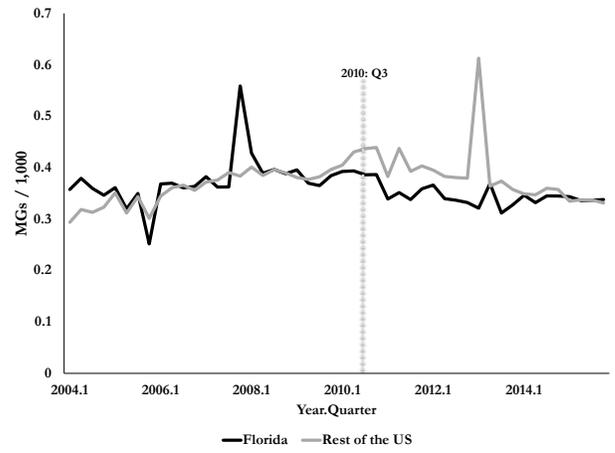
e: Pentobarbital



f: Oxymorphone



g: Hydromorphone



h: Fentanyl

Figure B1 (continued): Quarterly Shipments of Pharmaceuticals in MGs per 1,000 Residents, Florida and the Rest of the United States, 2004.1 – 2015.4, ARCOS Data

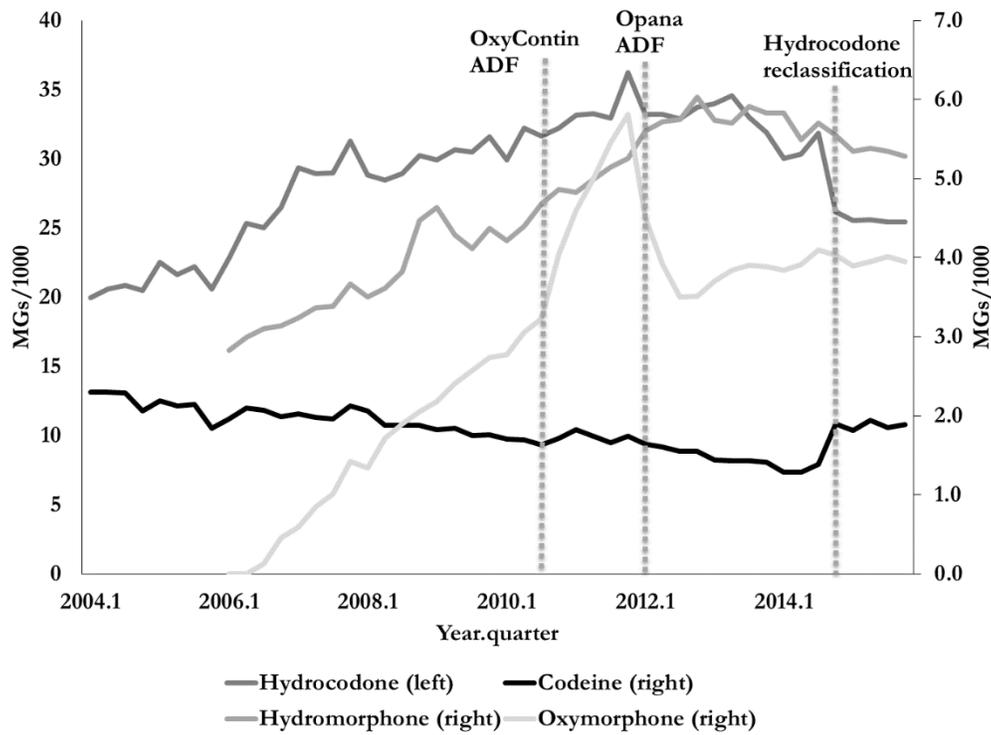


Figure B2: Quarterly Shipments of Selected Opioids in Florida, 2004.1 – 2015.4, ARCOS Data

Table B1: The Pill Mill Crackdown in Florida

Date	Event
06/2009	State Prescription Drug Monitoring Program (PDMP) adopted, but not funded. Due to go into effect 12/2010
03/2010	American Pain and two other clinics raided by the DEA
10/2010	Legislation requires pain clinics to register with state, restricts advertising, and limits length of prescriptions
12/2010	Governor Scott fires entire staff of the Office of Drug Control
01/2011	Governor Scott shuts down the Office of Drug Control
05/2011	PDMP funded
07/2011	Legislation barring doctors from dispensing drugs
09/2011	PDMP becomes operational
10/2011	Doctors can access data in the PDMP, but are not required to use it
06/2012	DEA raids more pill mills

See text for sources for each event.

Table B2: Fitting Splines to Florida and Rest of the U.S., Oxycodone and Other Pain Killers

Dependent variable	Means in 4 quarters prior to 2010:3		Regression coefficients (standard errors)				R ²	p-value on test		
			Pre-reformulation trend		Post-reformulation trend			(a)=(b)	(c)=(d)	(a)=(b) (c)=(d)
			Florida (a)	Rest of US (b)	Florida (c)	Rest of US (d)				
oxycodone	158.3	42.2	4.69 (0.27)	0.92 (0.27)	-5.96 (0.35)	-0.01 (0.34)	0.88	<0.001	<0.001	<0.001
Hydrocodone	26.7	31.2	-0.02 (0.04)	0.61 (0.04)	-0.35 (0.06)	-0.33 (0.06)	0.77	<0.001	0.800	<0.001
Morphine	21.4	18.0	0.36 (0.03)	0.30 (0.03)	0.00 (0.03)	-0.14 (0.03)	0.89	0.099	0.0045	<0.001
Codeine	9.7	13.4	0.06 (0.004)	0.06 (0.004)	0.008 (0.005)	0.008 (0.005)	0.90	0.64	0.95	0.81
Pentobarbital	5.9	7.3	0.25 (0.05)	0.29 (0.05)	-0.27 (0.07)	-0.25 (0.07)	0.40	0.58	0.76	0.64
Meperidine	2.1	2.0	0.06 (0.022)	0.06 (0.022)	-0.14 (0.03)	-0.11 (0.03)	0.28	0.98	0.48	0.67
Hydromorphone	1.6	1.0	0.09 (0.01)	0.05 (0.01)	0.05 (0.01)	0.001 (0.001)	0.89	<0.001	<0.001	<0.001
Oxymorphone	1.0	0.9	0.057 (0.004)	0.060 (0.004)	0.008 (0.005)	0.008 (0.005)	0.90	0.64	0.95	0.81
Fentanyl	0.4	0.4	0.001 (0.001)	0.005 (0.001)	-0.003 (0.001)	-0.004 (0.001)	0.35	0.001	0.45	0.002

Dependent variables are all measured in milligrams per 1,000 people. All regressions include separate splines for Florida and for the rest of the US. Standard errors are in parentheses and values are calculated assuming regression errors are correlated at the state level. Each regression has quarterly data for 50 states and DC from 2004 through 2014 for a total of 2,244 observations. Other control variables are state fixed-effects, month effects, the fraction of the population that is ≤19 years of age, 20-34 years of age, 35-40 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 B3: How Distance to Florida Affects Estimated Impact of Reformulation on Heroin Death Rates

Covariates	Distance in Miles (thousands)		Driving Time (10s of hours)	
	All States	Drop Alaska	All States	Drop Alaska
A: Linear distance measure				
Trend before	0.0008 (0.0009)	0.0007 (0.0009)	0.0008 (0.0009)	0.0007 (0.0009)
Trend before * distance	0.0000 (0.0002)	0.0001 (0.0002)	0.0001 (0.0001)	0.0001 (0.0002)
Trend break	0.0033 (0.0015)	0.0036 (0.0016)	0.0033 (0.0015)	0.0035 (0.0015)
Trend break * distance	-0.0006 (0.0009)	-0.0008 (0.0010)	-0.0004 (0.0006)	-0.0005 (0.0006)
B: 1 / distance				
Trend before	0.0013 (0.0010)	0.0015 (0.0010)	0.0016 (0.0010)	0.0016 (0.0010)
Trend before * distance	-0.0003 (0.0003)	-0.0004 (0.0004)	-0.0007 (0.0005)	-0.0007 (0.0005)
Trend break	0.0024 (0.0017)	0.0023 (0.0017)	0.0022 (0.0017)	0.0022 (0.0017)
Trend break * distance	0.0001 (0.0018)	0.0003 (0.0019)	0.0004 (0.0026)	0.0005 (0.0026)

Dependent variable is heroin deaths per 100,000 people in the state and month. Standard errors are in parentheses and values are calculated assuming regression errors are correlated at the state level. Each regression has monthly data for 49 states and DC from 2004 through 2012 for a total of 5,292 observations; columns that drop Alaska have 5,184 observations. Distance measure in the first two columns is thousands of miles between the centroid of the state and the centroid of Florida; in the second two columns, it is tens of hours of driving time between the centroids. Panel A shows results when the distance measure is interacted with the trend and trend break variables; Panel B shows results when one over the distance measure is interacted with the trend and trend break variables. Other control variables are state fixed-effects, month effects, the fraction of the population that is ≤ 19 years of age, 20-34 years of age, 35-50 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 5: OLS Estimates of Impact of Reformulation on the Trends in Heroin Death Rates, 2004-2012

Covariates	Low heroin/ Not exposed to pill mills	Low heroin/ Exposed to pill mills	High heroin/ Not exposed to pill mills	High heroin/ Exposed to pill mills
Trend before	0.0012 (0.0007)	0.0016 (0.0007)	0.0025 (0.0008)	0.0023 (0.0008)
Trend after	0.0023 (0.0007)	0.0037 (0.0011)	0.0046 (0.0009)	0.0070 (0.0017)
Diff: after-before	0.0012 (0.0005)	0.0021 (0.0010)	0.0019 (0.0010)	0.0047 (0.0017)
Diff: exposed-not exposed		0.0009 (0.0010)		0.0028 (0.0020)

Dependent variable is the heroin death rate. Standard errors are in parentheses and values are calculated assuming regression errors are correlated at the state level. Indicator for exposure to Florida's pill mills based on hospital admissions in Florida as described in text. Each regression has monthly data for 50 states and Washington D.C. for the years specified in the column headings. Other control variables are state fixed-effects, month effects, the fraction of the population that is ≤ 19 years of age, 20-34 years of age, 35-50 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.