How the Reformulation of OxyContin Ignited the Heroin Epidemic

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May 3, 2017

Abstract

We examine the recent rise in heroin poisoning deaths and attribute the increase to the reformulation of OxyContin, an extended-release painkiller that was at the center of the rise in opioid abuse. Prior to the reformulation, recreational users could easily crush the drug to create a powder that could be snorted or liquefied and injected. This allowed users to circumvent the extended-release mechanism and gain access to a high dose of the drug all at once. Without notice, an abuse-deterrent version of OxyContin replaced the old formulation in early August, 2010 making it difficult to abuse the drug in this way. In the first part of the paper, we use national time series data at the monthly and quarterly level and long-standing techniques from the macro literature to date regime changes. These results show that OxyContin use and deaths stop rising and/or decline in August 2010 while heroin use and deaths begin to climb the following month. We then use the pre-reform specifics of heroin markets and OxyContin use to break states up into areas with high and low substitution possibilities. The shift to heroin would be easier and more pronounced in areas with greater access to heroin or areas with a greater use of opioids in the pre-reform period. Using monthly data on mortality rates at the state level for heroin and opioid deaths, we find that high substitution states had a much larger increase in heroin death rates. However, nationally, the reformulation generated no change in total heroin and opioids mortality, though we do find that areas with less access to heroin see slight reductions in combined heroin and opioids mortality. This suggests that the FDA's push for more abuse-deterrent formulations of other opioids might have limited impact when there are readily-available alternatives and emphasizes the importance of considering consumers' equilibrium responses to interventions that affect the full price of opioids.

I.   Introduction

Over the past 15 years, deaths from drug overdoses have steadily increased and are now at epidemic levels. Figure 1 shows the national death rate (deaths/100,000) for drug poisonings from 1999 to 2014. Over that time period, the drug poisoning death rate doubled.[1] The bottom two lines in the graph illustrate the death rates for opioids and heroin (together) poisonings and all other drugs. These figures show that the rise in poisonings is driven primarily by opioid and heroin deaths[2] with these drugs representing 75 percent of the overall increase in deaths from drug poisonings.[3]

Opioids are narcotic pain relievers and are available only by prescription. When used as directed, they are an important component of fighting acute (e.g., post-surgery or cancer) or 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 in chronic pain. The efforts changed prescribing practices considerably and between 1991 and 2013, there was a three-fold increase in opioid prescriptions.[4] 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 Figure 2, we report time series, now familiar to many, for heroin and opioid death rates as well as the combined death rate for either. Between 1999 and 2009, opioid death rates were rising rapidly but heroin death rates were low and increasing slowly. In 2010, this changed; over the next four years, heroin death rates increased by a factor of four while opioid death rates remained fairly flat.

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[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).

[2] Heroin deaths are identified by the ICD10 code T40.1 while opioid deaths are T40.2, T40.3 and T40.4.

[3] Throughout the rest of the paper we will use opioid (heroin) poisoning mortality and the opioid (heroin) death rate synonymously.

[4] https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse

In this paper, we argue that the rapid rise in the heroin death rate since 2010 is 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 Oxycodone. 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 that made it much more difficult to extract the full dose of Oxycodone all at once. 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; Larochelle et al., 2015; Coplan et al., 2016; Chilcoat et al., 2016). Most of this work uses interrupted time-series analysis with annual or quarterly data and suggests that outcomes such as OxyContin prescriptions, deaths from opioids, fatalities reported to the makers of OxyContin, calls to poison control centers for opioids, and entrance into opioid treatment programs all have fallen since the third quarter of 2010. At the same time, 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 2 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 (Quandt, 1960; Andrews, 1993; Hansen, 2001), pinpoints the timing of the changes to the reformulation of OxyContin. The results of these analyses are illustrated in Figure 3 where the solid line displays the national, monthly heroin death rate. The grey dotted line shows the month that the structural break analysis chose as the month in which the trend break occurred. For the heroin death rate, this is the month immediately following the OxyContin reformulation. A number of national time series including shipments of oxycodone (an imperfect measure of consumption), prescriptions

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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 precisely 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. 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 (a lower shadow price) and markets with higher rates of pre-reform 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 heroin death rate and the latter with whether a state is above or below the median pre-reformulation 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, in differences-in-differences specifications (states below the median in both of our risk factors are the least treated group), 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 4 where we record the monthly heroin mortality rate from 2004 through 2014 for the four groups of states.[5] Note that pre-reform trends in heroin death rates are quite similar across the groups of states but in the 4.5 years after 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.[6] The results from these models suggest that across all state groups, opioid death rates were increasing rapidly before reformulation but were

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[5] There are gaps in the series because months in which there were fewer than 10 heroin deaths have been suppressed per CDC reporting requirements.

[6] 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.

flat afterwards. When we combine heroin and opioid deaths together, we find that states that were at lower risk of substitution saw declines in total mortality rates from heroin and opioids, but no change for states at the highest risk of substitution. Thus it appears that the intent behind the abuse-deterrent reformulation of OxyContin was completely undone in high substitution risk states 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 abuse-deterrent formulations (ADFs) of drugs. Currently, there are seven drugs on the market with ADFs, five of them opioids.[7] 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). This past year, 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.

We also present evidence that a number of alternative explanations do not appear capable of generating the patterns found in the data. First, we show that changes in the purity of heroin, changes in the quality-adjusted price of heroin, and changes in the price of Oxycodone are unlikely to explain the increase in heroin deaths and reductions in Oxycodone use. Second, we examine other leading hypotheses—the rise of the potent synthetic opioid fentanyl, the adoption of prescription drug monitoring programs, and changes to

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[7] http://www.fda.gov/newsevents/newsroom/factsheets/ucm514939.htm
[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-opiod-epidemic-with-abuse-deterrent-formulation-legislation/

the legal opioid market in Florida—and find that the timing of those events is not consistent with them being responsible for the national changes in heroin death rates.

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 over time, the authors hypothesize 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 construct a pre-reformulation measure of OxyContin abuse rates at the state level from the NSDUH 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 accurately date the changes in the heroin and opioid markets to the exact month in which the reformulation occurred—this makes it much more difficult to construct plausible alternative mechanisms unrelated to the reformulation. 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.

In the next section, we provide some background on the extent of the opioid and heroin crises, 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 with a lower shadow price of heroin or a higher 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 the Opioid and Heroin Crises, OxyContin, and the Reformulation

A. The Extent of the Opioid and Heroin Crises

As noted in Figure 2, opioid death rates have increased by a factor of four from 1999 to 2014. Since 2010, heroin deaths have increased dramatically as well. In the next series of figures, we show that the combined rise in opioid and heroin poisonings is concentrated more heavily in certain groups. In Figure 5a, we report the opioid and heroin death rate (deaths per 100,000) from 1999 to 2014 for five racial-ethnic groups: Non-Hispanic Native Americans/Alaskan Natives (NA/AN), White non-Hispanics, non-Hispanic African Americans, non-Hispanic Asians, and Hispanics. The death rates for the first three of these groups were essentially the same in 1999 but by 2014, the rates for non-Hispanic whites and NA/AN's increased by a factor of 5. Given the large difference in size between these groups, we will focus on white non-Hispanics in the next series of graphs. In Figure 5b, we graph the opioid/heroin death rates for white non-Hispanics for six age groups (15-24, 25-34, 35-44, 45-54, and 65-74). The increases are dramatically higher for those aged 24-54. For non-Hispanic whites in this age range, we graph the opioid/heroin death rates for males and females. As seen in Figure 5c, the death rate increased by a factor of more than 4 for males aged 25-54 and more than 6 for females in the same age range. Since the level for females was much lower at the start, rates were still considerably higher for males in 2014 than females.

Rising drug abuse rates for white, non-Hispanics has dramatically altered the time series of aggregate mortality rates for these groups. The role that rising drug overdose death rates have played in aggregate mortality rates for whites was first noted by Case and Deaton (2015) who showed that for white non-Hispanics aged 45-54, aggregate mortality has increased since 1999 with the rise being caused primarily by drug poisonings, suicides and liver damage. We replicate the basics of the Case and Deaton results but note that a large fraction of the increase in the deaths in their group of interest can be explained by rising opioid/heroin death rates alone, and the rising aggregate rates are present for non-Hispanic whites in other age groups as well.

In Figure 6a, we report the aggregate all-cause mortality rates (left axis) among those aged 25-34 for non-Hispanic whites and all other racial/ethnic groups, which we refer to as "all others." The graphs for

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these groups are the solid lines with the lighter line being for "all others." Note that for all others, aggregate rates have declined by 20 percent from 123/100,000 to 99/100,000. In contrast, rates for non-Hispanic whites over this time have increased by 25 percent, rising from 91/100,000 to 115/100,000, a staggering increase from an historical perspective.[11] On the right axis, we report mortality rates from opioid/heroin deaths only, which are shown as a dotted lined of the same color as the corresponding all-cause number. Note that in this graph, the left and right-hand-side vertical axes are on the same scale. For both groups we see a rise in opioid/heroin poisoning death rates but the increase for non-Hispanic whites is much larger. The increase in poisonings in this group represents 83 percent of the aggregate increase in mortality for non-Hispanic whites in this age group.

In Figures 6b and 6c, we produce the same figures for those aged 35-44 and 45-54, respectively. Among those 35-44, non-Hispanic white mortality increased by just under 5 percent but the same rate for the all other group declined by 35 percent. Opioid/heroin poisoning death rates for non-Hispanic whites increased by a factor of four and this increase represents 196 percent of the increase in all-cause mortality. For those aged 45-54 in Figure 6b, the decline in mortality for all others is 30 percent while all-cause mortality for non-Hispanic whites increased by 10 percent and the rise in opioid/heroin poisonings explains about half of this increase.

In the following subsection, we discuss changes to the opioid market, with emphasis on OxyContin, that are thought to have led to the increase in opioid deaths outlined above.

B.   **The Rise of OxyContin**

OxyContin is a name-brand opioid pain killer marketed by Purdue Pharma.[12] The active ingredient in OxyContin is Oxycodone, an opioid that has been in clinical use since 1917 (Kalso, 2005) and is the active ingredient in such pharmaceuticals as Percodan (Oxycodone and aspirin) and Percocet (Oxycodone and Tylenol). OxyContin is an extended-release formulation that allows for up to 12 hours of pain relief and

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[11] National vital statistics data indicate that for whites aged 25-34, mortality rates declined from 148.3 in 1950 to 96.4 in 1998. https://www.cdc.gov/nchs/nvss/mortality/hist290.htm
[12] We will refer to OxyContin ER simply as OxyContin for the duration of the paper.

hence there is typically a high milligram (mg) content of Oxycodone in the pills.[13] Since its release in 1996, OxyContin has been one of the most successful pharmaceuticals of all time with worldwide sales totaling $35 billion.[14]

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. Given the limited use of opioids, pain from chronic conditions often went untreated. 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 introduced the notion that pain is the "5th vital sign." Campbell (1995) argued that "Quality care means pain is measured. Quality of care means pain is treated." 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). The standards focused on the patient's rights to appropriate pain care and the standards encouraged hospitals to make pain evaluation a priority and introduce pain scales. The Joint Committee statement also urged that patients should be taught that pain management is a part of treatment and that the quality of care should be measured in part by how well organizations treat pain. The Centers for Medicare and Medicaid have been fielding the 32-question Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) among Medicare patients since 2006. Three questions on the survey ask 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 HCAHPS survey have encouraged "dangerous pain control practices, the endpoint of which is often the inappropriate provision of

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[13] According to the Physicians' Desk Reference online, Percocet 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
[14] http://www.latimes.com/projects/la-me-oxycontin-part3/

opioids."[15,16] During this time, state medical boards and state laws started to relax regulations about prescribing opioids to non-cancer patients (Alexander, Frattaroli, and Gielen, 2015). It is difficult to say what impact each of these changes had on prescribing practices, but it is the case that the environment was such that prescribing opioids for those in chronic pain was becoming more acceptable as a medical practice.

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 addition (Van Zee, 2009).[17]

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 increased from 76 to 211 million with Oxycodone-based products representing roughly a quarter of all of these prescriptions in the later years.[18]

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[15] http://www.supportprop.org/wp-content/uploads/2014/12/TJC-Letter-Final-04-11-16.pdf

[16] 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

[17] In 2007, Purdue Pharma agreed to pay $600 million in fines in Federal civil and criminal cases. They 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

[18] https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse

C.   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, 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 abuse-deterrent formulation 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.[19] A randomized controlled trial showed that the abuse-deterrent formulation, even when crushed or chewed, produced far less of a high than a crushed or chewed tablet of the old OxyContin formulation and when crushed, took hours longer to be absorbed into the body (Gudin et al., 2015). Purdue Pharma received FDA approval for their abuse-deterrent formulation 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).

The movement to an abuse-deterrent formulation made OxyContin less desirable for recreational use. A large literature in the medical and public health fields, mostly using interrupted time series designs, has shown that all measures of use and abuse, such as prescriptions, mortality, visits to emergency rooms, calls to poison control centers and entrance into treatment programs fall after August of 2010 (Severtson et al., 2012; Severtson et al., 2013; Butler et al., 2013; Sessler et al., 2014; Havens et al., 2014; Dart et al., 2015; Larochelle et al., 2015; Coplan et al., 2016; Chilcoat et al., 2016).

Unfortunately, at the time of the reformulation, there was a readily-available 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

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[19] http://www.nytimes.com/2011/06/16/health/16oxy.html

the past 30 years, there has been an increasing supply of heroin from Mexico. Many of the Mexican suppliers compete for market share by offering higher quality heroin (Quinones, 2015) which has increased purity levels. Of confiscated heroin, 79 percent is now from Mexico (DEA, 2016). When price is calculated per pure gram, this high quality has pushed the price down to very low levels. In Figure 7, the black line (left axis) shows the average purity level of heroin from the Drug Enforcement Administration (DEA) over the 1980 - 2012 period. In the same graph, the gray line (right axis) shows the average price per pure gram of heroin, also from the same source.

Between 1980 and the late 1990s, the purity level of heroin increased by a factor of four while the price of heroin fell by over 80 percent. The DEA notes that Mexican 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. 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." The entry into heroin is now much easier because of the purity 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 the 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 move 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, among heroin users, the vast majority started using pain medicine before switching to heroin. Using the same survey 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 empirical macroeconomics 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) $Y_t = \gamma + t_c(1 - A_t^c)\beta_1 + t_c^2(1 - A_t^c)\beta_2 + t_c A_t^c \alpha_1 + t_c^2 A_t^c \alpha_2 + \varepsilon_t$

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 minimizes the sum of squared errors (SSE). In most series, the break visually occurs between 2009 and 2011 so we allow c to vary between the start of 2008 to the end of 2012. Each of the figures that follows plots the time-series, the quadratic spline fit to the time-series, and the time period that is most likely to have had a trend break.

Figure 8a shows monthly data on Oxycodone prescriptions per 1,000 subscribers in the Truven Marketscan Research Database. This is a database of individual-level claims for inpatient, outpatient, and prescription drug use from over 350 payers. By the end of the period in our analysis, the data had claims for roughly 37 million covered clients per month.[20] We use data for the 2006 through 2013 period. Oxycodone prescriptions per 1,000 subscribers are rising between January, 2006 and the beginning of 2010. However, the growth in prescriptions levels off in August, 2010. In Table 1, we present information about the sample and the results from estimating equation (1). The data suggest that August, 2010 is the most likely month for a trend break in Oxycodone prescriptions. 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.[21]

Because the Marketscan data only represent the prescription drug use of a subset of the population, we run the same analysis using data from the Drug Enforcement Agency's (DEA) Automation of Reports and Consolidated Orders System (ARCOS). Within this system, drug manufacturers and distributers report controlled substance transactions from manufactures to points of sale or distribution to the DEA.[22] Many of the drugs tracked in the ARCOS system are opioids and we use data from Report 3 which 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.[23] These data tell a similar story to the Marketscan data. As seen in Figure 8b, Oxycodone shipments per 1,000 people were rising in the 2000s, but suddenly stopped and actually began to fall in the quarter in which the reformulated OxyContin hit the market. The second column of Table 1 shows that there is very strong statistical evidence of a trend break in the third quarter of 2010.

Although the data are considerably noisier, we also test whether there was a trend break in the percentage of individuals in the National Survey on Drug Use and Health who reported using pain

[20] Information about Marketscan data can be found at http://truvenhealth.com/your-healthcare-focus/analytic-research/Marketscan-research-databases
[21] The relevant critical values for the F-test are provided in Andrews (1993, 2003).
[22] More information about the ARCOS data can be found at https://www.deadiversion.usdoj.gov/arcos/retail_drug_summary/2015/index.html
[23] 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 smoothly across periods until the next period.

medications recreationally in the past thirty days. Figure 8c 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 Table 1, we lack the statistical power to 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 3 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 very quickly in 2010, we are unaware of any other studies that date the start of the rise so precisely. The fifth column of Table 1 shows strong evidence of a break in trend and that it is most likely to have occurred in September of 2010.

Figure 8d 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. The final column of 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.

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 available (i.e. a lower shadow price) 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

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first outline each measure individually and proceed to demonstrate graphically that there appear to be greater

shifts to heroin after the reformulation in areas where we would expect greater substitution. We then

aggregate the measures and estimate regression models that allow us to exploit the panel nature of our data,

removing state fixed effects and the impacts of a number of important demographic factors.

Our first measure is intended to capture the extent of Oxycodone use and 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

per 1,000 people shipped to states in 2008 and 2009, the two years preceding the reformulation. This

measure relies on areas where there is high Oxycodone use also having high abuse. Figure 9 provides

evidence that this is likely true. It plots the 2008-2009 opioid mortality rate for each state against the number

of milligrams of Oxycodone shipped to the state per 1,000 people in 2008 and 2009. There is a clear positive

association. In the corresponding regression, the shipments variable alone explains 25 percent of the

variation in opioid death rates.

Based upon the distribution of states' Oxycodone shipments per 1,000 people, we divide states into

two groups, those above the median and those below. As seen in Figure 10a, 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.[24] The two groups' heroin death rates track each other extremely well right up to the

reformulation. However, as soon as the reformulation occurs, the two groups immediately begin to diverge.

States with above median per-capita Oxycodone shipments saw their heroin death rates rise from just under

0.1 to more than 0.4; states with below median per-capita Oxycodone shipments 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, or shadow price, of using heroin. In areas

where it is very costly to find and purchase heroin, the reformulation is not likely to lead many people to

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[24] 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.

substitute towards heroin; in areas where there is an active heroin market, it is more likely that a person could find a dealer and begin to use heroin. The purchase of heroin occurs in an illegal market and hence the street price of the drug is but one aspect of the full price of consuming the drug. States with more lax enforcement, a greater number of suppliers, or less strict penalties for use, will all have lower shadow prices. These variables are of course difficult to measure so we must use proxies instead. Our measure of the shadow price of heroin is based on a state's heroin death rate in the two years preceding the reformulation, 2008 and 2009. High heroin death rates indicate greater availability of the drug—it likely easier to find and purchase heroin in an area where a high fraction of individuals are abusing the drug.

Death rates are an extreme outcome of abuse that could be affected by changes in underlying drug quality, both across states and over time. If the death rate is primarily driven by heroin's purity, then the pre-reformulation death rate will not be a useful measure for our purposes. To assess this concern, 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.[25] Figure 11 plots this measure of drug quality and shows that deaths per use of heroin were fairly steady in the pre-reformulation period. There is an uptick in heroin deaths per use starting in 2013 that the DEA (2016) suggests is due to suppliers mixing the drug with fentanyl, but this was not a problem in the pre-reformulation period; we will discuss this trend later in the paper. As a result, we will view heroin death rates as reflecting the underlying rate of heroin abuse.

We divide states into two categories according to their pre-reformulation heroin death rate. 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 10b 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, indicated with the vertical

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[25] 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 11 that the purity of heroin did not significantly change when OxyContin was reformulated.

line, 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 are graphed in Figure 4. Once the reformulation

occurs, every group experiences a noticeable increase in its heroin death rate with the greatest change

appearing to occur 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

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

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 Wonder Multiple Cause of Death database and range from January, 2004 through December of 2014 for all states and the District of Columbia. CDC Wonder 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 actual number of heroin deaths in each state and month, including those states and months in which there were fewer than 10. 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.[26]

The regression results with heroin death rates as the outcome of interest are shown in Panel A of Table 2. The first row presents the estimated trends for each of the four groups—each group gets its own column—prior to the reformulation. In all cases, the point estimates are positive, but quite small and nowhere near statistically distinguishable from zero. The trends after the reformulation are all positive and 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 and statistically significant at conventional levels. The point estimate for the high Oxy, high heroin death rate trend break is 0.0067. It would have taken these states only twelve months to have increased the death rate by the mean monthly heroin death rate before the reformulation (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. Based on this estimate, 0.0043, the high Oxy, high heroin group can account for more than 27 percent of the aggregate rise in the heroin death rate alone.

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[26] We linearly interpolate monthly population numbers from the annual SEER data.

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 2 present the same analysis seen in Panel A, but for opioid death rates as well as for deaths that involved opioids, heroin, or a combination 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, though only half of the estimates are statistically distinguishable from zero. In Panel C, the estimates do not provide strong evidence of a decline in the death rates from heroin and opioids.[27]

We do not want to overemphasize the exact magnitudes found in Table 2 because the final two years of our sample are potentially affected by the rise of fentanyl. Fentanyl, a synthetic opioid 50 times stronger than heroin, has been included in counterfeit Oxycodone pills and used to increase heroin's potency. Beginning in 2013, the DEA noted an increase in fentanyl related deaths (DEA, 2016) and has suggestive, but not definitive, evidence that the fentanyl used to lace heroin is distributed by the Mexican gangs selling heroin. Anecdotal evidence in the documentary *Death by Fentanyl* is consistent with the DEA's suggestions;[28] 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. Figure 12a shows that there was a stark increase in synthetic opioid deaths, including fentanyl, starting in the middle of 2013.[29] Because fentanyl is often used in conjunction with heroin or other opioids, it could be affecting our opioid or heroin deaths series. Figure 12b shows that of deaths that include a synthetic opioid, the fraction that also include heroin increases precipitously beginning in 2013.

To separate out the impacts of fentanyl from those of the reformulation, we estimate our previous specifications and exclude the data from 2013 forward. This approach is preferable to excluding all deaths that include 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

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[27] Because an individual's death can be classified as both an opioid death as well as a heroin death, the results in Panel C need not be the sum of the results from Panels A and B.
[28] http://interactive.fusion.net/death-by-fentanyl/
[29] This graph is produced from the CDC wonder data and reports deaths with a T40.4 code, the code for synthetic opioid poisonings.

grown the fastest could be more likely to have fentanyl-laced heroin because dealers might need to stretch their supply in the short run—our differences-in-differences estimates would be biased towards zero. The results from our regression analysis where the years 2013 and 2014 have been excluded are shown in Table 3. Qualitatively, the estimated impacts of the reformulation on heroin death rates and opioid death rates are very similar to what we found previously, though the former are slightly attenuated while the latter are slightly larger in magnitude.

The main result of accounting for the rise of fentanyl occurs for the combined heroin and opioid death rates. For every group except the high Oxy, high heroin group, we estimate negative and statistically significant breaks in trend. This suggests that in the absence of well-developed opioid and heroin markets, the reformulation would have reduced the combined heroin and opioid death rates. The point estimates indicate that the combined heroin and opioid death rates fell by approximately 10 percent per year in the low Oxy, low heroin and the low Oxy, high heroin states while the combined heroin and opioid death rates fell by nearly 17 percent per year with the reformulation. Thus even if heroin deaths rose somewhat in those areas, those increases were more than offset by reductions in opioid deaths. However, in areas that had high rates of Oxycodone shipments and high heroin death rates, there was no change in the growth of combined heroin and opioid deaths. In those states, consumers changed their behavior enough to completely undo the intended effects of the reformulation, at least as measured by death rates.

V. Other Influences on the Heroin Epidemic

There are a number of potential alternative explanations for the observed increase in heroin deaths. First, a reduction in the price of heroin or an increase in its purity could lead heroin death rates to rise. Figure 7, displayed previously, shows that prices for heroin have declined dramatically since the early 1980s. However, there has been very little decline since the early 2000s. There actually appears to be a slight increase in the purity-adjusted prices in 2010 which, ceteris paribus, would tend to reduce heroin deaths. The DEA data also suggest that heroin's purity did not change in a way consistent with the increase in heroin deaths. Figure 7 shows that the average purity of heroin in the United States began falling in the early 2000s and has

declined fairly regularly. Although there is a slight dip in 2010, the recovery in 2011 suggests that changes in quality were not responsible for the steady climb in heroin death rates. As seen in the Figure 11, heroin deaths per thousand days of use, does not seem to have changed in August, 2010. This alternative measure of heroin's purity suggests that quality was very similar before and after the reformulation, at least until fentanyl's rise.

Another potentially important change in recent years has been the adoption of state-level prescription drug monitoring programs (PDMP). A PDMP is essentially a database 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, 2016). 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.

Although the average price and purity of heroin does not appear to be able to explain the observed changes, a large increase in the price of Oxycodone in August, 2010 could. Such a price increase would likely have led to a reduction in Oxycodone use and substitution to heroin. We can address this possibility by examining drug prices in the Marketscan data. Figure 13 shows the average price per kilogram of Oxycodone (left axis) as well as the average out-of-pocket price per kilogram of Oxycodone (right axis) on a monthly basis.[30] It is clear from the figure that neither the out-of-pocket nor the price inclusive of what the insurer

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[30] The out-of-pocket price is the price that the consumer must pay for the prescription when it is purchased. The price series in Figure 13 includes both the consumer's out-of-pocket payment as well as the payment made by the insurer.

pays rises sharply at the same time that OxyContin was reformulated. As such, it is unlikely that movements in the price of Oxycodone were the main driver of the observed changes in the heroin and opioid markets.

A final alternative explanation for our results is that the crackdown on Florida's "pill mills" reduced access to Oxycodone and may have encouraged the shift to heroin. 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 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), Kennedy-Hendricks et al. (2016), Chang et

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The out-of-pocket price series has a sawtooth pattern because of annual deductibles and other cost-sharing features of private drug coverage.

[31] http://myfloridalegal.com/pages.nsf/Main/AA7AAF5CAA22638D8525791B006A30C8

[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

[34] https://www.youtube.com/watch?v=wGZEvXNqzkM

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.

It is easy to generate suggestive evidence that the pill mill crackdown worked. The papers listed in the previous paragraph are mostly versions of interrupted time series analysis showing that opioid poisoning deaths in Florida started to fall after 2010. In Figure 14a, 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.[35]

We investigate the pill mill hypothesis but find it insufficient to explain the timing of the national shift to heroin for a few reasons. 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 4. 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.[36] 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.[37] The PMDP however does not go into effect when scheduled for a variety of reasons. First, there were insufficient funds for the project.[38] Second, in December of 2010, incoming governor Rick Scott fires all of the full-time

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[35] 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. Although the break is much greater for Florida than the rest of the United States (-10.7 and -0.93 respectively), both are highly statistically significant with t-statistics greater than 10.

[36] http://www.tampabay.com/news/politics/stateroundup/new-law-may-crack-down-on-florida-illegal-prescription-drug-market/1011527

[37] http://www.tampabay.com/news/health/prescription-pain-pill-monitoring-limited-by-delay-in-reporting/1110710. Buchmueller and Carey (2016) 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.

[38] http://www.tampabay.com/features/humaninterest/pill-mills-demise-brings-relief-to-neighbors/1098705

employees of the governor's Office of Drug Control, the agency that was responsible for the PDMP.[39]   In

January of 2011, the governor-elect shuts down the Office of Drug Control and, using and administrative

orders, freezes "all new regulations" which shelve the new standards for pain clinics.[40]

In March of 2010, the Federal Drug Enforcement (DEA) executes raids on the largest pain clinics in

Florida.[41],[42] In October of 2010, various components of the law passed in 2009 that established the 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. [43], [44]

In July of 2011, Governor Scott signed into law HB 7095.[45] 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 September[46] and on October 17th, physicians can

register on the PMDP for the first time.[47]

The text above suggests that there were a number of changes in legislation over a two-year period from

2009 to late 2011 designed to reduce the impact of pill mills. 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."[48]

A second reason the pill mill crackdown does not seem likely to explain the time series pattern in

heroin use is that it is not clear the pill mill crackdown had much of an impact. Customers of pill mills could

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[39] http://www.tampabay.com/news/politics/gubernatorial/rick-scott-moves-to-eliminate-floridas-office-of-drug-control/1141510
[40] Temple (2015).
[41] http://abcnews.go.com/Business/PersonalFinance/feds-raid-alleged-pill-mills-florida/story?id=10022791
[42] http://www.mcclatchydc.com/news/crime/article24575644.html#!
[43] http://www.gray-robinson.com/Elerts/03_05_12_Health_Elert_Florida_Legislation_Regarding_Pain_Management_Clinics.pdf
[44] http://www.palmbeachpost.com/news/news/crime-law/32-new-florida-laws-take-effect-today/nMBP2/
[45] http://www.flgov.com/governor-rick-scott-signs-pill-mill-bill-that-will-be-a-model-for-the-nation/
[46] http://www.huffingtonpost.com/entry/florida-legislation-opioid-prescriptions_us_55d244a3e4b055a6dab11c23
[47] http://www.palmbeachpost.com/news/news/state-regional/law-requiring-florida-pharmacists-to-send-drug-inf/nLxZy/
[48] http://www.nytimes.com/2011/09/01/us/01drugs.html

get prescriptions for many drugs, not just OxyContin. In Figures 14b through 14h, we report the milligrams of shipments per 1,000 people for Florida and the rest of the US for seven other pain killers: hydrocodone, morphine, codeine, pentobarbytal, 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. More importantly, there is no sharp decrease in drug use for *any* of these seven drugs. In fact, two drugs (hydromorphone and oxymorphone) show sharp increases soon after the reformulation of OxyContin. More telling however is that the time series patterns of shipments for these seven other drugs look very similar to what is happening in the rest of the US.

Using the 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 5. Each row is the result 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

A third reason that pill mills seem unlikely to be driving the national changes in heroin deaths is that states that appear to have been much less exposed to the Florida pill mills still have large increases in their heroin death rates immediately following the reformulation. We take two approaches to estimating how exposed a state was to Florida's pill mills. First, we use distance from Florida as a proxy for whether or not a state was affected by Florida's pill mills. We augment our standard regression specification, interacting

distance from Florida with each section of the spline, and test whether states that are further away from Florida have statistically different breaks in their heroin death rate trends. Table 6 presents the pre-reformulation trend, the break in trend, and each of those terms interacted with a distance measure. States further from Florida were not on systematically different trends prior to the reformulation and there is no discernible difference in trend breaks for states further away from Florida. These findings are consistent 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.

Our second approach is based on anecdotal evidence from *The OxyContin Express* which suggests that individuals who traveled to Florida to obtain opioids for distribution in their home states were also using opioids. Using the universe of emergency department and hospital admissions in Florida from 2007 through the second quarter of 2010, for each state of residence, we calculate the admissions per capita for people aged 18-64 in Florida due to opioids (labeled as OPCs). We then calculate the fraction of non-opioid per capita admissions for the same group (NOPC$_s$), then 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. Interstate 75 (I-75) travels from south east Florida, to the Gulf coast, then through the center of the state and north through Georgia, Tennessee, Kentucky, Ohio, Michigan and ends at The Canadian border in Sault St Marie. This interstate is commonly known as the Oxy Express as those using the Florida Pill Mills frequently use this interstate to travel to and from Florida. Our procedure identifies all states served by I-75 as in the top third, and five states contiguous to states served by I-75 (Alabama, Indiana, North Carolina, West Virginia, Pennylvania), plus six other states (Rhode Island, Maine, New Jersey, Maryland, Mississippi and New York). As a reality check, we include NO states west of the Mississippi as being served by Florida Pill Mills.

In Figure 15, we graph the monthly heroin mortality for the one-third of states that are likely users of Florida Pill Mills as a supplier of opioids (black line) and all other states (grey line). The time trend for both series is very similar with both showing 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

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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. It is clear from the graph that the closing of pill mills have changed the trajectory in October 2011 so

the reduction in supply in opioids had an impact of also encouraging heroin use. That said, the initial impetus

for the increase in heroin use occurs in both series in August of 2010 – when the reformulaiton of OxtContin

occurred.

And finally, it is unlikely that changes to pill mills are driving the results in the Marketscan data. In

part to avoid detection, pill mills were run as cash-only businesses (Miller, 2015; Norton, 2016). As a result,

prescriptions filled at a pill mill would not show up in databases of insurers' claims. Thus, the observed

change in opioid prescribing in the Marketscan data must have come from some other source, in our view,

from the reformulation of OxyContin. Taken as a whole, our evidence suggests that while these other

changes to the opioid or heroin markets could have had important effects, they are not capable of explaining

the increase in heroin deaths that began towards the end of 2010.

VI. Conclusion

The dramatic increase in heroin deaths since 2010 and the impacts of the OxyContin reformulation

on outcomes related to opioid abuse have been studied thoroughly, but the links between these events have

largely been circumstantial. We provide quantitative evidence that the switch to the abuse-deterrent

formulation of OxyContin in August of 2010 led to the increase in the heroin death rate. Moreover, 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.

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. This provides an important counterpoint to the push for the development of

abuse-deterrent formulation 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.

The economic costs of the heroin and opioid abuse crisis are high. These costs include increased medical care use, worker absenteeism, lost productivity, the direct costs of police enforcement and interdiction, and of course, the lost earnings due to mortality. Therefore, a formal cost-benefit of ADFs in this instance would need to take into consideration these other factors, something we do not do in this paper. There are clearly some benefits of ADFs. As we noted above, about 80 percent of heroin users moved from pain medicine abuse to heroin but it is the case that a small minority of pain medicine users switch to heroin in any given period. At the end of our sample period, there are about ten times as many abusers of pain medicine as heroin users. Looking at Figure 8c, there are fewer opioid abusers now after the reformulation of OxyContin and given the small number of heroin users in aggregate, it is the case that the total number of opioid or heroin abusers is most likely lower now than before. That said, the costs of the opioid crisis seem to be driven primarily by the costs associated with mortality. Inocencio et al. (2013) put the total costs at $20.4 billion in 2011 dollars, but 89 percent of these costs, more than $18 billion, are due to lost earnings from higher mortality. Although we do not do a formal cost-benefit analysis, the fact is that Purdue Pharma's abuse-deterrent formulation of OxyContin was unable to affect the vast majority of the crisis's costs.

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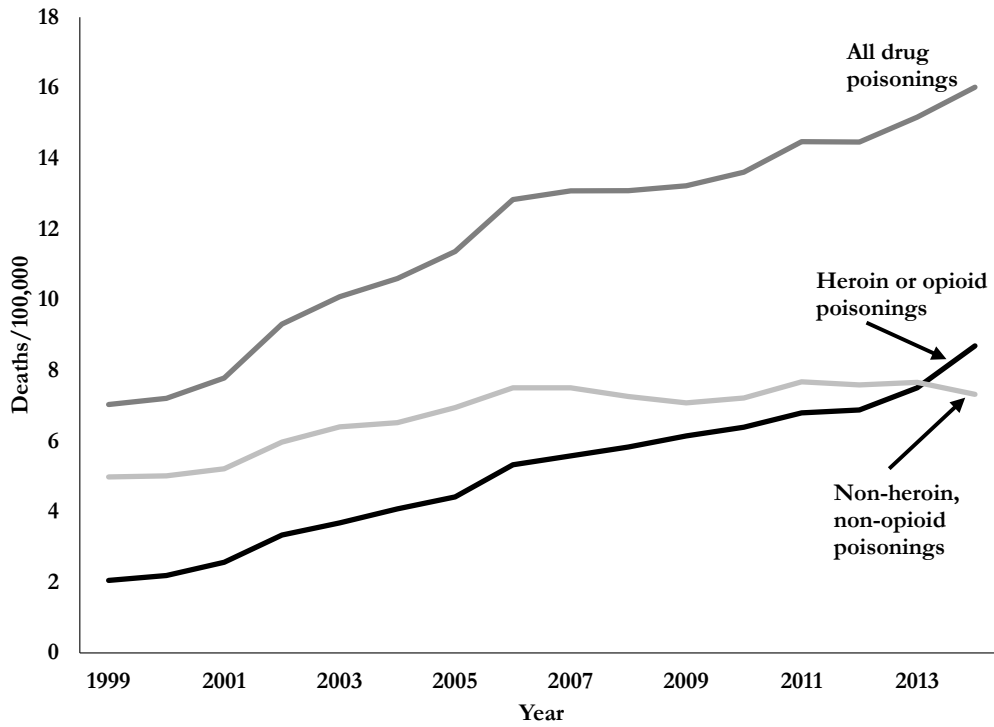
Figure 1: Drug Poisoning Mortality Rate, 1999-2014
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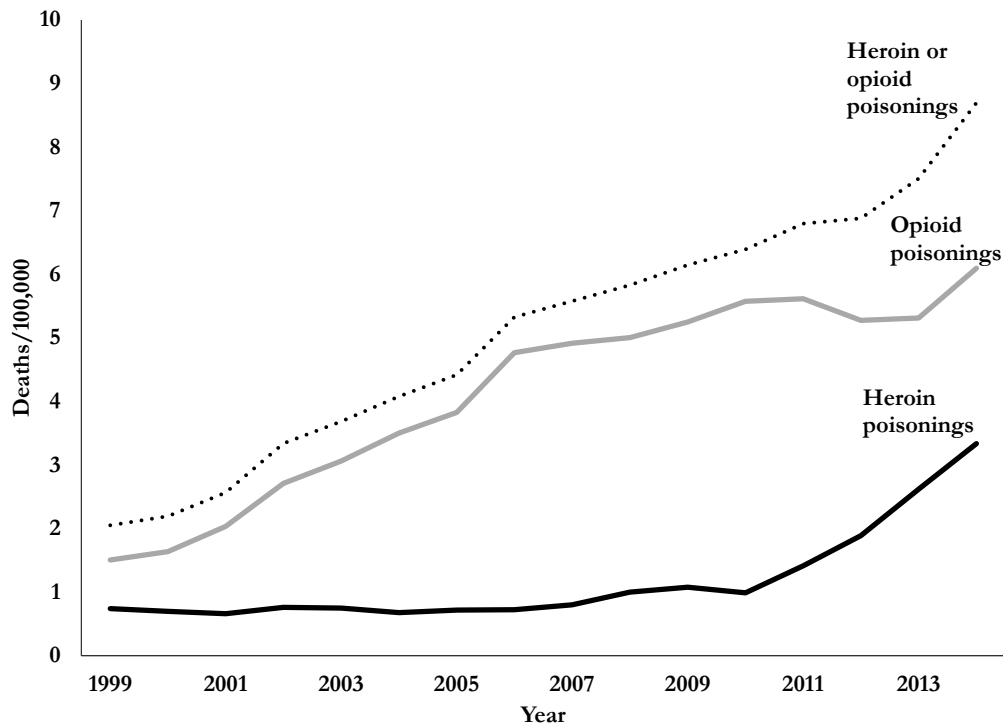
Figure 2: Opioid and Heroin Drug Poisoning Mortality Rate, 1999-2014
CDC Wonder Multiple Cause of Death Data

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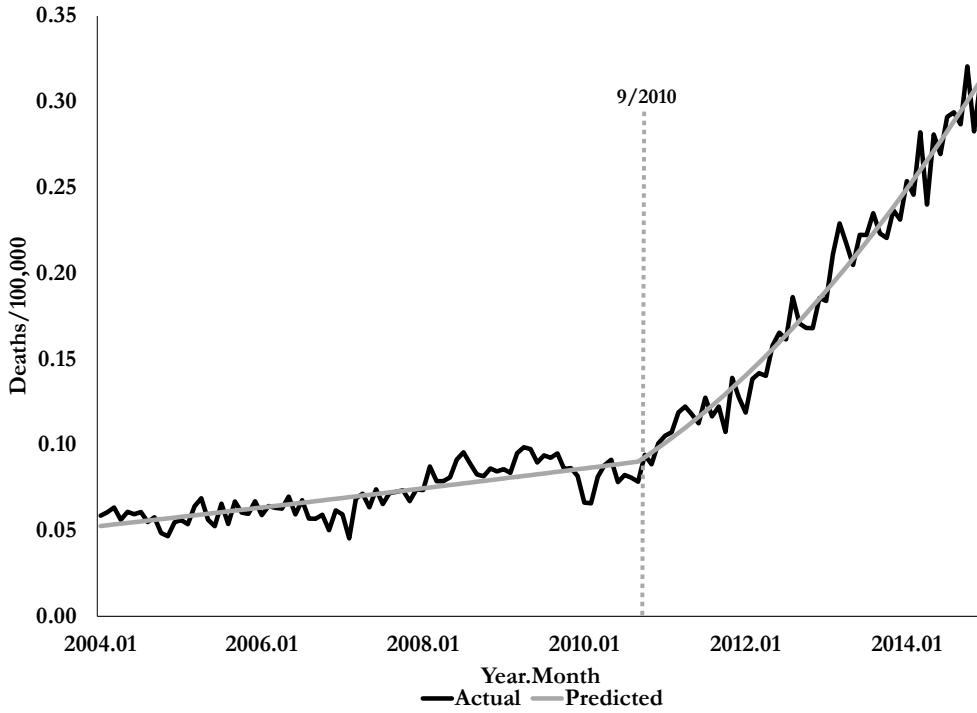
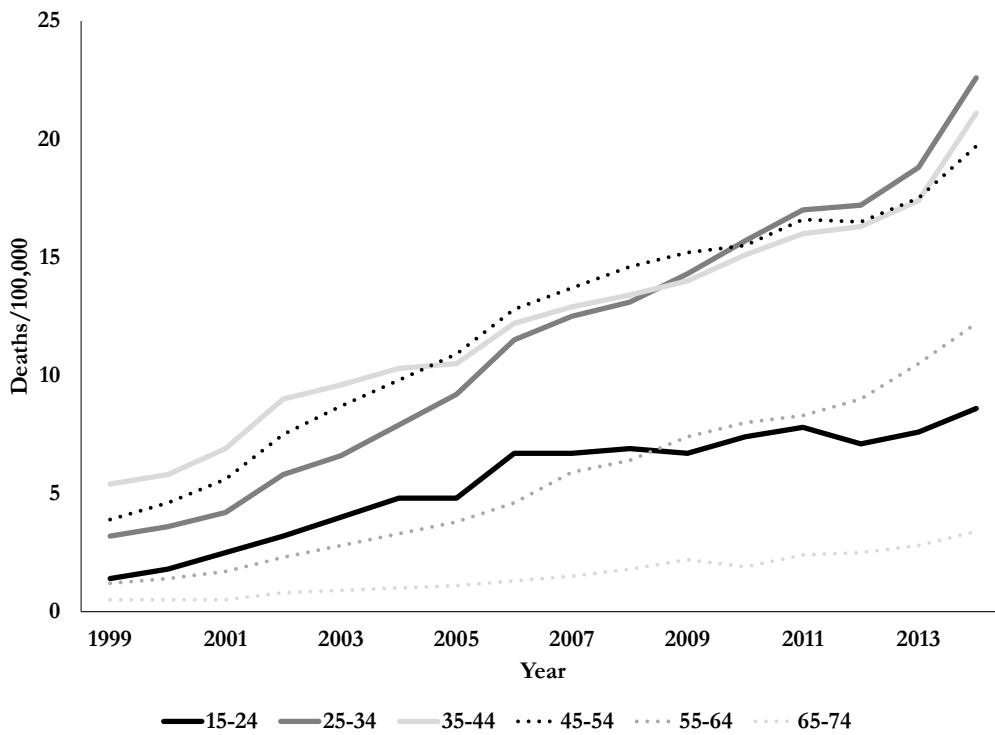Figure 3: Monthly Heroin Poisoning Mortality Rate, 2004.01 − 2014.12,
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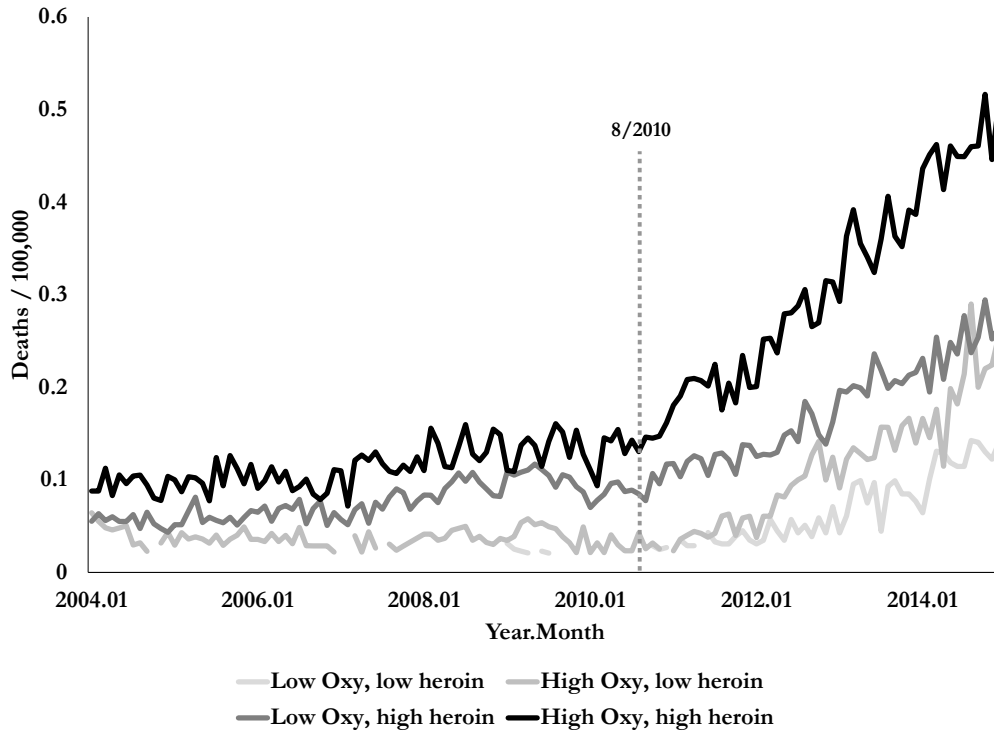
Figure 4: Monthly Heroin Poisoning Mortality Rate, 2004.01 − 2014.12, by State Substitution Risk
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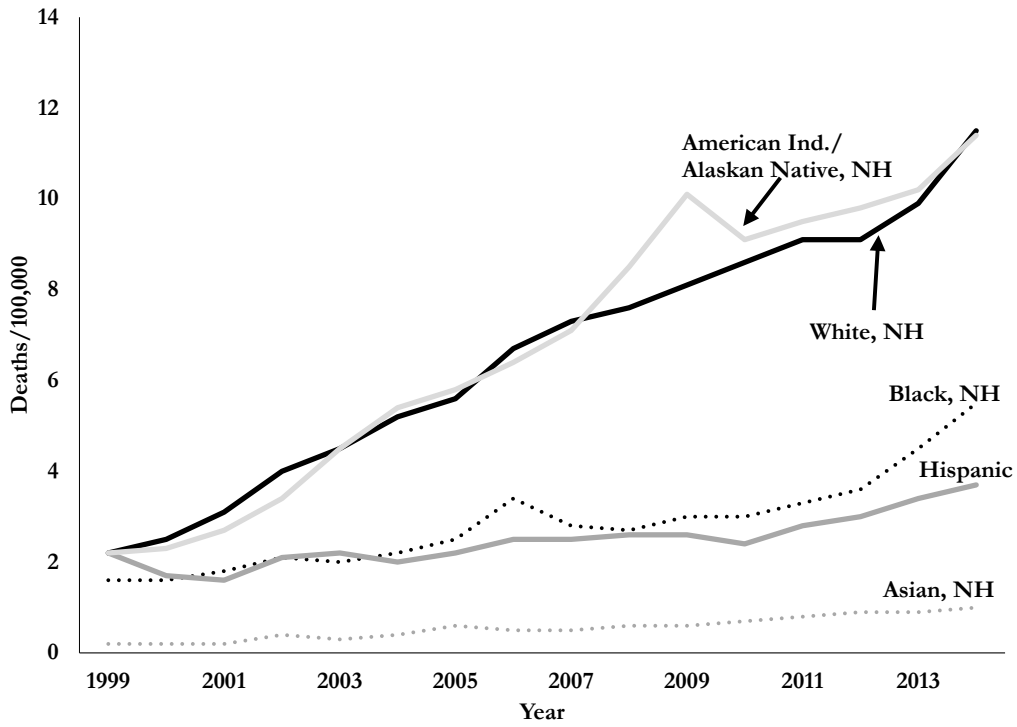
Figure 5a: Heroin or Opioid Poisoning Mortality Rate by Race/Ethnicity, 1999-2014
CDC Wonder Multiple Cause of Death Data

Figure 5b: Heroin or Opioid Poisoning Mortality Rate by Age for White non-Hispanics, 1999-2014
CDC Wonder Multiple Cause of Death Data
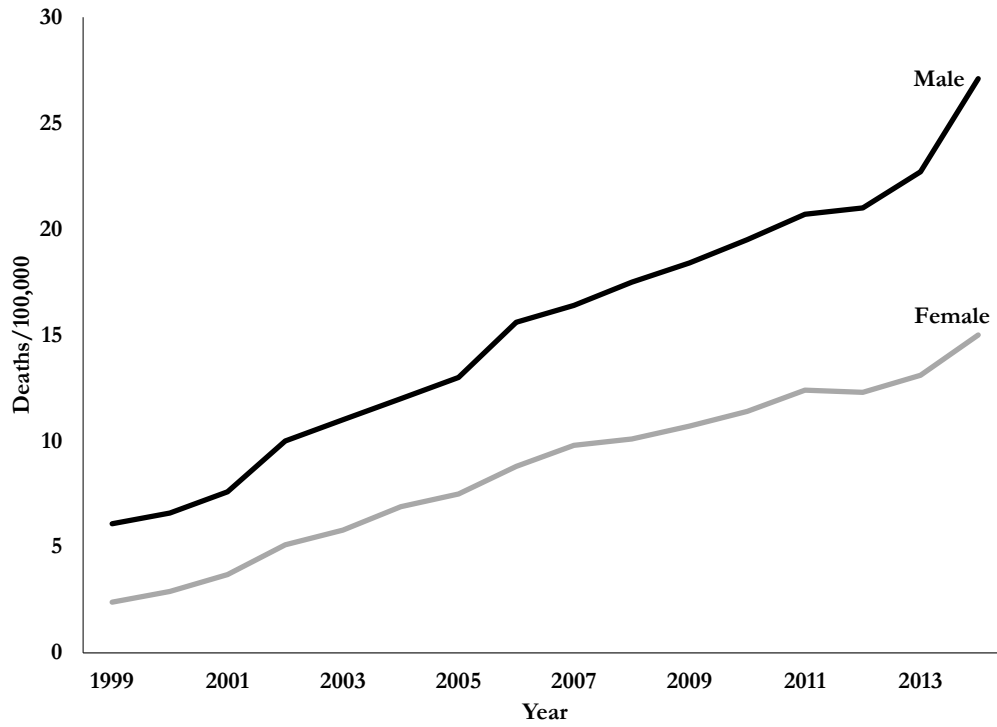
Figure 5c: Heroin or Opioid Poisoning Mortality Rate by Sex for White non-Hispanics Aged 25-54, 1999-2014, CDC Wonder Multiple Cause of Death Data
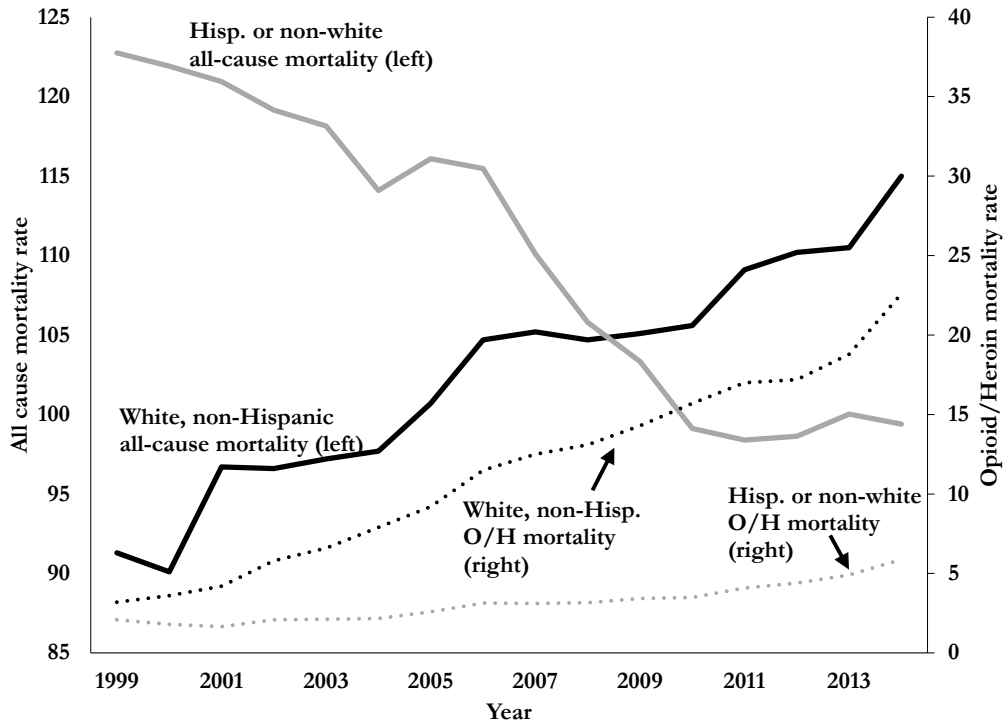
Figure 6a: Mortality Rates, Ages 25-34, By Race/Ethnicity and by Cause,
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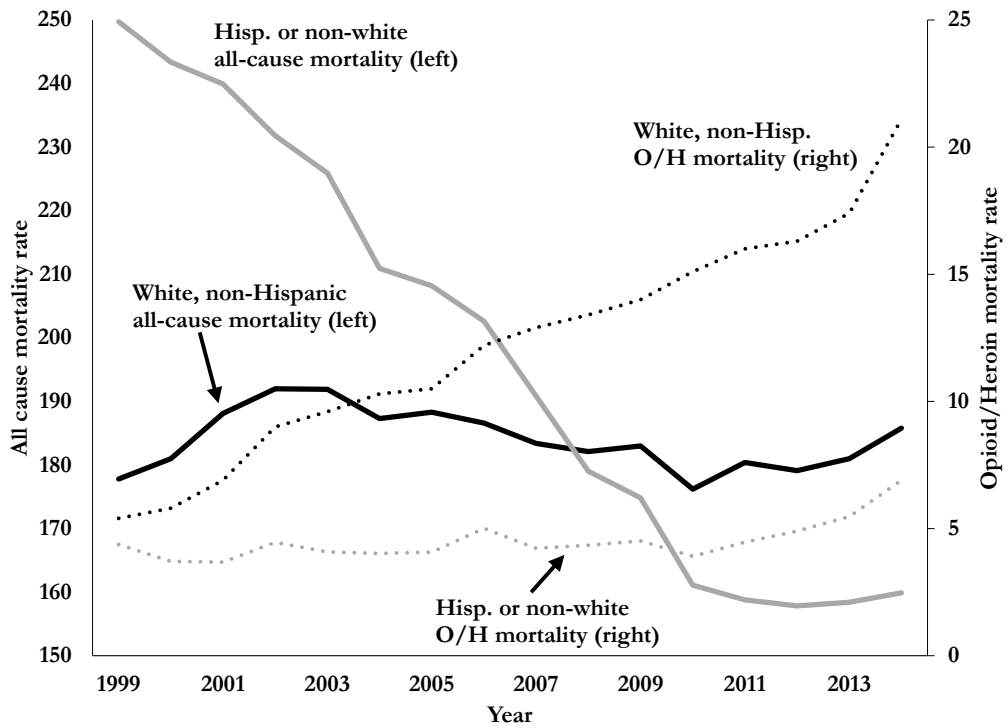
Figure 6b: Mortality Rates, Ages 35-44, By Race/Ethnicity and by Cause,
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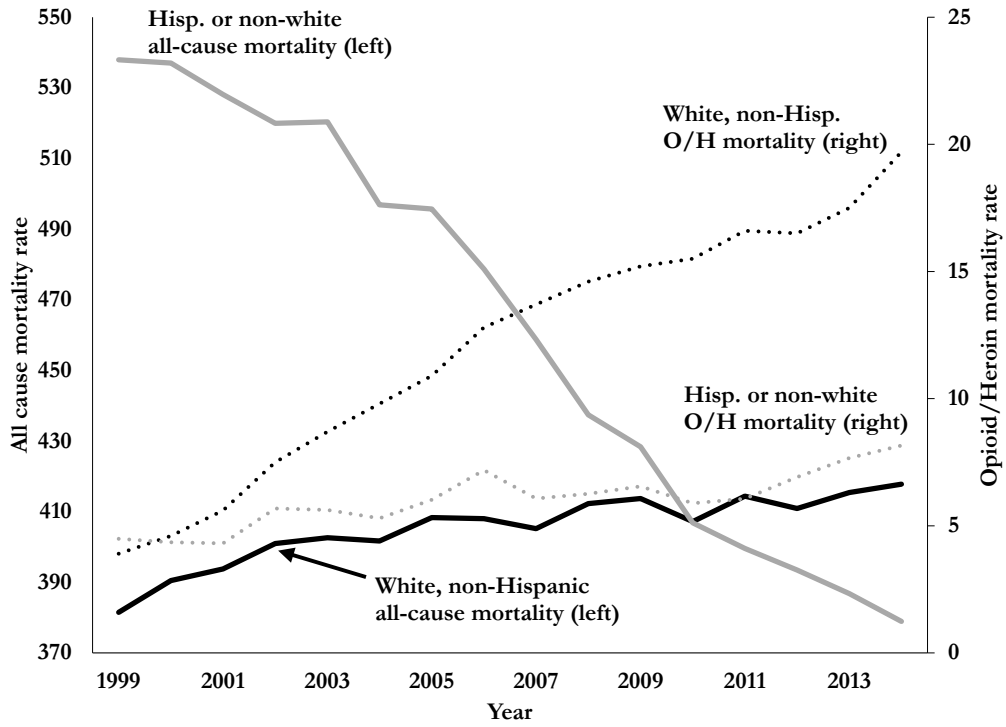
Figure 6c: Mortality Rates, Ages 45-54, By Race/Ethnicity and by Cause,
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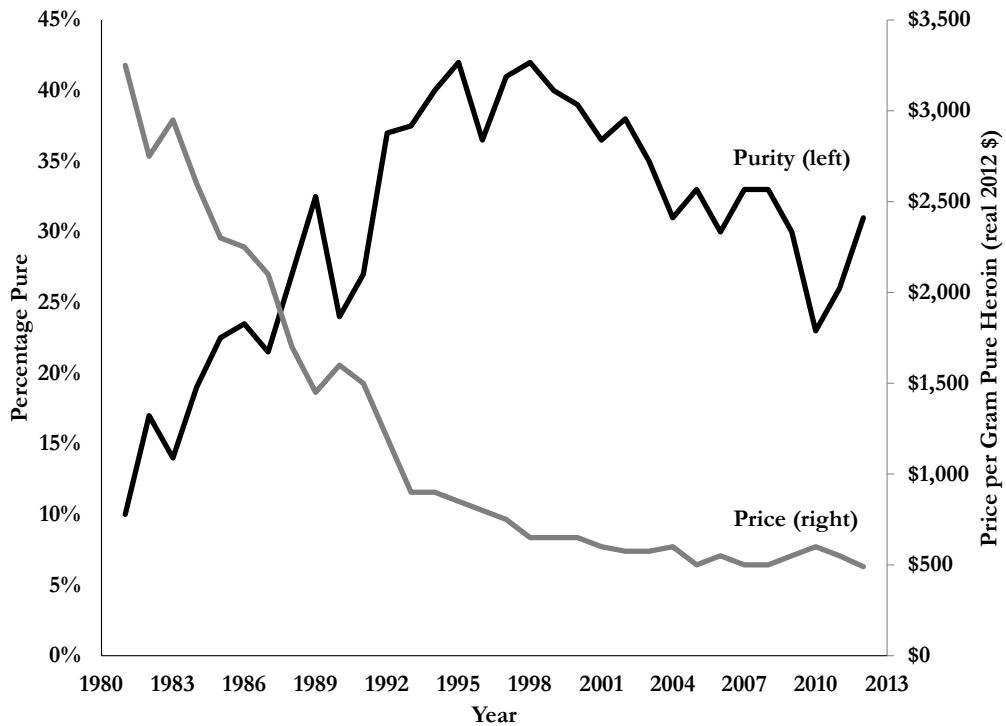
Figure 7: Average Price per Pure Gram (real 2012 $) and Purity of Heroin, 1981-2012
DEA Intelligence Report
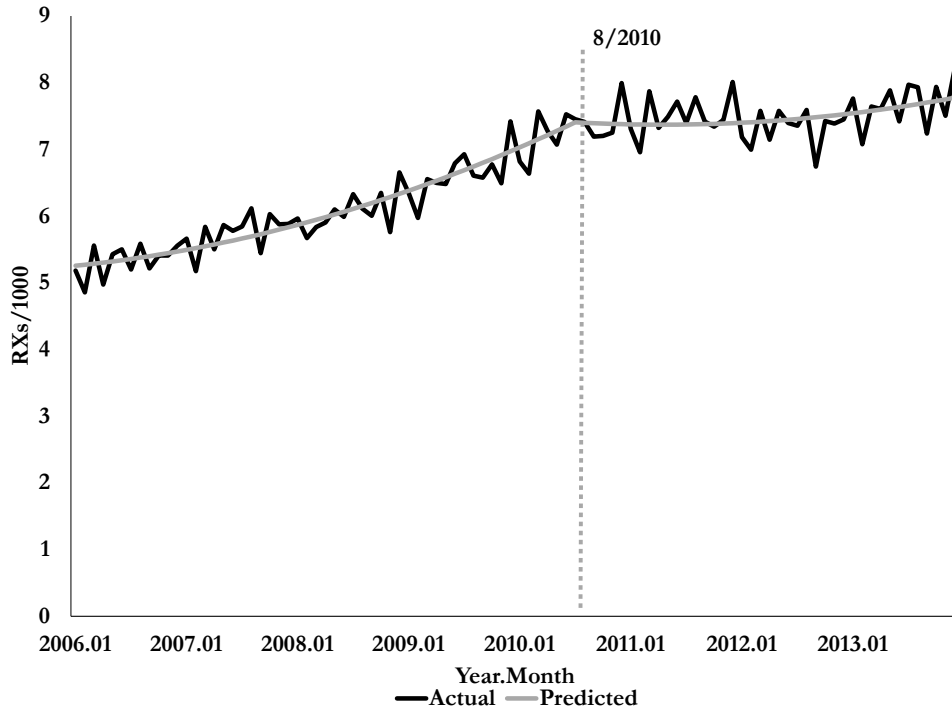
Figure 8a: Monthly Prescriptions for Oxycodone per 1,000 Subscribers, 2006.01 – 2013.12, Marketscan Data
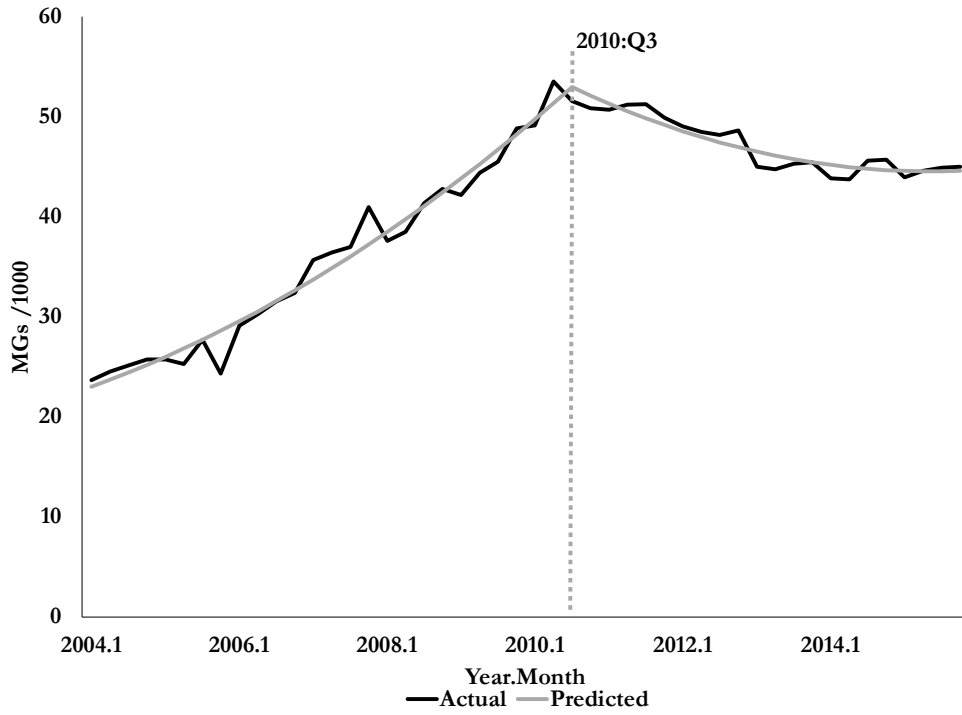
Figure 8b: Quarterly Shipments of Oxycodone, 2004.1 – 2014.4
ARCOS Data
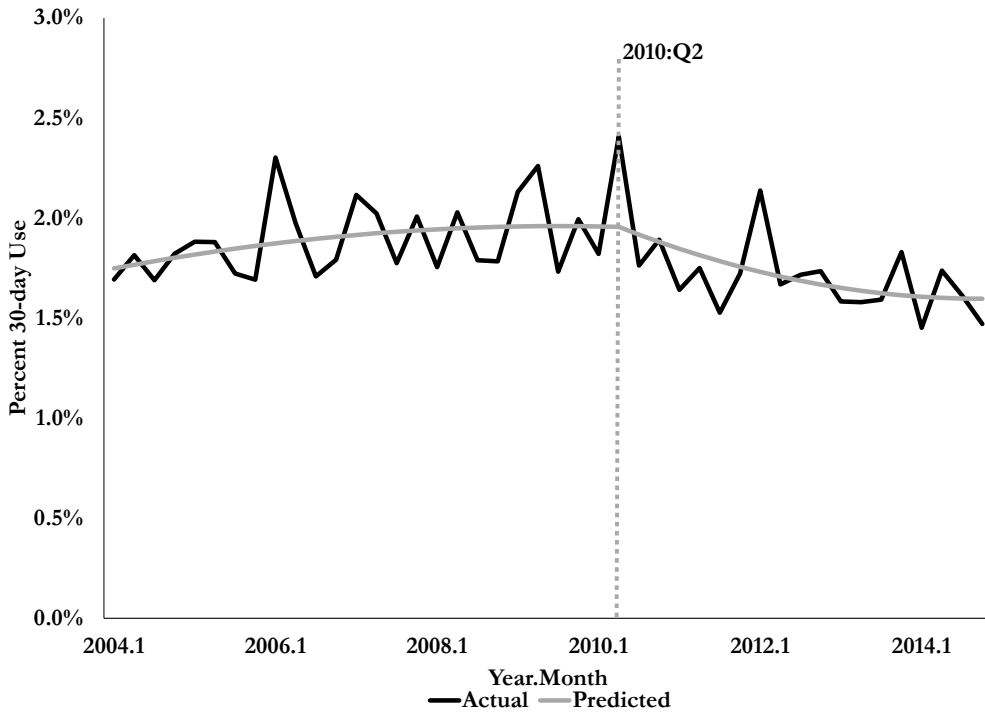
Figure 8c: Percent that use Pain Medicine Recreationally, by Quarter, 2004.1 – 2014.4
National Survey on Drug Use and Health
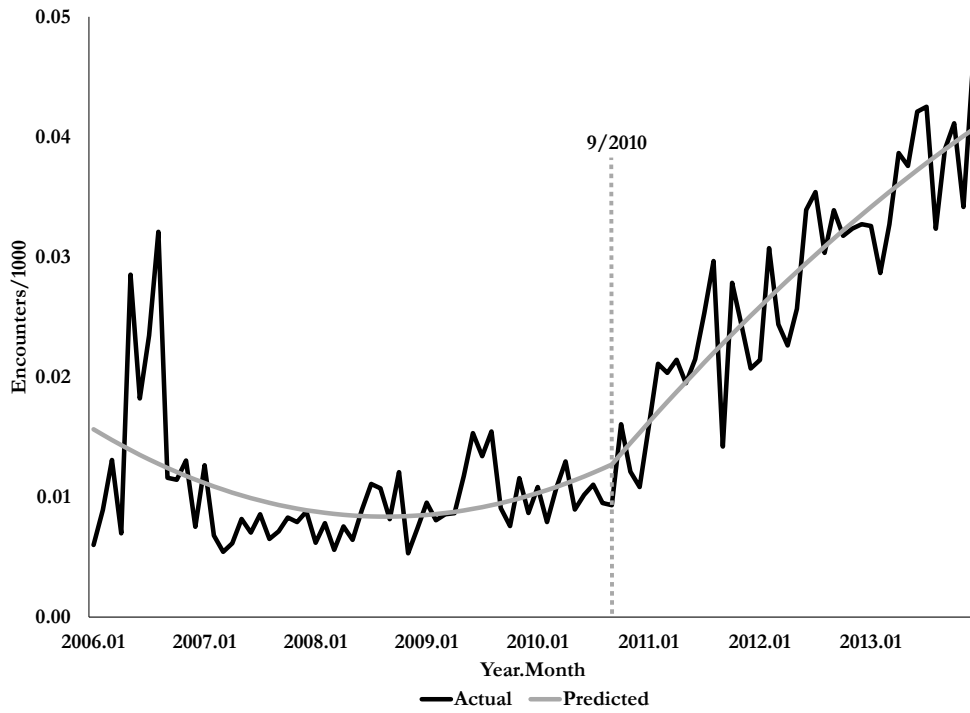
Figure 8d: Quarterly Medical Encounters for Heroin Poisonings per 1,000 Subscribers, 2006.1 – 2013.4
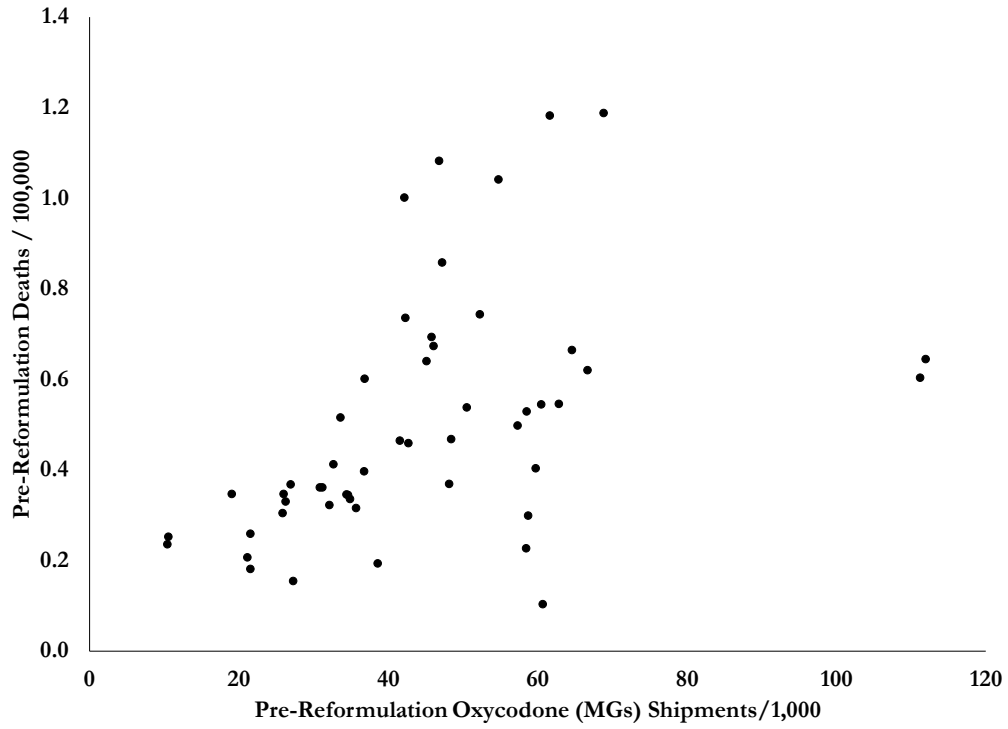Marketscan Data

Figure 9: 2008-2009 Opioid Poisoning Mortality Rate by Oyxcodone Shipments per 1,000 Population
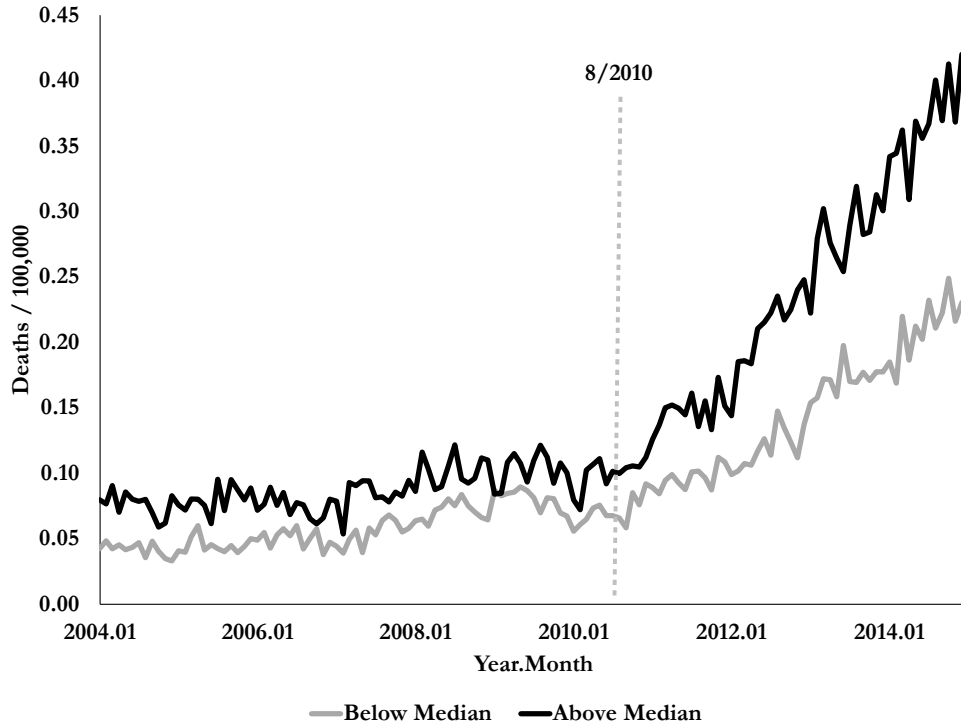CDC Wonder Multiple Cause of Death Data and ARCOS Data

Figure 10a: Heroin Mortality Rates by 2008-2009 Oyxcodone Shipments per 1,000 Population
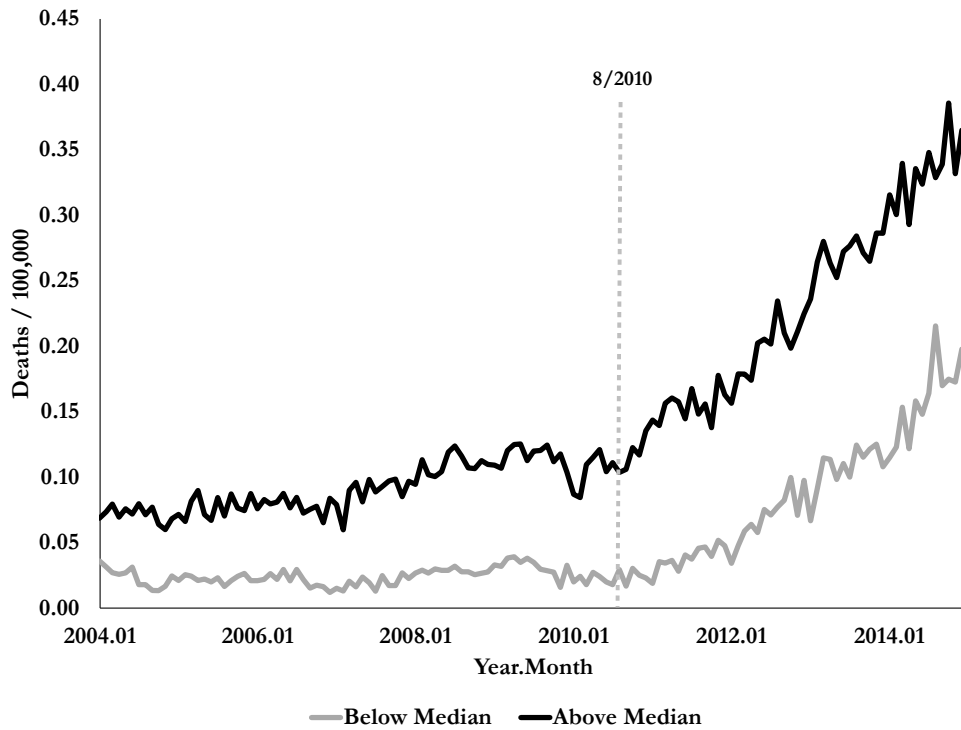CDC Wonder Multiple Cause of Death Data and ARCOS Data

Figure 10b: Heroin Mortality Rate by 2008-2009 Heroin Mortality Rate
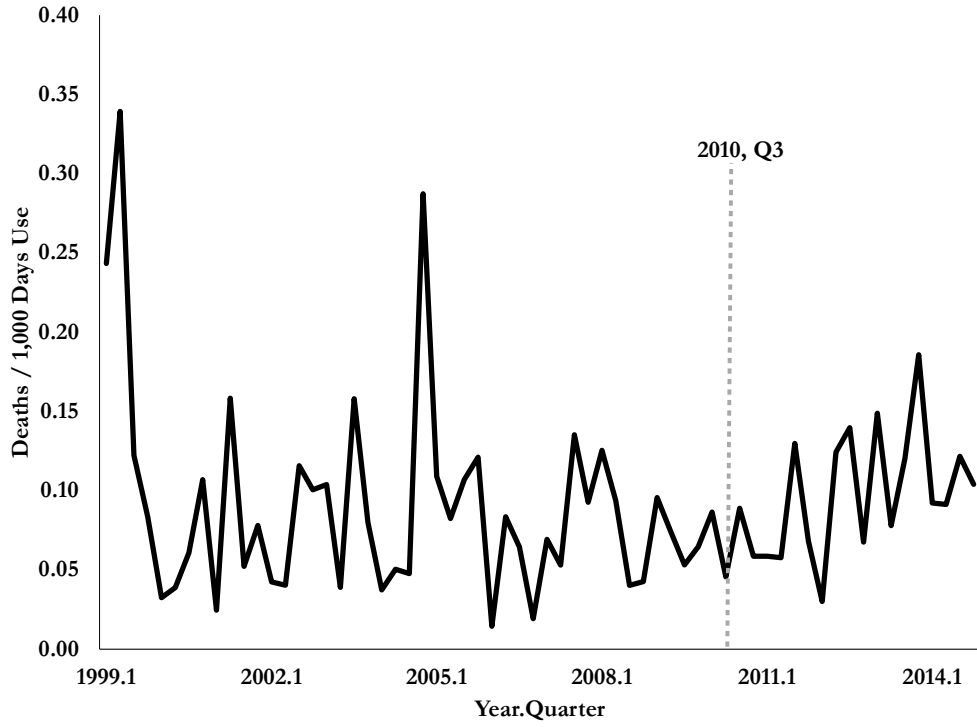CDC Wonder Multiple Cause of Death Data and ARCOS Data

Figure 11: Heroin Deaths per 1,000 Days of Heroin Use, Quarterly, 1999.1 – 2014.4
National Survey on Drug Use and Health and CDC Wonder Multiple Cause of Death Data
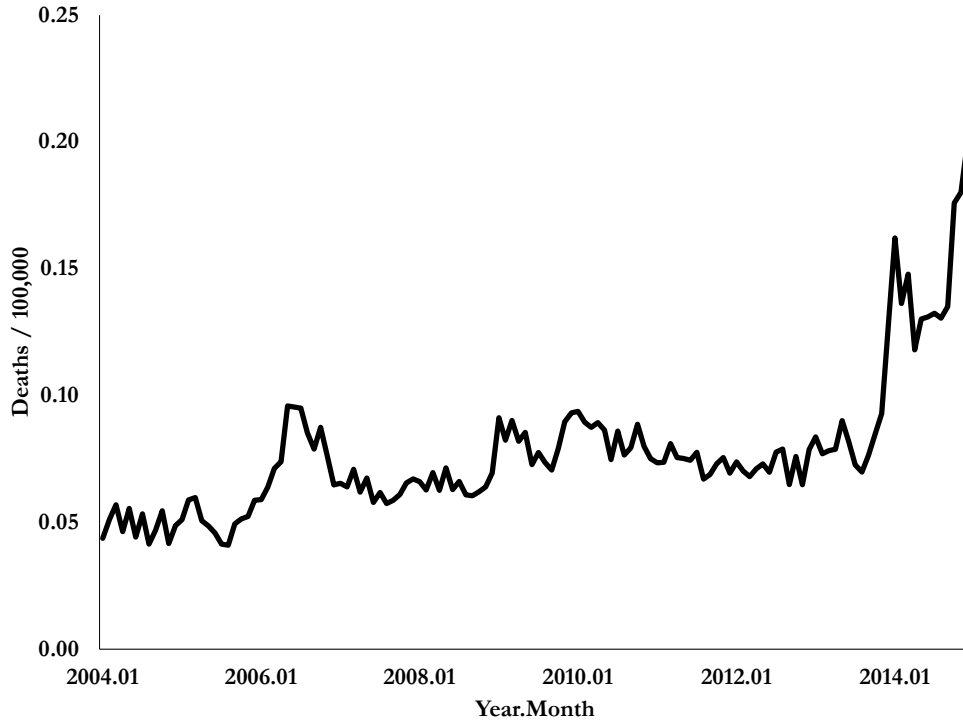
Figure 12a: Monthly Synthetic Opioid Poisoning Mortality Rate, 2004.01 – 2014.12,
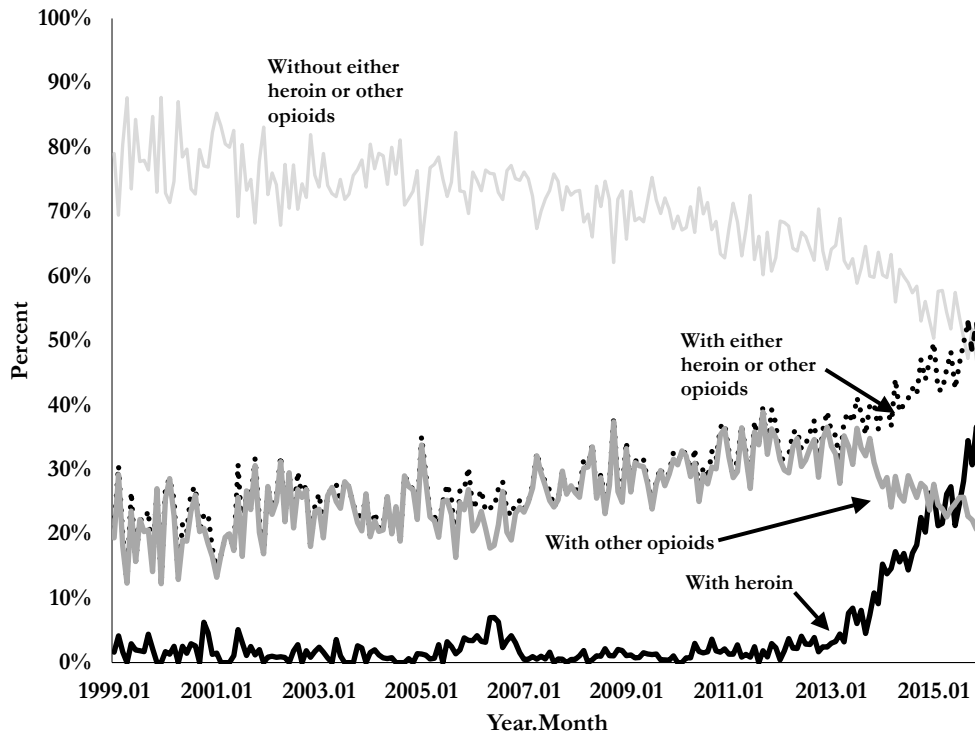CDC Wonder Multiple Cause of Death Data

Figure 12b: Monthly Synthetic Opioid Poisoning Mortality Rate, Alone and in Conjunction with Other
Drugs 2004.01 – 2014.12,
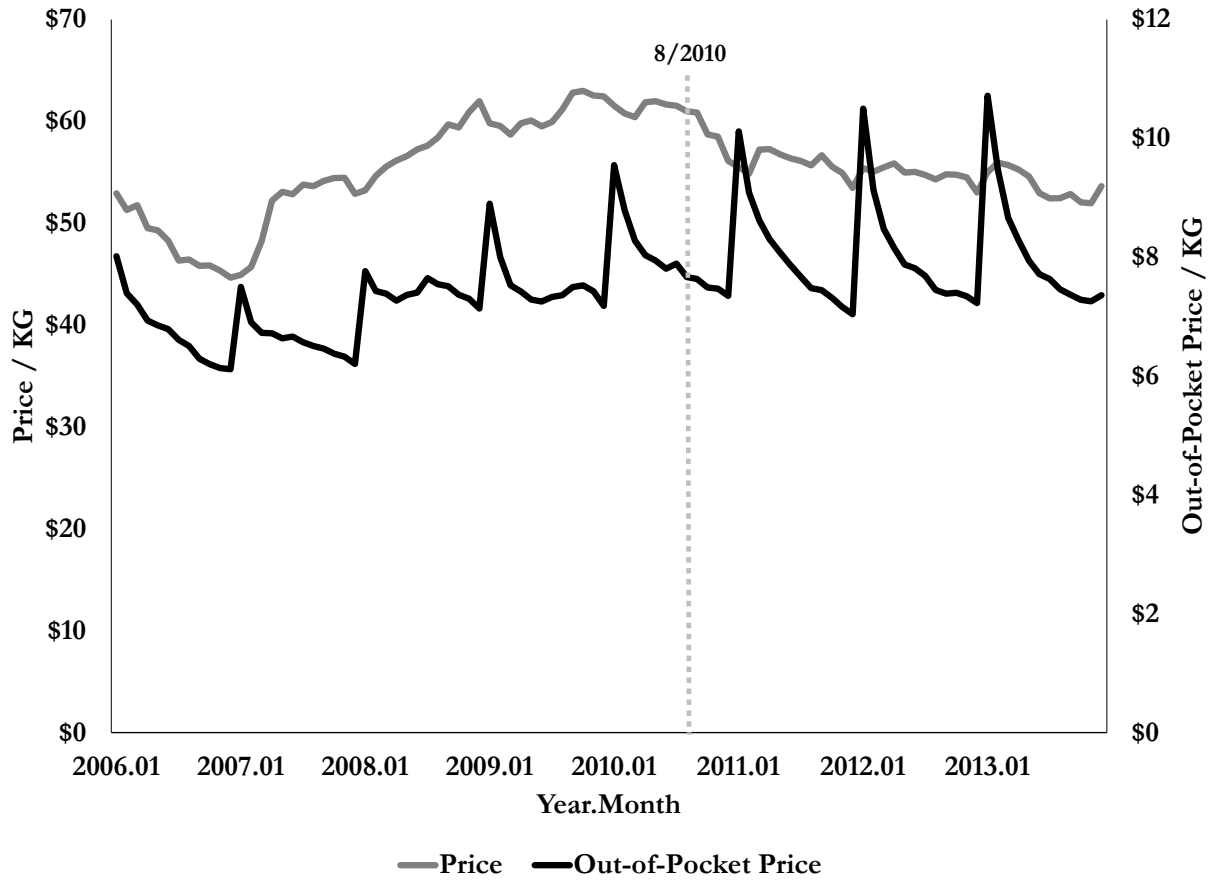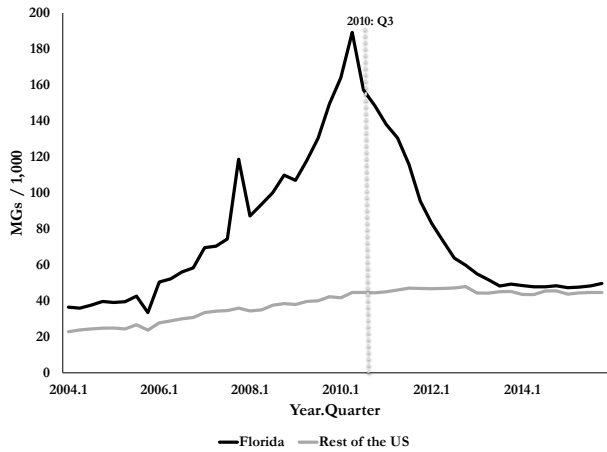CDC Wonder Multiple Cause of Death Data

Figure 13: Average Monthly Price per KG of Oxycodone, 2006.01 – 2013.12, Marketscan Data

a: Oxycodone
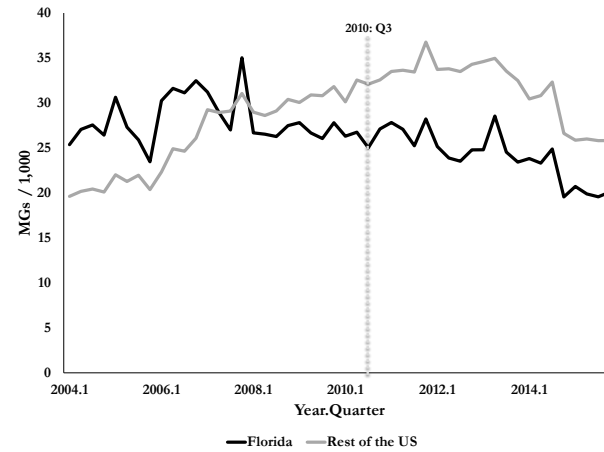
b: Hydrodocone
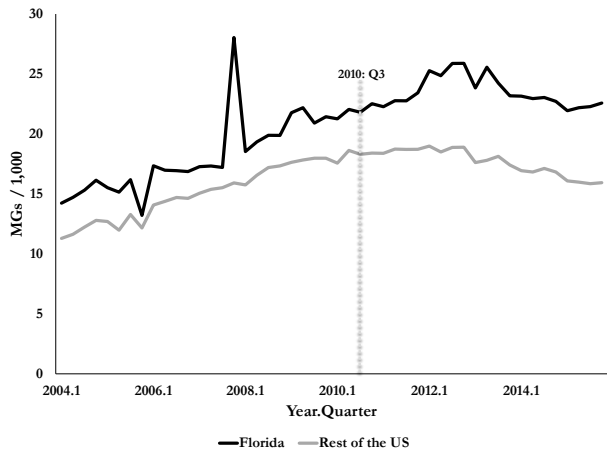
c: Morphine
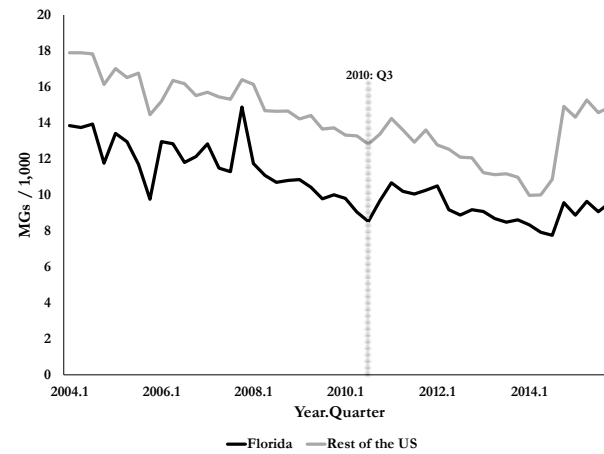
d: Codeine

Figure 14: 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
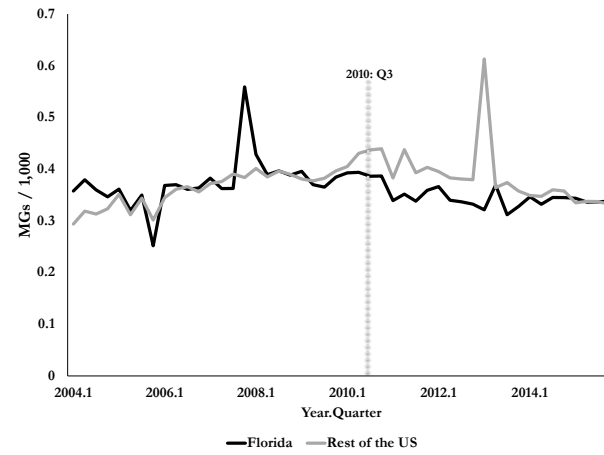
h: Fentanyl

Figure 14 (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
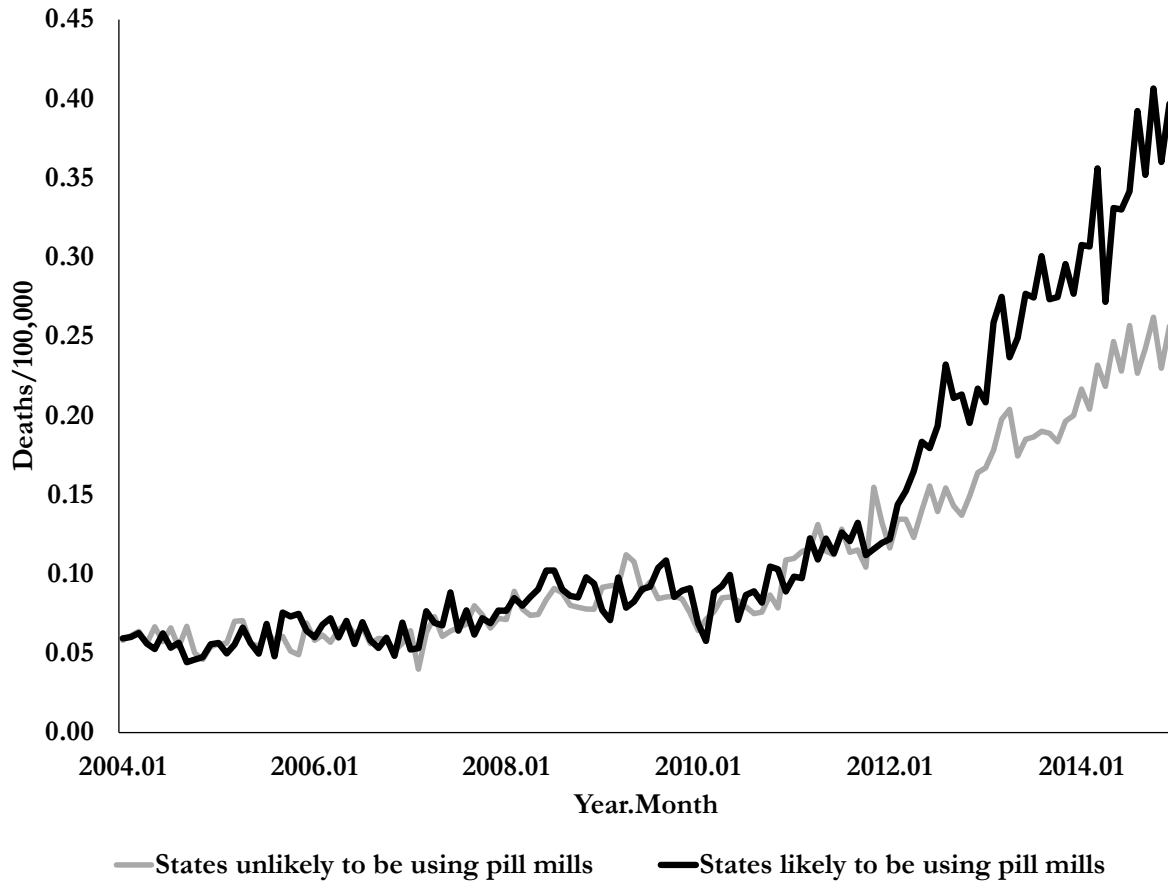
Figure 15: Heroin Mortality Rate by whether States are Likely Users of Florida pill mills

Table 1: Estimated Structural Break Points in National Time Series

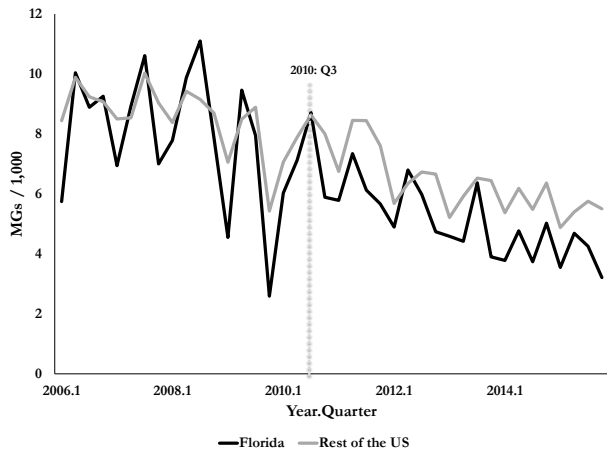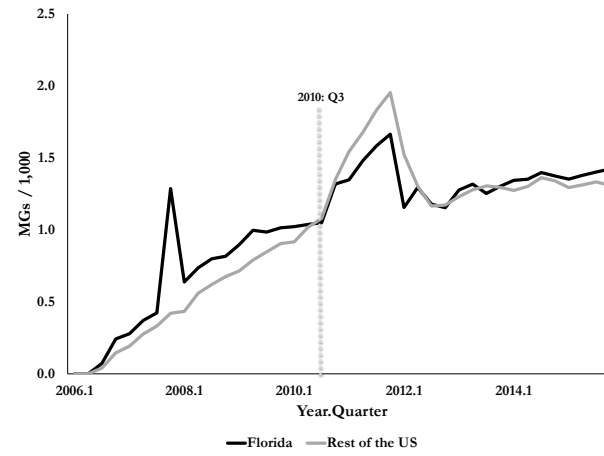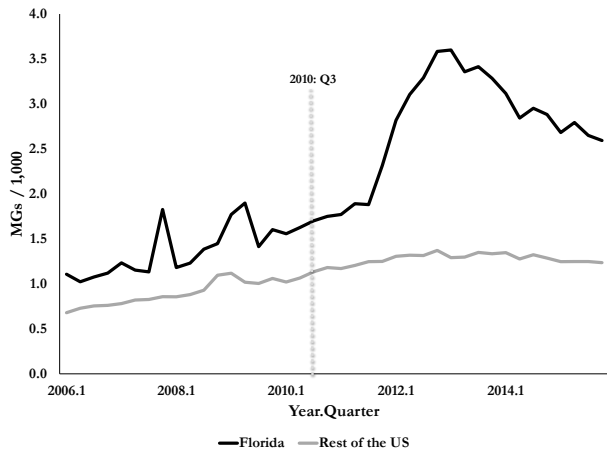| Outcome	Oxycodone RXs/1000	MGs of Oxycodone Shipments/ 1000	30-day recreational pain med use	Heroin deaths/ 100,000	Heroin poisonings/ 100,000
Frequency	Monthly	Quarterly	Quarterly	Monthly	Monthly
Years in sample	2006-2013	2004-2014	2004-2014	2004-2014	2006-2013
Observations	96	44	48	132	96
Break point	8/2010	Q3/2010	Q2/2010	9/2010	9/2010
R^2	0.911	0.980	0.34	0.981	0.847
F test/trends the same	13.52	67.54	0.84	99.79	4.15
λ	19.88	5.44	5.44	7.62	19.88
Critical value Of F (Andrews: 2003)	5.69	5.09	5.09	5.27	5.69

Each column presents results from a different regression. Frequency indicates whether the time dimension of the data is in months or quarters. 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 (2003), presented in the final row.

Table 2: OLS Estimates of Impact of Reformulation on the Trends in Heroin and Opioid Death Rates, Not Accounting for Fentanyl

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	0.0004	0.0014	0.0009
	(0.0010)	(0.0012)	(0.0012)	(0.0011)
Trend after	0.0024	0.0042	0.0044	0.0076
	(0.0008)	(0.0013)	(0.0014)	(0.0017)
Difference: after-before	0.0024	0.0038	0.0029	0.0067
	(0.0007)	(0.0011)	(0.0013)	(0.0011)
Difference group-Low Oxy/Low heroin		0.0013	0.0005	0.0043
		(0.0009)	(0.0011)	(0.0013)
B: Opioid death rates {0.74} [0.464]				
Trend before	0.0030	0.0057	0.0038	0.0037
	(0.0017)	(0.0021)	(0.0020)	(0.0020)
Trend after	0.0012	-0.0007	0.0012	0.0036
	(0.0014)	(0.0022)	(0.0017)	(0.0018)
Difference: after-before	-0.0017	-0.0063	-0.0026	-0.0001
	(0.0014)	(0.0021)	(0.0013)	(0.0014)
Difference group-low risk		-0.0046	-0.0009	0.0016
		(0.0021)	(0.0011)	(0.0016)
C: Combined Heroin/opioid death rate {0.74} [0.532]				
Trend before	0.0025	0.0055	0.0044	0.0040
	(0.0021)	(0.0026)	(0.0026)	(0.0025)
Trend after	0.0028	0.0019	0.0045	0.0088
	(0.0017)	(0.0026)	(0.0024)	(0.0026)
Difference: after-before	0.0003	-0.0036	0.0001	0.0048
	(0.0017)	(0.0026)	(0.0019)	(0.0018)
Difference group-low risk		-0.0039	-0.0002	0.0046
		(0.0026)	(0.0017)	(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 3: OLS Estimates of Impact of Reformulation on the Trends in Heroin and Opioid Death Rates, Accounting for Fentanyl

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

Table 4: 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 5: Fitting Splines to Florida and Rest of the U.S., Oxycodone and Other Pain Killers

| | | | Regression coefficients (standard errors) | | | | | | | |
| Dependent variable | Means in 4 quarters prior to 2010:3 | | Pre-reformulation trend | | Post-reformulation trend | | | p-value on test | | |
	Florida	Rest of US	Florida (a)	Rest of US (b)	Florida (c)	Rest of US (d)	R²	(a)=(b)	(c)=(d)	(a)=(b) (c)=(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
Pentobarbytal	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
Meperdine	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 6: 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	-0.0013	-0.0014	-0.0014	-0.0014
	(0.0012)	(0.0012)	(0.0013)	(0.0013)
Trend before * distance	0.0001	0.0001	0.0001	0.0001
	(0.0002)	(0.0003)	(0.0002)	(0.0002)
Trend break	0.0054	0.0057	0.0054	0.0056
	(0.0015)	(0.0017)	(0.0016)	(0.0016)
Trend break * distance	-0.0011	-0.0013	-0.0007	-0.0008
	(0.0008)	(0.0009)	(0.0006)	(0.0006)
B: 1 / distance				
Trend before	-0.0010	-0.0008	-0.0007	-0.0006
	(0.0017)	(0.0017)	(0.0017)	(0.0017)
Trend before * distance	-0.0003	-0.0004	-0.0007	-0.0007
	(0.0006)	(0.0006)	(0.0009)	(0.0009)
Trend break	0.0037	0.0035	0.0038	0.0037
	(0.0017)	(0.0017)	(0.0017)	(0.0017)
Trend break * distance	0.0007	0.0008	0.0008	0.0008
	(0.0019)	(0.0019)	(0.0026)	(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 50 states and DC from 2004 through 2014 for a total of 6,732 observations. Distance measure first two columns is thousands of miles between the centroid of the state and the centroid of Florida; in 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.