Supply-Side Drug Policy in the Presence of Substitutes: Evidence from the Introduction of Abuse-Deterrent Opioids[*]

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Overdose deaths from prescription opioid pain relievers nearly quadrupled between 1999 and 2010. We study the consequences of one of the largest supply disruptions to date to abusable opioids – the introduction of an abuse-deterrent version of OxyContin in 2010. Supply-side interventions which limit access to opioids may have the unintended consequence of increasing use of substitute drugs, including heroin. Exploiting cross-state variation in OxyContin exposure, we find that states with the highest initial rates of OxyContin misuse experienced the largest increases in heroin deaths. Our results imply that the recent heroin epidemic is largely due to the reformulation of OxyContin.

JEL Codes: I12, I18

Keywords: supply-side drug policy, abuse-deterrence, opioids, heroin

Drug overdose deaths have risen dramatically over the past 15 years, increasing by 137% between 2000 and 2014 (Rudd et al., 2016). By 2009, they were the leading cause of death from injuries in the United States, exceeding deaths from motor vehicles and firearms (Paulozzi, 2012). Overdose deaths from prescription opioid pain relievers are the primary driver behind this upward trend,

[*] We would like to thank seminar and conference participants at the Conference of the American Society of Health Economists, APPAM Fall Research Conference, ASSA Annual Meetings, Bates White Life Sciences Symposium, Caribbean Health Economics Symposium, NBER Summer Institute, Rutgers University, UCLA, and the U.S. Food and Drug Administration for helpful comments, especially from our discussants Melinda Buntin, Dean Lillard, and David Meltzer. We thank Sarah Dykstra for excellent research assistance. Powell and Pacula gratefully acknowledge financial support from NIDA (R21DA041653) and the Bing Center for Health Economics.

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nearly quadrupling since 1999 (CDC, 2016). Since this time, there have been nearly 200,000 deaths due to opioids. The unprecedented rise in opioid overdose deaths has prompted the Centers for Disease Control and Prevention (CDC) to call this the worst drug overdose epidemic in U.S. history (Kolodny et al., 2015). The harmful effects of prescription opioids are particularly acute in the U.S., the largest consumer of these drugs.[1] In 2014, nearly 2 million Americans abused or were dependent on prescription opioids, and 10.3 million had used prescription opioids for non-medical purposes in the past year (SAMHSA, 2015).

Given the severity of the opioid epidemic, the federal government and states have implemented a vast array of policies aimed at curbing prescription opioid abuse. These policies have disproportionately targeted the supply-side of the market by limiting access to opioids, including Prescription Drug Monitoring Programs (PDMPs), Medicaid Lock-In Programs, pain clinic laws, diversion control, black box warnings, and abuse-deterrent drug formulations. Less attention and funding have been directed to demand-side interventions, such as prevention and substance abuse treatment, which aim to reduce the prevalence of addiction.[2] While supply-side interventions often dominate the discussion surrounding drug policy, evidence of their effectiveness is mixed with many studies finding limited effects across a wide range of drugs (e.g., Dobkin and Nicosia, 2009; Dobkin et al., 2014; Pollack and Reuter, 2014).

In this paper, we study the consequences of a massive nationwide supply disruption for opioid abuse: the introduction of abuse-deterrent OxyContin. OxyContin is one of the most widely abused opioids (Cicero et al., 2005). In

[1] The U.S. consumes more than 80% of the world supply of oxycodone and 99% of hydrocodone—the main ingredients in the majority of prescription opioids (International Narcotics Control Board, 2008).

[2] Although, the recently signed 21st Century Cures Act will provide $1 billion in funding for these types of programs. In addition, the Comprehensive Addiction and Recovery Act of 2016 budgets $181 million annually to address the opioid epidemic, including resources to expand prevention and addiction services.

2010, the FDA approved a reformulated, abuse-deterrent version of OxyContin designed to make the pill difficult to crush or dissolve. The most dangerous methods of abuse occur when OxyContin is crushed for ingestion, inhalation or injection. The original formulation was then discontinued, marking a substantial reduction in the supply of abusable prescription pain relievers. Indeed, time series evidence suggests that the OxyContin reformulation reduced non-medical OxyContin use by as much as 40% (Cicero, et al. 2012; Butler, et al. 2013; Cicero, et al. 2015).

However, by raising the cost of OxyContin abuse, this intervention may have also had the unintended effect of increasing the abuse of substitute drugs, including even more harmful opiates such as heroin. To the extent that this substitution occurred, it would undermine the effectiveness of this type of intervention. While prescription opioids and heroin are pharmacologically similar, this relationship does not inherently imply that individuals will switch to the more dangerous illegal substance given the additional costs associated with acquiring and abusing illegal drugs. The existence and magnitude of actual substitution patterns are determined by individual characteristics as well as access to substitutes, and therefore are empirical questions.

We quantify how the OxyContin reformulation impacted overdoses involving heroin and other types of opioids. We leverage data from multiple sources including the National Survey on Drug Use and Health (NSDUH) and administrative data from the Drug Enforcement Administration (DEA) to measure OxyContin and pain reliever use and data from the National Vital Statistics System (NVSS) to measure overdose deaths. We study mortality both as an important outcome on its own and as an indicator of substitution to heroin. While our primary focus is on understanding the role of the OxyContin reformulation in explaining recent overdose trends— especially the dramatic rise in heroin-related mortality— we also assess the net effects of the reformulation on overall overdose

deaths. The impacts of this intervention are particularly relevant as the FDA is encouraging the development of more abuse-deterrent opioids.

Following the OxyContin reformulation in 2010, abuse of prescription opioid medications and overdose deaths decreased for the first time since 1990 (Warner et al., 2014; Dart et al., 2015). However, this drop coincided with an unprecedented rise in heroin overdoses (see Figure 1). Heroin-related overdoses more than *tripled* between 2010 and 2014 (from 1.0 to 3.4 deaths per 100,000), after remaining relatively constant between 1999 and 2010. In 2014 alone, heroin was responsible for over 10,000 deaths. This time series evidence is consistent with the hypothesis that the reformulation led individuals to substitute away from OxyContin to heroin. Indeed, prior studies in the medical literature— which have been limited to before and after evaluations of the reformulation (e.g., Coplan et al., 2013; Larochelle et al., 2015)— have suggested there is a relationship between these recent trends. However, it is difficult to isolate the effects of the OxyContin reformulation from other concurrent changes in state and federal policies that have sought to address the rise in opioid abuse during the same time period.

[Figure 1 about here]

We address the challenge of identifying the effects of a national intervention separately from other policy and secular trends by exploiting cross-state variation in pre-reformulation rates of OxyContin misuse. The reformulation should have more "bite" in states with higher initial rates of OxyContin misuse. Consistent with our hypothesis, we show that states with high initial OxyContin misuse experience larger declines in OxyContin misuse immediately following the reformulation. We exploit this differential exposure to the reformulation across states to quantify its effects on heroin and opioid deaths.

We find that the OxyContin reformulation significantly reduced OxyContin misuse, but also led to a large increase in heroin deaths. States with the highest initial rates of OxyContin misuse experienced the largest increases in heroin deaths. Event study results show that this differential increase in heroin deaths began precisely in the year following reformulation. Moreover, heroin deaths were uncorrelated with OxyContin misuse prior to the reformulation: both the levels and trends in heroin deaths were nearly identical across states with high or low initial rates of OxyContin misuse before 2010. Our estimates show that each percentage point reduction in the rate of OxyContin misuse due to reformulation leads to 3.1 more heroin-related deaths per 100,000. Extrapolating our estimates to the national trend implies that as much as 80% of the three-fold increase in heroin mortality between 2010 and 2013 may be due to the OxyContin reformulation.

On the other hand, we find little evidence of differential reductions in overall opioid mortality in states with high initial OxyContin misuse. This may be partially due to substitution from OxyContin to other opioids. Studying synthetic opioids independently, we find suggestive evidence of a relative increase in fentanyl deaths. On net, the reformulation had no effect on total overdose deaths since heroin and opioid deaths largely offset each other.

Given the considerable policy efforts to reduce opioid abuse during this time period, we conduct several tests to verify that our results represent a causal effect of the reformulation. We show that our results are not sensitive to controlling for the differential adoption of PDMPs or excluding Florida— which experienced a significant crackdown on "pill mills" in 2010-2011. Furthermore, we find that nonmedical use of OxyContin, specifically, is predictive of growth in heroin mortality while nonmedical use of pain relievers more generally is not. These tests suggest that the reformulation is the main driver of the rise in heroin overdoses and not other policies broadly affecting opioids.

I. Background

A. Background on OxyContin

OxyContin was introduced by Purdue Pharma in 1996 and is the brand-name drug for the extended-release formulation of oxycodone. Oxycodone is a semi-synthetic opioid, similar to morphine, used for the management of acute and chronic pain. The key innovation of OxyContin was its long-acting formula which provided 12 hours of continuous pain relief, significantly improving the quality and ease of pain management over previous drugs. However, the timed-release aspect of OxyContin is contingent on taking the pill whole. Crushing or dissolving the pill causes the high dose of oxycodone, which is intended to be released slowly over 12 hours, to be delivered all at once. This property made OxyContin especially easy to abuse. Individuals who intended to abuse OxyContin could chew, snort or inject the crushed pill for maximum euphoric effects. This method of abuse is arguably the most dangerous, as this high level of potency comes with a heightened risk for addiction and overdose death.[3]

Prior to the reformulation, OxyContin was one of the highest selling prescription drugs in the U.S. (ranking 15th in sales) with more than $3 billion in annual sales in 2010 (Bartholow, 2011). OxyContin sales grew rapidly due to an aggressive marketing campaign[4] that promoted the drug for a wide range of conditions, including non-cancer chronic pain, and as a first line therapy (GAO, 2003). This departed from previous clinical recommendations to prescribe

[3] Ironically, the time-released aspect of OxyContin led FDA officials to initially believe that OxyContin would be less attractive to abusers since absorption of the drug would be delayed. The original product label included the false statement that OxyContin had a lower potential for abuse. This claim was central to the marketing campaign.

[4] In 2007, Purdue pleaded guilty to misleading users about the addiction risk, leading to a $600 million settlement.

opioids only after other drugs had failed (WHO Expert Committee, 1986) and primarily for acute and cancer pain (Max et al., 1995).[5] The increased market presence of OxyContin led to high levels of diversion to non-medical use, making it one of the leading drugs of abuse (Cicero et al., 2005).[6] Indeed, many experts have implicated OxyContin as a key cause of the opioid epidemic, as its introduction coincided with the origin of the epidemic in the mid-1990s (Kolodny et al., 2015).

B. The OxyContin Reformulation

In April 2010, Purdue Pharma introduced a reformulated version of OxyContin which was designed to make the drug more difficult to abuse. It was the first drug product to ever receive an "abuse-deterrent" designation from the FDA.[7] The abuse-deterrent version uses physicochemical barriers to make the pill hard to break, crush or dissolve, thus deterring the most harmful methods of abuse while still maintaining the pain-relieving benefits for legitimate medical users who take the drug orally. In August 2010, Purdue Pharma stopped distributing the original formulation of OxyContin to pharmacies. It should be noted that the reformulation is not entirely "abuse-proof," since it cannot eradicate oral misuse (i.e., taking more pills or higher doses than prescribed), and some users have even found ways to counteract the abuse-deterrent properties of the new version.[8] The FDA recently announced its intent to encourage the

[5] In 1995, the American Pain Society recommended that pain should be the "fifth vital sign" and national pain organizations revised treatment guidelines to recommend opioids for cancer and non-cancer pain (Phillips, 2000).

[6] OxyContin was the first drug targeted for monitoring by the DEA by its brand name, specifically (GAO, 2003).

[7] This reformulated version received an official "abuse-deterrent" designation from the FDA in April 2013.

[8] Highly sophisticated methods were shared on websites for how to counteract the abuse-deterrent properties of the drug involving baking, freezing, or soaking the pill in solvents (Goodnough and

development of more opioid formulations with abuse-deterrent properties.[9] To date, the FDA has approved abuse-deterrent versions for several brand name extended-release opioids (e.g., Targiniq, Embeda, Hysingla, MorphaBond, Xtampza, and Troxyca), though OxyContin remains the most important given its large market size.

There was an immediate reduction in OxyContin misuse and oxycodone distribution after the reformulation, as shown in Figure 2. Self-reported misuse of OxyContin declined by about 40 percent nationally between 2010 and 2014 in the National Survey on Drug Use and Health (NSDUH).[10] Total legal distribution of oxycodone—as recorded by the DEA— also declined for the first time after the reformulation, following a steady increase since 2000. This is consistent with several medical studies showing that the reformulation was effective at reducing OxyContin abuse among recreational users by as much as 40 percent (Cicero et al., 2012; Butler et al., 2013; Cicero et al., 2015).[11]

[Figure 2 about here]

Prior medical studies find evidence of an immediate rise in heroin use after the OxyContin reformulation. Cicero and Ellis (2015) surveyed opioid users enrolled in substance abuse treatment programs finding that OxyContin use declined after 2010, but heroin use increased among this population. Coplan et al. (2013) find an uptick in calls to national poison centers for heroin exposure after the reformulation and Larochelle et al. (2015) show an increase in heroin

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Zezima, 2011; Becker and Fiellin, 2017). However, as noted by Cicero and Ellis (2015), given the significant time effort required, these methods may prove too costly for most users.

[9] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm492237.htm (accessed May 21, 2016)

[10] The NSDUH is our main data source for measuring the prevalence of nonmedical use of OxyContin and is described in more detail in the next section.

[11] Other studies show a reduction in calls to poison control centers for OxyContin (Coplan et al., 2013), adverse event reports of death (Sessler et al., 2014), and drug diversion reports (Severtson et al., 2013).

overdoses using claims data from a large national insurer. On the other hand, a review article (Compton et al., 2016) argues that the reformulation and other policies are not the main drivers of the heroin epidemic because heroin use began to rise prior to 2010. Consistent with this observation, we observe a slight increase in heroin deaths beginning in 2007 (see Figure 1), though their reasoning does not explain why there was a massive trend break precisely in 2010.

More generally, survey evidence documents fluid transitions between opioids and heroin. Between 50-85% of recent heroin users report abusing opioids before initiating heroin (e.g., Siegal et al., 2003, Pollini et al., 2011).[12] Similarly, in Cicero and Ellis (2015), a small sample (N=153) of OxyContin users were asked how they responded to the reformulation: 33% indicated that they replaced OxyContin with other drugs. Of this group, 70% reported that they had switched to heroin and a smaller proportion switched to other opioids (primarily other forms of oxycodone). Only 3% reported that they stopped abusing drugs altogether.

These medical studies support the plausibility of a causal link between the reformulation and the rise in heroin deaths. However, they rely exclusively on time-series trends, so they are unable to disentangle the OxyContin reformulation from the many other policies that were implemented concurrently. Moreover, since most of these studies are based on survey data, they cannot estimate how the reformulation contributed to the dramatic rise in heroin *deaths*. Finally, their analyses on small, non-random samples may not generalize to explain national trends.

In contrast, we are the first to exploit cross-state variation in exposure to the reformulation in a difference-in-difference framework—isolating the causal

[12] Studies on the trajectory of abuse show that individuals typically abuse opioids orally first, then transition to inhalation/injection as they build tolerance, and then heroin which is more potent and often cheaper.

relationship between the reformulation and heroin deaths. Our approach permits us to control for common national shocks that occurred around 2010, account for fixed differences across geographic areas, and test for pre-existing trends in heroin deaths across areas. Further, unlike prior work, we use nationally representative data on OxyContin misuse (NSDUH), administrative data on the legal supply of oxycodone (ARCOS), and the census of U.S. deaths. These data provide a more representative view of the nationwide effects of the reformulation, while also permitting analysis of mortality effects.

C. Related Literature on Supply-Side Drug Policy

Supply-side interventions have largely dominated the set of policies aimed at reducing drug abuse (Pollack and Reuter, 2014). Economic theory predicts that policies that reduce the supply of drugs should lead to increased drug prices, lowering demand for the drug (Caulkins and Reuter, 2010; Reuter and Kleiman, 1996). However, substitution responses may partially undo the benefits of these policies. In general, there are two possible substitution responses by producers and consumers which limit the scope for these policies to reduce drug abuse.

First, the increase in price may attract new suppliers to the market (or increased production by existing suppliers), thereby reducing or even eliminating the supply shortfall.[13] As just one example, in the market for methamphetamine, interventions that targeted the supply of specific drug precursors were found to have only short term effects on prices because producers could substitute away from using the regulated inputs towards unregulated ones (Cunningham and

[13] The reduction in observed use in response to a supply shock should depend on the slope of the demand curve for that specific drug. If demand is inelastic, then total use (and supply) will remain the same.

Finlay, 2016; Dobkin et al., 2014). Thus, substitution across producers enables the continued production or distribution of the drug.

Second, there may be consumer-level substitution responses. By increasing the cost of OxyContin abuse, the reformulation reduced consumption of OxyContin, but may have also led existing users to substitute to heroin or other similar drugs. The magnitude of the response will depend on cross-price elasticities of demand as well as the supply of alternative drugs. The economics literature has long recognized the importance of substitution patterns across drugs, showing fluid substitution in response to supply changes for alcohol, smoking, and marijuana.[14]

We add to this literature by exploiting the introduction of abuse-deterrent OxyContin as a large national shock to the supply of abusable opioids to understand its ramifications for overdose deaths involving substitute drugs. The reformulation represents one of the largest disruptions to the nonmedical market for opioids and presents a rare opportunity to isolate the effects of consumer-level substitution from producer-level substitution (since the latter response is not possible in this context[15]). Studies of other opioid interventions, such as PDMPs, could potentially confound producer- and consumer-side responses.[16] Understanding such substitution patterns are especially important given the current focus on using supply-side policies to combat opioid abuse.

[14] For example, DiNardo and Lemieux (2001) and Crost and Guerrero (2012) find substitution between alcohol and marijuana. In more closely related work, medical marijuana laws led to substitution from opioids to marijuana (Powell et al., 2015). Other studies find evidence of complementarities across drugs (e.g., Williams et al, 2004; Saffer and Chaloupka, 1999; Pacula 1998).

[15] The OxyContin reformulation is a unique intervention in this respect since Purdue Pharma is the sole legal producer of this compound and altogether reduced the supply of its abusable drug formulation immediately and permanently across all markets. Thus, the reformulation did not have a producer-level substitution response.

[16] For example, a PDMP may reduce the supply of opioids diverted from the medical side of the market (e.g., pharmacies). However, the black market could compensate for this supply reduction by funneling in opioids from out-of-state pharmacies with less stringent PDMPs. In this case, we would predict less substitution to heroin.

II. Data and Descriptive Statistics

To estimate the impact of the introduction of abuse-deterrent OxyContin, we combine several data sources to measure: 1) OxyContin and prescription pain reliever use and 2) heroin and opioid-related overdose deaths and overall overdose deaths. These data sets all provide state-level information and we conduct our analyses at this level.[17]

A. Nonmedical Opioid Use

To measure nonmedical use of OxyContin and pain relievers, we use state-level data from the National Survey on Drug Use and Health (NSDUH). The NSDUH, sponsored by SAMHSA, is a nationally representative household survey of individuals ages 12 and older and is the largest annual survey collecting information on substance use in the U.S. The survey provides information on self-reported "nonmedical OxyContin use" within the past year beginning in 2004 as well as "nonmedical pain reliever use." The publicly available NSDUH data are available in two year waves.[18] We use nonmedical OxyContin use rates from the

[17] While some sub-state information is available (e.g., county-level mortality), sub-state data is not available for our primary measure of OxyContin misuse (our source of variation in exposure to the reformulation). Our empirical strategy requires that we have cross-sectional variation in misuse, and we will show that there is sufficient state-level variation. In principle, performing this analysis using sub-state areas (if such data were available) could improve precision. However, using state-level data should not bias our estimates.

[18] SAMHSA recently restricted access to the individual level NSDUH data. Specifically, the portal allowing access to geographically identifiable individual level data in the NSDUH has been closed for over two years, making it impossible to conduct this work on the NSDUH microlevel data. We use the only NSDUH data that were available to researchers which is aggregated to the state level and available in two year waves. These data are sufficient for the purposes of constructing state-level measures of pre-reformulation OxyContin misuse.

2004-2005, 2006-2007, 2008-2009, 2010-2011, and 2012-2013 waves, and we will often refer to each wave by its first year.

We use the NSDUH data to construct our main measure of OxyContin misuse for two reasons. First, it specifies OxyContin in the survey question, which is the exact drug product affected by the reformulation. Second, it specifies nonmedical use. In the NSDUH, nonmedical use is defined as use by individuals who either (a) were not originally prescribed the medication or (b) use such medications "only for the experience or feeling they caused."[19] Given the sensitive nature of pain reliever misuse, NSDUH provides respondents with a highly private and confidential method for responding to questions in effort to increase honest reporting.[20] Nevertheless, self-reported data on drug use is subject to some under-reporting error. Prior validation studies have shown that reporting of illicit drug use (e.g., marijuana, cocaine, and heroin) in the NSDUH is accurate in 68% to 96% of responses (Harrell, 1997), though data on the degree of pain reliever under-reporting is not available.[21] Since the focus of our analysis is on geographic patterns in OxyContin misuse, the misreporting error will not confound our estimates if it is not systematically correlated with state-level changes in heroin use. We will provide evidence that state-level OxyContin misuse rates from the NSDUH are correlated with both administrative data on the

[19] Specifically, the respondent is shown cards with the names of different types of pain relievers (including OxyContin) and photos of the pills. They are asked to identify "which of the pain relievers…have you used when they were not prescribed for you or that you took only for the experience or feeling they caused?" This section of the questionnaire is preceded by the following introduction, which further emphasizes non-medical use: "Now we have some questions about drugs that people are supposed to take only if they have a prescription from a doctor. We are only interested in your use of a drug if the drug was not prescribed for you, or if you took the drug only for the experience or feeling it caused."

[20] NSDUH collects data using audio computer-assisted self-interviewing (ACASI) in which respondents read or listen to the questions on headphones and respond using a NSDUH laptop computer, rather than to an interviewer.

[21] Under-reporting due to missing values is not a concern with the NSDUH. For example, in 2004, less than 0.4% of responses to the OxyContin question are missing values. NSDUH uses statistical imputation to account for nonresponse (which is rare) in constructing state-level averages of misuse.

legal supply of oxycodone from ARCOS and opioid prescriptions in the geocoded Medical Expenditure Panel Survey (MEPS), which is reassuring that the NSDUH data accurately identifies geographic variation in OxyContin misuse.

Despite the limitations of self-reported data, the main advantage of this survey is that it captures "nonmedical use." Alternative data sources on OxyContin use through legal channels, such as pharmacy claims data or reports of legal distribution of oxycodone, may not fully capture the differential effects of the reformulation across states—which we would expect to affect nonmedical users more than medical users. Thus, we consider "nonmedical use" as our preferred measure. However, our results are robust to using alternative data sources and measures of OxyContin use including legal distribution, which we show in Section IV.

We define exposure to the reformulation as the population-weighted rate of OxyContin misuse in each state combining the 2004-2005 through 2008-2009 waves. We select these years because they precede the 2010 introduction of abuse-deterrent OxyContin and aggregate the waves together to obtain more precise measures of OxyContin misuse rates, reducing concerns about measurement error. The nonmedical pain reliever use variable is constructed similarly. We will also present sensitivity analyses where we construct our measure of initial OxyContin misuse using only one wave. We do not measure heroin use because NSDUH heroin data are currently unavailable at the state-level. However, we will measure substance abuse treatment admissions for heroin as an alternative measure of abuse using the Treatment Episode Data Set (TEDS), described further in Section IV.

We complement these data with information about the legal supply of opioids at the state-level from the DEA's Automation of Reports and Consolidated Orders System (ARCOS). The Controlled Substance Act of 1970 requires all manufacturers and distributors to report their transactions and

deliveries of all Scheduled II-V substances to the Attorney General. ARCOS is the system that monitors and records the flows of these controlled substances as they move from manufacturers to retail distributors at the state level.[22] Only the active ingredients are reported in this dataset, so we observe the total distribution of oxycodone by state, but not OxyContin specifically. However, OxyContin accounts for a large share of oxycodone distribution.[23] We will use ARCOS data to define alternative measures of exposure to the reformulation based on the relative importance of oxycodone in the state compared to hydrocodone, prior to the reformulation. Hydrocodone (e.g., Vicodin) is another Schedule II prescription opioid which is a clinical substitute for oxycodone and is also commonly abused.[24] States which disproportionately prescribe oxycodone relative to hydrocodone should be more affected by the reformulation.

B. Mortality

We use the National Vital Statistics System (NVSS) Multiple Cause of Death mortality files—the census of deaths in the U.S.— to study annual overdose deaths from 1999-2013. We use restricted data to access state identifiers. We follow the coding used by the CDC to categorize deaths as opiate-related. First, we code deaths as overdoses by using the ICD-10 external cause of injury codes X40-X44, X60-64, X85, or Y10-Y14. Second, we use drug

[22] While ARCOS reports supply in grams, we convert oxycodone and hydrocodone into morphine equivalent doses using standard conversions into morphine milligram equivalents [https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-March-2015.pdf (last accessed August 15, 2017)] and then dividing by 60 (to convert to doses).

[23] OxyContin accounted for about 70% of oxycodone distribution in 2000 and 2002 (Van Zee, 2009; Paulozzi, 2006). Other products containing oxycodone include OxyIR, Percocet, Percodan, and Tylox.

[24] In a study of opioid-dependent subjects entering drug treatment programs, oxycodone and hydrocodone were the drugs of choice for 75% of patients (Cicero et al., 2013).

identification codes, which provide information about the substances found in the body at death. There are four drug identification codes related to opiates. T40.1 indicates poisoning by heroin. Opioid-related deaths (excluding heroin) are identified as: T40.2 for natural and semisynthetic opioids (e.g., oxycodone and hydrocodone), T40.3 for methadone, and T40.4 for synthetic opioids excluding methadone (e.g., fentanyl and tramadol). Following the CDC, we combine T40.2-T40.4 as our measure of total opioid-related deaths. We also study more disaggregated measures of opioid deaths, such as examining T40.2 alone (since the OxyContin reformulation should have the most direct effect on this category) and examining substitution across categories.

The mortality estimates that we present reflect any presence of the drug, unless otherwise noted. While this approach does not allow us to attribute the death to a single drug when multiple drugs are mentioned on the death certificate, increases or decreases in the presence of a drug are indicative of substitution patterns. Since multiple drugs are often mentioned, and this has occurred at an increasing rate over time (Ruhm, 2016), we will also compute mortality rates based on the exclusive presence of a particular drug (e.g., heroin only) in sensitivity analyses.[25] While variation in reporting rates across states and time may lead us to understate the prevalence of deaths from specific drugs (Ruhm, 2016), we do not expect that there were sharp systematic changes in reporting that occurred precisely after 2010.

C. Variation in Initial OxyContin Misuse

There is significant geographic variation in initial nonmedical OxyContin use, which is illustrated in Figure A.1. We exploit this geographic variation in our

[25] Comparing the results from any mention of a drug to an exclusive mention bounds the contribution of each specific drug in explaining trends in overdose deaths.

analysis. There are some clusters of misuse (such as Indiana, Kentucky, and West Virginia), but we see high propensities to misuse throughout different parts of the country. The OxyContin misuse rate ranges from 0.26% in Illinois to 1.15% in Rhode Island. Variation in OxyContin misuse could be driven by many factors including: variability in prescribing of specific opioids (not unlike the observed geographic variation in health care services more generally) due to a lack of consensus on best practices for treating pain patients (Paulozzi et al., 2014); or variability in consumer brand preferences.[26]

Alternative measures of initial OxyContin misuse are correlated with our chosen measure, as shown in Figures A.2 and A.3. These figures show that our measure is strongly correlated with the 2004-2005 misuse rate and the 2008-2009 misuse rate (Panel A of Figure A.2), demonstrating that the measure is stable over time.[27] Using ARCOS data, we also show that there is a strong correlation between OxyContin misuse and the per capita legal supply of oxycodone (Panel A of Figure A.3). Finally, rates of OxyContin misuse are also positively correlated with OxyContin prescription claims from the MEPS (Panel B of Figure A.3).[28,29] We would not expect that these alternative measures would be perfectly correlated with our OxyContin misuse measure given that only a fraction of the

[26] For example, OxyContin is more expensive than other opioids, but also delivers a preferred high over hydrocodone. Hydrocodone is often preferred by more risk-averse recreational users such as women and the elderly; while OxyContin is often preferred by more risk-tolerant young men (Cicero et al., 2013).

[27] Year-to-year correlations of OxyContin misuse within a state are also relatively strong (see Figure A.2, Panel B), suggesting that misuse was quite stable within states over time. Indeed, our main results are similar whether we use the two-year waves or the full pre-period to measure initial misuse.

[28] We accessed the restricted MEPS with state identifiers at the AHRQ Data Facility. We computed the fraction of individuals ages 12 and above from 2004-2009 with at least one prescription with the drug name "oxycodone" or "OxyContin" (we excluded combination products such as oxycodone/acetaminophen, which are not OxyContin).

[29] We also find a high level of year-to-year stability within states in the ARCOS and MEPS measures. These measures are slightly more stable over time than the NSDUH measures, as they are based on administrative data or validated claims rather than self-reports.

legal supply of oxycodone (ARCOS) or medically-intended prescriptions (MEPS) are diverted to nonmedical use.

We will also present analyses where we exploit differences in states' total supply of oxycodone relative to hydrocodone to isolate independent variation in OxyContin misuse. As shown in Table A.1, states with high shares of oxycodone relative to hydrocodone distribution have higher rates of OxyContin misuse but *not* higher rates of misuse of other types of pain relievers. Our analysis will proceed by using OxyContin misuse rates from the NSDUH as our main measure of exposure because we hypothesize that this is the margin determining substitution to heroin. However, we will also show results using variation in the oxycodone-relative-to-hydrocodone share to further isolate changes due to the reformulation rather than other policies.

D. Descriptive Statistics

States with higher misuse rates of OxyContin differ from states with lower misuse rates. Table 1 shows mean outcomes and control variables before the reformulation for states with above and below-median rates of initial OxyContin misuse as measured in the NSDUH. As we would expect, high OxyContin misuse states have more oxycodone doses per capita, more opioid overdoses, and more drug overdoses from all causes. However, there is no statistically significant difference in heroin mortality rates between the two groups of states prior to the OxyContin reformulation. The age composition is relatively similar across states as are the economic indicators as measured in 2000. However, high OxyContin misuse states have smaller populations and a higher proportion of whites. These differences motivate the inclusion of state fixed effects in our analyses.

[Table 1 about here]

III. Empirical Strategy

We estimate the causal impact of the OxyContin reformulation by exploiting variation in states' exposure to the reformulation due to differences in their initial prevalence of OxyContin misuse. We examine whether states with higher rates of OxyContin misuse experienced larger changes in heroin and opioid-related deaths by estimating the event-study specification:

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

where Y_{st} is the number of heroin or opioid deaths per 100,000 in state *s* and year *t*. $OxyRate_s^{Pre}$ is the fixed rate of OxyContin misuse in state s in the pre-reformulation period (using the 2004-2009 NSDUH) and is interacted with a full set of year fixed effects. We control for state fixed effects α_s to account for fixed cross-sectional differences across states as well as year fixed effects γ_t to account for national shocks and trends in heroin availability, enforcement, prices, and other factors common across states. Standard errors are clustered at the state level to account for serial correlation.

The main variables of interest are the full set of δ_t estimates, which we will show graphically, normalizing the 2009 coefficient to zero. These estimates identify the differences in mortality rates across states with higher and lower initial rates of OxyContin misuse in each year and we will test for a trend break after the reformulation in 2010. For heroin deaths, we expect the estimates of δ_t to increase beginning after 2010 if higher initial OxyContin misuse in the state predicts a larger increase in heroin deaths after the OxyContin reformulation. The

identifying assumption is that in the absence of the reformulation, differences across states would have continued along the same trends.

We also parameterize the above model to estimate the average effect of the reformulation. Specifically, we estimate a trend-break specification limiting the analysis sample to the years 2008-2013. We focus on the time period close to the reformulation to estimate the linear trend more precisely, although we show that results are similar if we use a longer pre-period. Our specification is as follows:

$$(2) \qquad Y_{st} = \alpha_s + \gamma_t + \delta_1[Post_t \times OxyRate_s^{Pre}] + \delta_2[t \times OxyRate_s^{Pre}] + \delta_3[Post_t \times (t - 2011) \times OxyRate_s^{Pre}] + X'_{st}\beta + \varepsilon_{st},$$

where $Post_t$ is an indicator that turns on in 2011 and later and t is a linear time trend—i.e., $(t - 2011)$ equals 1 in 2012 and 2 in 2013. This specification controls for pre-existing trends while allowing for both a level shift and trend break beginning in 2011. We restrict the trend break to occur in 2011 since the discontinuation of the original formulation occurred late in 2010 and we expect that patients still had some access to this formulation as pharmacies drew down their inventories.[30] To the extent that a partial effect occurred in 2010, our estimates should be biased towards zero, which we examine in robustness tests. Equation (2) is a less flexible version of equation (1) but provides easier to interpret magnitudes for the relationship between initial nonmedical OxyContin use and changes in mortality. After estimating the parameters in equation (2), we report the effects of the OxyContin reformulation through 2013 ($\delta_1 + 2\delta_3$), our last year of data.

[30] Prescriptions filled at pharmacies for the original formulation of OxyContin accounted for 7.4%, 1.8%, and 0.6% of total OxyContin prescriptions in January 2011, June 2011, and December 2011, respectively (Butler, et al. 2013).

In the parameterized specification, we also include a vector of state and time-varying covariates X_{st}. In the basic set of covariates, we include the log unemployment rate, share of the population in 6 age groups (0-11, 12-17, 18-24, 25-44, 45-64, 65+), share female, share white, share with high school degree or less, some college, and college degree or more, and log population.[31] We also control for state policy variables that may independently impact opioid and heroin deaths including indicators for PDMP adoption (controlling for any PDMP and a "must access" PDMP[32]), indicators for whether the state has a medical marijuana law (MML) and for the presence of active and legal dispensaries (since opiates and medical marijuana may be substitutes), and an indicator for whether the state has pill mill legislation.[33] In robustness tests, we test for the independent contribution of each of these policy variables.

In some specifications, we also provide estimates where we control separately for initial nonmedical pain reliever use, parameterized in the same manner as initial OxyContin misuse.[34] Including both variables allows us to isolate the effect of the OxyContin reformulation relative to other policies, such as PDMPs, which affect opioid abuse more broadly. If OxyContin reformulation is the driving force behind the change in opioid and heroin mortality rates, then we would expect that the changes in these outcomes would load on the OxyContin misuse variable rather than on the more encompassing nonmedical pain reliever use variable.

[31] The unemployment rate is from the Bureau of Labor Statistics (BLS); education and race variables are from the American Community Survey (ACS); population totals, age shares, and share female are from the Census.

[32] Buchmueller and Carey (2017) find that "must access" PDMPs may be more effective in reducing opioid abuse.

[33] Medical marijuana law and dispensary data is taken from Powell et al. (2015); PDMP information and pill mill legislation is derived from LawAtlas and Buchmueller and Carey (2017).

[34] This measure is constructed similarly to initial OxyContin misuse and is included in equation (2) on its own by interacting the initial rate with a post-2010 indicator, a linear time trend, and a post-2010 time trend.

IV. Results

Our analysis proceeds in three steps. First, we provide evidence for our key underlying assumption that OxyContin misuse declined more after the reformulation in states with higher initial OxyContin misuse. Second, we estimate the causal impact of this reduction in OxyContin misuse due to the reformulation on overdose deaths involving heroin. We also separately identify deaths caused by different types of opioids as well as the impact on overall overdose deaths. Third, we investigate alternative channels for the observed substitution patterns across drugs, including other state-level opioid policies, changes in heroin prices, and economic shocks.

A. First Stage Effects of Reformulation on OxyContin Use

We begin by showing graphically that the initial rate of OxyContin misuse in a state is strongly predictive of differential changes in OxyContin misuse after the 2010 reformulation. This relationship is necessary for using variation in initial OxyContin misuse to identify the reformulation's impact.[35] Figure 3 shows the "first stage" relationship between the pre-reformulation OxyContin misuse rate and the change in the OxyContin misuse rate between the 2008 and 2012 waves in the NSDUH data. We divide states into quartiles based on their initial OxyContin misuse and plot the histogram of rate changes. We observe a monotonic relationship between initial OxyContin misuse and reductions in misuse after the reformulation. In states with the highest initial OxyContin

[35] While the underlying relationship is necessary, it is possible – in principle – that it may be difficult to detect this relationship statistically given the size of the NSDUH. However, we find statistically significant differential reductions.

misuse, the rate of OxyContin misuse declined by nearly 50 percent after the reformulation, while OxyContin misuse actually increased slightly in states with the lowest rates of initial OxyContin misuse.

[Figure 3 about here]

Figure A.4 shows an analogous event study version of the first stage by estimating equation (1) using OxyContin misuse as the outcome variable. We should expect to observe a partial effect in 2010-2011, since the reformulation occurred in late 2010, followed by a full effect for 2012-2013. We observe a relative decrease in 2010-2011 for states with higher initial misuse rates followed by an even larger decrease in 2012-2013. The 2012-2013 estimate indicates that each percentage point increase in initial nonmedical OxyContin use is associated with a statistically significant decrease in misuse of 0.8 percentage points after reformulation relative to 2008-2009 and 0.4 percentage points relative to 2004-2005 or 2006-2007.[36] As complementary evidence, we also present a scatterplot (Figure A.5) which shows the state-by-state relationship between initial OxyContin misuse and changes in misuse after reformulation.

B. Effects of OxyContin Reformulation on Heroin Mortality

Main Results.— Next, we examine whether the differential decrease in OxyContin misuse led to changes in heroin mortality. Figure 4 presents the full set of coefficients from estimating our baseline event-study specification (equation 1) for several mortality outcomes. The first graph in Panel A shows the point

[36] We can reject that the 2012-2013 estimate is equal to the 2004-2005 estimate at the 5% level, the 2006-2007 estimate at the 10% level, the (omitted) 2008-2009 estimate at the 1% level, and the (partially-treated) 2010-2011 estimate at the 1% level. A joint test that the 2012-2013 estimate is equal to each of the pre-reformulation estimates (2004-2005, 2006-2007, and 2008-2009) is rejected at the 1% level. A parametric specification in which we permit a differential pre-trend (similar to equation 2) also estimates statistically significant reductions at the 1% level.

estimates and 95% confidence intervals for heroin mortality. The effect of the reformulation on heroin overdose deaths is striking. The event study coefficients are close to zero and statistically insignificant in every year before the reformulation. This indicates that there were no differences in pre-reformulation trends in heroin deaths per capita across states with high and low initial rates of OxyContin misuse. Moreover, as previously shown in Table 1, there was no difference in the *levels* of per capita heroin deaths across these states. In fact, the correlation between our OxyContin misuse measure and per-capita heroin deaths before 2010 is only 0.019.[37] However, following the reformulation in 2010, there is a sudden statistically significant relative increase in heroin deaths in states with the highest initial rates of OxyContin misuse. The magnitude of this differential effect grows larger in 2012 and 2013. The timing of this effect, which coincides precisely with the reformulation, and the fact that this effect is concentrated among states with the highest initial OxyContin use strongly suggests a causal relationship between the OxyContin reformulation and the sharp increase in heroin deaths.[38] We further explore the causality of this relationship below.

[Figure 4 about here]

In Table 2, we present the parameterized estimates from equation (2) to quantify the total magnitude of the impacts of the reformulation on heroin deaths. We report the "three-year effect" of the reformulation (i.e., the effect through 2013), combining the intercept and slope shift coefficients from equation (2). Specifically, we report estimates of $\delta_1 + 2\delta_3$.[39] Standard errors in Table 2 are

[37] Figure A.6 shows a scatter plot of this cross-sectional relationship.

[38] The growth over time is notable since we may hypothesize that substitution to heroin would cause an immediate rise in deaths due to the lack of experience of first-time heroin users. In other words, first-time users may be more vulnerable to purchasing heroin with unknown purity (i.e., tainted with other substances) or have less experience using it which may increase the risk of death. However, we observe larger effects even three years later.

[39] We report the δ_1, δ_2, and δ_3 estimates separately in Table A.2.

clustered by state. We report block-bootstrapped confidence intervals in Table A.3.[40]

In Column (1), we report an effect of 2.2, implying that a 1 percentage point higher rate of initial OxyContin misuse leads to an additional 2.2 heroin deaths per 100,000 in 2013, which is statistically significant at the 5% level. This estimate indicates that each standard deviation increase in the initial OxyContin misuse rate is associated with an additional 0.50 heroin deaths per 100,000 in 2013, a 47% increase relative to the baseline mean of 1.06. In Column (2) of Table 2, we include time-varying state-level covariates (excluding policy variables). The estimate increases in magnitude to 2.8 and is statistically different from zero. Column (3) adds policy variables (i.e., PDMPs, Must Access PDMPs, MMLs, and pain clinic laws). The estimate is relatively unaffected by the inclusion of these additional controls.

Column (4) presents the results when both initial OxyContin misuse and initial pain reliever use are included. This test is important because the two variables are correlated[41] and our initial OxyContin measure is potentially picking up some effects related to initial pain reliever misuse more generally. By controlling for the overall pain reliever misuse variable, we can isolate the effects of the OxyContin reformulation from other opioid policies affecting pain relievers. We find that the positive effect on heroin deaths does indeed "load" on the OxyContin measure. We estimate that an additional percentage point of nonmedical OxyContin use before reformulation increases heroin deaths by 3.6

[40] We generate confidence intervals for the linear estimates using a block bootstrap procedure where we bootstrap the *t*-statistics. This approach provides asymptotic refinement. To create symmetric confidence intervals, we compare the absolute value of the sample *t*-statistic to the distribution of the absolute value of *t*-statistics generated by the bootstrap. The bootstrapped confidence intervals are generally tighter than those implied by the standard errors in Table 2.

[41] The correlation between initial OxyContin misuse and initial pain reliever misuse is 0.457 (see Panel C of Figure A.3 for a scatter plot of the relationship).

deaths per 100,000 in 2013.[42] Thus, not accounting for pain reliever misuse actually biases the estimates downward. The coefficient on initial pain reliever misuse—controlling for OxyContin misuse— is negative, suggesting that policies and programs (e.g., substance abuse treatment programs, naloxone access laws, etc.) were disproportionately targeted to areas with high overall pain reliever misuse and led to a small decline in heroin deaths. We will show below that opioid deaths may have also declined more in these states, consistent with the systematic adoption of policies broadly reducing opioid- and heroin-related harms.

[Table 2 about here]

In the final two columns of Table 2, we test the sensitivity of the results to functional form by implementing Poisson regression (the corresponding event studies are shown in Figure A.7). Since states have different initial mortality rates, it may be useful to model the effect of reformulation as having a proportional effect from these different baselines.[43] For heroin deaths, this is less of a concern since these baseline differences are not systematically related to initial nonmedical OxyContin use, though proportional effects are important for opioid deaths in the next section. In Column (5), we estimate a positive and statistically significant relationship between initial OxyContin misuse and heroin deaths. The Poisson coefficients are not directly comparable to OLS, but the estimate implies that a one percentage point higher initial OxyContin misuse rate leads to 2.8 more heroin deaths per 100,000 in 2013, similar to the estimates from the linear specification estimated above. In Column (6), we include both pre-

[42] This estimate implies that each standard deviation increase in the initial nonmedical OxyContin misuse rate increased heroin deaths per 100,000 people in 2013 by 0.78.

[43] Poisson regression permits the estimation of proportional effects and has several advantages over estimating a linear specification with a log outcome variable (Santos Silva and Tenreyro, 2006), especially when the outcome includes zeros (which occurs for about 12% of state-years in the full sample and 6% in the 2008-2013 sample).

reformulation misuse measures. The estimated relationship between initial OxyContin misuse and heroin deaths increases and is statistically significant at the 1% level.

In Panel B, we compute heroin mortality rates based on the exclusive presence of heroin at the time of death. Both panels are indicative of substitution patterns, however, the heroin-only measure allows for a more exact attribution of the death to heroin. We find similar results for both measures. Figure A.8 presents an event study using heroin-only overdoses as the outcome.

Alternative Measures of Exposure to the Reformulation.— We also show that our results are robust to alternative measures of exposure to the reformulation. We present these results as graphical event studies in Figure 5 (the corresponding regression estimates are shown in Table A.4). First, in Panel A, we define a state's exposure to the reformulation as the initial rate of OxyContin misuse divided by the initial rate of pain reliever misuse. This variable captures the fraction of individuals misusing pain relievers who are misusing OxyContin specifically. Thus, it accounts for differences in the rate of overall pain reliever misuse across states. Second, in Panel B, we use ARCOS data to define a state's exposure as the initial supply of oxycodone (in morphine equivalent doses) divided by the total supply of oxycodone and hydrocodone combined. While oxycodone and hydrocodone are generally considered substitutes, there is state variation in the relative size of the supplies of these drugs. Finally, Panel C replicates Panel B but uses the ratio of initial oxycodone supply to initial hydrocodone supply.

[Figure 5 about here]

Using all three measures, the event study pattern is very similar to our previous results using our preferred NSDUH OxyContin misuse measure. The

magnitudes of the effects are also stable across measures as shown in Table A.4.[44] Overall, we find that our results are not sensitive to how we construct the measure of exposure to the reformulation. Moreover, these alternative measures suggest that our results are due to policies targeting OxyContin/oxycodone specifically, and not due to policies (or concurrent shocks) for opioids overall.

Heterogeneity in the Heroin Mortality Effect.— In Table 3, we examine heterogeneity in the effect of the reformulation across subgroups by age, gender, race, and education. It should be noted that our initial OxyContin misuse rate does not vary based on demographics, so we associate the overall rate in initial OxyContin misuse to changes in heroin deaths for specific groups.[45] We find the largest increases in heroin deaths for individuals ages 25-64, though there is also a statistically significant increase for those under age 25. There is no statistically significant effect of the reformulation for the elderly ages 65 and over. The effect is larger for men than for women. Further, the rise in heroin deaths is concentrated among whites. We find statistically significant increases in heroin deaths for the more highly educated, though the point estimate is also large for those with less education, albeit not statistically significant.[46] These results show that the rise in heroin deaths due to the reformulation is driven largely by working-age, white men—which is precisely the demographic group that has been hit the hardest by the opioid epidemic, as noted in Case and Deaton (2015).

[Table 3 about here]

[44] Since the alternative measures of exposure to the reformulation are each in different units, we present the effect of a one standard deviation increase in exposure on the heroin death rate.

[45] Some caution in interpretation is warranted since the estimates represent a combination of variation in misuse for a subgroup across states and the transition rates for that group from nonmedical use to heroin overdoses.

[46] The national time series rise in heroin mortality after 2010 is also larger (in percentage terms) for the highly-educated relative to the less-educated, suggesting that this group substituted to heroin at a higher rate after reformulation.

C. *Effects of OxyContin Reformulation on Opioid Mortality*

We also examine the effect of the reformulation on opioid deaths. Figure 4 (second figure in Panel A) presents the main event-study specification for overall opioid deaths. Event-studies for each opioid subtype (e.g. synthetic vs. non-synthetic) are discussed below and presented in Appendix Figure A.9. There is an upward trend in overall opioid overdose deaths as a function of initial OxyContin misuse before the reformulation. This shows, not surprisingly, that opioid deaths per capita were growing faster in states with high initial OxyContin misuse, motivating our use of a regression specification which accounts for pre-existing trends.

Following the 2010 reformulation, we observe some evidence of a leveling off and a small relative decline in opioid deaths in states with higher initial OxyContin misuse. However, while the point estimates decline, the confidence intervals widen in 2010, making it difficult to reject that the reformulation had no effect on opioid mortality. It should be noted that this figure includes all opioid overdoses, not just those specifically involving OxyContin, adding noise to our overdose measure and encompassing substitution to other types of opioids. Below, we will examine disaggregated measures of opioid deaths to study within-opioid substitution.

To quantify the magnitude of the reformulation effects, Table 4 presents estimates from the parameterized model for opioid-related mortality (Table A.5 presents heterogeneous effects by demographic subgroup). In Panel A, we estimate the effects of the reformulation for total opioid deaths per 100,000 (drug codes T40.2-T40.4). The point estimates suggest that the reformulation differentially decreased overall opioid deaths in areas with high initial OxyContin

misuse, but the estimates are too noisy to statistically reject that there is no effect. In Column (1), we find that each percentage point of nonmedical OxyContin use in the pre-period is associated with a decrease of 1.1 opioid deaths per 100,000 after reformulation, but this relationship is not statistically significant. Recall that in the corresponding event study shown in Figure 4 we observed a flattening trend around the time of reformulation, though the confidence intervals were wide. Adding covariates in Column (2) decreases the magnitude of the estimate to 0.3. The estimate is similar when the policy variables are included in the model (Column 3). When we jointly estimate the effects of initial OxyContin and pain reliever misuse in Column (4), we find that high OxyContin misuse is associated with a statistically insignificant *increase* in opioid-related deaths after reformulation. Initial pain reliever use leads to a decrease in opioid-related mortality, which may be due to the effects of other policies aimed at opioid abuse, as noted above, though neither effect is statistically significant. The Poisson estimates in Columns (5) and (6) also find no statistical relationship between initial OxyContin misuse and changes in opioid-related mortality, and the point estimates are positive.[47]

[Table 4 about here]

Panel A represents the broadest definition of opioids, possibly explaining these null results, at least in part. The analysis combines all types of opioids (T40.2-T40.4), though we might expect the reformulation to have a negative effect on deaths due to oxycodone (T40.2) and a positive effect on deaths involving synthetic opioids (T40.4) due to substitution effects. This may cause offsetting effects which mask changes in opioid deaths for specific types of

[47] For heroin mortality, there was almost no correlation between initial OxyContin misuse and the death rate. This is not the case for opioid deaths, which is one possible reason that the OLS and Poisson estimates have different signs.

opioids. We explore this heterogeneity below by separately examining natural and synthetic opioids.

Moreover, given differential trends in opioid deaths before reformulation, it is more difficult to precisely estimate post-reformulation effects for opioid outcomes— especially when compared to the heroin analysis in which pre-reformulation levels and trends are nearly identical across states. While our regression specification does account for differences in pre-reformulation levels (state fixed effects) and trends (OxyContin misuse rates interacted with linear trends), we use some caution in interpreting the null effects for opioids and view these results as more suggestive when compared to the heroin analysis.

Opioid Mortality due to Natural Opioids.— In Panel B, we present estimates for deaths from natural opioids (T40.2), which includes drugs such as oxycodone and hydrocodone (the corresponding event study is in Figure A.9). For natural opioids, the point estimates generally become more negative, but we still cannot statistically reject that there is no effect in the OLS specifications. The Poisson estimates, however, are statistically different from zero and suggest reductions in overdoses involving natural opioids.

Parsing the data further, in Panel C, we consider the effects of the reformulation on natural opioid-only mortality (the event study is also in Figure A.9). Specifically, we construct deaths due to natural opioids excluding deaths that also involve heroin (T40.1), methadone (T40.3) or synthetic opioids (T40.4). The linear estimates again increase in magnitude. They are statistically significant at the 10% level until we control for initial pain reliever misuse in Column (4). The Poisson estimates are statistically significant at the 1% level. The pattern across Panels A through C shows that as we more precisely isolate deaths involving OxyContin, we find greater evidence of a differential reduction

in opioid deaths following the reformulation. However, there are limits to this exercise and we consider the evidence largely suggestive.

In summary, the opioid mortality results are noisy, but suggestive of a reduction in natural opioid deaths. It is important to note that we would not expect the reduction in opioid deaths to be equal in magnitude to the rise in heroin deaths. Heroin is more lethal than OxyContin so even a small amount of substitution from OxyContin to heroin—which may have little impact on prescription opioid deaths—could plausibly lead to a large increase in heroin deaths.[48] Since data on heroin use is not available, we cannot differentiate between a small fraction of individuals switching to heroin with a high probability of overdosing and a larger fraction with a smaller probability of overdosing. However, as a complementary measure, we examine changes in substance abuse treatment admissions for heroin in the Treatment Episode Data Set (TEDS), which covers all treatment facilities receiving public funding.[49] We estimate the event study specification (equation 1) from 1999-2012[50] for heroin treatment admissions per 100,000 as the outcome variable (see Figure A.10). We find a similar pattern as heroin deaths. There was a statistically significant increase of 50.76 admissions per 100,000 in 2012, relative to the 2009 baseline. For the corresponding 2012 mortality estimate, we estimate an increase of 1.66 deaths per 100,000— much smaller than the rise in treatment admissions. The large

[48] Moreover, it may also be the case that naive users of heroin are more susceptible to overdoses (e.g., obtaining deadly forms of heroin or using the drug in a way that may increase the probability of overdosing).

[49] While TEDS is often used in research, there are concerns about underreporting of admissions. Some states may not report in each year or may not report admissions in the same manner over time (SAMHSA, 2013). However, there is little reason to believe that such underreporting would correlate with initial OxyContin misuse and change after 2010. We tested this assumption explicitly by replicating the analysis for other substances (e.g., marijuana, alcohol) and do not observe a similar pattern, suggesting that reporting issues are not driving the heroin results.

[50] 2012 is the most recent year of TEDS micro-data, which are necessary to construct our measures of admissions.

increase in heroin treatment admissions is suggestive of a sizeable increase in heroin use.

Opioid Mortality due to Synthetic Opioids.— In addition to substitution to heroin, we also hypothesize that the reformulation may have caused substitution to other types of opioids. If this occurred, it may explain part of the recent rise in deaths due to fentanyl and other synthetic opioids (categorized as T40.4), which are more dangerous than oxycodone.

Table 5 presents the estimates for synthetic opioid deaths. In Column (1) of Panel A, the effect of the reformulation is positive, but not statistically significant. As we include additional control variables and control for initial pain reliever use, we estimate positive effects which are statistically significant at the 10% level. When we estimate proportional effects using Poisson regression, we find statistically significant effects for synthetic opioid deaths. Given that there are large cross-sectional differences in synthetic opioid mortality correlated with initial OxyContin misuse, estimating proportional effects is more appropriate and explains the more precise estimates. In Column (6), we estimate that a one standard deviation higher initial OxyContin misuse rate leads to an additional 28% increase in synthetic opioid mortality. The graphical event study using Poisson regression presents complementary evidence (see Figure A.7), implying statistically significant increases with little evidence of differential pre-existing trends. In Panel B of Table 5, we estimate the effects for deaths due to synthetic opioids only. The linear estimates decrease in magnitude, but the Poisson estimates remain statistically significant at the 1% level. Taken together, this evidence is suggestive that the OxyContin reformulation may have increased deaths involving synthetic opioids.

[Table 5 about here]

D. Effects of OxyContin Reformulation on Total Overdose Deaths

Finally, we examine the net effects of the reformulation on total drug overdose deaths. We have previously shown evidence that reformulation increased heroin mortality, but we also find negative (though mostly insignificant) effects on natural opioid deaths. The overall effect is of special interest to understand the net impact of reformulation on drug abuse and mortality—arguably, the outcomes that the intervention seeks to address.

In Figure 4 (Panel B), we present event-studies combining opioid and heroin deaths. There is an increasing trend in the coefficients before the reformulation which flattens slightly in 2012. We observe a similar trend for all drug overdoses, which includes non-opiate drugs (e.g., cocaine). However, in both figures the confidence intervals widen in 2011, which makes it difficult to statistically reject that there is no effect, as we discuss below. In Table 6, we estimate the magnitudes of these net effects. In Panel A, we first replicate our previous tables, but using opioid and heroin deaths combined per 100,000 as the outcome. We estimate *positive* effects of the reformulation on deaths from opioids and heroin across all models, though these estimates are never statistically distinguishable from zero at the 5% level. We also examine total overdose deaths for all drugs, including non-opiate drugs. We find that initial nonmedical OxyContin use is not statistically significantly related to changes in drug overdoses overall, regardless of specification or estimation technique. The estimates are positive which is consistent with the heroin and synthetic opioid effects dominating. However, for both outcome variables in Table 6, there is too much noise to estimate the effects precisely. Overall, the results suggest that the increase in deaths from heroin and fentanyl offset any reductions in natural opioid deaths, leading to no net reduction in total overdoses from the reformulation.

[Table 6 about here]

E. Robustness Tests

Alternative Specifications.— In this section, we explore the robustness of our findings. We focus our discussion on heroin deaths, but find that the results for opioids deaths are also robust to alternative specifications. These robustness tests are presented in Table A.6. Panel A shows the results for heroin deaths and Panel B for opioid-related deaths.

In Column (1), we present our preferred estimate for heroin deaths (from Table 2, Column 3) of 2.52 to compare to alternative specifications. In Column (2), we exclude 2010 from the analysis, since this is a partially treated year, and estimate a larger effect. In Column (3), we test for the importance of weighting by state population. Without weights, we estimate a statistically significant effect of 3.76. In Column (4), we include state-specific trends and estimate a statistically significant effect of 2.52. In Column (5), we use the full sample period 1999-2013. We used 2008-2013 in our primary analyses to restrict to the years around reformulation and avoid fitting the pre-existing linear trend on data from over a decade before the intervention. Using the full sample, we estimate an effect of 2.04.

In Column (6), we replace our initial OxyContin misuse measure, constructed using the 2004-2008 NSDUH waves, with a similar measure constructed using the 2004-2005 wave only. One advantage of using this wave is that it pre-dates the 2008-2013 analysis sample. States which experience a transitory shock to opioid abuse might experience different changes in heroin abuse over time due to mean reversion. Using data further from the time of treatment reduces mean reversion concerns. Moreover, these years have the

advantage of preceding the Great Recession, which is a possible confounder if variation in misuse was partially driven by economic conditions. The disadvantage of using only one year of data is that it exacerbates measurement error. Using the 2004-2005 measure, we estimate an effect of 2.70, similar to our main estimate. In Column (7), we show the corresponding estimate using the 2008-2009 wave— the year before reformulation—and estimate an effect of 1.26, statistically significant from zero at the 10% level. The decrease in magnitude results partially from the noisiness of the measure constructed from one wave and partially because the standard deviation of the misuse measure is larger in 2008-2009 than in other years.[51] Mean reversion issues may also be a factor.

In general, measurement error in our measure of OxyContin misuse should attenuate our estimates. To explore this further, in a separate analysis, we replicate the Column (7) estimate in an instrumental variables framework to address measurement error concerns. We use the rates of initial OxyContin misuse from 2004 to instrument the rates from 2008.[52] This analysis, shown in Table A.7, provides further evidence that the single wave results contain measurement error, motivating the aggregation of waves in our main analysis.

Finally, it may be important to account for differences in age composition across states and time when studying overdose rates, beyond the age composition control variables we include in the regression model. Our summary statistics suggest that a state's age distribution is not predictive of OxyContin misuse, but

[51] For the main result (Column 1 of Table A6), a one standard deviation higher OxyContin misuse rates leads to an additional 0.57 heroin deaths per 100,000. When the 2008-2009 OxyContin misuse rate is used (Column 7), we estimate that a one standard deviation higher misuse rate leads to an additional 0.42 heroin deaths per 100,000.

[52] We replicate the Table A6, Column (7) model but estimate it using 2SLS with the 2004 misuse measure to generate the excluded instruments. The 2SLS estimate (see Column 1 of Table A7) implies that each percentage point increase in nonmedical OxyContin misuse in 2008 leads to an additional 5.2 heroin-related deaths per 100,000 people. The estimate is larger than the size of the OLS estimate, which is suggestive that the year-by-year measures have measurement error. The corresponding event study is included in Appendix Figure A.11.

we verify that age composition differences are not driving our results by age-adjusting our mortality rates. In Column (8), we use an age-adjusted heroin overdose rate and find a similar effect as our main result.

Alternative Explanations.— In Table 7, we consider an array of alternative explanations for the relationship between initial OxyContin misuse rates and changes in heroin deaths (Table A.8 replicates Table 7 for opioid-related mortality, finding similar results). In Column (1), we repeat our estimate of 2.80 (from Table 2) from the model with all covariates except for the policy variables. In the subsequent columns we include our policy variables one by one to test for the independent contributions of each variable. In Column (2) we include a time-varying indicator variable for whether the state has a PDMP. Including this variable in the model has little effect on the estimate. Evidence on the effectiveness of PDMPs is mixed, with a recent study suggesting that "must access" PDMPs reduce opioid abuse while PDMPs without such provisions have limited effects (Buchmueller and Carey, 2017). In Column (3), we control for whether a state had a "must access" PDMP and find similar effects. In Column (4), we control for an indicator for whether the state had medical marijuana laws (MMLs) as well as an indicator for whether the state has legal and operational dispensaries (since marijuana and opioids may be substitutes). In Column (5), we also control for an indicator for pill mill laws. We estimate effects similar to our main effect.

[Table 7 about here]

Another concern is whether pill mill laws enacted in Florida, specifically, around the time of the reformulation may explain part of the observed heroin effect. Florida experienced a dramatic rise in opioid supply in the 2000s due to lax regulations permitting the spread of "pill mills" throughout the state. In

response, a package of laws was passed in 2010 and 2011 which shut down many of these pain clinics (see Surrat et al., 2014 and Johnson et al., 2014). Given that the timing of this crackdown coincided with the reformulation of OxyContin, we address whether the rise in heroin mortality is primarily due to Florida policies. In Column (6) we exclude Florida from the sample, and the estimate increases slightly to 2.73. The Florida pill mills prescribed and sold opioids to out-of-state residents as well. There is some anecdotal evidence that a large share of these opioids were sold to residents of Kentucky[53] and West Virginia. When we exclude Florida, Kentucky, and West Virginia (Column 7), the estimate decreases to 2.24 but remains statistically significant from zero at the 5% level. More generally, the pill mills primarily affected the eastern portion of the United States and there is little evidence of noteworthy diversion to the western region. In Column (8), we include only the West Census Region and estimate a coefficient of 2.73, similar to our main estimate, though much noisier given the 75% reduction in sample size. Overall, the estimated relationship between initial nonmedical OxyContin misuse rates and growth in heroin deaths does not appear to be driven by other policies.

We also estimate our event study specification for heroin prices using the DEA's System to Retrieve Information from Drug Evidence (STRIDE) database which includes information from drug seizures, such as the type of drug, the purity, and the price. We construct state-level purity-adjusted measures of heroin prices for 2000-2012.[54] Heroin prices dropped nationally during our time period, continuing the long term downward trend observed over the past two decades (Kilmer et al., 2014). Our time fixed effects account for these national price changes. However, a reduction in heroin prices could explain the rise in heroin

[53] http://www.nytimes.com/2011/09/01/us/01drugs.html?_r=1 (last accessed October 3, 2016)
[54] We adjusted for purity and coverage rates using methods developed in Kilmer et al. (2014) and Arkes et al. (2004).

abuse if the price change was differential across areas with higher initial rates of OxyContin misuse. We present the results in Figure 6. We find that state-level heroin price changes are uncorrelated with initial OxyContin misuse, so they are unlikely to explain the differential rise in heroin deaths.[55]

[Figure 6 about here]

Similarly, differential economic shocks across states— in particular, the Great Recession from 2008-2010— may also have an independent influence on OxyContin misuse and drug overdose deaths. Previous work found that opioid deaths increase during time periods with high unemployment rates (Hollingsworth, et al. 2017). In Figure A.12, we repeat the event-study exercise using the log of the unemployment rate and housing price index[56] as outcome variables.[57] While opioid deaths may have risen overall during the Great Recession, we do not observe that the unemployment rate or housing price index changed systematically over time in a way that would be expected to confound our estimates.[58] The Great Recession does not appear to have had a greater negative impact in areas with high initial OxyContin misuse, suggesting that it cannot explain the differential rise in heroin deaths.[59]

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[55] While we might expect to observe a price increase due to the demand shock, the absence of a relationship is reassuring that other confounding shocks are not affecting our analysis. The lack of a price response may also occur if both demand and supply curves are shifting outwards.

[56] The data source is Federal Housing Finance Agency (https://www.fhfa.gov/DataTools/Downloads/pages/house-price-index-datasets.aspx, last accessed July 20, 2017), discussed in Bogin et al. (2016).

[57] Clemens and Wither (2014) consider the housing price index as a strong state-level proxy for the severity of the housing crisis during this time period.

[58] For the unemployment rate, the post-reformulation estimates suggest that economic conditions got differentially *better* in high OxyContin misuse states relative to 2009, which should work against finding any effects (Hollingsworth et al., 2017). However, the 2011-2013 estimates are statistically insignificant from every other pre-reformulation year estimate, which is consistent with our findings that controlling for the unemployment rate has little effect on any of our estimates.

[59] As shown before in Table A.6, our main results for heroin and opioid deaths are also robust to using 2004-2005 (before the recession) as the measure of initial OxyContin misuse. This is

Placebo Tests.— We also conduct placebo tests estimating our event study specification for cocaine overdose deaths and, separately, for all drug overdoses excluding heroin and opioids. These estimates are presented in Figure A.13. We find little evidence of effects for other drugs. Other drugs may be complements or substitutes for opioids so it is not clear whether we would expect to observe any relationship, but the statistical absence of any effect is reassuring that the heroin effect is not driven by concurrent demand shocks for drugs more generally.

F. Counterfactual Growth in Heroin Deaths

Finally, we quantify the effect of the reformulation in explaining the dramatic increasing national trend in heroin deaths after 2010. We use the event study estimates shown in Figure 4 to predict per capita heroin deaths. To make this counterfactual prediction, we set the initial OxyContin misuse rate to zero and calculate the heroin death rate in each year.[60] We estimate that reformulation can explain 0.37 heroin deaths per 100,000 in 2011, 0.94 deaths in 2012, and 1.10 deaths in 2013. Between 2010 and 2013, the actual heroin death rate increased by 101%. We predict that in the absence of reformulation, we would have observed only a 21% increase. Thus, our estimates imply that OxyContin reformulation is responsible for as much as 80% of the recent growth in heroin deaths.

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reassuring that the Great Recession is not differentially affecting initial OxyContin exposure in a way that is correlated with opiate mortality. Also, as shown in Tables 2-6, controlling for the unemployment rate does not alter the main results.

[60] We consider a hypothetical state with no pre-reformulation OxyContin misuse as "untreated", representing the counterfactual growth in heroin that would occur if there were no scope for substitution from OxyContin to heroin. In other words, the predicted mortality growth for this untreated state results only from "all other factors" contributing to heroin mortality growth during this time period. Of course, there are no states without any pre-reformulation misuse so this calculation is, by necessity, an out-of-sample extrapolation.

V. Conclusion

The reformulation of OxyContin represents one of the largest disruptions to date to the supply of abusable opioids. However, the benefits of any market disruption may unravel as producers and consumers respond to the supply shock by substituting to different suppliers (producers) or to other drugs (consumers). In this paper, we isolate the effects of consumer-level substitution responses to understand their role in the recent dramatic rise in heroin overdoses.

While the prior literature has relied on time series evidence to estimate the effects of the reformulation, we examine differential effects across states based on their pre-reformulation prevalence of OxyContin misuse. We estimate that initial OxyContin misuse rates are predictive of large and statistically significant increases in heroin mortality. This increase begins precisely in the year following the reformulation. Moreover, more general nonmedical pain reliever use does *not* predict an increase in heroin mortality – the increase loads entirely on OxyContin misuse specifically. Each additional percentage point of initial OxyContin misuse is associated with a decrease in OxyContin misuse of 0.8 percentage points and 2.5 additional heroin deaths per 100,000 (using our Table 2, Column 3 estimate). The implied instrumental variable estimate is that each percentage point reduction of OxyContin misuse due to reformulation increases heroin mortality by 3.1 deaths per 100,000.

Furthermore, we find no evidence that the reformulation reduced opioid deaths or overall overdose deaths (across all drugs), at least in the three years following the reformulation. We also find suggestive evidence that consumers substituted to synthetic opioids such as fentanyl. This combination of results demonstrates that the reformulation simply shifted deaths from one drug to another without reducing total mortality— suggesting that consumer-side substitution completely unraveled the benefits of the reformulation.

The findings from this study provide yet another example of how supply-side strategies alone are often inadequate for dealing with the drug problem, particularly when substitute drugs exist. This is evident in the large increase in heroin deaths (and deaths from other substitute opioids) following the reformulation. As summed up by Cicero and Ellis (2015), "as long as there is a demand for a drug, that demand will be met in some way." Treating underlying demand (e.g., through medication assisted treatment) may prove to be the more effective strategy for dealing with the current opioid epidemic, particularly because substitutes are readily available. Demand-side interventions as well as harm reduction strategies are likely to be more robust in the presence of close substitutes. Additionally, government policy may be able to implement broader supply-side interventions which are also more robust to substitution. We study a supply disruption which was narrow in its focus as it only affected one drug. Broader supply-side policies which jointly address the supply of opioids and its substitutes (including heroin) are potentially more effective than narrow market disruptions.

It is also important to recognize that opioid policies, such as the OxyContin reformulation, may have different effects in the short and long run since the composition of new and existing users will change over time. While the reformulation may lead to substitution across drugs for existing users (mitigating its effectiveness in the short run), the reformulation may achieve long run effectiveness by deterring new abuse. This may be particularly relevant for other countries whose opioid problems are now just emerging (Karanges et al., 2016; van Amsterdam and van den Brink, 2015); supply-side policies, such as the reformulation, may have higher effectiveness in these cases. Our study can only examine the effects in the first three years, but we find sizable effects in the short-term and these effects only grow over our time period. Moreover, we might expect that these trends could be exacerbated in the near future as the introduction

of other abuse-deterrent opioids could cause more users to switch from opioids to heroin.

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Figures and Tables

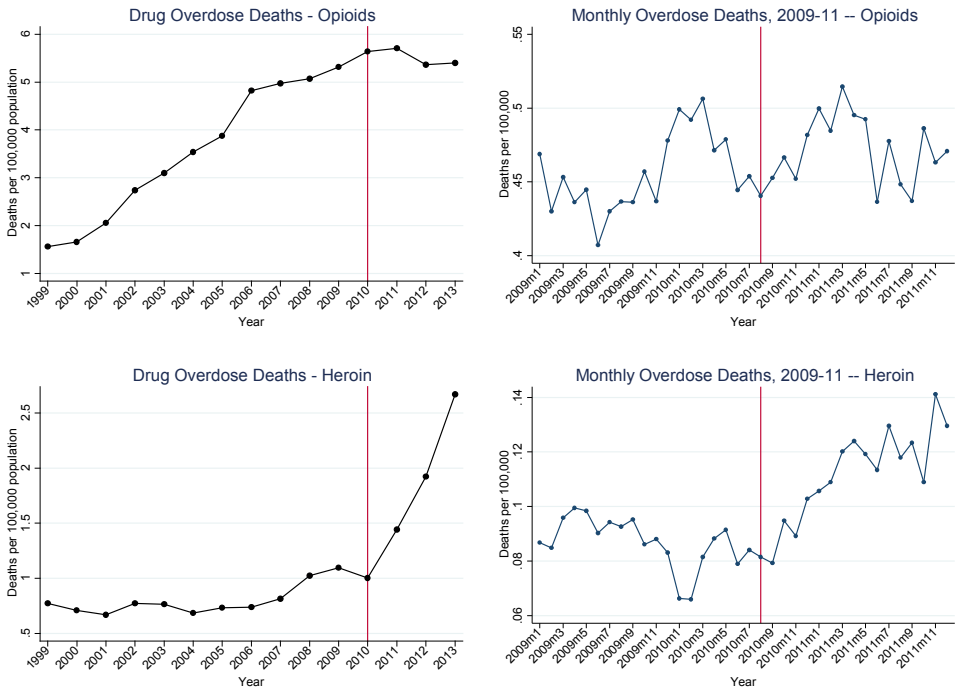


Figure 1: Trends in Drug Overdose Deaths: Prescription Opioids and Heroin

Notes: Deaths per 100,000 population from the National Vital Statistics System (NVSS). Opioid overdose deaths are coded using ICD-10 codes for underlying cause of death X40–X44, X60–X64, X85, and Y10–Y14 with a multiple cause code of T40.2 for natural and semisynthetic opioids (e.g., oxycodone and hydrocodone), T40.3 for methadone, and T40.4 for synthetic opioids excluding methadone (e.g., fentanyl and tramadol). Heroin deaths are coded using T40.1 and a drug poisoning underlying cause of death.

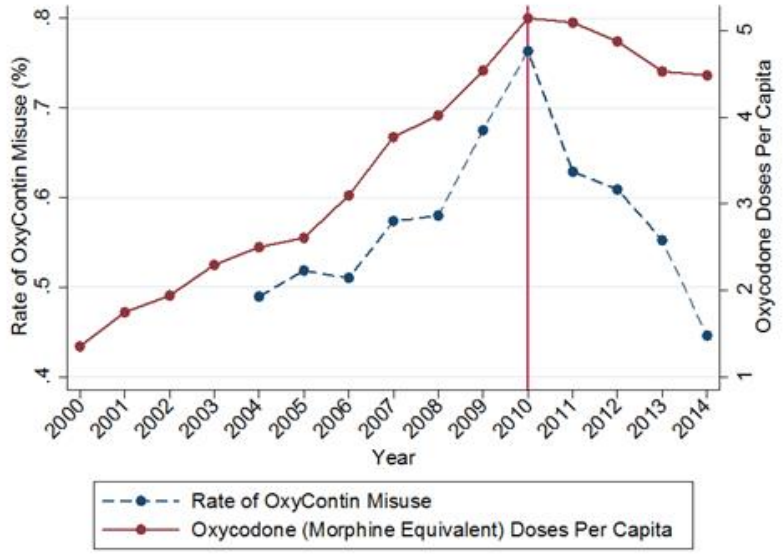


Figure 2: National Trends in Prescription Opioid Use

Notes: Rate of OxyContin misuse is the percentage of the population ages 12+ "using OxyContin for nonmedical use" in the National Survey on Drug Use and Health (NSDUH). We use the NSDUH Public Use Files individual level data without state-identifiers (available for each year, rather than 2-year waves) to construct the weighted mean rate of OxyContin misuse. Oxycodone doses are from the DEA's Automation of Reports and Consolidated Orders System (ARCOS) and have been converted into morphine-equivalent doses per capita. Oxycodone is the primary ingredient in OxyContin and is also contained in other opioid pain relievers.

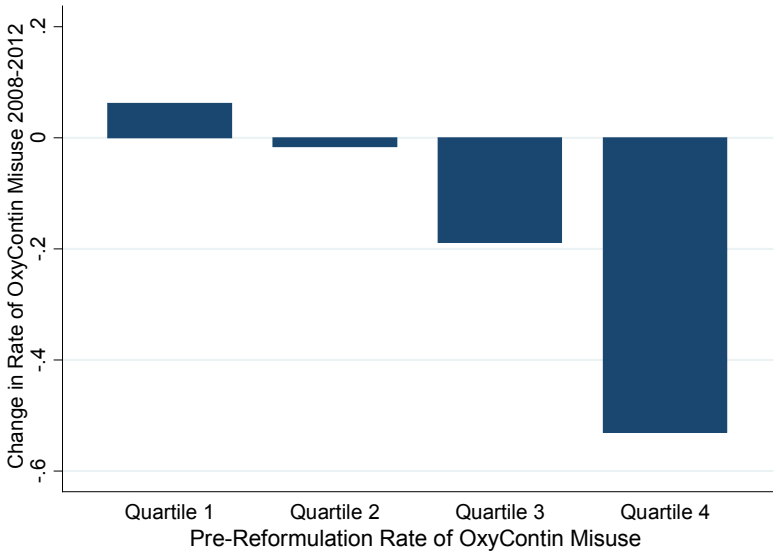
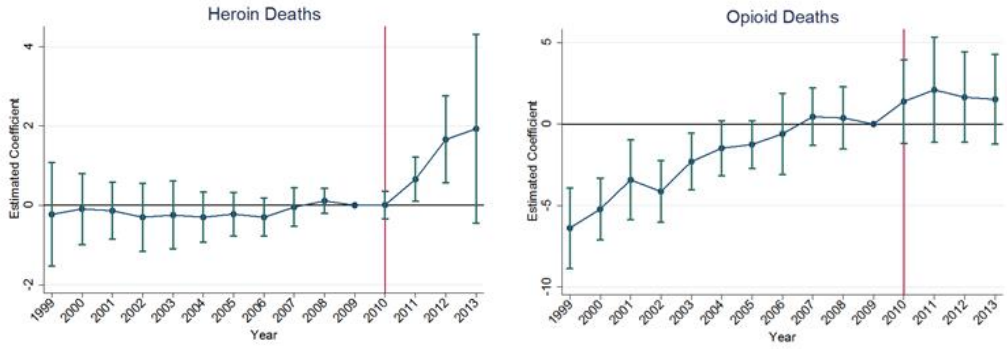


Figure 3: Relationship between Pre-Reformulation Rate of OxyContin Misuse and Change Between 2008-2012

Notes: Quartiles represent states with the highest and lowest pre-reformulation rates of OxyContin misuse (Quartile 4 includes the 25% of states with the highest pre-reformulation rates of OxyContin misuse). The change in the rate of OxyContin misuse is weighted by state population.

Panel A: Heroin and Opioid Mortality



Panel B: Net Impact on Mortality

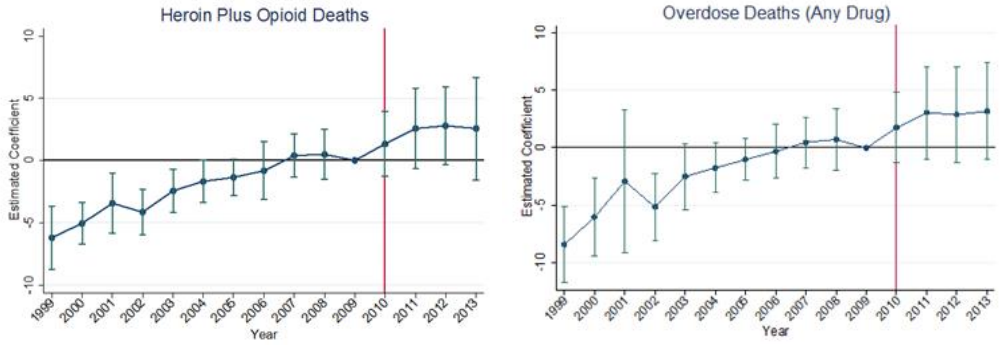


Figure 4: Effect of OxyContin Reformulation on Overdose Deaths– Baseline Event Study Specification

Notes: Each graph includes point estimates from event study (normalized to 0 in 2009) and 95% confidence intervals which are adjusted for within-state clustering.

A: OxyContin Misuse/Pain Reliever Misuse **B: Oxycodone/(Oxycodone+Hydrocodone)** **C: Oxycodone/Hydrocodone**

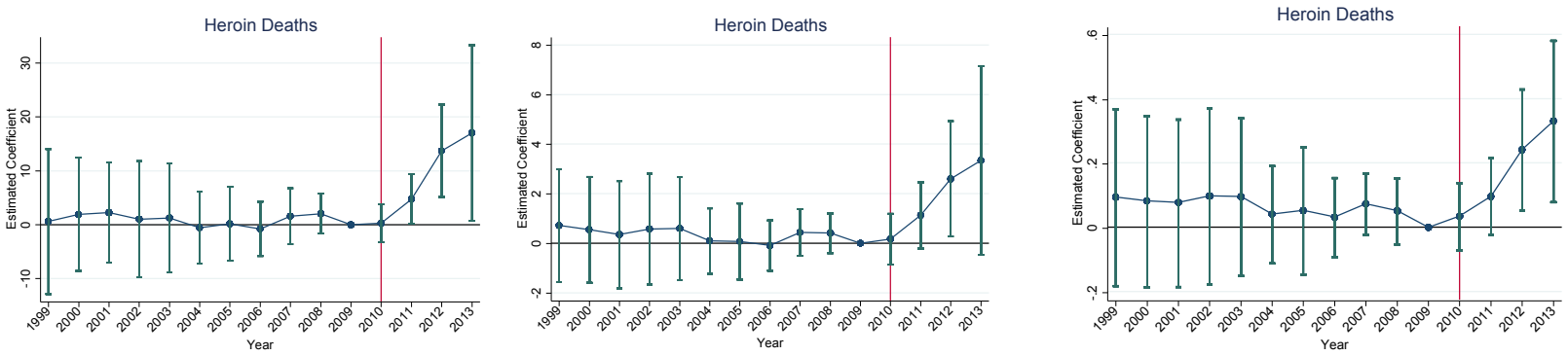


Figure 5: Event Study Results for Heroin Deaths using Alternative Measures of the "Bite" of OxyContin Reformulation

Notes: Each graph includes point estimates from event study (normalized to 0 in 2009) and 95% confidence intervals which are adjusted for within-state clustering. Figure A uses NSDUH data to construct the "bite" measure; Figures B and C use ARCOS data.

Figure 6: Event Study Results for Heroin Prices

Notes: Point estimates from event study (normalized to 0 in 2009) with 95% confidence intervals. Heroin prices calculated using STRIDE data.

Table 1: Summary Statistics, 2000-2009

Variable (Mean)	All States	States with Low OxyContin Misuse Rate	States with High OxyContin Misuse Rate	Test of Equality of Means (p-value)	Source
Outcomes					
Oxycontin Misuse Rate (%)	0.567	0.447	0.842	0.000	NSDUH, 2004-2008
Oxycodone (Morphine-Equivalent) Doses per Capita	2.812	2.309	3.970	0.001	ARCOS, 2000-2009
Deaths per 100,000:					
Opioids	3.747	3.001	5.460	0.000	Vital Statistics, 2000-2009
Heroin	0.803	0.787	0.839	0.769	Vital Statistics, 2000-2009
All Drug Overdoses	10.832	9.907	12.958	0.000	Vital Statistics, 2000-2009
Demographics Characteristics					
Population	5,532,597	7,888,831	3,266,986	0.007	Census, 2000
Age (%):					
0-17	25.65	25.98	24.88	0.087	Census, 2000
18-64	61.92	62.08	61.55	0.259	Census, 2000
65+	12.43	11.94	13.57	0.082	Census, 2000
Race (%):					
White	80.99	78.64	86.45	0.000	Census, 2000
Black	12.69	14.41	8.70	0.021	Census, 2000
Other Race	6.31	6.94	4.85	0.249	Census, 2000
Unemployment Rate (%)	4.01	4.12	3.76	0.162	BLS, 2000
Personal Income Per Capita	30,318.88	30,840.44	29,107.92	0.199	BEA, 2000
Poverty Rate (%)	11.32	11.55	10.79	0.320	Census, 2000
Number of States	51	25	26		

Notes: Means are weighted by state population and pooled for 2000-2009 unless otherwise noted. Column 4 shows the p-value from a test of equality of means for Columns 2 and 3.

Table 2: Relationship Between OxyContin Misuse and Changes in Heroin Death Rates

Outcome:	Heroin Deaths per 100,000					
	(1)	(2)	(3)	(4)	(5)	(6)
A. Total Heroin Deaths per 100,000						
Initial OxyContin (3 Year Effect)	2.212**	2.804***	2.523**	3.581***	1.420***	1.591***
	(1.016)	(1.041)	(1.065)	(1.074)	(0.616)	(0.608)
Initial Pain Reliever (3 Year Effect)				-0.495**		-0.210*
				(0.241)		(0.114)
Mean of Dep. Variable (2008-09):	1.060					
B. Heroin-Only Deaths per 100,000 (T40.1 but not also T40.2-T40.4)						
Initial OxyContin (3 Year Effect)	1.497	2.068**	1.849**	2.694***	1.518**	1.727***
	(0.911)	(0.879)	(0.920)	(0.894)	(0.647)	(0.649)
Initial Pain Reliever (3 Year Effect)				-0.392*		-0.194*
				(0.198)		(0.116)
Mean of Dep. Variable (2008-09):	0.876					
State and Time-Varying Covariates	No	Yes	Yes	Yes	Yes	Yes
Policy Variables	No	No	Yes	Yes	Yes	Yes
Estimator	OLS	OLS	OLS	OLS	Poisson	Poisson

Notes: Standard errors in parentheses adjusted for clustering at the state-level. State fixed effects and year fixed effects included in all specifications. Each model also includes a linear trend interacted with initial nonmedical OxyContin misuse as well as a post-2011 indicator interacted with initial nonmedical OxyContin misuse. Finally, a separate post-2011 linear trend interacted with initial nonmedical OxyContin misuse is also included. We report the 3 year post-2011 effect of the initial OxyContin variable. Regressions are weighted by population. Years 2008-2013 are used.

***Significant at the 1% level; **Significant at the 5% level; *Significant at the 10% level.

Table 3: Heterogeneity in Heroin Effects

Outcome:	Heroin Deaths per 100,000								
By Subgroup:	Age Group			Gender		Race		Education	
	Ages 0-24	Ages 25-64	Ages 65+	Female	Male	White	Non-White	HS degree or less	More than HS
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Initial OxyContin (3 Year Effect)	1.159**	3.935**	0.191	0.864*	4.164**	2.353**	1.812	3.123	2.411***
	(0.469)	(1.752)	(0.307)	(0.459)	(1.768)	(0.953)	(1.315)	(2.105)	(0.864)
Mean of Dep. Variable (2008-09):	0.490	1.670	0.064	0.375	1.769	1.193	0.810	1.980	0.595

Notes: Standard errors in parentheses adjusted for clustering at the state-level. State fixed effects and year fixed effects and the full set of covariates are included in all specifications. Each model also includes a linear trend interacted with initial nonmedical OxyContin misuse as well as a post-2011 indicator interacted with initial nonmedical OxyContin misuse. Finally, a separate post-2011 linear trend interacted with initial nonmedical OxyContin misuse is also included. We report the 3 year post-2011 effect of the initial OxyContin variable. Regressions are weighted by population. Years 2008-2013 are used. Columns 8 and 9 include only individuals ages 25+ to exclude those without completed education.

***Significant at the 1% level; **Significant at the 5% level; *Significant at the 10% level.

Table 4: Relationship Between OxyContin Misuse and Changes in Opioid Death Rates

Outcome:	Overdose Deaths per 100,000					
	(1)	(2)	(3)	(4)	(5)	(6)
A. Total Opioid Deaths per 100,000 (T40.2-T40.4)						
Initial OxyContin (3 Year Effect)	-1.135	-0.266	-0.420	0.789	0.089	0.146
	(1.921)	(1.765)	(1.698)	(1.836)	(0.219)	(0.253)
Initial Pain Reliever (3 Year Effect)				-0.554		-0.067
				(0.358)		(0.052)
Mean of Dep. Variable (2008-09):	5.192					
B. Natural Opioid Deaths per 100,000 (T40.2)						
Initial OxyContin (3 Year Effect)	-2.699	-2.243	-2.388	-1.700	-0.652**	-0.629**
	(1.888)	(1.810)	(1.700)	(1.821)	(0.293)	(0.312)
Initial Pain Reliever (3 Year Effect)				-0.304		-0.023
				(0.342)		(0.067)
Mean of Dep. Variable (2008-09):	3.233					
C. Natural Opioid-Only Deaths per 100,000 (T40.2, but not also T40.1, T40.3, or T40.4)						
Initial OxyContin (3 Year Effect)	-3.015*	-2.636*	-2.742*	-2.337	-0.794***	-0.807***
	(1.671)	(1.555)	(1.392)	(1.423)	(0.305)	(0.309)
Initial Pain Reliever (3 Year Effect)				-0.167		0.016
				(0.275)		(0.063)
Mean of Dep. Variable (2008-09):	2.593					
State and Time-Varying Covariates	No	Yes	Yes	Yes	Yes	Yes
Policy Variables	No	No	Yes	Yes	Yes	Yes
Estimator	OLS	OLS	OLS	OLS	Poisson	Poisson

Notes: Standard errors in parentheses adjusted for clustering at the state-level. State fixed effects and year fixed effects included in all specifications. Each model also includes a linear trend interacted with initial nonmedical OxyContin misuse as well as a post-2011 indicator interacted with initial nonmedical OxyContin misuse. Finally, a separate post-2011 linear trend interacted with initial nonmedical OxyContin misuse is also included. We report the 3 year post-2011 effect of the initial OxyContin variable. Regressions are weighted by population. Years 2008-2013 are used.

***Significant at the 1% level; **Significant at the 5% level; *Significant at the 10% level.

Table 5: OxyContin Misuse and Changes in Synthetic Opioid Death Rates

Outcome:	Overdose Deaths per 100,000					
	(1)	(2)	(3)	(4)	(5)	(6)
A. Synthetic Opioid Deaths per 100,000 (T40.4)						
Initial OxyContin (3 Year Effect)	0.454	0.616*	0.641*	0.869*	1.137***	1.223***
	(0.405)	(0.366)	(0.349)	(0.444)	(0.262)	(0.339)
Initial Pain Reliever (3 Year Effect)				-0.106		-0.085
				(0.108)		(0.082)
Mean of Dep. Variable (2008-09):	0.887					
B. Synthetic Opioid-Only Deaths per 100,000 (T40.4, but not also T40.1, T40.2, or T40.3)						
Initial OxyContin (3 Year Effect)	0.124	0.245	0.267	0.363	0.933***	0.944***
	(0.257)	(0.223)	(0.214)	(0.243)	(0.234)	(0.240)
Initial Pain Reliever (3 Year Effect)				-0.044		-0.023
				(0.063)		(0.066)
Mean of Dep. Variable (2008-09):	0.624					
State and Time-Varying Covariates	No	Yes	Yes	Yes	Yes	Yes
Policy Variables	No	No	Yes	Yes	Yes	Yes
Estimator	OLS	OLS	OLS	OLS	Poisson	Poisson

Notes: Standard errors in parentheses adjusted for clustering at the state-level. State fixed effects and year fixed effects included in all specifications. Each model also includes a linear trend interacted with initial nonmedical OxyContin misuse as well as a post-2011 indicator interacted with initial nonmedical OxyContin misuse. Finally, a separate post-2011 linear trend interacted with initial nonmedical OxyContin misuse is also included. We report the 3 year post-2011 effect of the initial OxyContin variable. Regressions are weighted by population. Years 2008-2013 are used.

***Significant at the 1% level; **Significant at the 5% level; *Significant at the 10% level.

Table 6: Relationship Between OxyContin Misuse and Changes in Overall Overdose Death Rates

Outcome:	Overdose Deaths per 100,000					
	(1)	(2)	(3)	(4)	(5)	(6)
A. Opioid and Heroin Deaths						
Initial OxyContin (3 Year Effect)	0.362	1.802	1.429	3.483	0.257	0.378*
	(2.385)	(2.060)	(2.148)	(2.129)	(0.214)	(0.225)
Initial Pain Reliever (3 Year Effect)				-0.947*		-0.123**
				(0.475)		(0.053)
Mean of Dep. Variable (2008-09):	6.068					
B. All Overdoses						
Initial OxyContin (3 Year Effect)	0.205	2.353	1.322	3.713	0.041	0.123
	(2.974)	(3.064)	(2.824)	(2.914)	(0.157)	(0.169)
Initial Pain Reliever (3 Year Effect)				-1.017*		-0.078*
				(0.602)		(0.047)
Mean of Dep. Variable (2008-09):	13.097					
State and Time-Varying Covariates	No	Yes	Yes	Yes	Yes	Yes
Policy Variables	No	No	Yes	Yes	Yes	Yes
Estimator	OLS	OLS	OLS	OLS	Poisson	Poisson

Notes: Standard errors in parentheses adjusted for clustering at the state-level. State fixed effects and year fixed effects included in all specifications. Each model also includes a linear trend interacted with initial nonmedical OxyContin misuse as well as a post-2011 indicator interacted with initial nonmedical OxyContin misuse. Finally, a separate post-2011 linear trend interacted with initial nonmedical OxyContin misuse is also included. We report the 3 year post-2011 effect of the initial OxyContin variable. Regressions are weighted by population. Years 2008-2013 are used.

***Significant at the 1% level; **Significant at the 5% level; *Significant at the 10% level.

Table 7: Alternative Explanations for Increase in Heroin Deaths

Outcome:	Heroin Deaths per 100,000							
	Main Result	Add PDMP	Must Access	Add MMLs	Add Pill Mill Laws	No FL	No Pill Mill States	West Only
Initial OxyContin (3 Year Effect)	2.804***	2.815***	2.469**	2.374**	2.523**	2.731**	2.239**	2.727
	(1.041)	(1.047)	(1.009)	(0.974)	(1.065)	(1.050)	(1.006)	(1.710)
Mean of Dep. Variable (2008-09)	1.060	1.060	1.060	1.060	1.060	1.091	1.101	1.187
Number of Observations	306	306	306	306	306	300	288	78

Notes: Standard errors in parentheses adjusted for clustering at the state-level. State fixed effects, year fixed effects, and the full set of state and time-varying covariates (excluding policy variables) are included in all specifications. Each model also includes a linear trend interacted with initial nonmedical OxyContin misuse as well as a post-2011 indicator interacted with initial nonmedical OxyContin misuse. Finally, a separate post-2011 linear trend interacted with initial nonmedical OxyContin misuse is also included. We report the 3 year post-2011 effect of the initial OxyContin variable. Regressions are weighted by population. "No Pill Mill States" means that Florida, Kentucky, and West Virginia are excluded. "West Only" means that only states in the West Census Region are included in the sample.

***Significant at the 1% level; **Significant at the 5% level; *Significant at the 10% level.

Online Appendix

Supply-Side Drug Policy in the Presence of Substitutes: Evidence from the Introduction of Abuse-Deterrent Opioids

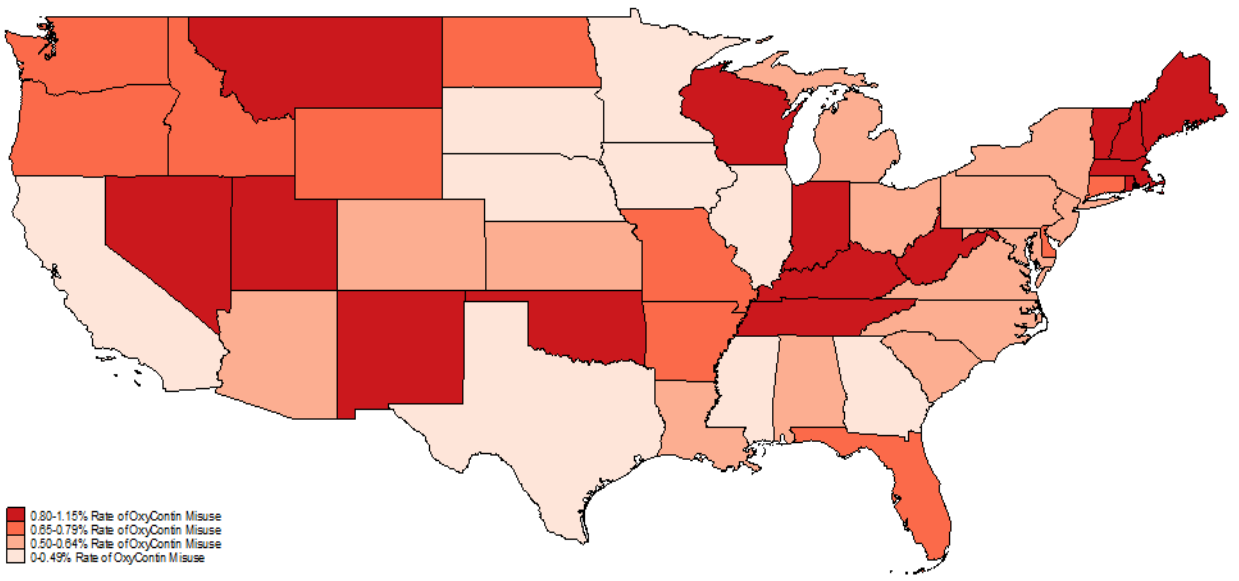
Abby Alpert, David Powell, Rosalie Liccardo Pacula

Appendix Figure A.1: Geographic Variation in Rate of OxyContin Misuse, 2004-2008

Panel A: States with highest and lowest rates of OxyContin misuse

Top 10 Rates of OxyContin Misuse (%)		Bottom 10 Rates of OxyContin Misuse (%)	
Rhode Island	1.15	Washington D.C.	0.47
West Virginia	1.13	Minnesota	0.47
Utah	1.04	Georgia	0.39
Wisconsin	0.98	Nebraska	0.39
Massachusetts	0.97	Mississippi	0.37
Kentucky	0.97	California	0.30
Montana	0.96	Texas	0.29
Indiana	0.96	Iowa	0.27
Nevada	0.95	South Dakota	0.26
Alaska	0.94	Illinois	0.26

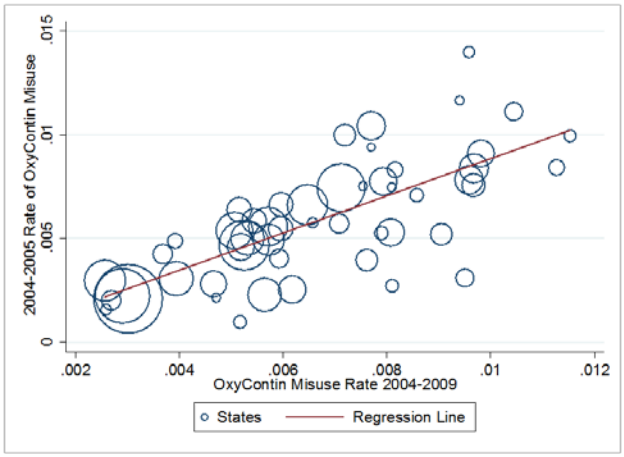
Panel B: State variation in Rate of OxyContin Misuse



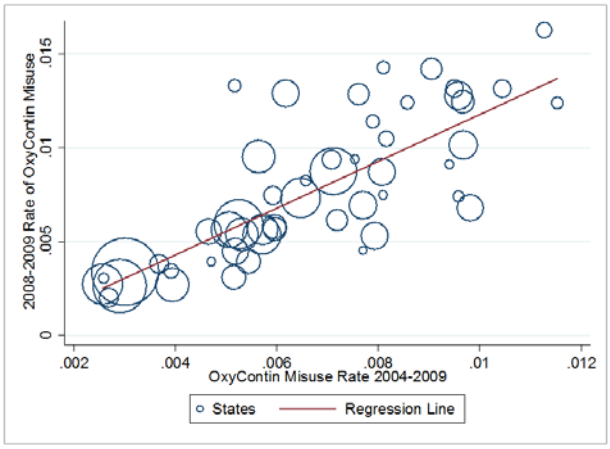
Appendix Figure A.2: Robustness of OxyContin Misuse Rate

Panel A: Relationship between 2004-2009 OxyContin Misuse Measure and 2004 or 2008 OxyContin Misuse Measures (NSDUH)

2004 Misuse: Correlation= 0.811



2008 Misuse: Correlation= 0.835



Panel B: Year-to-Year Correlations in OxyContin Misuse (NSDUH)

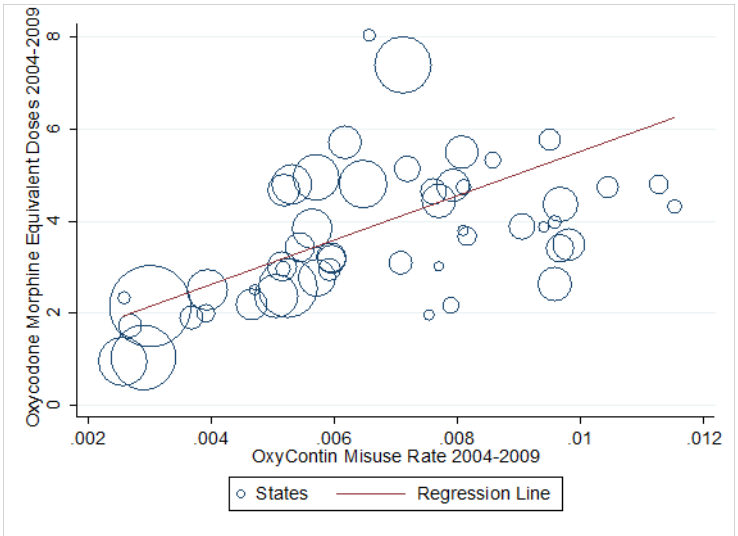
NSDUH	2004	2006	2008
2004	1		
2006	0.4445	1	
2008	0.4631	0.6144	1

Note: Each year represents a 2-year wave (e.g. "2004" is 2004-2005)

Appendix Figure A.3: Alternative Measures of OxyContin Misuse Rate

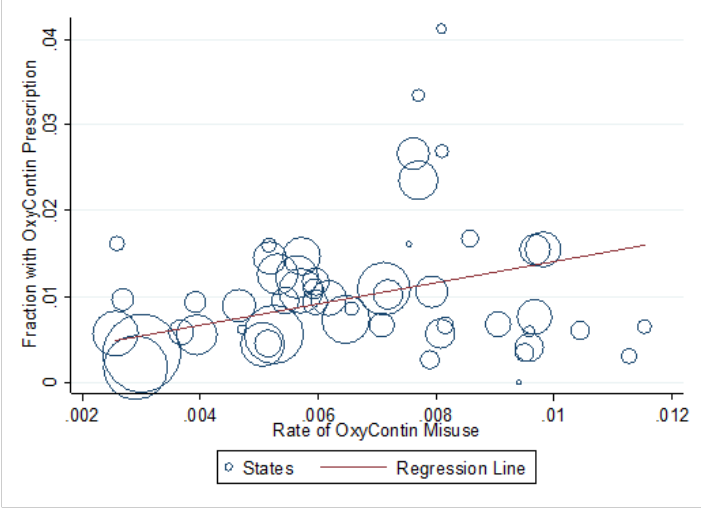
Panel A: Relationship between 2004-2009 OxyContin Misuse (NSDUH) and 2004-2009 Oxycodone Doses (ARCOS)

Correlation=0.638

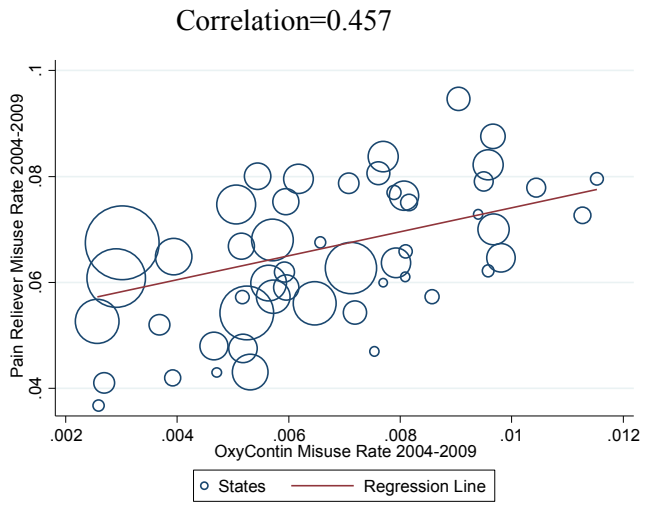


Panel B: Relationship between 2004-2009 OxyContin Misuse (NSDUH) and 2004-2009 Proportion with OxyContin/Oxycodone Prescription (MEPS)

Correlation= 0.466

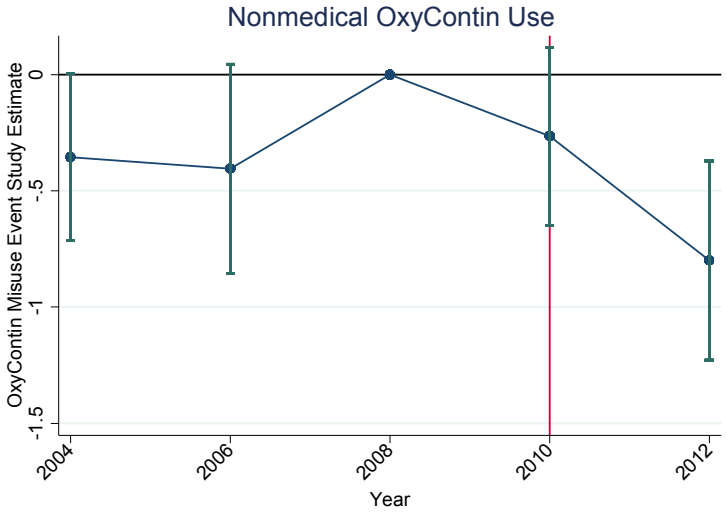


Panel C: Relationship between 2004-2009 OxyContin Misuse (NSDUH) and 2004-2009 Pain Reliever Misuse (NSDUH)



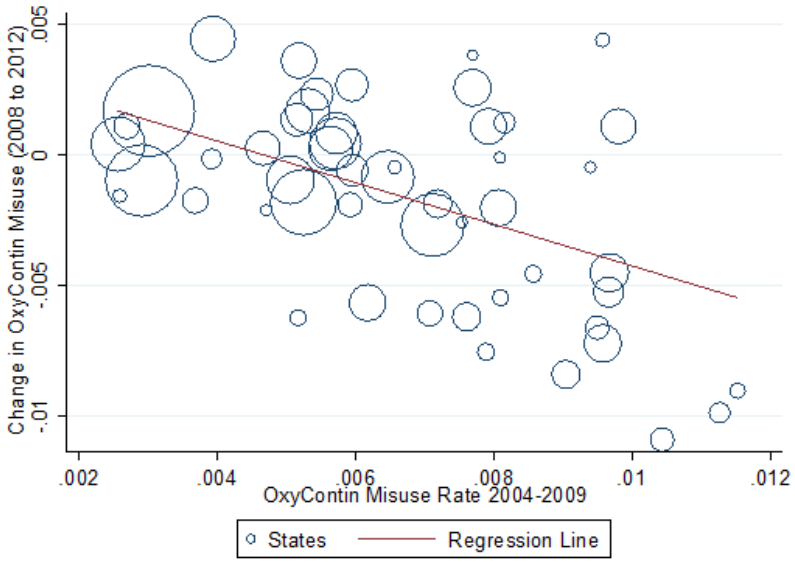
Notes: Size of marker reflects population size.

Appendix Figure A.4: Relationship Between Initial OxyContin Misuse and Changes in OxyContin Misuse – Event Study Specification



Notes: Each year on the x-axis refers to that year and the following year since each NSDUH wave includes two years. Consequently, we should expect a partial effect in 2010 (which includes post-reformulation year 2011) and a full year effect for 2012 (and 2013). The graph reports point estimates and 95% confidence intervals (which are adjusted for within-state clustering) from the event study in Equation 1 using OxyContin misuse as the outcome variable. We can reject that the 2012-2013 estimate is equal to the 2004-2005 estimate at the 5% level, the 2006-2007 estimate at the 10% level, the (normalized to 0) 2008-2009 estimate at the 1% level, and the (partially-treated) 2010-2011 estimate at the 1% level. A joint test that the 2012-2013 estimate is equal to each of the pre-reformulation estimates (2004-2005, 2006-2007, and 2008-2009) rejects at the 1% level.

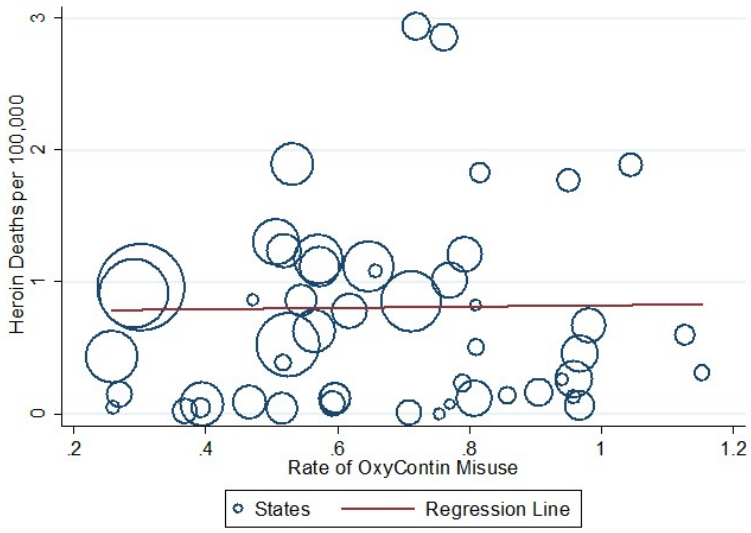
Appendix Figure A.5: Relationship Between Initial OxyContin Misuse and Changes in OxyContin Misuse – Scatterplot



Notes: Size of marker reflects population size.

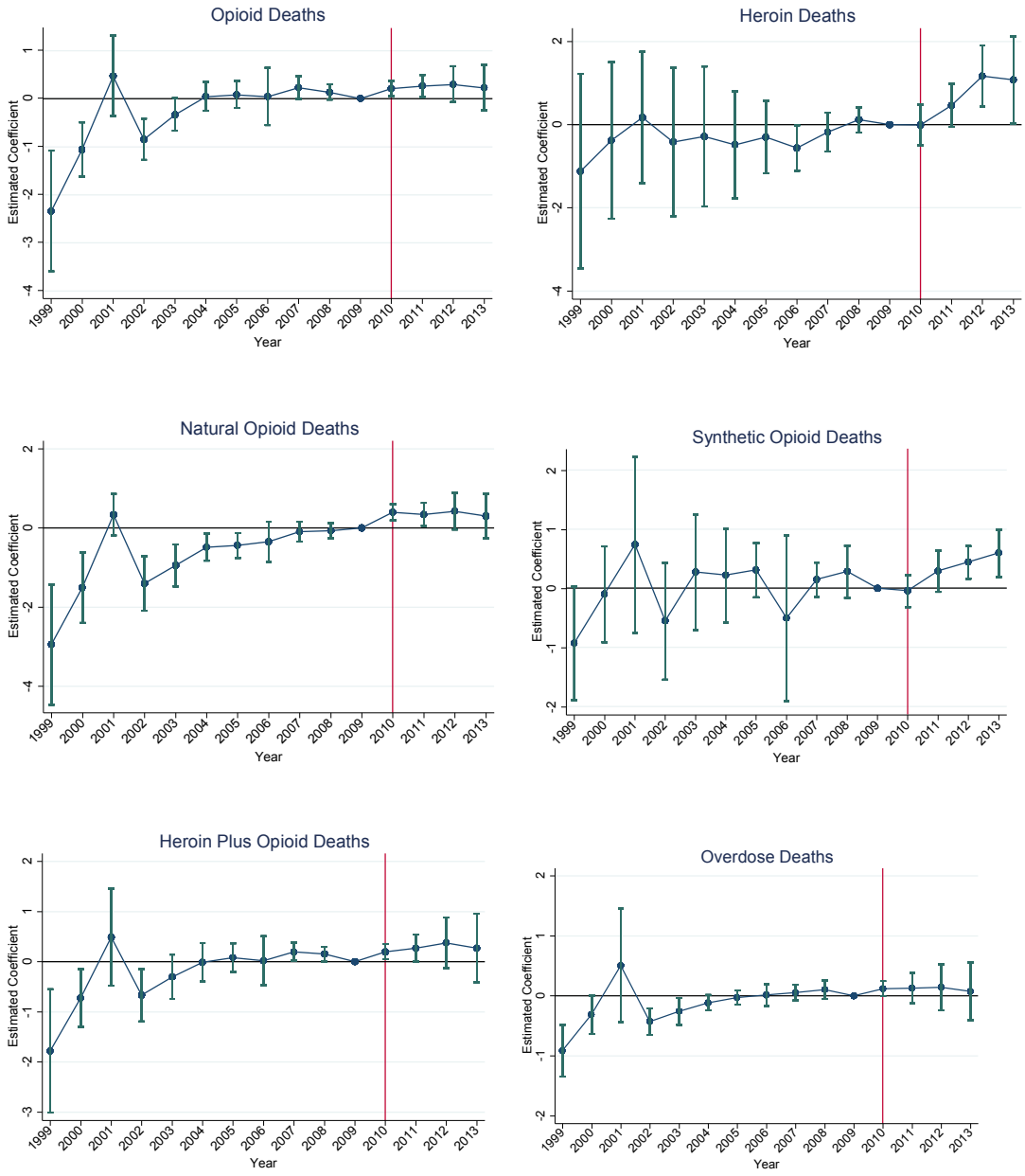
Appendix Figure A.6: Relationship Between Initial Rate of OxyContin Misuse and Heroin Deaths Before the OxyContin Reformulation

Correlation=0.0185



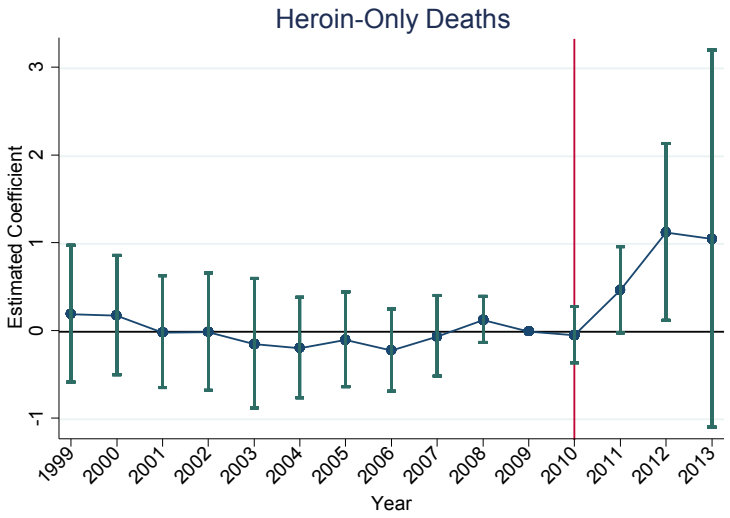
Notes: This figure shows the correlation between the heroin death rate from 1999-2009 with the initial rate of OxyContin misuse in each state. The size of the marker corresponds to the state population and the regression line is population-weighted.

Appendix Figure A.7: Poisson Event Study Specification



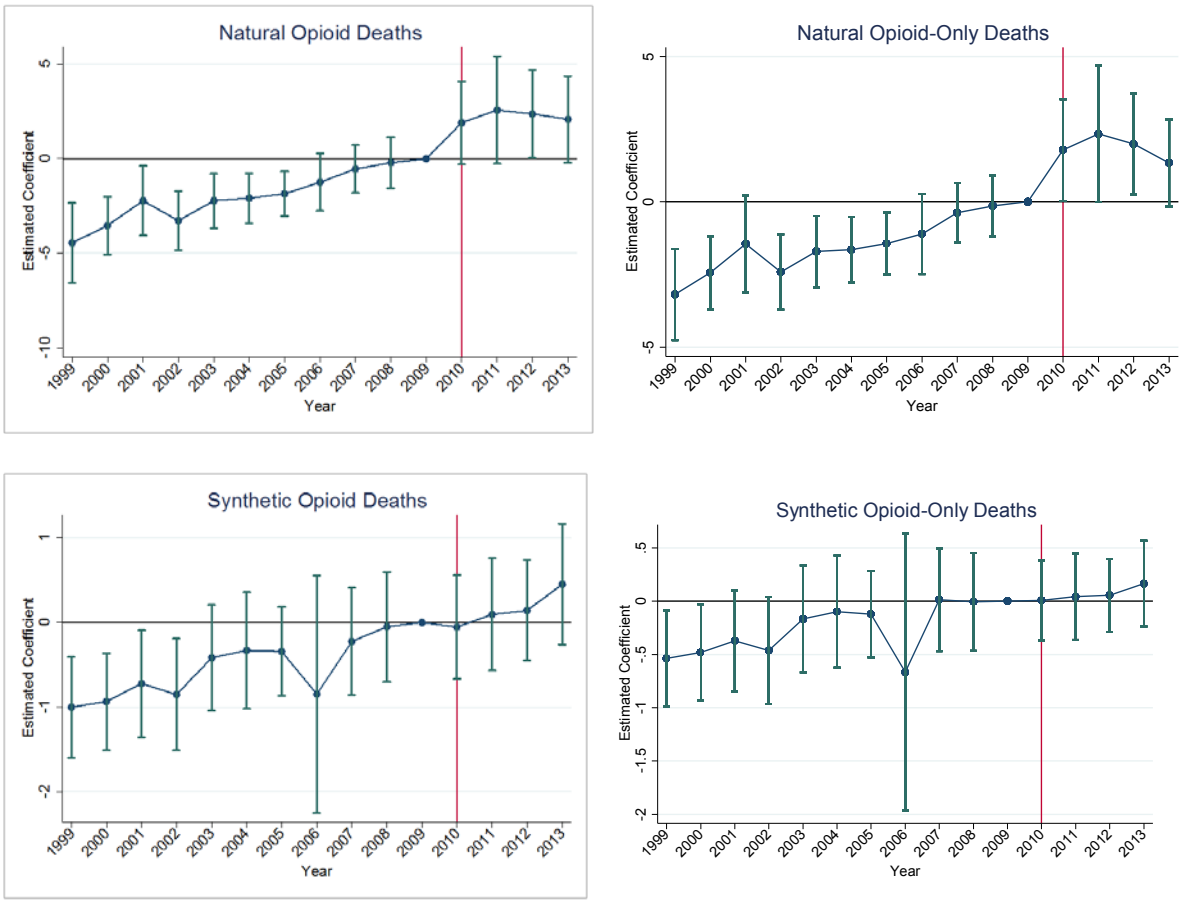
Notes: Each graph includes point estimates from event study (normalized to 0 in 2009) and 95% confidence intervals which are adjusted for within-state clustering.

Appendix Figure A.8: Event Study Specification for Heroin-Only Deaths



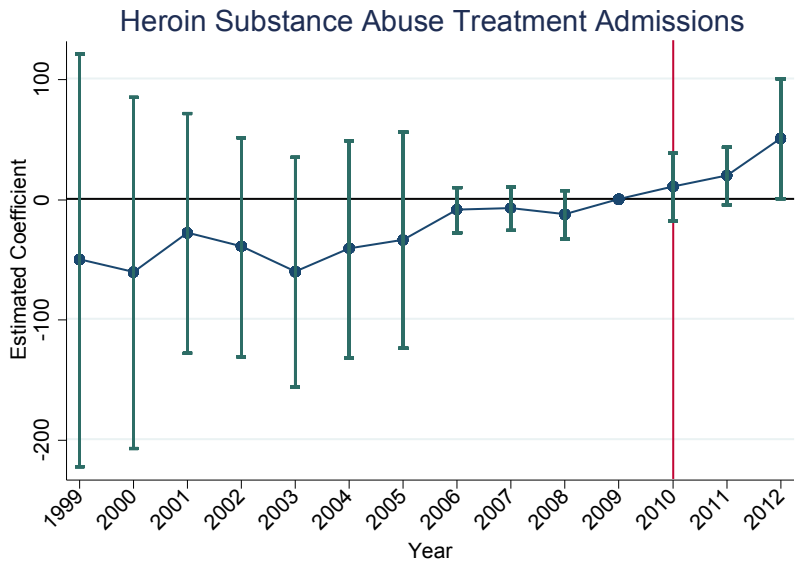
Notes: We exclude deaths also involving other opioids (T40.2-T40.4). Graph includes point estimates from event study (normalized to 0 in 2009) and 95% confidence intervals which are adjusted for within-state clustering.

Appendix Figure A.9: Baseline Event Study Specification for Different Types of Opioid Deaths



Notes: In the top figures, the left figure includes all drug overdoses involving T40.2 and the right figure uses the same outcome but excludes overdoses that also involve T40.1, T40.3, or T40.4. In the bottom figures, the left figure includes all drug overdoses involving T40.4 and the right figure uses the same outcome but excludes T40.1, T40.2, or T40.3.

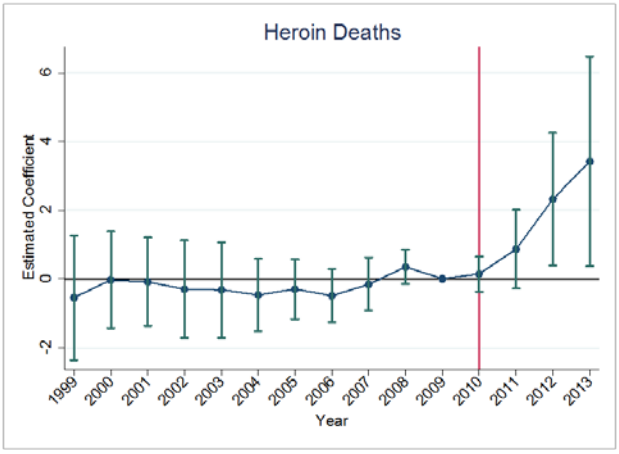
Appendix Figure A.10: Relationship Between Initial Rate of OxyContin Misuse and Heroin Substance Abuse Treatment Admissions



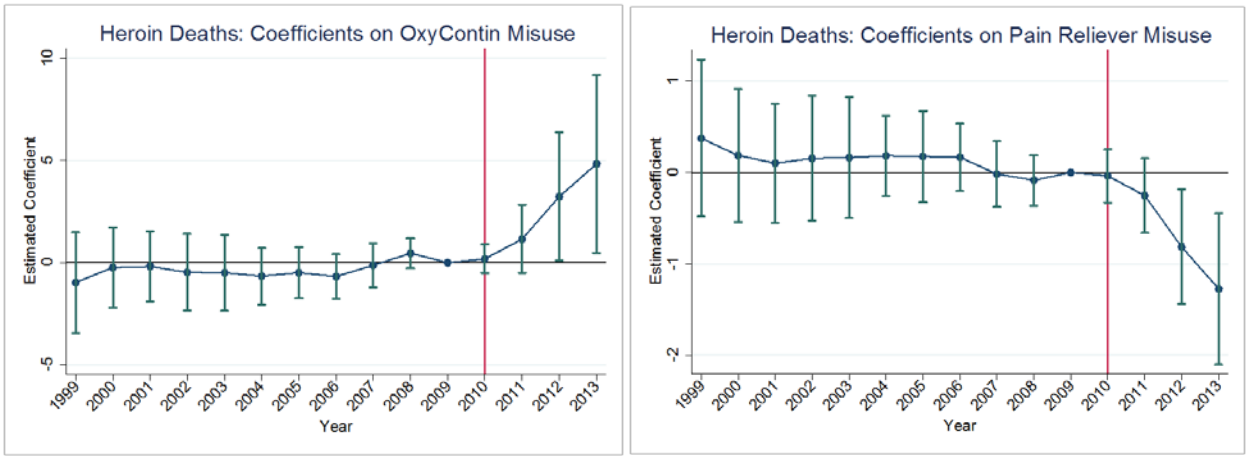
Notes: Outcome variable is number of treatment admissions in the TEDS involving heroin per 100,000. 95% confidence intervals adjusted for clustering at state-level.

Appendix Figure A.11 – Instrumental Variables Event Study Specification for Heroin Deaths

Panel A: Effects of Initial (2008) OxyContin Misuse



Panel B: Jointly Estimating Effects of Initial OxyContin and Pain Reliever Misuse



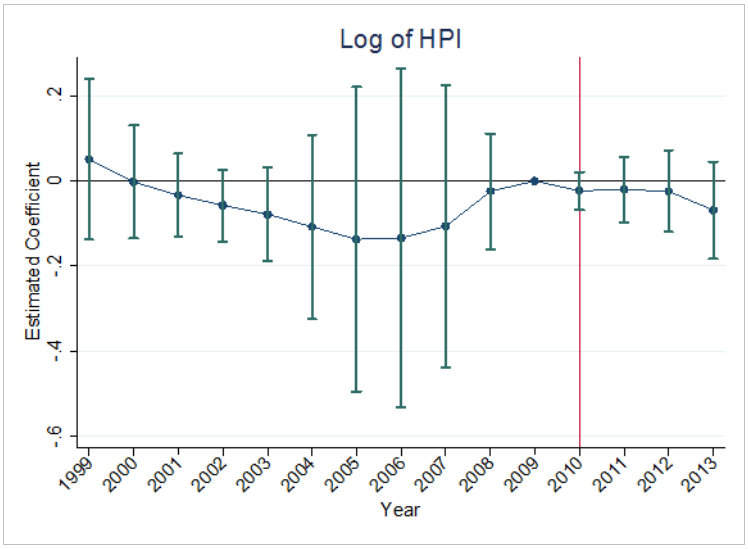
Notes: The graph on the left shows the estimates and 95% confidence intervals for the 2008 nonmedical OxyContin misuse variable for each sample. The graph on the right shows the estimates and 95% confidence intervals for the 2008 nonmedical pain reliever misuse variable for each sample. The estimates in both figures are jointly estimated. The specification uses the 2004 nonmedical OxyContin misuse rates and 2004 nonmedical pain reliever misuse rates interacted with year indicators as instruments.

Appendix Figure A.12 – Alternative Explanations: Event Study Results for Economic Conditions

Panel A: Unemployment Rate

Notes: 2011-2013 estimates are not statistically different from any pre-reformulation estimate except for the (excluded) 2009 estimate (smallest p-value=0.3492).

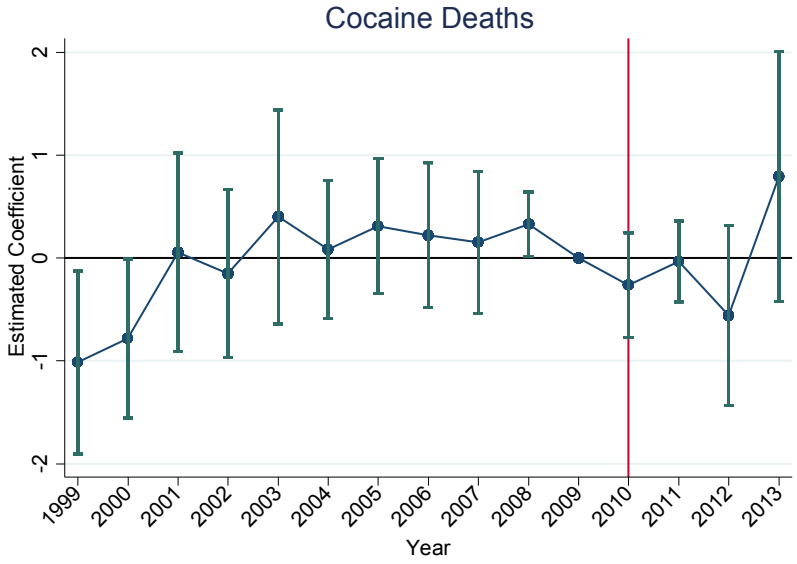
Panel B: Housing Price Index



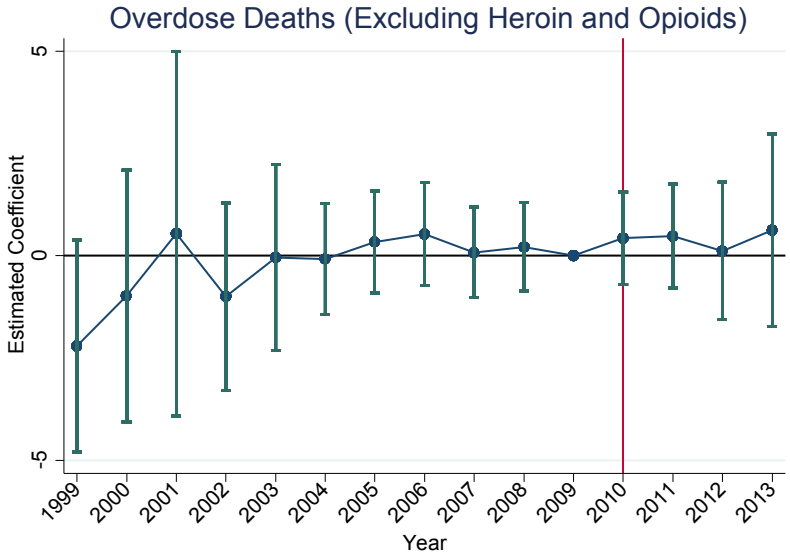
Source: Federal Housing Finance Agency

Appendix Figure A.13: Placebo Tests – Effect of Reformulation on Other Types of Drug Overdoses

Panel A: Cocaine Overdoses



Panel B: All Drug Overdoses, Excluding Heroin and Opioids



Appendix Table A1: Relationship between Legal Opioid Supply (ARCOS) and Pain Reliever Misuse Rates (NSDUH)

	OxyContin misuse	Other Pain Reliever misuse
Per Capita oxycodone MED	0.085***	0.035
	(0.022)	(0.083)
Per Capita hydrocodone MED	0.041	0.656***
	(0.028)	(0.160)
N	51	51

Notes: *10% Significance, **5% Significance, ***1% Significance. Heteroskedastic-robust standard errors shown in parentheses. MED = morphine equivalent doses. Results are from cross-sectional regressions. All variables are constructed by averaging over 2004-2009 data.

Appendix Table A2: Relationship Between OxyContin Misuse and Changes in Heroin Death Rates –Coefficient Estimates

Outcome:	Heroin Deaths per 100,000					
	(1)	(2)	(3)	(4)	(5)	(6)
Coefficient from Equation (2):						
delta1	0.839**	0.964***	1.218***	1.366***	1.015***	1.089***
	(0.323)	(0.335)	(0.365)	(0.372)	(0.230)	(0.208)
delta2	-0.049	-0.301	-0.224	-0.335	-0.339**	-0.439***
	(0.122)	(0.273)	(0.244)	(0.261)	(0.163)	(0.154)
delta3	0.687	0.920*	0.653	1.107**	0.202	0.251
	(0.528)	(0.538)	(0.497)	(0.498)	(0.274)	(0.269)
Implied 1 year effect (delta1)	0.839**	0.964***	1.218***	1.366***	1.015***	1.089***
	(0.323)	(0.335)	(0.365)	(0.372)	(0.230)	(0.208)
Implied 2 year effect (delta1 + 1*delta3)	1.526***	1.884***	1.870***	2.473***	1.217***	1.340***
	(0.537)	(0.555)	(0.622)	(0.631)	(0.376)	(0.367)
Implied 3 year effect (delta1 + 2*delta3)	2.212**	2.804***	2.523**	3.581***	1.420**	1.591***
	(1.016)	(1.041)	(1.065)	(1.074)	(0.616)	(0.608)
State and Time-Varying Covariates	No	Yes	Yes	Yes	Yes	Yes
Policy Variables	No	No	Yes	Yes	Yes	Yes
Control for Initial Pain Reliever	No	No	No	Yes	No	Yes
Estimator	OLS	OLS	OLS	OLS	Poisson	Poisson

Notes: *10% Significance, **5% Significance, ***1% Significance. Standard errors in parentheses adjusted for clustering at the state-level. This table replicates Table 2, reporting the underlying "delta" coefficients used to compute the 3-year effect. Coefficients for initial pain reliever use variables (not shown) are constructed similarly.

Appendix Table A3: Relationship Between OxyContin Misuse and Changes in Heroin Death Rates -- Block-Bootstrapped Confidence Intervals

Outcome:	Heroin Deaths per 100,000			
	(1)	(2)	(3)	(4)
A. Total Heroin Deaths per 100,000				
Initial OxyContin (3 Year Effect)	2.212**	2.804***	2.523**	3.581***
	[0.419, 4.005]	[1.026, 4.582]	[0.483, 4.563]	[1.791, 5.371]
Initial Pain Reliever (3 Year Effect)				-0.495**
				[-0.909, -0.080]
Mean of Dep. Variable (2008-09):	1.060			
State and Time-Varying Covariates	No	Yes	Yes	Yes
Policy Variables	No	No	Yes	Yes
Estimator	OLS	OLS	OLS	OLS

Notes: *10% Significance, **5% Significance, ***1% Significance. This table replicates Table 2 using a block-bootstrapped procedure for inference. 95% confidence intervals are shown in brackets adjusted for block-bootstrapping at the state-level, using a percentile-*t* bootstrap and creating symmetric confidence intervals. State fixed effects and year fixed effects included in all specifications. Each model also includes a linear trend interacted with initial nonmedical OxyContin misuse as well as a post-2011 indicator interacted with initial nonmedical OxyContin misuse. Finally, a separate post-2011 linear trend interacted with initial nonmedical OxyContin misuse is also included. We report the 3 year post-2011 effect of the initial OxyContin variable. Regressions are weighted by population. Years 2008-2013 are used.

Appendix Table A4: Heroin Effects Using Alternative Measures of Exposure to the Reformulation

Outcome:	Heroin Deaths per 100,000			
	Main Result	OxyContin Misuse/ Pain Reliever Misuse	Oxycodone/ (Oxycodone+Hydrocodone)	Oxycodone/ Hydrocodone
Exposure Measure:	2.523**	22.804***	4.079**	0.360***
	(1.065)	(7.594)	(1.666)	(0.132)
Effect of One Std Dev Increase:	0.568	0.709	0.668	0.702

Notes: *10% Significance, **5% Significance, ***1% Significance. Standard errors in parentheses adjusted for clustering at the state-level. State fixed effects, year fixed effects, and additional covariates are included in all specifications. Each model also includes a linear trend interacted with the exposure measure (e.g. initial nonmedical OxyContin misuse) as well as a post-2011 indicator interacted with the exposure measure. Finally, a separate post-2011 linear trend interacted with the exposure measure is also included. We report the 3 year post-2011 effect of the exposure variable. Regressions are weighted by population. Since units are different for each exposure measure, the effect of a one standard deviation increase in exposure to the reformulation is shown in the bottom row.

Appendix Table A5: Heterogeneity in Opioid Effects

Outcome:	Opioid Deaths per 100,000								
By Subgroup:	Age Group			Gender		Race		Education	
	Ages 0-24	Ages 25-64	Ages 65+	Female	Male	White	Non-White	HS degree or less	More than HS
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Initial OxyContin (3 Year Effect)	-0.774	-0.510	0.798	0.837	-1.764	0.049	1.860	-0.334	0.990
	(0.706)	(2.872)	(1.081)	(1.169)	(2.545)	(2.155)	(1.438)	(4.000)	(2.093)
Mean of Dep. Variable (2008-09):	1.601	8.453	1.310	4.008	6.417	6.899	1.992	10.254	4.655

Notes: *10% Significance, **5% Significance, ***1% Significance. Standard errors in parentheses adjusted for clustering at the state-level. State fixed effects and year fixed effects and the full set of covariates are included in all specifications. Each model also includes a linear trend interacted with initial nonmedical OxyContin misuse as well as a post-2011 indicator interacted with initial nonmedical OxyContin misuse. Finally, a separate post-2011 linear trend interacted with initial nonmedical OxyContin misuse is also included. We report the 3 year post-2011 effect of the initial OxyContin variable. Regressions are weighted by population. Years 2008-2013 are used. Columns 8 and 9 include only individuals ages 25+ to exclude those without completed education.

Appendix Table A6: Robustness Tests for Baseline Estimates for Opioid and Heroin Deaths

Panel A: Heroin Deaths

Outcome:	Heroin Deaths per 100,000							
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Initial OxyContin (3 Year Effect)	2.523**	3.725**	3.759***	2.523**	2.035*	2.700***	1.256*	2.637**
	(1.065)	(1.801)	(1.229)	(1.008)	(1.018)	(0.804)	(0.731)	(1.100)
State Linear Trends	No	No	No	Yes	No	No	No	No
Weighted	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Years	2008-2013	No 2010	2008-2013	2008-2013	1999-2013	2008-2013	2008-2013	2008-2013
Initial Abuse Measure	2004-2008	2004-2008	2004-2008	2004-2008	2004-2008	2004	2008	2004-2008
Age-Adjusted	No	No	No	No	No	No	No	Yes

Panel B: Opioid Deaths

Outcome:	Opioid Deaths per 100,000							
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Initial OxyContin (3 Year Effect)	-0.420	4.250	1.391	-0.261	-2.813***	1.402	-1.229	-0.463
	(1.698)	(5.883)	(1.960)	(1.892)	(0.917)	(1.525)	(1.258)	(1.809)
State Linear Trends	No	No	No	Yes	No	No	No	No
Weighted	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Years	2008-2013	No 2010	2008-2013	2008-2013	1999-2013	2008-2013	2008-2013	2008-2013
Initial Abuse Measure	2004-2008	2004-2008	2004-2008	2004-2008	2004-2008	2004	2008	2004-2008
Age-Adjusted	No	No	No	No	No	No	No	Yes

Notes: *10% Significance, **5% Significance, ***1% Significance. Standard errors in parentheses adjusted for clustering at the state-level. State fixed effects, year fixed effects, and the full set of covariates are included in all specifications. Each model also includes a linear trend interacted with initial nonmedical OxyContin misuse as well as a post-2011 indicator interacted with initial nonmedical OxyContin misuse. Finally, a separate post-2011 linear trend interacted with initial nonmedical OxyContin misuse is also included. We report the 3 year post-2011 effect of the initial OxyContin variable. Regressions are weighted by population unless noted otherwise. "Age Adjusted" uses an age-adjusted version of the outcome variable by weighting age-specific mortality rates, holding the weights constant across states and time.

Appendix Table A7: IV Estimates using Alternative Measures of OxyContin Misuse

	Heroin		Opioids	
Initial OxyContin (3 Year Effect)	5.218**	6.447**	2.272	4.172
	(2.156)	(3.012)	(2.942)	(4.276)
Initial Pain Reliever (3 Year Effect)		-1.814*		-1.568
		(0.884)		(1.131)
Years	2008-2013	2008-2013	2008-2013	2008-2013
Initial Abuse Measure	2008	2008	2008	2008
Estimator	IV	IV	IV	IV

Notes: *10% Significance, **5% Significance, ***1% Significance. Standard errors in parentheses adjusted for clustering at the state-level. State fixed effects, year fixed effects, and additional covariates are included in all specifications. Each model also includes a linear trend interacted with initial (2008) nonmedical OxyContin misuse as well as a post-2011 indicator interacted with initial (2008) nonmedical OxyContin misuse. Finally, a separate post-2011 linear trend interacted with initial (2008) nonmedical OxyContin misuse is also included. We report the 3 year post-2011 effect of the initial OxyContin variable. Regressions are weighted by population. IV estimation is used in which the instruments are the same variables using the 2004 measures of initial nonmedical use.

Appendix Table A8: Alternative Explanations: Opioid Deaths

Outcome:	Opioid Deaths per 100,000							
	Main Result	Add PDMP	Must Access	Add MMLs	Add Pill Mill Laws	No FL	No Pill Mill States	West Only
Initial OxyContin (3 Year Effect)	-0.266	-0.231	-0.211	-0.360	-0.420	0.349	1.475	-1.445
	(1.765)	(1.751)	(1.717)	(1.728)	(1.698)	(1.742)	(1.549)	(4.498)
Mean of Dep. Variable (2008-09)	5.192	5.192	5.192	5.192	5.192	5.012	4.895	6.262
Number of Observations	306	306	306	306	306	300	288	78

Notes: *10% Significance, **5% Significance, ***1% Significance. Standard errors in parentheses adjusted for clustering at the state-level. State fixed effects, year fixed effects, and the full set of state and time-varying covariates (excluding policy variables) are included in all specifications. Each model also includes a linear trend interacted with initial nonmedical OxyContin misuse as well as a post-2011 indicator interacted with initial nonmedical OxyContin misuse. Finally, a separate post-2011 linear trend interacted with initial nonmedical OxyContin misuse is also included. We report the 3 year post-2011 effect of the initial OxyContin variable. Regressions are weighted by population. "No Pill Mill States" means that Florida, Kentucky, and West Virginia are excluded. "West Only" means that only states in the West Census Region are included in the sample.