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Essays on Health and Public Policy

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This dissertation examines the economic and health impacts of policies which affect access to useful but potentially addictive substances.

The first chapter examines how the availability of prescription opioids affects the labor market. I provide new evidence on this question by leveraging a natural experiment which sharply decreased the supply of hydrocodone, the most commonly prescribed opioid in the US, relative to other opioids. I identify the causal impact of this decrease by exploiting pre-existing variation in hydrocodone prescribing patterns to compare areas differentially exposed to the treatment over time. Areas with larger reductions in hydrocodone prescribing experienced relative improvements in labor force participation and employment. These findings suggest that policies which reduce opioid misuse may also have positive spillovers on the labor market.

The second chapter, previously published in Health Economics, examines how efforts to reduce the abuse potential of prescription opioids affect population health. In response to rising opioid overdose deaths, pharmaceutical companies have begun introducing abuse-deterrent painkillers, pills with properties that make the drug more difficult to misuse. The first such painkiller, a reformulated version of OxyContin, was released in 2010. Previous

research has found no net effect on opioid mortality, with users substituting away from OxyContin toward heroin. This paper explores health effects of the reformulation beyond mortality. In particular, heroin is substantially more likely to be injected than OxyContin, increasing exposure to blood-borne diseases. Exploiting variation across states in OxyContin misuse prior to the reformulation, I find large relative increases in the spread of hepatitis B and C in states most likely to be affected by the reformulation. In aggregate, the estimates suggest that absent the reformulation we would have observed approximately 76% fewer cases of hepatitis C and 53% fewer cases of hepatitis B from 2011-2015. This finding has important implications for future policies addressing the opioid crisis.

The third chapter examines whether state-level decisions to liberalize access to medical marijuana have spillover effects on neighboring states. Previous research on medical marijuana laws (MMLs) has assumed that the effects of MMLs are only present in the states that adopt them. However, anecdotal evidence from politicians and law enforcement officials suggests that MMLs lead to increases in drug-related activity in neighboring states. In this paper I utilize a difference-in-differences strategy to test whether the effects from MMLs spill over across state lines. I present indirect evidence that MMLs do affect nearby states. Most importantly, I find a substantial reduction in opioid abuse in states which border MML states, suggesting substitution away from prescription opioids and heroin toward marijuana.

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Chapter 1

The Impact of Opioids on the Labor Market: Evidence from Drug Rescheduling

1.1 Introduction

Over the last two decades the opioid epidemic has claimed over 370,000 lives, driving the most deadly drug overdose crisis in US history. Despite numerous interventions by state and federal governments, pharmaceutical companies, and healthcare providers, the crisis shows no signs of abating. The number of opioid overdose deaths in each year since 1999 has exceeded the prior year's total, with 2017 as the deadliest year yet with over 47,000 deaths. This dramatic rise in opioid abuse and overdose deaths has garnered attention from academics, policy makers, media outlets, and politicians alike (Janet Yellen, 2017; The New York Times, 2019; Donald J Trump, 2018).

Coincident with the onset of the opioid crisis in the late 1990s and early 2000s, the national labor force participation rate fell from an all-time high of about 67 percent to under 63 percent by 2014, the lowest level since 1983. Further, the areas most affected by the crisis have typically also been the hardest hit by worsening labor market conditions (Alan B Krueger, 2017). For example, in 2011 West Virginia—the state with the highest rates of both opioid prescriptions and overdose deaths per capita—also had the lowest rate of labor

force participation of any state, nearly 10 percentage points below the national average.[1]

Observations like these have led researchers to ask the question: does opioid abuse cause poor economic conditions, or does declining economic activity drive individuals toward opioid abuse (e.g., Anne Case and Angus Deaton (2017); Christopher J Ruhm (2018); Janet Currie, Jonas Jin and Molly Schnell (2019); Krueger (2017))?[2] Despite the strong cross-sectional and time series correlations between overdose deaths and poor economic conditions, the answers to these questions regarding causality have proved elusive, in part due to the difficulty of identifying exogenous variation in either opioid prescribing or economic conditions.

In this paper, I focus on estimating the causal impact of opioid prescribing on labor market outcomes. In order to overcome difficulties faced by previous papers in identifying plausibly exogenous variation in opioid prescriptions, I rely on variation resulting from a regulatory change which suddenly and dramatically decreased the supply of hydrocodone, one of the most commonly prescribed opioids, relative to other similar drugs. Specifically, the Drug Enforcement Agency (DEA) classifies controlled substances into one of five schedules. Lower numbered schedules consist of drugs which are considered more dangerous and are subject to increasingly stringent prescribing and dispensing regulations. On October 6, 2014, hydrocodone combination products (HCPs) were "rescheduled" from Schedule III to Schedule II, leading to an approximately 36 percent decrease in the amount of hydrocodone distributed in the years following the rescheduling.

[1]Sources: CDC State Prescribing Maps, CDC WONDER Online Database, and BLS Local Area Unemployment Statistics.

[2]See section 1.2 for a review of the relevant literature.

Concurrent with this supply shock, the approximately 15-year fall in labor force participation stopped abruptly, with the labor force participation rate stabilizing at around 63 percent. I provide a variety evidence that the simultaneous reduction in opioid prescriptions and trend break in the labor force participation rate reflect a causal effect of opioid prescriptions on labor force participation.

To estimate the effect of the rescheduling on labor market outcomes, I employ a difference-in-differences framework leveraging variation in the extent to which different zip codes were exposed to the reform. Areas which relied heavily on hydrocodone prior to the rescheduling had more scope to be affected than places that used less hydrocodone to begin with. Similar methodology has been employed in previous work to study interventions with no variation in the timing of treatment, such as the eradication of hookworm from the American South (Hoyt Bleakley, 2007) and the reformulation of OxyContin (Abby Alpert, David Powell and Rosalie Pacula, 2018; David Beheshti, 2019). Utilizing this variation in pre-intervention hydrocodone consumption, I create a difference-in-differences style estimator to compare differentially treated areas before and after the rescheduling. I first show that the places which prescribed relatively more hydrocodone prior to the rescheduling were indeed the places which saw the largest declines in hydrocodone prescribing after the rescheduling. I find no evidence of substitution towards other opioids, indicating that the effects of the rescheduling were not simply undone via substitution.

Next, I present the main result of the paper: areas that were more exposed to the rescheduling saw relative increases in labor force participation compared to less exposed areas. I find that this result is driven almost entirely by increases in employment; there are no significant effects of the rescheduling on unemployment. In total, the regression estimates

indicate an aggregate increase of about 0.8 percent (0.52 percentage points) in the labor force participation rate and a 1 percent (0.61 percentage point) increase in the employment-to-population ratio relative to a counterfactual scenario without the rescheduling. Consistent with higher participation in the labor market, I also find a decrease in Social Security Disability Insurance (SSDI) claimants following the rescheduling.

A series of robustness tests supports a causal interpretation of these findings. I find that the results are driven specifically by areas with high levels of pre-reformulation exposure to hydrocodone as opposed to high opioid consumption more generally. I also present regression results explicitly controlling for other opioid related policy changes and find similar effects. Finally, I show that the results are not sensitive to the specific measure of hydrocodone consumption, nor alternate methods to measure exposure to the rescheduling.

These findings have important policy implications. The results indicate that more cautious opioid prescribing may have the ancillary benefit of improving local labor market conditions and reducing disability claims. Furthermore, the paper suggests a relatively low-cost policy lever with which to reduce opioid prescribing, namely, moving drugs to stricter regulatory categories. Although the majority of opioids are now in the most strictly regulated category of prescription drugs, there are still several commonly prescribed opioids which are subject to more lenient restrictions such as Tramadol, certain codeine formulations, and buprenorhpine. This could also be relevant for several increasingly commonly abused benzodiazepines, most of which are currently in a less strictly regulated category.

The paper proceeds as follows: Section 1.2 discusses the relevant institutional background, as well as the related literature. Section 1.3 outlines the research design, while section 1.4 discusses the data. The results are presented in section 1.5. Section 1.6 investigates the

robustness of the main results. Section 1.7 concludes.

1.2 Background

1.2.1 Background on the Opioid Crisis and Related Literature

Opioid Crisis Opioids refer to a class of drugs derived from opium or with opium-like effects. These drugs are generally used to treat acute and chronic pain, although they are also commonly misused for their recreational effects. Taking opioids in large quantities or in combination with alcohol or other sedative medications (e.g., muscle relaxants or benzodiazepines) enhances the recreational effects of the drug, but also causes respiratory depression which can lead to death. Opioids include prescription painkillers such as OxyContin, Vicodin, and Fentanyl, as well as illegal drugs like heroin. Beginning in the mid 1990s, a combination of factors including philosophical changes in the way healthcare providers viewed optimal pain management and aggressive marketing by pharmaceutical companies led to a rapid increase in the frequency with which these drugs were prescribed (James N Campbell, 1996; Art Van Zee, 2009). Unfortunately, painkiller overdose deaths rose in lockstep with the increase in opioid prescriptions, increasing from about 2,600 in 1999 to more than 14,600 in 2017, an increase of more than 500 percent.[3] Anne Case and Angus Deaton (2015); Case and Deaton (2017) find that opioid overdose deaths constitute one of the two largest factors in the recent increase in mortality rates among middle-aged non-Hispanic whites in the US. Opioid overdose deaths are currently the leading cause of death from accidents in the US, exceeding the number of car accident fatalities in each year since 2009.

[3]Refers to deaths with MCD Codes T40.2 and T40.3. Including deaths from heroin and synthetic opioids (e.g., Fentanyl) makes the rise even more dramatic, with the number of total opioid overdose deaths increasing by more than eight times over the same period.

Related Literature In reaction to the growing death toll, numerous policies and interventions have been enacted in an attempt to reduce opioid misuse.[4] The sudden rise in opioid abuse and related policies has engendered a growing literature examining different facets of opioid prescribing and misuse such as physician education (Molly Schnell and Janet Currie, 2017), the introduction of Medicare Part D (David Powell, Rosalie Liccardo Pacula and Erin Taylor, 2015), and access to marijuana (David Powell, Rosalie Pacula and Mireille Jacobson, 2018). Related papers have examined the effectiveness of various interventions such as prescription drug monitoring programs (Thomas C Buchmueller and Colleen Carey, 2018; Dhaval M Dave, Anca M Grecu and Henry Saffer, 2017; Leonard J Paulozzi, Edwin M Kilbourne and Hema A Desai, 2011), increased access to Naloxone (Jennifer L Doleac and Anita Mukherjee, 2018; Daniel I Rees, Joseph J Sabia, Laura M Argys, Joshua Latshaw and Dhaval Dave, 2017), Good Samaritan Laws (Rees et al., 2017), the introduction of abuse-deterrent painkillers (Alpert, Powell and Pacula, 2018; Beheshti, 2019; William N Evans, Ethan Lieber and Patrick Power, 2018), and quantity limits for opioid prescriptions (Daniel W Sacks, Alex Hollingsworth, Thuy D Nguyen and Kosali I Simon, 2019). This paper is the first in the economics literature to examine the impact of one of the single largest interventions to the prescription opioid market, the rescheduling of hydrocodone.[5] The results of this paper indicate that this type of low-cost intervention can have large ef-

[4]See Jennifer Doleac, Anita Mukherjee and Molly Schnell (2018) for a review of the recent literature regarding the opioid epidemic.

[5]Several papers in the medical literature also investigate the rescheduling and find reduced access to hydrocodone, consistent with the findings in this paper (e.g. Jan Chambers, Rae M Gleason, Kenneth L Kirsh, Robert Twillman, Lynn Webster, Jon Berner, Jeff Fudin and Steven D Passik, 2015; Christopher M Jones, Peter G Lurie and Douglas C Throckmorton, 2016). This paper further expands on these papers by considering the effects of the rescheduling on outcomes beyond prescribing behavior, specifically labor market outcomes.

fects, suggesting another policy-lever with which to address not only opioid misuse, but also drug abuse more generally.

A closely related strain of the literature has focused on the relationship between opioids and the labor market. Motivating this segment of the literature are two broad stylized facts. First, the onset of the opioid crisis coincided with the start of a nearly 15-year decline in labor force participation (Figure 1.1, panel (A)). Second, the areas which have experienced the largest deteriorations in labor market conditions are also the areas which have been hit hardest by the opioid crisis (Krueger, 2017). Suggesting a causal mechanism driving this observation, Krueger (2017) finds that almost half of prime-age men not in the labor force take pain medication every day. Several different papers have investigated whether there exists a causal relationship between opioid use and labor market conditions, in either direction, using a variety of identification strategies.

Most closely related to this work are papers which investigate the causal effect of opioids on the labor market. Many of these papers instrument for opioid prescriptions in order to alleviate concern of an omitted variable bias (e.g., underlying patient demand). For example, Currie, Jin and Schnell (2019) instrument opioid prescriptions for the young with prescriptions for the elderly and find that increased opioid prescriptions lead to modest increases in the employment-to-population ratio for women, although they do not find any effects for men. In contrast, Matthew C Harris, Lawrence M Kessler, Matthew N Murray and M Elizabeth Glenn (2017) instrument for county level opioid prescriptions using the prevalence of high-volume prescribers in Medicare Part D and find that increases in opioid prescriptions lead to decreases in labor force participation. Relatedly, Bogdan Savych, David Neumark and Randall Lea (2018) find that injured workers who receive long-term

opioid prescriptions have longer absences from work following an injury, instrumenting for an individual's opioid prescription with county-level opioid prescribing patterns.

In this paper, I make two primary contributions relative to this existing literature. First, I provide transparent evidence on the impact of opioids on the labor market by utilizing sharp variation in prescribing behavior induced by a regulatory change. In contrast, prior work has largely relied on observational variation in prescribing patterns, making causal inference challenging.[6] Second, this paper provides estimates which are particularly relevant for public policy, as it analyzes the effects of a regulatory change that both state and federal governments can affect to influence future prescribing.[7,8]

Other work investigates the causal relationship between the labor market and opioids in the opposite direction, i.e., the effect of labor market conditions on opioid prescriptions, misuse, and mortality. Currie, Jin and Schnell (2019) use a shift-share instrument based on industry composition to examine the effects of economic conditions on opioid prescriptions and find no effects. This is consistent with work by Ruhm (2018), who finds that only a small fraction of drug mortality can be explained by medium-run changes in economic conditions.

[6]One exception is Jessica Laird and Torben Nielsen (2016), which examines outcomes of individuals in Denmark who move to high opioid prescribing areas and finds that these movers consume more opioids and reduce their labor force participation after the move. However, opioid use and abuse in the US is substantially higher in both levels and growth rates than in Denmark. Related work by Amy Finkelstein, Matthew Gentzkow and Heidi Williams (2018) find that SSDI beneficiaries in the US who move to high prescribing areas are substantially more likely to receive an opioid prescription. However, given the population they are studying Finkelstein, Gentzkow and Williams (2018) are not able to examine labor market outcomes.

[7]States can add additional requirements regarding the prescribing and dispensing of controlled substances above and beyond federal regulations.

[8]Angela Kilby (2015) considers another policy-relevant intervention, the introduction of prescription drug monitoring programs (PDMPs). She finds that states which implement PDMPs see decreases in opioid prescriptions but more absences from work for injured workers, highlighting the tradeoffs involved in stricter prescription regulations.

However, Alex Hollingsworth, Christopher J Ruhm and Kosali Simon (2017) find that short-term increases in the unemployment rate lead to increased emergency department visits related to opioids. On net, these papers suggest that transitory changes in unemployment may lead to increases in opioid abuse, although long-running trends in economic conditions do not explain much of the variation in opioid misuse and mortality.

Finally, this paper closely relates to other work which has investigated the effects of pharmaceuticals on the labor market. Specifically, Craig L Garthwaite (2012) and Aline Bütikofer and Meghan M Skira (2018) both exploit the sudden withdrawal of Cox-2 inhibitors (Vioxx, Celebrex, Bextra) to examine how changes in drug use affect labor force participation.[9] These papers find large and statistically significant reductions in labor force participation and increases in the number of absences due to sickness, indicating that this medication allowed some individuals to participate in the labor market who would otherwise be incapable of working. In principle, this could be the case with prescription opioids. However, opioids are much more likely to be abused, which would presumably drive individuals out of the labor market. It is theoretically ambiguous which of these effects would be larger. This paper investigates these competing effects by leveraging variation from a large, plausibly exogenous change in opioid consumption stemming from a policy change. Empirically, I find that the latter effect dominates, with fewer opioid prescriptions leading to higher labor force participation and employment.

[9]Cox-2 inhibitors are anti-inflammatory drugs used to treat a variety of conditions, especially arthritis.

1.2.2 Hydrocodone Background and Rescheduling

Hydrocodone is an opioid analgesic synthesized from codeine, a naturally occurring substance in opium poppies. Like many other opioids, it is used in the treatment of both acute and chronic pain. Clinically, hydrocodone has been shown to work as well in the treatment of acute pain as oxycodone (Catherine A Marco, Michael C Plewa, Nancy Buderer, Cheryl Black and Alisa Roberts, 2005), although a slight majority of recreational users prefer oxycodone (Theodore J Cicero, Matthew S Ellis, Hilary L Surratt and Steven P Kurtz, 2013).[10] It is commonly sold under the brand names such as Vicodin, Lortab, and Norco, although it is also available in generic form. In 2013, hydrocodone was the most frequently prescribed opioid in the US with about 137 million prescriptions (Drug Enforcement Agency, 2014). In the same year, hydrocodone was the most commonly prescribed drug *overall* (not just among opioids) in Medicare Part D.[11] It was the third highest selling of all generic drugs, generating almost 1.1 billion dollars in 2013.[12] Due to its ubiquity, hydrocodone is one of the most commonly misused painkillers in the US. Approximately 4.9 percent of National Survey on Drug Use and Health (NSDUH) respondents in 2013 reported misusing hydrocodone at some point in their lives. Interestingly, this is more than a percentage point higher than the fraction of NSDUH respondents reporting any lifetime OxyContin misuse at in 2009 (3.6 percent), the peak year of OxyContin misuse. Hydrocodone has been a key contributor to the opioid crisis, implicated in around 3,000 deaths per year from 2011-2016 (Holly Hedegaard,

[10] Hydrocodone was ranked the as the second most preferred opioid among recreational users, and was the drug of choice among around 30 percent of those surveyed.

[11] Authors calculation using the 2013 Part D Prescriber Public Use File, available here: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/Part-D-Prescriber.html.

[12] Source: https://www.pharmacytimes.com/publications/issue/2014/july2014/top-drugs-of-2013.

Brigham A Bastian, James P Trinidad, Merianne Spencer and Margaret Warner, 2018).[13]

Although similar to many other opioids in both usage and effects, hydrocodone has historically been less stringently regulated. In the US, the Drug Enforcement Agency (DEA) classifies prescription drugs into one of four categories, Schedules II-V.[14] The classifications have important implications for prescribers and patients, as lower numbered schedules (e.g., Schedule II) are much more strictly regulated relative to other schedules, making these drugs more difficult to obtain. For example, Schedule II drugs require a new prescription each time a patient obtains the drug, while Schedule III drugs can be refilled up to five times in a six month period.[15] Schedule II prescriptions must be handwritten, as opposed to Schedule III prescriptions which can be faxed to a pharmacy. Additionally, many individual states have laws which further restrict access to Schedule II drugs. For example, some states prohibit mid-level practitioners such as physician assistants and nurse practitioners from prescribing Schedule II drugs, while many emergency departments do not distribute Schedule II drugs as a matter of policy (Drug Enforcement Agency, 2014).

Historically, most high potency narcotic painkillers have been placed in the most restrictive category, Schedule II. Although hydrocodone by itself was also classified as Sched-

[13]Despite being the most commonly prescribed opioid in the US, hydrocodone is less frequently mentioned in popular accounts of the opioid crisis, which have mainly focused on the role of OxyContin in driving opioid abuse and mortality (Sam Quinones, 2015). This is due at least in part to the ease with which OxyContin could be abused prior to its reformulation in 2010 (Alpert, Powell and Pacula, 2018; Evans, Lieber and Power, 2018; Beheshti, 2019). This ease of abuse led to oxycodone playing an outsized role in opioid-related mortality relative to its prescribing and reported misuse. Hydrocodone was the fourth leading cause of death among painkillers from 2011-2016, following oxycodone, morphine, and methadone.

[14]Schedule I drugs are those which are considered to have no accepted medical use and high potential for abuse, and are therefore not available via prescription.

[15]Title 21 Code of Federal Regulations, available here: https://www.deadiversion.usdoj.gov/21cfr/cfr/1306/1306_22.htm. Also see: https://www.deadiversion.usdoj.gov/faq/prescriptions.htm.

ule II, if combined with another non-narcotic analgesic such as acetaminophen (Tylenol) or ibuprofen (Advil), it was classified as Schedule III. Likely because of this exception, all hydrocodone drugs sold in the US prior to the rescheduling were hydrocodone combination products (HCPs), i.e., hydrocodone with acetaminophen or ibuprofen.[16] This "Vicodin loophole" made HCPs such as Vicodin, Norco, and Lortab substantially easier for providers to prescribe relative to non-hydrocodone based painkillers such as oxycodone (e.g., OxyContin) or hydromorphone (e.g., Dilaudid). On October 6, 2014, the DEA closed this loophole by rescheduling all hydrocodone drugs— regardless of whether or not they were combined with other drugs— as Schedule II. Consistent with the rescheduling making hydrocodone more difficult to prescribe, panel (B) of Figure 1.1 demonstrates an immediate decline in the distribution of hydrocodone beginning in the first quarter of the rescheduling.[17] By the end of 2017, the quarterly amount of hydrocodone distributed had fallen by more than 36 percent of its 2013 level. In the following section, I discuss how I use variation in exposure to this drop in hydrocodone prescriptions to estimate the causal effects of the rescheduling.

1.3 Research Design

The aggregate drop in the distribution of hydrocodone (Figure 1.1 panel (B)) and coincident trend break in falling labor force participation (Figure 1.1 panel (A)) around the date of the rescheduling are suggestive of a relationship between the two. However,

[16]Currently, two extended release hydrocodone (only) drugs are available in the US, Zohydro ER and Hysingla ER. These were not released until after the rescheduling.

[17]Similar figures are shown with the number of hydrocodone prescriptions and tablets dispensed immediately before and after the rescheduling in Jones, Lurie and Throckmorton (2016) using proprietary pharmacy data from the IMS Health National Prescription Audit. Their data cover the period between 2011 Q4 and 2015 Q3.

it is difficult to draw strong conclusions based solely on this type of time series evidence. Evaluation of the causal effect of the rescheduling is further complicated by the fact that the rescheduling took place everywhere on the same date, disallowing a typical difference-in-differences research strategy comparing treated and untreated units. Instead, I use a similar research strategy to several previous papers investigating the effects of aggregate level events including the eradication of hookworm from the American South (Bleakley, 2007) and the reformulation of OxyContin (Alpert, Powell and Pacula, 2018; David Powell, Abby Alpert and Rosalie L Pacula, 2019; Beheshti, 2019) by comparing units which were differentially exposed to the treatment of interest. In this instance, I exploit pre-existing cross-sectional variation in the distribution of hydrocodone to compare places which were more heavily exposed to the rescheduling to places which were less exposed. For example, an area which typically received large shipments of hydrocodone each quarter prior to the rescheduling had much more scope to be affected than a place which typically received very little hydrocodone.

Non-Parametric Event Study Formalizing the idea described above, I begin by estimating non-parametric difference-in-differences regressions of the form

$$y_{zt} = \alpha_z + \gamma_t + \sum_{T \neq \text{ Sept. } 2014} \beta_T \cdot 1(t = T) \times \text{Hydro}_z^{pre} + \delta X_{zt} + \epsilon_{zt}, \tag{1.1}$$

where y_{zt} is the outcome in three-digit zip code (zip3) z and period t. Zip3 and time fixed effects are represented by α_z and γ_t, respectively. Time varying control variables are included in X_{zt}. The baseline model does not include any additional control variables, although I explore the sensitivity of the regression coefficients to the inclusion of more controls in section 1.6. Hydro_z^{pre} is the average number of milligrams of hydrocodone per person

quarter prior to the rescheduling, which is the proxy for exposure to treatment. The primary coefficients of interest are the β_Ts, the coefficients of the interaction of Hydro_z^{pre} with time fixed effects. Each of these coefficients can be interpreted as the difference in the outcome variable at time t across zip3s with differing pre-rescheduling rates of hydrocodone exposure. I normalize $\beta_{\text{Sept. 2014}}$ to zero, so all coefficients can be interpreted as changes relative to the month (or quarter) prior to the rescheduling. Standard errors are clustered at the zip3 level throughout.

The standard identifying assumption for regressions like equation 1.1 is that the post-period dynamics of the less treated observations trace out the dynamics that we would have observed in the more treated observations absent the treatment. This is commonly referred to as the parallel trends assumption. This assumption is fundamentally untestable as we do not observe the state of the world in which the treatment never occurs. However, researchers often assess the plausibility of this assumption by examining the β_T coefficients in the pre-period. Pre-period β_T coefficients that are close to zero indicate that the more and less treated observations were trending similarly prior to the treatment taking place, which lends plausibility to the assumption that they would have trended in parallel in the post-period absent the treatment.

1.3.1 Parametric Event Study

As will be shown in Section 1.5, there exist strong, differential time trends in several of the outcome variables across zip3s related to their level of exposure to hydrocodone. This manifests itself as non-zero β_T coefficients in the pre-period, which violates the standard parallel trends assumption of this type of difference-in-differences model. Motivated by

these results, I follow Carlos Dobkin, Amy Finkelstein, Raymond Kluender and Matthew J Notowidigdo (2018) and also estimate a more parametric model which directly controls for these pre-existing trends. Specifically, I estimate

$$y_{zt} = \lambda_z + \psi_t + \sum_{T>\text{Sept. '14}} \theta_T \cdot 1(t = T) \times \text{Hydro}_z^{pre} + \sum_Z \phi_Z \cdot 1(z = Z) \cdot t + \eta X_{zt} + \nu_{zt}. \quad (1.2)$$

The key differences between this and equation 1.1 are the inclusion of zip3 specific linear time trends, included as $\sum_Z \phi_Z \cdot 1(z = Z) \cdot t$, and the fact that the coefficients on the interaction of Hydro_z^{pre} with time fixed effects are only estimated for the post period. Conceptually, this fits a linear trend based on the pre-period for each zip3 and then allows deviations from this trend in the post-period via the interactions of the time fixed effects and the Hydro_z^{pre} variable.

The identifying assumption necessary for this model to reveal the causal effect of the hydrocodone rescheduling is a slight modification of the identifying assumption discussed above. Rather than assuming that the dynamics of the more heavily treated areas would have followed those of the less treated areas in the absence of treatment, this model requires that we would have observed similar deviations from a linear trend fit based on the pre-period in the more or less treated areas absent the treatment. This assumption is closely related to that of equation 1.1. In fact, it is equivalent to the standard parallel trends assumption after controlling for zip3 specific linear trends.

Because equation 1.2 only estimates the interaction terms for the post-period, examining the θ_T coefficients does not provide a sense of how well the the linear pre-trend fits the data. Therefore, I follow Dobkin et al. (2018) and rescale the β coefficients from equation

1.1 to equal the θ coefficients when presenting the results from this model.[18] This rescaling allows the reader to easily see whether the linear trends fit the data well by examining whether the rescaled β coefficients differ from zero in the pre-period.

1.4 Data and Identifying Variation

1.4.1 Data

ARCOS Data on the distribution of various opioids come from the Automated Reports and Consolidated Ordering System (ARCOS) of the Drug Enforcement Agency (DEA). By law, manufacturers and distributors of certain controlled substances are required to report their transactions to the DEA.[19] The DEA compiles these reports into an annual publication. Data are currently available from 2000-2017, at the quarter by 3-digit zip code (zip3) level.[20]

There are several major advantages to these data. First, they are available at the active ingredient level (e.g., oxycodone, hydrocodone, etc.) for most commonly prescribed opioids.[21] This allows the researcher to observe the geographic distribution of different types

[18] In principle, this just subtracts the implied time trend out from the non-parametric model. More specifically, equations 1.1 and 1.2 imply $\beta_t - \theta_t = a + b \cdot t \ \forall t >$ Sept. 2014, where a, b are constants. Using this relationship I can recover the implicit pre-period θ_t coefficients, i.e., $\theta_t = \beta_t - a - b \cdot t \ \forall t$. Dobkin et al. (2018) do this in reverse, superimposing the θ coefficients onto the β coefficients and plotting the implied time trend along with the non-parametric coefficients.

[19] Title 21, United States Code, Section 827(d)(1), and Title 21, Code of Federal Regulations, Section 1304.33.

[20] Data can be downloaded here: https://www.deadiversion.usdoj.gov/arcos/retail_drug_summary/index.html.

[21] Data include hydrocodone, oxycodone, remifentanil, oxymorphone, powdered opium, morphine, methadone, meperidine (pethidine), levorphanol, hydromorphone, fentanyl base, dihydrocodeine, codeine, buprenorphine, sufentanil, and opium tincture. One notable omission is tramadol, for which ARCOS does not publish any data. Data at the ingredient level is also available through the Medicare Part D prescriber files (available here: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/Part-D-Prescriber.html), although this is only reflective of prescriptions to Medicare beneficiaries enrolled in Part D.

of opioids, as opposed to summary measures which pool across all types of opioids, such as the data on number of prescriptions per capita published by the CDC. This is especially useful in the context of this paper, which examines the effects of a policy intervention which in practice only directly affected opioids which contain hydrocodone. Second, the data is published at the zip3 level. Zip3's are an aggregation of all zip codes with the same first three digits. Generally, these are continuous geographic areas slightly larger than a typical county. This is beneficial as there is not only significant interstate, but also intrastate variation in the distribution of many opioids which would be overlooked with more aggregate (e.g., state-level) measures. Third, the data do not rely on survey responses from individuals, but are created from data reported directly from drug manufacturers and distributors to the DEA.

However, these data are not without disadvantages. Most notably, the data measure the distribution of various drugs to different locations, but not necessarily the sale or consumption of the drug. If pharmacies or hospitals stockpile large amounts of opioids differentially across geographies, then this data could misrepresent the areas with the most exposure to the drug. However, to the extent that the distribution of the drug is correlated with consumption, this data will reflect meaningful differences in drug consumption patterns. In order to examine the extent to which the distribution of an opioid is correlated with consumption, I compare data on the amount of various opioids prescribed in Medicare Part D across the US to the amount distributed as reported by ARCOS. Drawing from the ARCOS dataset, panel A of Figure A.1 shows the number of milligrams of hydrocodone distributed per capita in 2013, while panel B shows the number of 'hydrocodone days supplied' per capita in Medicare Part D, both at the zip3 level. As the figure shows, in general the zip3s with large amounts of hydrocodone shipments are also the zip3s with large amounts of

hydrocodone prescribed in Medicare Part D. To quantify this correlation further, I regress the measure of hydrocodone distribution from ARCOS on the Medicare Part D consumption measure and report the results in Table A.1. Column (1) shows that Medicare prescriptions for hydrocodone are strongly predictive of the aggregate distribution, with an R^2 of 0.58 (correlation coefficient of 0.76). Columns (2)-(7) repeat this exercise for several of the other most commonly prescribed opioids, and generally reveal the same pattern. While Medicare Part D is only a subset of the hydrocodone using population, this is suggestive that the distribution of hydrocodone is strongly predictive of consumption.[22]

Another difference between ARCOS and other measures of opioid consumption, although not necessarily a disadvantage, is that the ARCOS data measure the amount of the drug distributed (in grams) and do not contain information about the number of prescriptions written. In some ways this is an improvement on other data which only reports the number of prescriptions, as the amount of the drug prescribed can vary widely across patients. However, a drawback of this is that I am unable to separately identify changes in the consumption of hydrocodone (or other opioids) along the intensive versus extensive margin. It should be noted that this problem is not unique to this data, as most other datasets only contain information about the number of prescriptions.[23]

LAUS Labor market data come from the Local Area Unemployment Statistics (LAUS). These data are created by the Bureau of Labor Statistics from several different sources

[22]Because of this, for the remainder of the paper I use the terms distribution and consumption interchangeably.

[23]Medicare Part D is an exception, although again this only provides information about a segment of the population.

including the Current Population Survey (CPS), Current Employment Statistics, Quarterly Census of Employment and Wages, and the American Community Survey (ACS).[24] Data on the number of people employed, unemployed, and participating in the labor force are available at the county-by-month level. The major advantage of these data relative to other sources such as the CPS or ACS is that there is no suppression of small counties. The CPS and ACS censor all counties with a population under about 100,000 and 65,000, respectively.[25] Because of this, about 91.06 and 74.32 percent of counties are censored in the CPS and ACS, respectively.[26] The LAUS, on the other hand, reports for every county in each month. This is particularly important in this context, as much of the variation in hydrocodone exposure is driven by these smaller counties. A disadvantage of these data, however, is that they cannot be disaggregated, so I am unable to examine demographic heterogeneity in labor force responses to the rescheduling.

SSA The Social Security Administration (SSA) administers multiple programs which provide benefits to those with disabilities. Social Security Disability Insurance (SSDI) and Supplemental Security Income (SSI) both provide benefits to disabled individuals with limited work capacity. Both programs have the same medical requirements, while SSDI requires a sufficiently long work history and previous payment of Social Security taxes. In contrast, SSI is based solely on disability status and financial need; SSI beneficiaries must fall below

[24]For more information, see: https://www.bls.gov/lau/laumthd.htm.

[25]The CPS does not explicitly report a population threshold for data suppression, although all but seven of the counties identified in the CPS have a population greater than 100,000. The Census Bureau explicitly states that CPS estimates are not reliable (or even available) for most counties: https://www.census.gov/programs-surveys/cps/about/faqs.html#Q3.

[26]This corresponds to approximately 51.85 and 16.43 percent of the population, respectively. The counties identified are shown in Figure A.2.

certain income and asset thresholds but do not need to have previously paid Social Security taxes. The SSDI payments crowd out SSI payments among those who qualify for both programs.[27] While the number of applications are only available at the state level, the number of SSI and SSDI beneficiaries are available at the county and zip code levels, respectively, although this data is reported annually as opposed to monthly.[28]

HUD The availability of opioid distribution data at the zip3 level is a major improvement over state-level data; however, it introduces an additional complication as most local area labor force data is measured at the county level. Counties and zip code boundaries are created independently and frequently overlap, which makes mapping between them a non-trivial exercise. Counties for the entire US are shown in panel (A) of Figure A.3 in various shades of red, while zip3s are shown in shades of blue in panel (B).[29] These panels demonstrate two facts: first, zip3s are generally (although not always) larger than counties. Second, many (but again not all) counties are nested entirely within a single zip3. In order to highlight these facts more clearly, panel (C) shows county boundaries in white and zip3 boundaries in black for just the state of Texas. Panel (D) zooms in even further on the central Texas region, in order to demonstrate how zip3s are constructed from zip5s. Zip5 bounaries are shown in gray, with zip3s shown in different colors. As this map makes clear, zip5s are nested entirely within zip3s (by construction). County boundaries are again shown in white. When

[27] See Manasi Deshpande, Tal Gross and Yalun Su (2019) for a more detailed discussion of the institutional background of both programs.

[28] SSI data available here: https://www.ssa.gov/policy/docs/statcomps/ssi_sc/index.html. SSDI data available here: https://www.ssa.gov/policy/docs/statcomps/oasdi_zip/index.html.

[29] The colors represent randomly generated data; they are only included to help visually identify county and zip3 boundaries.

counties are nested entirely within zip3s, it is relatively straightforward to create zip3 level labor force statistics. However, this is often not the case.

Fortunately, there exist crosswalks which make this type of merge possible. Since 2010, the Office of Policy Development and Research at the Department of Housing and Urban Development (HUD) has published crosswalks to allow researchers to map between various geographies created by the US Postal Service and the Census Bureau.[30] These crosswalks are updated quarterly and indicate the fraction of individuals in a particular geographic area (e.g., county) who live in each intersecting geography of a different type (e.g., zip code). In order to produce labor force statistics at the zip3 level, I utilize these crosswalks to create counts of employment, unemployment, and labor force participation.[31] Specifically, let Z be the set of all 5-digit zip codes and C be the set of all counties, with z and c representing individual zip codes and counties, respectively. I define ϕ_{cz} to be the fraction of people in county c who reside in zip code z. I define $Z \cap c = \{z : \phi_{cz} \neq 0\}$. In order to map counts from county to zip code, I calculate $X_z = \sum_{c \in C} \sum_{z \in Z \cap c} X_c \cdot \phi_{cz}$, where X is the count of individuals employed, unemployed, or in the labor force.[32] Given the estimate of X at the 5 digit zip code, I simply aggregate up to create the zip3 counts. I then convert these into rates by dividing by the population older than 16.

[30] Data available here: https://www.huduser.gov/portal/datasets/usps_crosswalk.html#data.

[31] It is also possible to map from zip3s to counties. However, since counties are typically smaller than zip3s, mapping from county to zip3 is less reliant on the HUD crosswalks since many counties are nested within zip3s. In practice this does not significantly affect the regression results.

[32] This calculation assumes that employment and unemployment counts are distributed uniformly throughout each county, which likely introduces some measurement error.

1.4.2 Identifying Variation

There exists substantial cross-sectional variation in opioid prescribing patterns across the US. This fact is widely know and has been the subject of a great deal of discussion among academics and policymakers, although the precise causes of this variation are not well understood.[33] Panel (A) of Figure 1.2 demonstrates this variation in prescribing, pooling data on several of the most commonly prescribed opioids from 2010-2013. Darker shades indicate more opioid consumption per capita, with lighter colors showing areas which consumed fewer opioids.

While the variation in overall opioid prescribing has been widely documented, there has been less focus on the variation in prescribing of specific types of opioids. For example, there existed considerable cross-sectional variation in the distribution of hydrocodone prior to the rescheduling. Panel (B) of Figure 1.2 shows the average milligrams of hydrocodone per capita per quarter for each zip3 pooled from 2010-2013, the four years preceding the rescheduling, which I define as my primary treatment variable, Hydro_z^{pre}. As in panel (A), darker shades indicate more hydrocodone per capita with lighter colors showing areas which used less hydrocodone. On average, each zip3 received around 36 milligrams per person-quarter, about the maximum recommended daily dosage for someone over 18.[34] Zip3s in the 75th quartile consumed approximately two and a half times more hydrocodone each quarter than zip3s in the 25th percentile. The maximum value observed in my sample

[33] Most surprisingly, the variation in opioid prescribing does not appear to be driven by underlying differences in patient pain across locations (https://www.aaaceus.com/courses/nl0116a/nl0116a_Article2.pdf).

[34] A typical hydrocodone prescription is one or two 5 milligrams hydrocodone/ 325 milligrams acetaminophen tablets every 4-6 hours as needed, with a maximum of 8 pills in a day. Source: https://www.healthline.com/health/acetaminophen-hydrocodone-oral-tablet.

is about 409 milligrams, enough for each person in the zip3 to be medicated around the clock for about 10 days of each quarter, or 40 days per year. Interestingly, the variation in hydrocodone prescribing does not simply mirror the variation in overall opioid prescribing. Even conditional on the total amount of opioids prescribed, there exists significant variation in the composition of opioids (e.g., hydrocodone versus non-hydrocodone).

This map reveals several geographic clusters where hydrocodone use is especially prevalent, including parts of the Southeast and most of Appalachia, as well as parts of Texas and the Western US. However, even within these regions there still exists considerable variation in hydrocodone use. Because of this geographic clustering, more heavily treated zip3s likely differ on average from less treated zip3s.[35] Of course, given the difference-in-differences design outlined in equations 1.1 and 1.2, average differences across zip3s related to the treatment variable are not important for identification. In order to identify the causal impact of the rescheduling, equation 1.2 only requires that pre-existing differences in trends in the outcome variable would have continued absent the rescheduling. For example, a sudden improvement in labor market conditions in places with more pre-period hydrocodone use for reasons unrelated to the rescheduling would violate this assumption. In Table A.3 I report the results from a series of placebo tests in which I examine whether I observe deviations from trend across zip3s coincident with the rescheduling for variables which would not plausibly be affected by the rescheduling. Each row reports the coefficient analogous to θ from equation

[35] I explore whether several different characteristics such as population, racial composition, Hispanic origin, and age distribution differ by pre-period exposure to hydrocodone in Table A.2. Columns (1)-(4) display summary statistics each of these demographic variables broken down by quartile of Hydro_z^{pre}. Interestingly, none of these variables seem to vary systematically in relation to Hydro_z^{pre}.

1.2, except that in these regressions all of the post periods are pooled together.[36] The first row demonstrates that there is no change in population trends coincident with the rescheduling, while rows (2)-(5) show that there are no changes in the gender, racial, or ethnic composition. Finally, rows (6) and (7) demonstrate that there are no changes in the age distribution. The small and statistically insignificant coefficients for these placebo regressions provide some assurance that the following regression results are not picking up spurious trend breaks which are not actually caused by the rescheduling.

1.5 Results

1.5.1 First-Stage

A necessary condition for the identification strategy outlined above to reveal the causal effect of the rescheduling is that areas with differing pre-period levels of hydrocodone consumption were differentially affected by the rescheduling, which I refer to as the 'first-stage'. Specifically, I expect that areas with high consumption of hydrocodone prior to the rescheduling were more affected than areas with lower consumption. I begin by presenting evidence that this was indeed the case. To do so, I estimate equation 1.1 with the amount of hydrocodone distributed per person-quarter as the outcome variable. For this regression I standardize the treatment variable to have a mean of zero and a standard deviation of one, so each coefficient can be interpreted as the treatment effect of a one standard deviation increase in pre-period hydrocodone exposure. The β_T coefficients are presented graphically

[36] Explicitly, I report the θ coefficient from the regression

$$Y_{zt} = \lambda_z + \psi_t + \sum_Z \phi_Z \cdot 1(z = Z) \cdot t + \theta \cdot 1(t > Oct.'14) \times \text{Hydro}_z^{pre} + \eta X_{zt} + \nu_{zt}$$

.

in panel (A) of Figure 1.3, with the mean of the outcome variable shown in the bottom left corner. Prior to the rescheduling in the 4th quarter of 2014 (indicated by the vertical red dashed line) the coefficients are generally close to zero, although they do exhibit a slight downward trend. However, beginning with the first quarter after the rescheduling, the coefficients show a dramatic and persistent drop in the amount of hydrocodone distributed, especially in the zip3s with higher pre-period levels of hydrocodone consumption. The post-period coefficient indicate that a one standard deviation increase in exposure to treatment is associated with more than a 10 milligram per person drop in the distribution of hydrocodone each quarter, over a third of the mean value. Panel (B) shows the regression results from equation 1.2, which directly controls for linear pre-trends. This attenuates the magnitudes slightly, although there is still a clear drop of nearly 22 percent of the mean value immediately following the rescheduling in places with one standard deviation higher levels of pre-period exposure. Figure A.4 demonstrates the mechanics of equation 1.2 using a discretized version of the raw data. Panel (A) shows the quarterly distribution of hydrocodone per capita, broken down by the 1st and 4th quartile of exposure to treatment. This figure reveals that the zip3s in the 4th quartile were trending down slightly faster than those in the 1st quartile prior to the rescheduling. Panel (B) fits a linear trend to each quartile based on the pre-period, while Panel (C) shows deviations from these linear trends.

Of course, hydrocodone is just one of many different opioids. Ex ante, it is plausible that the drop in hydrocodone distribution was offset by substitution towards other opioids. In order to investigate this, I run a simpler version of equation 1.2 which only interacts Hydro_z^{pre} with a post indicator and then plot these coefficients for all of the opioids reported in ARCOS. These coefficients are shown graphically in Figure 1.4. Panel (A) shows the coef-

ficients for a variety of opioids, all of which are converted to morphine milligram equivalents. Consistent with Figure 1.3, Figure 1.4 shows a reduction of a little under 10 milligrams of hydrocodone per person-quarter after the rescheduling in places with one standard deviation more exposure to hydrocodone in the pre-period. Interestingly, there appears to be almost no substitution toward other opioids. The only statistically significant positive estimate is for codeine, although the magnitude is far too small to compensate for the decrease in hydrocodone.

For several of the opioids tracked by the DEA, there was no straightforward conversion into morphine milligram equivalents, so I leave them in milligrams per capita. These coefficients, along with the coefficient for hydrocodone, are reported in in panel (B).[37] None of these coefficients are statistically significant, and all are very close to zero.

In order to explore the possible dynamic responses of other opioids, I present the coefficients from equation 1.1 pooling all opioids which can be converted into morphine equivalent doses in panel (A) of Figure 1.5. This figure shows no break around the date of the rescheduling, indicating that there was no immediate substitution toward other opioids after the rescheduling. In fact, the coefficients become negative and statistically significant several quarters after the rescheduling, indicating that if anything there was less consumption of possible substitute opioids. However, the coefficients reveal a steady decline in the pre-period as well. Adjusting for this pre-trend in panel (B) shows that there is no effect on other non-hydrocodone opioids.

Taken together, these results demonstrate that areas with high levels of hydrocodone

[37]The hydrocodone coefficient is identical in both panels since a milligram of hydrocodone is equivalent to a milligram of morphine.

consumption were in fact the areas most affected by the rescheduling. Furthermore, these effects were not simply undone via substitution toward other prescription opioids.[38] It is possible, however, that some substitution could have occurred toward illegal drugs such as heroin or illicitly manufactured Fentanyl, although I do not have any data with which to test this. Given the large number of individuals outside of the labor force taking prescription painkillers (Krueger, 2017), this lends plausibility to the idea that this intervention may have had effects in the labor market, which I document in the next sub-section.

1.5.2 Labor Market Results

Given the large, differential reduction in hydrocodone consumption in areas with higher pre-period consumption of hydrocodone, I now investigate whether the rescheduling affected the labor market. First, I examine the effects of the rescheduling on the labor force participation (LFP) rate. Panel (A) of Figure 1.6 graphically presents each β_T coefficient from estimating equation 1.1, with $\beta_{\text{Sept. 2014}}$ normalized to zero and 95 percent confidence intervals indicated by gray shading. Each of these coefficients can be interpreted as the expected difference in the LFP rate in zip3s which had one standard deviation higher levels of per capita hydrocodone consumption in the pre-period. Examining these coefficients reveals a striking pattern: LFP rates were falling substantially faster in areas with more

[38] I cannot directly examine substitution toward Tramadol using my regression framework. Tramadol was a previously unscheduled synthetic opioid which was placed in Schedule IV in August of 2014. Because of its late addition to the Controlled Substances Act, Tramadol was not reported by the DEA. However, I am able to pull data on the annual distribution of Tramadol from IQVIA (taken from a report by US Food and Drug Administration (2018)) and compare it to the quarterly distribution of hydrocodone. This is shown in Figure A.5 and suggests that there wasn't significant substitution toward Tramadol after the rescheduling. Unfortunately I don't have access to these data at any other level of geography and so cannot test for substitution using my regression strategy.

hydrocodone exposure in the pre-period. However, following the rescheduling this differential trend disappears immediately, suggesting that the rescheduling affected the LFP rate differentially in areas with differing levels of exposure to the rescheduling.[39]

In order to interpret the post-period regression coefficients as the causal effect of the policy in question, the standard difference-in-difference model requires the assumption that outcomes in differentially treated areas would have continued trending similarly in the absence of the treatment, conditional on the included controls. This is commonly referred to as the 'parallel trends' assumption, and is generally tested by examining whether the pre-period coefficients differ from zero. The underlying idea is that if outcomes are trending differentially prior to the treatment and these same trends continue into the post-period, a typical difference-in-differences model will erroneously estimate a treatment effect when in reality the policy had no effect. In this context, the typical parallel trends assumption is clearly not met. However, the regression coefficients demonstrate a sharp break in trend coincident with the date of the rescheduling. Interpreting this trend break as the impact of the rescheduling requires the assumption that in the absence of the rescheduling, the pre-existing (differential) trends in the outcome variable would have continued. Put slightly differentially, this model assumes that deviations from a linear trend among the observations less exposed to the treatment provide a reasonable counterfactual for the observations which were more exposed to treatment had the treatment not taken place. Conceptually, this is equivalent to the familiar parallel trends assumption after controlling for zip3-specific pre-trends.

[39]This pattern is demonstrated with the raw data in panel (A) of Figure A.6, where I plot the LFP rate broken down by the 1st and 4th quartiles of exposure to treatment.

I formally describe this regression in equation 1.2 and graphically present the regression coefficients in panel (B) of Figure 1.6.[40] Each of these coefficients can be interpreted as the average difference from trend in zip3s one standard deviation apart in pre-period hydrocodone consumption. The pre-period coefficients are all close to zero in magnitude and statistically insignificant, indicating that there was very little deviation from trend in the pre-period. However, immediately following the rescheduling the coefficients become positive, indicating a relative increase in the LFP rate in areas which were more heavily exposed to the rescheduling.[41] About two and a half years after the rescheduling, the LFP rate was about 0.44 percentage points above trend in areas with an additional standard deviation of exposure to the treatment. Relative to the mean LFP rate (shown in the bottom left corner of panel (A)) this suggests around a 0.7 percent increase in the LFP rate. A more extreme treatment, for example moving from the 10th to the 90th percentile in terms of pre-period hydrocodone consumption, is associated with over a 0.88 percentage point increase in the LFP rate, about a 1.4 percent increase above the mean.

In order to characterize the magnitude of this result directly in terms of the reduction in hydrocodone, I scale the treatment effect on the LFP rate by the treatment effect on hydrocodone. Specifically, a one standard deviation increase in pre-period exposure to treatment is associated with a 22 percent decrease in hydrocodone and a 0.7 percent (0.44 percentage point) increase in the LFP rate two and a half years later. Dividing these estimates indicates that a ten percent decrease in hydrocodone prescriptions is associated with about a 0.32 percent increase in the LFP rate. Extrapolating from this estimate to the

[40] The process for inferring the pre-period coefficients is described in section 1.3.1.

[41] Panel (B) of Figure A.6 shows an analogous plot using the raw data. The lines in this figure show the deviations from a linear trend fit separately for the 1st and 4th quartile of exposure to treatment.

36 percent aggregate reduction in hydrocodone consumption since the rescheduling suggests that the rescheduling could account for an aggregate increase in the LFP rate of about 1.8 percent (1.15 percentage points).

Mechanically, the increase in LFP could be driven by either increases in employment or by increases in unemployment.[42] In order to investigate what is causing the change in the LFP rate, I begin by examining the effects of the rescheduling on the employment-to-population ratio (EPR). Panel (C) of Figure 1.6 plots each coefficient from regression equation 1.1. These coefficients show an almost identical pattern to the analogous regressions examining the LFP rate: the EPR was falling at a faster rate in places with more exposure to the treatment in the pre-period, although this pattern stops immediately after the rescheduling. In addition to duplicating the same pattern as the LFP rate, the EPR coefficients are nearly identical in magnitude. This indicates that nearly the entire relative rise in the LFP rate can be explained by the change in the EPR. The results from the parametric model which allows for linear pre-trends are shown in panel (D). Again, this approximately duplicates the results from panel (B) of Figure 1.6. Prior to the rescheduling there was little deviation from a linear trend, although in the post period all of the coefficients become positive, indicating differential increases in the EPR in places more exposed to the treatment.[43]

Although the change in EPR can almost completely account for the increase in the

[42]In addition, a drop in population holding the number of people in the labor force constant would have the same effect. However, column (1) of Table A.3 shows that this is not the case.

[43]Raw data plots of the EPR by quartile of exposure to treatment are shown in panels (C) and (D) of Figure A.6. Although the pre-trends in panel (C) are not as obvious as panel (A), the detrended data in panel (D) shows a very similar pattern as panel (B).

LFP rate, I also examine the effects of the rescheduling on the unemployment-to-population ratio (UPR) for the sake of completeness. The nonparametric regression results with the UPR as the dependent variable are shown in panel (A) of Figure A.7. Unlike the EPR or LFP rate, the UPR does not exhibit any clear trends either before or after the rescheduling. While some of the coefficients are statistically different from zero, they are typically small in magnitude and move somewhat erratically. Although there is no evidence of a linear pre-trend, I still run the parametric regression and report the coefficients in panel (B). Taken together, these estimates suggest that the large changes in LFP are driven primarily by changes in employment as opposed to unemployment.

1.5.3 SSDI

The previous two subsections indicate that the rescheduling of hydrocodone led to a reduction in the supply of hydrocodone and a corresponding increase in the LFP rate and EPR in areas which saw larger reductions in hydrocodone consumption. More individuals participating in the labor market could have an added effect of reducing disability claims if those entering (or not leaving) the labor market would have otherwise enrolled in SSI/SSDI. Krueger (2017) reports that approximately half of prime aged males outside of the labor market regularly take pain medication, suggesting that opioids may play a significant role in disability claims. In light of this, I now investigate the effects of the rescheduling on disability outcomes. First, I examine the effects of the rescheduling on the rate of SSDI beneficiaries per 1000 population. The results from equation 1.1 are shown in panel (A)

of Figure 1.7.[44] As before, the treatment variable is scaled so that all coefficients can be interpreted as the effect of a one standard deviation increase in Hydro_z^{pre}. For this variable, the pre-period coefficients are generally small in magnitude and not significantly different from zero, indicating no differential trends in outcomes in the pre-period. Beginning with 2014, however, the coefficients begin to fall. In 2017, the coefficient is approximately -0.5, indicating that a standard deviation increase in exposure to the treatment is associated with a reduction of .5 SSDI beneficiaries per 1000 population, about a 1.5 percent decrease relative to the mean. [45]

1.5.4 Counterfactuals

In order to further contextualize the magnitude of the labor market results, I conduct a simple simulation to estimate the aggregate impact of the rescheduling on the labor market. Using the estimates from equation 1.2, I predict the paths of the aggregate LFP rate and EPR under the observed levels of pre-period hydrocodone exposure as well as the under the counterfactual that every zip3 had zero pre-period exposure. This counterfactual can be thought of as an estimate of what may have happened had hydrocodone not been rescheduled, since if every zip3 had no pre-period hydrocodone exposure there would have been no scope for the rescheduling to affect the outcome variables. Mathematically, I estimate

[44] As this outcome is only available annually, I normalize 2013, the last full year before the rescheduling, to zero.

[45] While there is no evidence of a pre-trend, for completeness I also show the parametric results allowing for a linear pre-trend in panel (B). Not surprisingly, the results look very similar. I do not, however, find any reduction in the number of SSI beneficiaries.

$$Y_{zt}^{cf} = \hat{\lambda}_z + \hat{\psi}_t + \sum_{Z} \hat{\phi}_Z \cdot 1(z = Z) \cdot t + \sum_{T>\text{Sept. '14}} \hat{\theta}_T \cdot 1(t = T) \times \overline{\text{Hydro}}_z^{pre} + \hat{\eta} X_{zt} \quad (1.3)$$

where $\overline{\text{Hydro}}_z^{pre}$ is either the actual level of pre-period hydrocodone consumption or zero. The results of this exercise are shown in panels (A) and (B) of Figure 1.8 for the LFP rate and EPR, respectively. In both panels the solid black line shows the predicted outcome variable under the observed level of hydrocodone exposure, while the dashed blue line shows the counterfactual estimate. The estimates in panel (A) indicate that the LFP rate would have declined at a steeper rate absent the rescheduling, resulting in about a half of a percentage point (0.8 percent) lower LFP rate two and a half years after the rescheduling than what was actually observed. In the case of the EPR, this exercise suggests that the rescheduling can account for an approximately 0.61 percentage point (1 percent) increase in the EPR in the two and a half years following the rescheduling.[46] This suggests that high levels of opioid prescribing may depress local labor market conditions, and reducing unnecessary prescriptions could have positive spillover effects on the labor market.

1.6 Robustness

The primary explanatory variable measuring the intensity of treatment used throughout section 1.5 is drawn from ARCOS. This has the advantage of being compiled from administrative reports filed by drug manufacturers directly to the DEA, measuring the entire legal supply of hydrocodone in the US. However, these data do not directly measure consumption

[46] For completeness, I show the results for the UPR in Figure A.8. Consistent with the discussion in Section 1.5.2, this figure shows no real effects of the rescheduling on the UPR.

of hydrocodone, but rather shipments of the drug. Furthermore, they are only available at the zip3 level, necessitating an imperfect transformation of the county level labor force statistics. In light of these potential issues, I investigate the robustness of the main regression results to the use of an alternate treatment variable, namely, per capita hydrocodone consumption from Medicare Part D. While these data only measure hydrocodone consumption among the Medicare Part D population, it can be measured at the county level and therefore does not require any changes to the labor force data. The regression results using this treatment variable are shown in Figure A.9. Panels (A) and (B) show the non-parametric and parametric results for the LFP rate, respectively, while Panels (C) and (D) present the results for the EPR. Overall, the results look very similar to those with the ARCOS treatment variable shown in Figure 1.6, albeit slightly larger in magnitude. This provides some assurance that measurement error introduced from the transition from county to zip3 labor force statistics or differential stockpiling of hydrocodone across zip3s are unlikely to significantly influence the regression results.

Next, I investigate the sensitivity of the results to the inclusion of controls for other non-hydrocodone opioids. Specifically, I convert several of the other most commonly prescribed opioids into morphine equivalent dosages and then aggregate them together in an 'other' opioid variable, pooled over the same period as the primary treatment variable.[47] I then include interaction terms for both the pre-period hydrocodone treatment variable as well as the measure of pre-period use of other opioids with time fixed effects in the regressions. The purpose of this exercise is that in principle it is possible that the results presented

[47]This variable combines oxycodone, morphine, hydromorphone, meperidine (pethidine), methadone, oxymorphone, codeine, dihydrocodeine, and levorphanol.

in the previous section were not driven by the rescheduling of hydrocodone, but rather some omitted factor which changed coincident with the rescheduling. In order for this to be the case the omitted factor would need to have differentially affected areas with higher pre-period consumption of hydrocodone. If areas which consume large amounts of hydrocodone also tend to consume larger amounts of other opioids, it is possible that this omitted factor was not directly related to hydrocodone consumption, but rather opioid consumption more generally.[48] For example, some set of policies enacted in late 2014 in areas with high levels of opioid consumption which changed labor market conditions could have generated a similar set of results to those reported above. If this was the case we would expect the hydrocodone variable to have little additional explanatory power once we control for other opioids. However, Figure A.10 demonstrates that the inclusion of these additional controls has almost no impact whatsoever on the regression results. The top panels (A and B) show the coefficients on the interaction of the hydrocodone variable with month fixed effects with the LFP rate as the dependent variable, while the bottom panels (C and D) show the same coefficients with the EPR as the dependent variables. Panels (A) and (C) show the non-parametric results for each outcome, while panels (B) and (D) show the coefficients from the parametric model. These coefficients are nearly identical to those shown in Figure 1.6, suggesting that these results are in fact driven by the rescheduling of hydrocodone, and not other factors which may have affected opioid use more broadly.

A closely related concern is that these results are not driven by the hydrocodone rescheduling, but rather by relative improvements in economic conditions in areas which

[48]Figure 1.2 suggests that this is unlikely, as there is a weak correlation between hydrocodone and overall opioid consumption.

have historically consumed large amounts of oxycodone (e.g., OxyContin). If oxycodone consumption is highly correlated with hydrocodone consumption, then the regression coefficients may simply be picking up this pattern. I present two pieces of evidence which mitigate this concern. First, Figure A.11 demonstrates that the consumption of hydrocodone and oxycodone is largely uncorrelated. Each circle represents a zip3, weighted by population, and plots the per capita consumption of oxycodone (x-axis) against the per capita consumption of hydrocodone (y-axis) pooled from 2010-2013. The correlation coefficient is shown in the top right corner of the figure. Second, Figure A.12 presents regression coefficients analogous to those in Figure A.10, except only controlling for oxycodone prescribing instead of all non-hydrocodone opioid prescribing. Controlling for oxycodone prescribing makes almost no difference, which is not surprising given the lack of correlation between hydrocodone and oxycodone prescribing shown in Figure A.11.

Another alternative explanation for these findings is that areas which have historically consumed large quantities of opioids are also areas which were particularly affected by the Great Recession, and the trend break observed in the regressions is simply due to differentially slow recovery from the Recession in these areas. The fact that the trend break occurs around the time of the rescheduling is mere coincidence. However, the findings in Figures A.10 and A.12 cast doubt on this explanation. These figures show that the trend break occurs specifically in areas with higher reliance on hydrocodone even after controlling for the consumption of other opioids. It is difficult to rationalize why the Recession would differentially affect areas which consumed large amounts of hydrocodone as opposed to other non-hydrocodone opioids.

Furthermore, I present direct evidence that the differential labor market trends in the

pre-period do not appear to be driven by the Recession. The crosswalks to map between counties and zip3s do not exist prior to 2010, which means I cannot use the county-by-month LAUS data to include a longer pre-period in the regressions. However, state-by-year level labor force participation and employment-to-population ratio data exists in the ACS starting in 2005. I present regression results using this data in Figure A.13. Panels (A) and (C) show that the differential trends in labor market conditions pre-dated the Recession, going back to at least 2005. Furthermore, the regression coefficients do not appear to change significantly around the time of the Recession, implying that areas which were more reliant on hydrocodone were not differentially affected by the Recession. Panels (B) and (D) show the regression results explicitly controlling for state-specific linear pre-trends. Despite the loss of spatial variation in exposure to treatment that occurs from using state-level data, the results using the ACS data broadly mirror the main regression results presented in Figure 1.6.

As discussed in section 1.4, my primary treatment variable pools data on hydrocodone shipments from 2010-2013, the 4 years prior to the rescheduling. The purpose of this variable is to measure the extent to which different areas were likely to be affected by the rescheduling, and pooling over several years should act to reduce measurement error in this variable. However, the specific choice of years to include is somewhat arbitrary. If there are significant differences in the relative ordering of hydrocodone consumption across years in the pre-period, then the regressions may be sensitive to the particular choice of years included. In order to investigate whether this will likely have any effects on the results, I first rank each zip3 in terms of per capita hydrocodone consumption separately for 2010 and 2013 and plot these ranks against each other in Figure A.14. The red line represents the 45 degree line

while each black circle represents a specific zip3, with more populous zip3s indicated by larger circles. While there are some exceptions, most zip3s fall very close to the 45 degree line, indicating that there is little over-time shuffling in the ranking of hydrocodone consumption over the pre-period. This minimizes the concern that the specific choice of years to include in the variable definition will influence the results. Further illustrating this point, Figure A.15 presents the main regression results using several different alternative definitions of the treatment variable. The blue line shows the baseline regression coefficients from equation 1.1 in blue for the EPR in panel (A) and LFP rate in panel (B). The other colored lines show the same regression coefficients, but defining the treatment variable as the (normalized) per capita hydrocodone shipment for only a single year. The results are similar regardless of which year is used. The fact that using only data from as far back as 2010 gives similar results to those using data from 2013 alone should lessen concerns of the results being driven by mean reversion.

I explore the sensitivity of the regressions to the inclusion of additional control variables in Figure A.16. This figure again shows the baseline coefficients for the EPR and LFP rate in blue in panels (A) and (B), respectively. The gray dashed line adds in indicator variables for whether a state had a prescription drug monitoring program, Good Samaritan law, or law expanding access to Naloxone. The red line adds in more detailed information about these laws (e.g., whether physicians are required to access the prescription drug monitoring program prior to prescribing). The black line adds in demographic information about the age, sex, ethnic, and racial distributions of the zip3. The figures indicate that the inclusion of these additional controls has essentially no impact on the regression results, suggesting that the results are not simply picking up the effects of other laws or changes in underlying

population characteristics.

Finally, I present regression results including a richer set of fixed effects. Specifically, in Figure A.17 I show the regression coefficients from equations 1.1 (panels (A) and (C)) and 1.2 (panels (B) and (D)) with the inclusion of Census region-by-time fixed effects.[49] Results for the LFP rate and EPR are shown in the top two and bottom two panels, respectively. By including these fixed effects I net out any variation in labor market conditions across regions over time, relying only on within region variation. The regression coefficients here are almost identical to those shown in Figure 1.6, indicating that the pattern of results is not just picking up changing economic conditions across different regions of the county coincident with the rescheduling.

1.7 Conclusion

The proliferation of opioid prescriptions in the US coincided not only with rises in opioid abuse and mortality, but also with deteriorating labor market conditions. This labor market decay has been particularly pronounced in areas hit hardest by the opioid crisis, provoking researchers to ask whether opioids have a causal impact on the labor market. However, the lack of plausibly exogenous variation in opioid prescribing has made it difficult to answer this question. In this paper, I provide new evidence on how opioids affect the labor market by exploiting variation stemming from a natural experiment. I find that a ten percent drop in hydrocodone prescriptions causes a 0.7 percent increase in the labor force participation rate, which is driven almost entirely by relative increases in employment.

[49] Census regions are geographic groupings of states. There are four regions in the US.

These estimates suggest that the rescheduling of hydrocodone can account for around a half percentage point (about 0.8 percent) increase in the LFP rate and a one percent (0.61 percentage point) increase in the EPR. In total this amounts to about 800,000 additional individuals being employed relative to a counterfactual in which the rescheduling never happened.

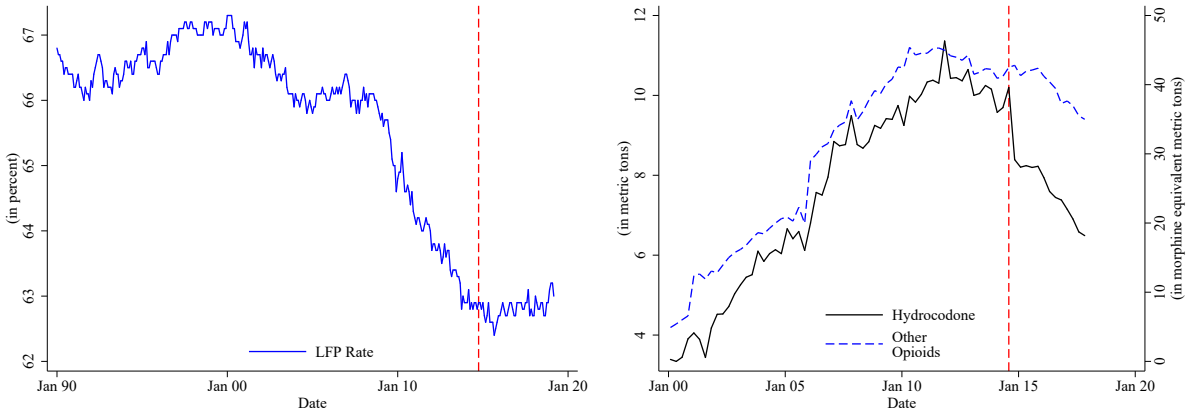
These findings inform several aspects of the academic discussion of correlates that affect opioid prescriptions, as well as the effects of opioids on a variety of different outcomes. For example, a variety of other interventions with the goal of reigning in opioid prescriptions have been implemented with varying degrees of success. The findings in this paper suggest a simple, low-cost intervention to decrease drug prescribing, namely, drug rescheduling. This type of intervention could be effective for any drugs that the DEA currently regulates, not just opioids. For example, there is growing concern surrounding stark increases in the abuse of benzodiazepines, almost all of which are currently in a less stringently regulated drug schedule (IV). Extrapolating from the rescheduling of hydrocodone combination products suggests that prescribing of benzodiazepines could be substantially reduced via rescheduling.[50] This paper further contributes to our understanding of how opioids affect the labor market. While previous evidence using a variety of different estimation strategies is mixed, this paper suggests that the effects of opioids on the labor market is primarily negative, i.e., reductions in opioid prescribing improve labor market conditions. This is consistent with several other papers (e.g. Harris et al., 2017; Savych, Neumark and Lea, 2018; Laird and Nielsen, 2016; Dionissi Aliprantis, Kyle Fee and Mark E Schweitzer, 2019), although it is qualitatively different than others (e.g. Currie, Jin and Schnell, 2019; Kilby, 2015). Further

[50]This is meant as an illustrative example, not an actual policy recommendation.

research is needed in order to understand what drives these differences.

The direct effects of policies geared toward reducing opioid prescriptions on the number of prescriptions ordered, as well as spillover effects onto the labor market are important components in evaluating these policies. However, they are not sufficient for a complete welfare analysis. There are two particularly salient concerns which suggest caution in taking further steps to reduce access to opioids. First, previous research has shown the potential for policies which restrict access to legal opioids to prompt some individuals to substitute toward more dangerous drugs such as heroin or illicitly manufactured Fentanyl, which I am unable to examine with my data. This could have positive or negative effects on overall mortality depending on how large the substitution toward these other drugs is relative to the reduction in legal opioid use. Second, improvements in the labor market need to be weighed against increased suffering among legitimate pain patients. Alarmingly, over a quarter of respondents to an online survey of hydrocodone patients reported thoughts of suicide after the rescheduling, highlighting the tradeoffs inherent in reducing access to pain medication (Chambers et al., 2015). New ways to help providers separately identify recreational users, diverters, and legitimate pain patients would be useful in developing targeted interventions that could reduce opioid abuse while continuing to provide pain relief to patients.

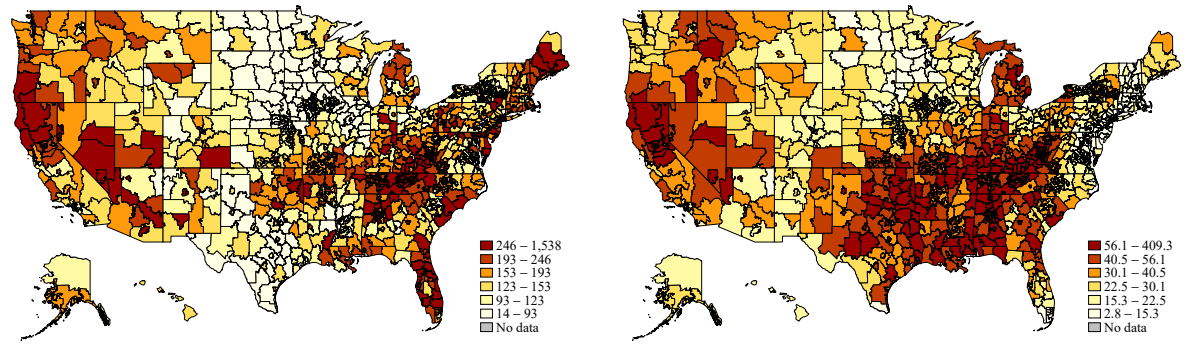
Figure 1.1: Labor Force Participation Rate and Opioid Distribution Over Time



(a) Labor Force Participation Rate (b) Hydrocodone and Other Opioids

Note: Panel (A) shows the aggregate labor force participation rate each month from January 1990 to December 2017. Panel (B) shows the quarterly distribution of hydrocodone (black line, left y-axis) and other non-hydrocodone opioids (blue dashed line, right y-axis) from 2000 to 2017. Non-hydrocodone opioids are pooled by converting each to morphine equivalents before adding. The vertical dashed red line in each sub-figure indicates the period immediately preceding the hydrocodone rescheduling.

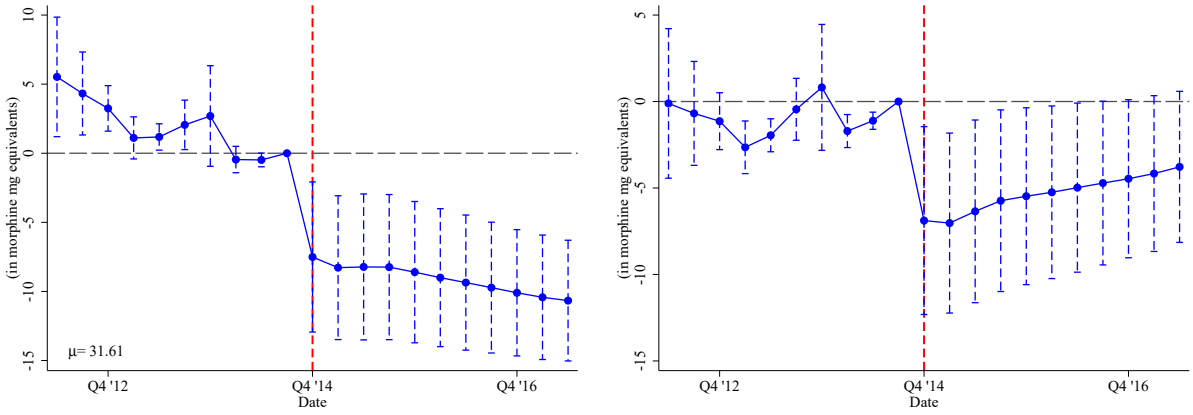
Figure 1.2: Identifying Variation: Pre-Period Morphine Milligram Equivalent Overall Opioid and Hydrocodone Distributions



(a) All Opioids, ARCOS (b) Hydrocodone, ARCOS

Note: These maps show the spatial variation in the distribution of opioids. Panel (A) shows the six quantiles of the distribution of all opioids in morphine milligram equivalents per capita-quarter, pooled from 2010-2013. Panel (B) recreates the same figure but for only hydrocodone. Darker shades of red indicate more consumption per capita, while lighter colors indicate less consumption.

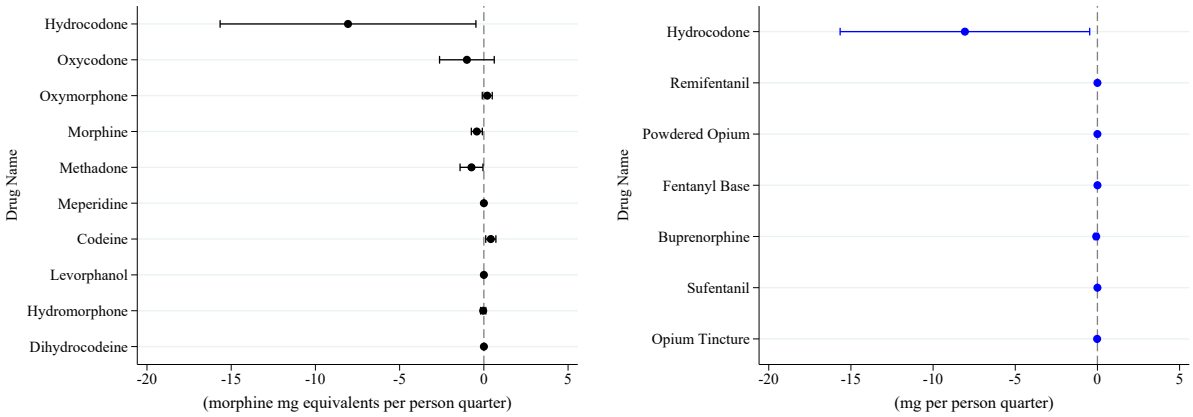
Figure 1.3: Hydrocodone Per Person-Quarter Regression Estimates: Impact of One Standard Deviation Increase in Hydro_z^{pre}



(a) Non-Parametric (equation 1.1) (b) Parametric (equation 1.2)

Note: These figures show the coefficients on the $\text{Hydro}_z^{pre}\times$ time interactions from regression equations 1.1 (panel (A)) and 1.2 (panel (B)) with the number of milligrams of hydrocodone per capita as the dependent variable. The dependent variable is measured at the zip3-by-quarter level. The coefficients can be interpreted as the effect of a one standard deviation increase in pre-period hydrocodone consumption.

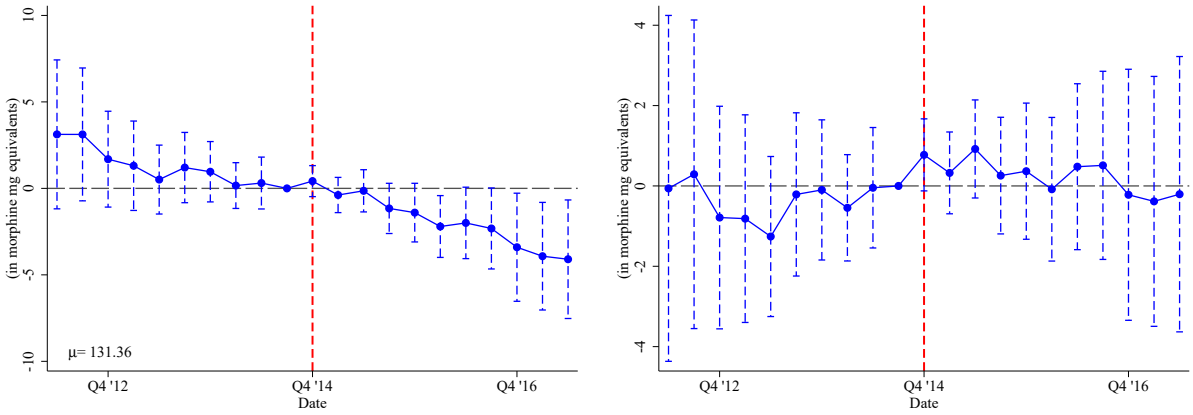
Figure 1.4: Other Opioids: Impact of One Standard Deviation Increase in Pre-Period Hydrocodone Exposure



(a) (b)

Note: These figures show the coefficients from a simple before and after difference-in-differences analogous to equation 1.2 for a variety of opioids in the ARCOS data. Explicitly, these are the θ coefficients from the regression $Y_{zt} = \lambda_z + \psi_t + \sum_Z \phi_Z \cdot 1(z = Z) \cdot t + \theta \cdot 1(t > Oct.'14) \times \text{Hydro}_z^{pre} + \eta X_{zt} + \nu_{zt}$. The coefficients in black (panel (A) are first converted to morphine milligram equivalents. The coefficients in blue (panel (B)) do not have obvious conversion factors and so are left in milligrams.

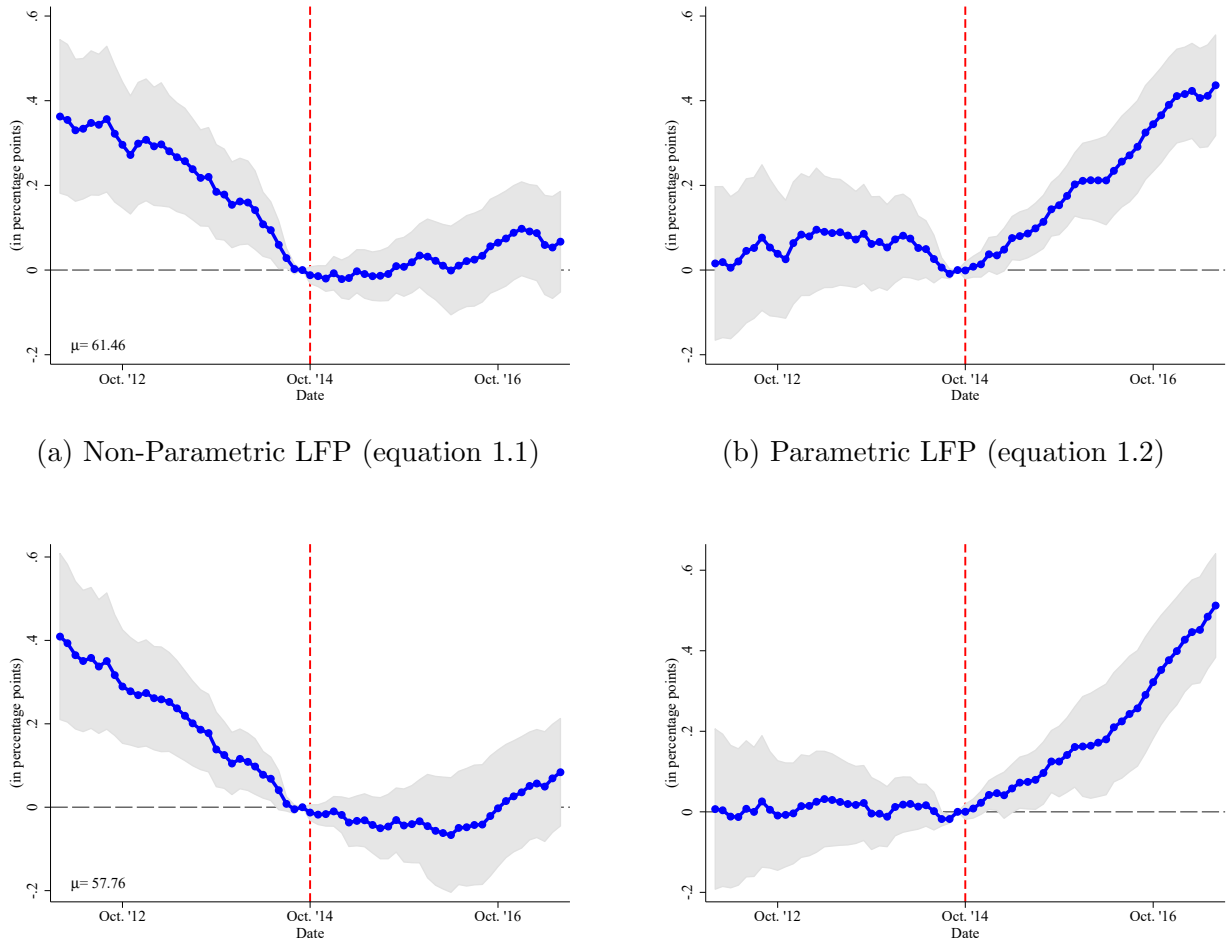
Figure 1.5: Other Opioids per Person-Quarter Regression Estimates: Impact of One Standard Deviation Increase in Hydro_z^{pre}



(a) Non-Parametric (equation 1.1) (b) Parametric (equation 1.2)

Note: These figures show the coefficients on the $\text{Hydro}_z^{pre} \times$ time interactions from regression equations 1.1 (panel (A)) and 1.2 (panel (B)) with the per capita morphine milligram equivalent distribution of non-hydrocodone opioids as the dependent variable. The opioids included in this variable are oxycodone, oxymorphone, morphine, methadone, meperidine, codeine, levorphanol, hydromorphone, and dihydrocodeine. The dependent variable is measured at the zip3-by-quarter level. The coefficients can be interpreted as the effect of a one standard deviation increase in pre-period hydrocodone consumption.

Figure 1.6: Labor Force Participation Rate and Employment-to-Population Ratio Regression Estimates: Impact of One Standard Deviation Increase in Hydro_z^{pre}



(a) Non-Parametric LFP (equation 1.1)

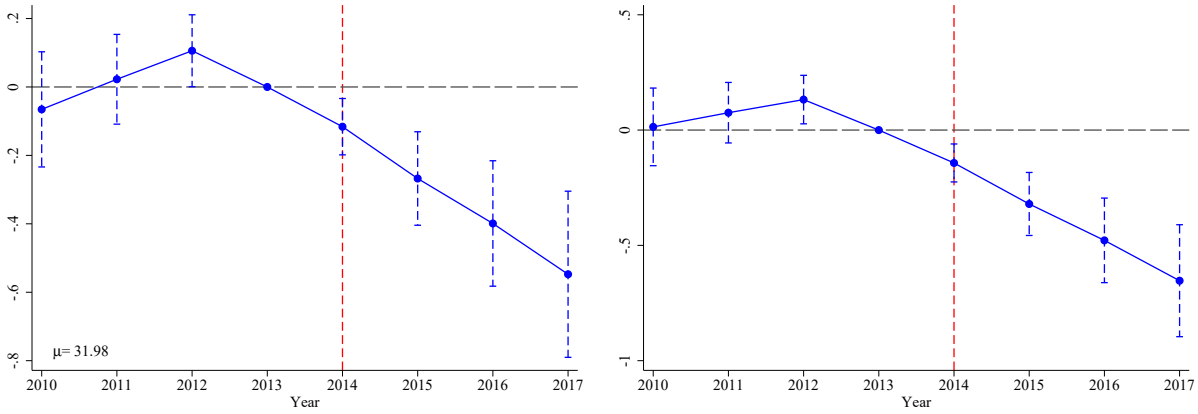
(b) Parametric LFP (equation 1.2)

(c) Non-Parametric EPR (equation 1.1)

(d) Parametric EPR (equation 1.2)

Note: These figures show the coefficients on the $\text{Hydro}_z^{pre}\times$ time interactions from regression equations 1.1 (panels (A) and (C)) and 1.2 (panel (B) and (D)). Panels (A) and (B) show the results for the labor force participation rate, while panels (C) and (D) show the results for the employment-to-population ratio. The dependent variables are measured at the zip3-by-month level. The coefficients can be interpreted as the effect of a one standard deviation increase in pre-period hydrocodone consumption.

Figure 1.7: SSDI Beneficiaries Regression Estimates: Impact of One Standard Deviation Increase in Hydro_z^{pre}



(a) Non-Parametric (equation 1.1) (b) Parametric (equation 1.2)

Note: These figures show the coefficients on the $\text{Hydro}_z^{pre} \times$ year interactions from regression equations 1.1 (panel (A)) and 1.2 (panel (B)) with the number of SSDI beneficiaries per 100,000 as the dependent variable. The dependent variable is measured at the zip3-by-year level. The coefficients can be interpreted as the effect of a one standard deviation increase in pre-period hydrocodone consumption.

Figure 1.8: Counterfactual Paths of the Labor Force Participation Rate and Employment-to-Population Ratio

(a) Labor Force Participation Rate (b) Employment-to-Population Ratio

Note: This figure shows the predicted and counterfactual labor force participation rate (panel (A)) and employment-to-population ratio (panel (B)). The counterfactual estimates use the regression coefficients from equation 1.2, but assume that each zip3 has $\text{Hydro}_z^{pre} = 0$. The black line shows the predicted values with the actual value of Hydro_z^{pre}, while the blue dashed line shows the counterfactual.

Chapter 2

Adverse Health Effects of Abuse-Deterrent Opioids: Evidence from the Reformulation of OxyContin

2.1 Introduction

The US is currently in the midst of the worst drug overdose crisis in its history, driven primarily by a massive increase in opioid abuse over the past two decades (Andrew Kolodny, David T Courtwright, Catherine S Hwang, Peter Kreiner, John L Eadie, Thomas W Clark and G Caleb Alexander, 2015).[1] In 2016, nearly 64,000 Americans died from a drug overdose, more than the total number of people killed by either gunshots or car accidents. Opioid overdoses were responsible for approximately two-thirds of these fatalities, with over 115 people dying every day. This increase in opioid abuse is so severe that it has contributed to a reversal of the long-run trend of falling midlife mortality for certain demographic groups, with mortality rates among middle-aged non-Hispanic whites actually rising (Case and Deaton, 2015, 2017). This has garnered widespread media attention and led former President Obama, President Trump, and the CDC to refer to opioid abuse as a nationwide epidemic (Barack Obama, 2016*b*; Trump, 2018).[2]

[1] This is the pre-peer reviewed version of the following article: "Adverse Health Effects of Abuse-Deterrent Opioids: Evidence from the Reformulation of OxyContin", which has been published in final form at https://doi.org/10.1002/hec.3944. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.

[2] https://www.cdc.gov/drugoverdose/epidemic/index.html (Accessed: 2018-05-22).

In response, the medical community, as well as federal and state governments, have implemented numerous interventions attempting to curb the abuse of opioids. For example, the 21st Century Cures Act set aside $1 billion in grants to combat opioid abuse. Several studies have investigated the impact of state-level interventions to curb opioid abuse or deaths, such as prescription drug monitoring programs (Buchmueller and Carey, 2018; Dave, Grecu and Saffer, 2017; Paulozzi, Kilbourne and Desai, 2011), Naloxone access laws (Doleac and Mukherjee, 2018), and Good Samaritan laws (Rees et al., 2017). An interesting non-government intervention is the introduction of abuse-deterrent painkillers– pills with physical properties that make the painkiller more difficult to misuse. There are currently 10 such painkillers on the market which implement a variety of novel mechanisms to deter abuse. Some examples include pills which are crush proof (to deter snorting), resistant to dissolving in water (to deter injection), or which release other drugs (opioid antagonists) to block the effects of the opioid if the pill is tampered with. The first abuse-deterrent painkiller, a reformulation of OxyContin (brand name extended-release oxycodone), was released in August of 2010, with the original formulation being simultaneously discontinued. While some evidence suggests that the reformulation led to a reduction in OxyContin misuse (Stephen F Butler, Theresa A Cassidy, Howard Chilcoat, Ryan A Black, Craig Landau, Simon H Budman and Paul M Coplan, 2013; Theodore J Cicero, Matthew S Ellis and Hilary L Surratt, 2012; Theodore J Cicero and Matthew S Ellis, 2015), recent papers in the economics literature have found that the reformulation also led to an increase in heroin overdose deaths (Alpert, Powell and Pacula, 2018; Evans, Lieber and Power, 2018). Importantly, these prior studies fail to reject the null hypothesis that there was no net effect on overall opioid mortality inclusive of heroin and prescription opioids.

In this paper, I examine the potential health impacts of substitution away from OxyContin beyond the immediate mortality effects previously documented. Specifically, I examine the transmission of blood-borne diseases which could be accelerated by increasing heroin use. While the reformulation of OxyContin may not have had an immediate impact on overall opioid-related mortality, differences in typical routes of administration for heroin versus OxyContin have likely affected other important health outcomes. In particular, drug users are substantially more likely to inject heroin relative to OxyContin, which was typically chewed (as opposed to swallowing whole as intended) or ground into a powder and snorted. Injection drug use greatly amplifies a drug user's risk of contracting contagious blood-borne diseases such as hepatitis B and C, both of which are substantial contributors to morbidity and mortality in the US. Since 2007, hepatitis C has surpassed HIV as the most deadly infectious disease in the US, killing over 18,000 people in 2016 (Kathleen N Ly, Jian Xing, R Monina Klevens, Ruth B Jiles, John W Ward and Scott D Holmberg, 2012).[3] Fortunately, recent advances in treatment for chronic hepatitis C have proven effective in curing over 90% of those treated, although there is still no cure for hepatitis B, which killed around 1,700 in 2016. In addition to the significant mortality impact, treatment for either disease can be financially devastating for an individual or impose large external costs if treatment is paid for by a third party (e.g., public insurance programs such as Medicare and Medicaid, private health insurers, family members, hospitals, etc.). For example, one recent estimate from the medical literature suggests that the total economic burden of hepatitis C could exceed $10 billion annually (Maria Stepanova and Zobair M Younossi, 2017), while another suggests that the annual costs of hepatitis B could be as high as $1.5 billion (W Kim, 2009). Heroin

[3] https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1 (Accessed: 2018-05-22).

overdose deaths, although obviously an extremely important outcome, do not fully encompass the potential negative health effects of the recent substitution away from OxyContin toward heroin. The most recent estimates from the National Survey of Drug Use and Health (NSDUH) suggest that on average around 894,000 individuals aged 12 and older used heroin each year from 2015-2016, with an average of 14,434 heroin overdose deaths each of these two years.[4] Taken together these estimates suggest that a relatively small fraction of heroin users suffered from an overdose death from 2015-2016, about 1.6%. In contrast, estimates from Louisa Degenhardt, Amy Peacock, Samantha Colledge, Janni Leung, Jason Grebely, Peter Vickerman, Jack Stone, Evan B Cunningham, Adam Trickey, Kostyantyn Dumchev et al. (2017) indicate that between 38.1-68.0% of injection drug users are infected with hepatitis C, making contraction of hepatitis C a much more likely (albeit less deadly) risk of heroin use. This paper, along with concurrent work by Powell, Alpert and Pacula (2019), are the first to examine the effect of abuse-deterrent opioids on these broader health outcomes beyond opioid-related mortality. The findings in this paper suggest that the reformulation of OxyContin was a key contributor to both the recent rise in the spread of hepatitis C and the stall in falling hepatitis B rates.

In order to identify the causal effects of the OxyContin reformulation, I follow Alpert, Powell and Pacula (2018) by comparing states with different levels of pre-reformulation OxyContin misuse before and after the reformulation. The idea underlying this strategy is that states with higher pre-period levels of OxyContin misuse had more scope to be affected by the reformulation than states with lower levels of misuse. Leveraging this variation in

[4]Authors calculation using the Substance Abuse and Mental Health Services Administration's restricted-use data analysis system (RDAS), available here: https://rdas.samhsa.gov/#/ (Accessed: 2018-08-20).

the extent of OxyContin misuse in the pre-period, I construct a difference-in-differences estimator for the effect of the reformulation on the outcomes of interest.

Comparing states with differing levels of pre-period OxyContin misuse before and after the reformulation, I present the main findings of the paper, which illustrate there were large and statistically significant increases in both hepatitis B and C due to the reformulation of OxyContin. Moving from the bottom to the top state in terms of pre-period OxyContin misuse is associated with an additional 17.95 cases of hepatitis C and 9.33 cases of hepatitis B per 100,000 each year. In aggregate, the estimates suggest that absent the reformulation we would have observed about 76% fewer cases of hepatitis C and 53% fewer cases of hepatitis B from 2011-2015. With the median cost of new hepatitis C cures about $65,000, a simple back-of-the-envelope calculation suggests the total cost of treating all new cases of hepatitis C attributable to the reformulation of OxyContin would cost approximately $6.69 billion. A similar calculation is much more difficult for hepatitis B, as there is no cure for hepatitis B and treatment costs vary greatly depending on patient risk factors and the extent of liver damage. Since many people initially infected with hepatitis B or C do not yet know they have it, substantial liver damage could have already occurred prior to treatment which would result in other expensive treatments or even death (Cindy M Weinbaum, Ian Williams, Eric E Mast, Susan A Wang, Lyn Finelli, Annemarie Wasley, Stephanie M Neitzel, John W Ward, Centers for Disease Control, Prevention (CDC) et al., 2008). Furthermore, this lack of awareness of one's hepatitis status could accelerate the infection's spread, as infected individuals unwittingly pass it along to others.

This paper makes several contributions. First, this paper contributes to the growing literature investigating the impact of policies aimed at addressing the opioid crisis, which

includes work on prescription drug monitoring programs (Buchmueller and Carey, 2018; Dave, Grecu and Saffer, 2017; Paulozzi, Kilbourne and Desai, 2011), Naloxone access laws (Doleac and Mukherjee, 2018), Good Samaritan laws (Rees et al., 2017), and the mortality effects of the OxyContin reformulation (Alpert, Powell and Pacula, 2018; Evans, Lieber and Power, 2018).[5] Currently, the FDA has approved 10 different abuse-deterrent painkillers and is encouraging the development of more abuse-deterrent formulations.[6] The results in this paper suggest that as the supply of abusable painkillers is further restricted, whether by the introduction of tamper-proof painkillers or other supply-side interventions, policymakers may also wish to consider actions to combat the spread of hepatitis B and C.[7] Second, this paper posits a plausible explanation for the rapid increase in hepatitis C infections and the break in trend of falling hepatitis B infections since 2010. These trends have been documented in the medical literature (Jon E Zibbell, Alice K Asher, Rajiv C Patel, Ben Kupronis, Kashif Iqbal, John W Ward and Deborah Holtzman, 2018; Ronald Valdiserri, Jag Khalsa, Corinna Dan, Scott Holmberg, Jon Zibbell, Deborah Holtzman, Robert Lubran and Wilson Compton, 2014; Aaron M Harris, 2016), although the precise cause has yet to be identified. Lastly, this paper contributes to the broader literature investigating spillovers from supply regulations in a variety of settings beyond opioids including gun regulations (Brian Knight, 2013), abortion regulations (Scott Cunningham, Jason M Lindo, Caitlin Myers and Andrea Schlosser, 2017; Stefanie Fischer, Heather Royer and Corey White, 2017; Silvie Colman and Ted Joyce, 2011),

[5]Relatedly, other papers have examined the relationship between opioid prescriptions and physician education (Schnell and Currie, 2017), the effects of expansions in the supply of opioids due to the introduction of Medicare Part D (Powell, Pacula and Taylor, 2015), and the impact of macroeconomic shocks on opioid abuse (Hollingsworth, Ruhm and Simon, 2017).

[6]https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337066.htm.

[7]For example, by expanding access to clean needles or drug addiction treatment centers.

cigarette taxes (Michael F. Lovenheim, 2008), and marijuana regulations (Yu-Wei Luke Chu, 2015*a*; Powell, Pacula and Jacobson, 2018; David Beheshti, 2017).

This paper is most closely related to the concurrent work of Powell, Alpert and Pacula (2019), who also examine the impact of the OxyContin reformulation on the spread of hepatitis C using the same identification strategy. This paper further contributes by also examining the effects of the reformulation on hepatitis B, which is not considered in other work. In addition, this paper provides further evidence on the mechanism behind these results by examining relative differences in routes of administration for OxyContin and heroin, lending plausibility to the main findings. Finally, this paper provides a series of robustness tests to rule out alternative explanations of the main findings.

The paper proceeds as follows: Section 2.2 provides background details on the history of OxyContin, as well as information about hepatitis B and C. Section 2.3 explains the research design. Section 2.4 describes the data and identifying variation. Results are then presented in Section 2.5. Section 2.6 concludes.

2.2 Background

OxyContin OxyContin was released by Purdue Pharma in 1996.[8] It was unique among painkillers in that its extended-release formulation allowed the active ingredient, oxycodone, to be released slowly over a period of twelve hours. This was seen as a major advancement over traditional immediate-release painkillers which the user would typically have to take

[8]For a more detailed exposition of the history of OxyContin and the opioid crisis more broadly, see Alpert, Powell and Pacula (2018) and Evans, Lieber and Power (2018). This section largely draws from these two papers.

throughout the day in order to manage chronic pain. However, many users discovered that they could bypass the extended-release mechanism by chewing the pill before swallowing, grinding the pill into a powder and snorting it, or dissolving the crushed pill in water and injecting it. In addition to delivering the user more oxycodone more quickly, more intense methods such as snorting or injecting allow the oxycodone to enter the bloodstream faster and provide a more intense high. Because of its large market share and ease of abuse, OxyContin became one of the most frequently misused painkillers. At its peak level in 2009, estimates from the National Survey of Drug Use and Health (NSDUH) indicate that over 3.5% of the population over the age of 12 had taken OxyContin recreationally at some point in their life, with about 1.35% misusing OxyContin in that year alone.

In response to this widespread misuse, Purdue Pharma released a new abuse-deterrent formulation of OxyContin in August of 2010 while simultaneously discontinuing the original formulation. The new drug was more difficult to crush and grind into a powder which made it less susceptible to abuse. Even if the pill was successfully crushed, this no longer broke the extended-release mechanism.[9] While recreational users could still misuse OxyContin by taking it without a prescription or taking more than prescribed, the efficacy of OxyContin as a recreational drug was severely reduced.[10]

[9]Some of these abuse-deterrent properties are demonstrated in Figure B.2. The first row of the figure shows the original and reformulated OxyContin pills side-by-side. The second row shows an attempt to crush each pill with a blunt object. While the original grinds into a fine powder which could be snorted, the new formulation does not. The third row shows each pill after being put through a coffee grinder. Still, the new formulation does not break down into a powder. The last row shows the crushed pill mixed with water. While the original formulation dissolves into a liquid which can be drawn into a syringe, the new formulation turns to a gel which cannot be injected.

[10]Some more persistent users developed sophisticated methods in an attempt to get around the new abuse-deterrent properties (http://www.bluelight.org/vb/threads/523580-Experiment-Thead-New-Formulation-Oxycodone-Extraction), although anecdotally these methods are difficult to implement.

Consistent with the new formulation being more difficult to misuse, the fraction of NSDUH respondents reporting OxyContin misuse fell dramatically beginning in 2010, with less than half the fraction of respondents reporting OxyContin misuse in 2014 as 2009. At the same time, the number of heroin deaths begin to rise alarmingly, more than tripling from 2009 to 2014.[11] Of course, this does not constitute causal evidence as many other things could have changed in 2010 which could have affected OxyContin misuse as well as heroin deaths. In Section 2.3, I discuss the methodology for identifying the causal effects of the reformulation.

Given the existing evidence that many OxyContin users switched toward heroin after the reformulation, I verify that heroin is more likely to be injected relative to OxyContin (Cicero, Ellis and Surratt, 2012; Alpert, Powell and Pacula, 2018; Evans, Lieber and Power, 2018).[12] In order to investigate this claim, I first utilize data from the Treatment Episodes Data Set (TEDS). TEDS collects data from every drug-abuse treatment center which receives any public funding, which accounts for about 75% of all cases. TEDS has information for up to three substances of abuse, and importantly for the purpose of this paper asks about typical routes of administration for each drug. Panel A of Table 2.1 shows the usual route of administration for those admitted for either heroin and painkiller abuse.[13] The highlighted column indicates that around 62% of heroin users report injecting heroin, while only about 10% of painkiller users report injecting painkillers. By far the most common way to use painkillers was to take them orally, although TEDS does not distinguish between taking the

[11]Figures demonstrating these trends are shown in Alpert, Powell and Pacula (2018) and reproduced here in Figure B.3.

[12]I build upon this existing evidence in Section 2.5.

[13]TEDS does not ask about the exact type of painkiller so I cannot examine OxyContin specifically using these data.

pill whole or chewing first.[14] It is important to note that those who appear in the TEDS data are not a random sample of drug users, but individuals who had a severe enough problem that they either sought out treatment or were ordered to enter treatment by the criminal justice system. Therefore, it is possible that the rate of painkiller injection is substantially higher among those in the TEDS data than the general population.

While the NSDUH has somewhat limited information about routes of administration for different drugs, it is a nationally representative sample and therefore more representative of average drug users' behavior than the TEDS data. Among those who reported misusing OxyContin at some point in their life in the 2004-2009 waves of the NSDUH, only about 3% reported ever injecting OxyContin.[15] In contrast, over 42% of those who report lifetime heroin use report injecting heroin at some point.[16]. The lower rates of painkiller injection among less heavy users is also consistent with Sean Esteban McCabe, James A Cranford, Carol J Boyd and Christian J Teter (2007), who find less than one percent of undergraduates at a large Midwestern university who misused prescription opioids reporting injection as their route of administration for OxyContin.[17] However, about 13% reported snorting painkillers, indicating that this was a fairly common route of administration even among less serious

[14]Anecdotally, chewing prior to swallowing was a common way to misuse OxyContin, although I am unaware of any surveys which distinguish between taking the pill whole versus chewing it first (http://www.bluelight.org/vb/threads/319328-Snorting-Vs-Eating-Oxycontin).

[15]The NSDUH does not ask any questions about other routes of administration for OxyContin.

[16]About 37% report smoking heroin, while 72% report sniffing or snorting heroin. Respondents were able to indicate multiple routes of administration, so percentages do not necessarily add to 100%.

[17]However, in a small survey of 212 prescription drug users in two Kentucky counties, April M. Young, Jennifer R. Havens and Carl G. Leukefeld (2010) found nearly 45% of the 101 rural respondents had injected OxyContin, although none of the 111 urban respondents reported injecting OxyContin. Deni Carise, Karen Leggett Dugosh, A Thomas McLellan, Amy Camilleri, George E Woody and Kevin G Lynch (2007) found 78% of OxyContin users who had entered treatment at any of 157 treatment facilities in their sample administered the pill orally, while 11% inhaled or snorted the crushed pill and 17% injected it.

users.

One potential concern is that these summary statistics may overstate the increase in probability of injection of those who switch from OxyContin to heroin. For example, if those who are induced by the reformulation to substitute toward heroin were those who were more likely to be injecting OxyContin anyway, then just reporting the average routes of administration for all users of these drugs will be misleading. In order to examine this further, I restrict the sample to those who reported both painkiller and heroin misuse in the TEDS data and report the typical routes of administration for this group in panel B of Table 2.1. While painkiller users in this sample are slightly more likely to inject painkillers than those in the general sample, it is still the case that heroin is substantially more likely to be injected. This same basic pattern also holds in the NSDUH. Among those who reported having used both OxyContin and heroin, nearly 12% reported having injected OxyContin, while over 45% reported injecting heroin.

Hepatitis C Hepatitis refers to inflammation of the liver, most commonly caused by the hepatitis virus.[18] Hepatitis C has been the most deadly infectious disease in the US since 2007, when its annual death toll surpassed that of HIV (Ly et al., 2012). In 2016, over 18,000 people died as a result of hepatitis C, more than the number killed by either painkiller or heroin overdoses.[19] Today hepatitis C is most commonly spread via needle sharing among injection drug users, although prior to the availability of blood screening in 1992, it was

[18]There are five different strains of hepatitis: A, B, C, D, and E. Only types B, C, and D can be spread via needle sharing. A person can only contract hepatitis D if they already have hepatitis B.

[19]https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1.

frequently spread via blood transfusions and organ transplants.[20] The prevalence of hepatitis C among injection drug users is particularly high, with estimates ranging from 38.1-68.0% (Degenhardt et al., 2017). Perhaps not surprisingly given the rates of hepatitis C infection among injection drug users, in 2015 about 65% of those diagnosed with hepatitis C reported injection drug use (NNDSS, 2015). Hepatitis C can also be transmitted by accidental needle sticks, from mother to baby, or via sexual contact. However, sexual transmission is thought to be a very rare occurrence among heterosexual couples in monogamous relationships, although individuals with multiple sex partners, infected with HIV, or engaging in risky sex may be at an increased risk (Rania A Tohme and Scott D Holmberg, 2010).[21]

In many cases people infected with acute viral hepatitis C are able to clear the infection within six months without treatment. After six months those who have not cleared the infection are diagnosed with chronic hepatitis.[22] If left untreated chronic hepatitis C can cause cirrhosis, liver failure, or liver cancer. While there is currently no vaccine for hepatitis C, recent medical advances have created treatments for hepatitis C which cure over 90% of those treated. However, the cost of these drugs can be prohibitively expensive, with the median price of a cure for chronic hepatitis C (after adjusting for average rebates/discounts on the list price) around $65,000, although list prices can be as high as $147,000 (Swathi Iyengar, Kiu Tay-Teo, Sabine Vogler, Peter Beyer, Stefan Wiktor, Kees de Joncheere and Suzanne Hill, 2016; Elana S Rosenthal and Camilla S Graham, 2016). Stepanova and Younossi (2017) estimate that the total economic burden associated with hepatitis C may be as high as $10

[20] https://www.cdc.gov/hepatitis/hcv/cfaq.htm#cFAQ11.

[21] Tohme and Holmberg (2010) note that the increased risk among those with multiple sex partners may be confounded by increased likelihood of injection drug use.

[22] Approximately 75-85% of those infected with viral hepatitis C will develop chronic hepatitis C.

billion every year.

Hepatitis C has a relatively long incubation period, with an average of about 45 days. Symptoms can include fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, gray-colored bowel movements, joint pain, and jaundice. However, many infected individuals never exhibit symptoms until serious liver damage has already occurred. Routine tests for hepatitis C are not recommended to the general public, and it is estimated that the majority of those infected with hepatitis C are unaware of their infection. Therefore, hepatitis C is thought to be severely underreported.[23] The CDC estimates that there are about 3.5 million individuals infected with hepatitis C currently living in the US, although the majority do not know that they are infected.

The estimated number of acute viral hepatitis C transmissions over time is shown in Figure 2.1. The estimated number of new infections remained relatively constant from 2004 until 2010; however, after the reformulation of OxyContin the number of new infections began to rise dramatically. While this time series provides suggestive evidence, in Section 2.5 I leverage a difference-in-differences analysis to identify the causal effect of the reformulation. Prior studies in the medical literature have also documented this increase and suggested a link to opioid abuse, although these papers only utilize time series evidence and do not explain the cause of the sudden increase (Zibbell et al., 2018; Valdiserri et al., 2014).

Hepatitis B Similar to hepatitis C, if left untreated hepatitis B can cause cirrhosis, liver failure, or liver cancer. Absent treatment, up to one quarter of those infected with chronic

[23]The CDC estimates that there are 13.9 actual cases of hepatitis C for every reported case (R Monina Klevens, Stephen Liu, Henry Roberts, Ruth B Jiles and Scott D Holmberg, 2014). Also available here: https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1.

hepatitis B will die of related complications (Tarissa Mitchell, Gregory L Armstrong, Dale J Hu, Annemarie Wasley and John A Painter, 2011). However, unlike hepatitis C there exists a vaccine which can prevent contraction of hepatitis B in over 90% of healthy individuals (Colin W. Shepard, Edgar P. Simard, Lyn Finelli, Anthony E. Fiore and Beth P. Bell (2006), FE Andre (1990)). First approved in 1981, the hepatitis B vaccine was initially only targeted at high-risk groups (e.g., health care providers, men who have sex with men, injection drug users, etc.). However, beginning in 1991, the US began a campaign attempting to immunize all infants, drastically reducing the number of new cases of hepatitis B (Henry Roberts, Deanna Kruszon-Moran, Kathleen N Ly, Elizabeth Hughes, Kashif Iqbal, Ruth B Jiles and Scott D Holmberg, 2016). In spite of these efforts, much of the population is still not immunized. In their analysis of the 2011-2015 National Health Interview Survey, Pengjun Lu, Alissa C O'Halloran, Walter W Williams and Noele P Nelson (2018) found that only 24.6% of adults over the age of 18 had received the complete series of the hepatitis B vaccine.[24] This varies substantially by age, with 39.1% of 18-25 year olds having received the complete vaccine series compared to 11.1% of adults over the age of 65. Once infected, there is currently no cure for hepatitis B.

Hepatitis B is spread in the same ways as hepatitis C, although only about 30% of those diagnosed in 2015 reported injection drug use. Symptoms are similar to those of hepatitis C, although the average incubation period is somewhat longer at around 120 days. However, many individuals are asymptomatic for years and can experience substantial liver damage prior to being diagnosed. The CDC estimates that there are 6.48 actual cases of hepatitis B for every reported case (Klevens et al., 2014), with estimates ranging from

[24]Series completion requires three doses. Some respondents reported only having received the first dosage.

850,000-2.2 million infected individuals currently living in the US (NNDSS, 2015). An estimated 1,700 individuals died from hepatitis B in 2016, and the cost of treatment has been estimated as high as $1.5 billion annually (Kim, 2009).

Figure 2.1 shows the estimated number of new cases of acute hepatitis B each year from 2004-2015. The number of infections falls rapidly during the first decade of the century as more of the population is protected against the infection due to the vaccine. However, this fall stops in 2011, with the number of new infections remaining steady for the next few years and even rising in 2015. While less dramatic than the rise in hepatitis C, this time series provides some suggestive evidence that the change in trend may be related to the reformulation of OxyContin. Motivated by this time series evidence, in Section 2.5 I leverage a difference-in-differences analysis to identify the causal effect of the reformulation.

2.3 Research Design

The primary difficulty in estimating the effects of the OxyContin reformulation arises from the fact that the abuse-deterrent formulation was released on the same date throughout the nation, so there is no cross-sectional variation in the timing of the treatment to exploit. To overcome this concern, I follow the methodology used by Alpert, Powell and Pacula (2018) to utilize variation in the extent of OxyContin misuse prior to the reformulation to compare states that were more or less exposed to the treatment. The intuition here is simply that a state which had very little OxyContin misuse prior to the reformulation has little scope to be affected by the reformulation, while a state with high levels of OxyContin misuse has a much larger fraction of its population which could be affected. This idea is formalized in equation 2.1:

$$y_{st} = \alpha_s + \gamma_t + \sum_{T \neq 2009} \beta_T \cdot \text{Oxy Misuse}_s^{pre} + \delta X_{st} + \epsilon_{st}, \tag{2.1}$$

where y_{st} is an outcome in state s and year t. State and year fixed effects are represented by α_s and γ_t, and are included to control for any time-invariant differences across states and secular trends common across all states, respectively. The Oxy Misuse$_s$ variable is a proxy for state OxyContin misuse in the pre-period, drawing from the National Survey of Drug Use and Health (NSDUH). Additional control variables are included in X_{st} and include the unemployment rate and log of the population. The coefficients of interest are the β_T's, which indicate the difference in the outcome variable among states with different levels of pre-reformulation OxyContin misuse. I normalize β_{2009} to zero, so all coefficients can be interpreted as changes relative to 2009. Standard errors are clustered at the state level.

The identifying assumption in this model is that absent the reformulation of OxyContin, outcomes in states with differing levels of OxyContin misuse in the pre-period would have continued to evolve in parallel. While this assumption is fundamentally untestable, one can assess its plausibility by examining the β_T's in the pre-period.

2.4 Data and Identifying Variation

Data Data on hepatitis diagnoses come from the CDC's Division of Viral Hepatitis and the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. I use data on the number of new reported cases of acute viral hepatitis B and C at the state-by-year level from 2004-2015. Because hepatitis B and C are thought to be severely under-diagnosed, I apply the CDC's adjustment factors to obtain the estimated number of new cases each year

(Klevens et al., 2014).[25] Control variables include the unemployment rate and log of the population. These variables are taken from the Bureau of Labor Statistics and the Census Bureau, respectively, at the state-year level from 2004-2015. I obtain estimates of OxyContin misuse from the National Survey of Drug Use and Health (NSDUH). The NSDUH provides a variable estimating the fraction of the population which used OxyContin non-medically and is available at the state level in two year averages from 2004-2005 through 2008-2009. [26]

Identifying Variation As discussed above in Section 2.3, this paper's research design exploits variation in the extent to which different states were "treated" by the reformulation of OxyContin. In order to measure this intensity of treatment, I replicate the measure from Alpert, Powell and Pacula (2018), which pools data on reported OxyContin misuse from the 2004-2005 to 2008-2009 wave of the NSDUH. A major advantage of this measure is that it comes from a question which specifically asks the respondent if they have used OxyContin for non-medical reasons over the past year, as opposed to other potential proxies such as the geographic distribution of oxycodone.

Figure 2.2 demonstrates the identifying variation in the NSDUH. In this figure darker shades of red indicate the states with higher levels of OxyContin misuse, which I compare over time to the states in lighter shades of red.

[25]Specifically, I multiply the number of reported cases of hepatitis C by 13.9 and the number of reported cases of hepatitis B by 6.48. The CDC's published estimates since 2011 reflect this adjustment. Prior to 2011, different (and unpublished) adjustment factors were used. Therefore, the estimates in this paper may differ slightly from the CDC's published estimates prior to 2011. However, this paper's results are identical if I use annual reported diagnoses instead of estimated cases, then apply the adjustment factor to the regression coefficients after 2011.

[26]See Alpert, Powell and Pacula (2018) for further discussion on this variable.

2.5 Results

Given the previous literature's finding that the reformulation of OxyContin led to substitution toward heroin and the evidence presented in Section 2.2 that heroin users are substantially more likely to inject than OxyContin users, I first present the main results of the paper, which investigate the impact of the reformulation on the transmission of hepatitis B and C.

2.5.1 Main Results

Before presenting the regression results, I first show suggestive evidence of the main findings in the raw data. To do this I plot the time series for the number of new diagnoses of hepatitis B and C per 100,000, broken down by whether states are above or below the median in terms of pre-period OxyContin misuse. The results from this exercise are shown in Figure 2.3. The left panel shows that prior to the date of the reformulation (indicated by the vertical gray bar), states with higher or lower levels of pre-period OxyContin misuse had fairly similar rates of hepatitis C diagnoses, both in levels and in trends. However, after the reformulation the rate of new hepatitis C diagnoses rose substantially faster in states above the median in terms of pre-period OxyContin misuse. From 2010 to 2015 the rate of hepatitis C infections nearly triples in states above the median, while in states below the median the growth is much more moderate.

The right panel recreates the same figure, this time looking at the rate of new hepatitis B infections. Here, the rate of new infections is falling at essentially the exact same rate in states above and below the median, and for most of the pre-period the levels are nearly identical. However, following the reformulation the rate of new hepatitis B infections continue

to fall at essentially the same rate in states below the median, but completely stop falling (and even rise a little) in states above the median. Taken together, these two sub-figures provide suggestive evidence that states which were more exposed to the reformulation saw increases in hepatitis B and C, consistent with the reformulation leading individuals to transition to injectable drugs. While this exercise mimics regression equation 2.1 and has the advantage of being transparent and easy to interpret, it pools states above and below the median OxyContin misuse measure and therefore does not utilize all of the available variation in pre-period OxyContin misuse. The regressions, on the other hand, interact a continuous measure of OxyContin misuse with each year fixed effect, taking full advantage of the cross-state variation in pre-period OxyContin misuse.

Motivated by the striking trends in the raw data presented in Figure 2.3, I now graphically present the coefficient estimates from the difference-in-differences specification outlined in equation 2.1. The left panel of Figure 2.4 plots the regression coefficients along with 95% confidence intervals with the number of new diagnoses of hepatitis C per 100,000 as the outcome variable.[27] Prior to the reformulation in 2010, the regression coefficients are all statistically insignificant and close to zero, suggesting that pre-period OxyContin misuse was unrelated to any differential trends in the spread of hepatitis C prior to the reformulation. This lends plausibility to the identifying assumption that absent the reformulation, rates of hepatitis C transmission would have continued to trend in parallel across more and less treated states. After the reformulation the coefficients all become positive, indicating that states which were more exposed to the reformulation experienced larger increases in hepatitis C infections than states which were less exposed. Each coefficient after 2010 is statistically

[27]Each coefficient is reported in table form in Table 2.2.

significant at the 1% level. In the bottom right corner of the sub-figure, I report the p-value from a test of the significance of the average of all the post-period coefficients, which allows me to reject the null hypothesis that the average effect of the reformulation in the post-period is zero.

Given the event study framework, the interpretation of the these regression coefficients warrants some additional discussion. Each coefficient represents the marginal effect of a one percentage point increase in pre-period OxyContin misuse on the outcome variable relative to 2009. For example, column (1) of Table 2.2 indicates that a state with one percentage point more OxyContin misuse in the pre-period would expect 13.81 more diagnoses of hepatitis C per 100,000 in 2011 than 2009, relative to a state with one percentage point less OxyContin misuse. Taking the mean of all the post-period interaction coefficients suggests that on moving from the bottom to the top state (Illinois to Rhode Island) in terms of pre-period OxyContin misuse is associated with about 17.95 additional cases of hepatitis C each year after the reformulation.

Next, I graphically present the regression results with the rate of new hepatitis B infections as the outcome variable in the right panel of Figure 2.4. Consistent with the evidence shown in the right panel of Figure 2.3, the pre-period coefficients are all small in magnitude and statistically insignificant, consistent with there being no differential trends in hepatitis B transmissions related to pre-period OxyContin misuse. However, beginning in 2010, the first partially treated year, the coefficients all become positive and relatively large in magnitude. Each point estimate is listed in column (2) of Table 2.2. Each post-period coefficient is significant at the 5 or 10% level except for the 2015 coefficient, which is more noisily estimated. Averaging across all the post-period interactions indicates that the

top state in terms of pre-period OxyContin misuse was expected to have an additional 9.33 diagnoses of hepatitis B per 100,000 each year relative to the bottom state, although this average estimate is only significant at the 10% level.

To further contextualize these magnitudes, I conduct a counterfactual simulation in which I estimate the number of cases of hepatitis B and C that would have occurred in the absence of the reformulation. This exercise is discussed in Appendix B, and indicates that absent the reformulation of OxyContin we would have observed approximately 76% fewer cases of hepatitis C and 53% fewer cases of hepatitis B from 2011-2015. Finally, I show that the main results are robust to an alternate measure of pre-period OxyContin misuse and the inclusion of indicators for other opioid related laws. I also show that the results do not appear to be driven by changes in testing for hepatitis, changes in drug use patterns more broadly, or changes in blood-borne diseases more commonly spread sexually than via injection (see Appendix B).

2.6 Conclusion

In response to alarming rates of painkiller abuse, pharmaceutical companies have begun developing painkillers which are more difficult to misuse. The FDA has officially labeled ten such painkillers as abuse-deterrent, and is encouraging the development of more abuse-deterrent opioids. The introduction of a new tamper-proof formulation of OxyContin and simultaneous discontinuance of the existing formulation provide an interesting natural experiment to study the effects of these abuse-deterrent painkillers. In this paper I build upon the prior literature's finding that the reformulation of OxyContin led to an increase in heroin deaths by showing that this substitution has led to an increase in the spread of

blood-borne diseases, particularly hepatitis B and C. A series of robustness checks supports a causal interpretation of this result.

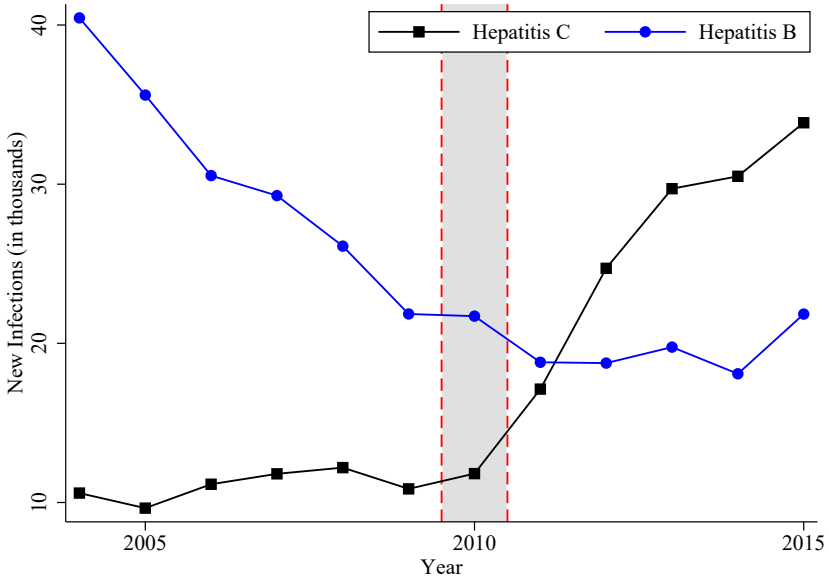
These findings have important policy implications. First, a simple back-of-the-envelope calculation reveals staggeringly large costs associated with the spread of hepatitis C: curing all of the new cases of hepatitis C since 2011 attributable to the reformulation of OxyContin would cost about $6.69 billion. Much of these costs will be borne by third parties, representing a substantial externality. Second, the results suggest that as more steps are taken to crack down on the distribution of abusable painkillers, we are likely to see increases in heroin use. In addition to increased risk of overdose, the fact that heroin is typically administered via injection will likely exacerbate the spread of blood-borne diseases, particularly hepatitis B and C. Ultimately, the issue of how to address painkiller misuse without driving those already addicted toward more dangerous behaviors is still an open question.

Table 2.1: Differences in Typical Routes of Administration for Heroin and Painkillers

Usual Route of Administration	A. All		B. Used Both	
	Heroin	Painkillers	Heroin	Painkillers
Oral	1.6	72.9	2.1	66.6
Smoking	2.8	2.1	3	1.7
Inhalation	33.1	14.1	30.6	17.3
Injection	61.8	10	63.5	13.6
Other	0.6	0.9	0.8	0.8
Observations	1,902,511	1,010,803	190,529	189,249

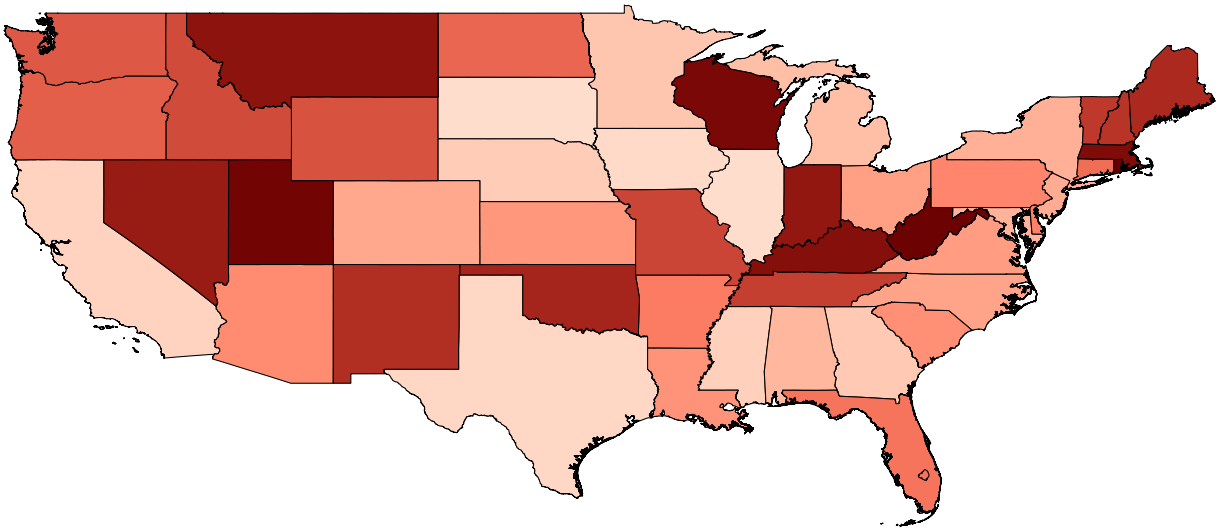
Note: This table displays the typical route of administration for heroin and painkiller users in the TEDS dataset. Data are pooled from 2004-2009 and include the fraction reporting each route of administration. Panel A includes the entire sample, while panel B is restricted to those who reported both heroin and painkiller abuse. The highlighted column demonstrates that heroin is injected with a much higher frequency than painkillers. The sample sizes in panel B are slightly different because the typical route of painkiller administration was missing for some individuals who reported both heroin and painkiller use.

Figure 2.1: Estimated Number of Acute Cases of Viral Hepatitis B and C by Year



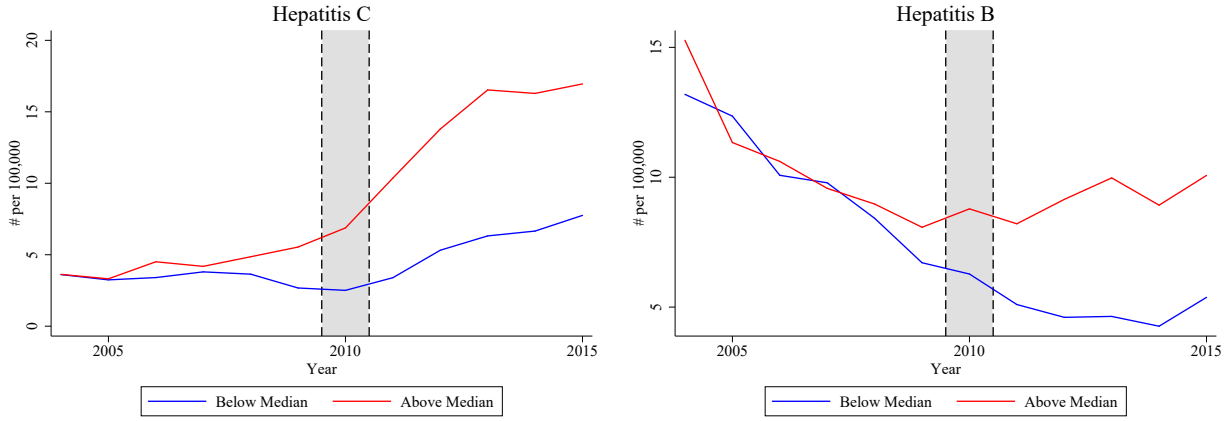
Note: This figure shows the estimated number of new acute cases of hepatitis B (in blue) and C (in black) in thousands from 2004-2015. The shaded region indicates the year that OxyContin was reformulated. The estimates in this figure may differ slightly from published estimates prior to 2011, which were calculated using a different (and unpublished) methodology. However, this figure exactly reflects the trends in annual diagnoses.

Figure 2.2: Identifying Variation: Fraction of NSDUH Respondents Reporting Pre-Period OxyContin Misuse



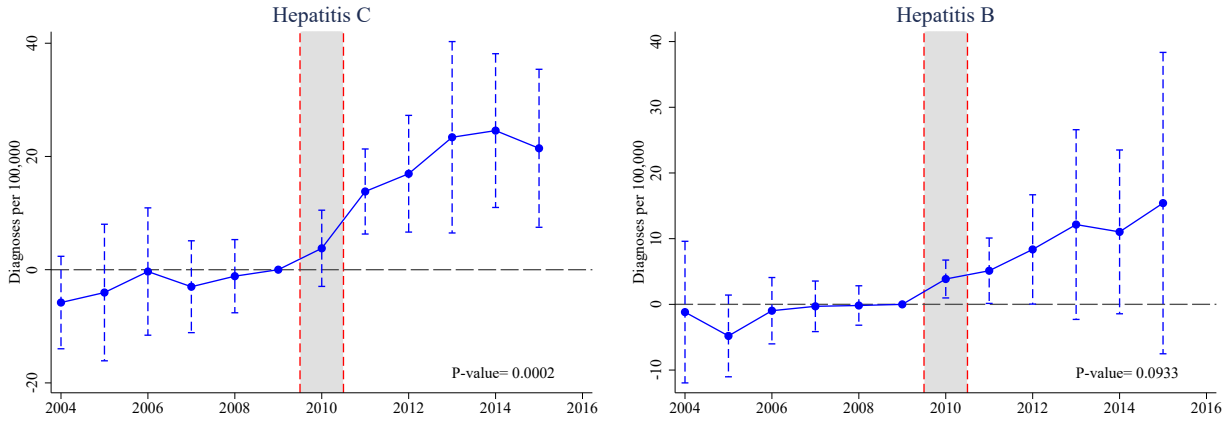
Note: This map shows the fraction of NSDUH respondents reporting past year OxyContin misuse pooled from 2004-2009, with darker shades of red indicating more misuse. The numbers underlying this map is included in Table B.2.

Figure 2.3: New Hepatitis Diagnoses Over Time for States Above and Below Median Pre-Period OxyContin Misuse



Note: This figure shows the average number of estimated cases of hepatitis C (left panel) and hepatitis B (right panel) per 100,000. In each panel the red line indicates states above the median, while the blue line represents states below the median.

Figure 2.4: Hepatitis Transmissions: Impact of One Percentage Point Increase in Pre-Period OxyContin Misuse



Note: This figure shows coefficients on Oxy Misuse$_s^{pre}\times$ year interactions from regression equation 2.1 for the number of hepatitis C (left panel) and hepatitis B (right panel) cases per 100,000. The coefficients can be interpreted as the effect of a one percentage point increase in pre-period OxyContin misuse. Dependent variables are measured at the state-year level.

Table 2.2: Main Regression

	(1) Hepatitis C	(2) Hepatitis B	(3) Hepatitis C	(4) Hepatitis B	(5) Hepatitis C	(6) Hepatitis B	(7) Hepatitis A	(8) Cocaine	(9) HIV
2004 * OxyPre	-5.8029	-1.1788	-0.0628	0.0445	-5.0285	-0.3971	0.6485	-0.5813	
	(4.0641)	(5.3657)	(0.1121)	(0.1013)	(3.6408)	(5.0921)	(1.0842)	(0.8387)	
2005 * OxyPre	-4.0359	-4.8049	-0.0492	0.0453	-3.2294	-4.2352	0.4380	-0.0651	
	(6.0021)	(3.0971)	(0.1260)	(0.0644)	(5.6115)	(2.9612)	(0.6027)	(0.6951)	
2006 * OxyPre	-0.3270	-0.9650	0.0230	0.0563	-0.1375	-1.1874	-0.0192	0.3621	
	(5.5968)	(2.5134)	(0.1419)	(0.0498)	(5.5062)	(2.4898)	(0.3777)	(0.9466)	
2007 * OxyPre	-3.0105	-0.2987	-0.0613	0.0341	-3.0776	-0.5919	-0.1414	0.3476	
	(4.0363)	(1.9156)	(0.0835)	(0.0331)	(3.9843)	(1.9317)	(0.2012)	(0.5931)	
2008 * OxyPre	-1.1483	-0.1708	-0.0649	0.0318	-1.2448	-0.5263	-0.4389	0.1467	1.6359
	(3.2156)	(1.4937)	(0.0612)	(0.0261)	(3.2301)	(1.5718)	(0.3998)	(0.4371)	(2.4916)
2010 * OxyPre	3.7749	3.8593***	-0.0068	0.0508**	4.0011	3.6742**	0.5318***	-0.1829	1.3367
	(3.3494)	(1.4346)	(0.0636)	(0.0223)	(3.4103)	(1.6291)	(0.1777)	(0.6603)	(1.1952)
2011 * OxyPre	13.8087***	5.1201**	0.1489**	0.0868**	13.5188***	4.4312*	0.4125**	0.0719	2.9953
	(3.7387)	(2.4776)	(0.0673)	(0.0378)	(3.7139)	(2.5213)	(0.1873)	(0.6682)	(2.3394)
2012 * OxyPre	16.9484***	8.3610**	0.1740	0.1316*	14.4347***	5.9958**	0.2936	-0.0694	2.9065
	(5.1295)	(4.1427)	(0.1082)	(0.0686)	(4.4513)	(2.9849)	(0.2134)	(0.5707)	(2.3526)
2013 * OxyPre	23.3885***	12.1457*	0.2431*	0.2035	20.6321***	9.7299*	0.3656*	0.4248	3.6138
	(8.4114)	(7.1889)	(0.1351)	(0.1317)	(7.4505)	(5.4887)	(0.2037)	(0.7820)	(2.5196)
2014 * OxyPre	24.5676***	11.0317*	0.3475***	0.2076*	20.5372***	7.4984*	0.5385***	0.1312	7.4798
	(6.7584)	(6.2069)	(0.1133)	(0.1115)	(5.4895)	(4.4558)	(0.1770)	(0.7756)	(5.7930)
2015 * OxyPre	21.4420***	15.4135	0.2426**	0.2914	17.0962**	11.5406	0.4097**	0.8353	3.6545
	(6.9441)	(11.4191)	(0.1139)	(0.2194)	(6.8399)	(9.9982)	(0.1931)	(1.0753)	(2.9848)
Observations	488	588	488	588	488	588	605	612	403
R^2	0.593	0.706	0.566	0.700	0.609	0.729	0.475	0.819	0.922
Other Laws	No	No	No	No	Yes	Yes	No	No	No
Treatment Var.	NSDUH	NSDUH	Google	Google	NSDUH	NSDUH	NSDUH	NSDUH	NSDUH

Note: This table shows regression coefficients from equation 2.1 for various outcome variables. The coefficients can all be interpreted as the effect of a one percentage point increase in pre-period OxyContin misuse. Columns (1) and (2) present the main regression coefficients. Columns (3) and (4) use an alternative measure of pre-period OxyContin misuse: Google searches for OxyContin. Columns (5) and (6) show regression results with additional controls for other related laws. Columns (7)-(9) are robustness tests looking at other outcome variables. Standard errors in parentheses are clustered at the state level. $*p < 0.10, **p < 0.05, ***p < 0.01$.

Chapter 3

Cross-State Spillovers from Medical Marijuana Laws

Over the past two decades nearly half of US states have passed laws permitting the sale and use of marijuana for medical purposes. A growing literature examines the effects of MMLs on a variety of outcome variables. Generally, the research strategy of these papers is a difference-in-differences strategy comparing outcomes in states with MMLs to states without MMLs before and after the law is passed. This research design implicitly assumes that only states with MMLs are affected by the passage of the law. However, given the ease of interstate travel in the United States, it is plausible that laws which increase the availability of marijuana in one state have spillover effects on neighboring states. This paper provides the first estimates of these potential cross-state spillovers.

I exploit variation in state and federal marijuana policy to compare the evolution of outcomes in states bordering states with relatively loose marijuana regulations (henceforth referred to as border states) to changes in non-border states both before and after the implementation of the MML and before and after a large change in federal marijuana prosecution practices. Implicit in this research design is the assumption that spatial proximity is an important determinant in interstate trafficking, which is consistent with both anecdotal evidence and previous research.

Using data on drug rehab treatment admissions, I find evidence of substantial spillovers from MMLs across state borders for several different outcomes. Specifically, I find a reduction in opioid[1] abuse in border states relative to non-border states, which is consistent with previous research that indicates marijuana can substitute for potentially dangerous painkillers. I also find that total admissions to treatment facilities fall, which implies substitution toward marijuana from more addictive drugs that are more likely to lead someone to enter a treatment facility. Surprisingly, I find a decrease in marijuana-related admissions. However, this does not necessarily imply a reduction in marijuana use in border states since this could reflect a smaller perceived risk of marijuana use in response to legal changes, leading fewer marijuana users to seek treatment. It is also plausible that the legalization of medical marijuana led to the availability of higher quality marijuana which caused fewer adverse reactions leading to treatment[2]. I find mixed evidence for alcohol abuse and a small decrease in heroin abuse. Finally, I find an increase in admissions for cocaine use which may imply that an increase in the size of the illegal marijuana market leads to a 'gateway' effect which causes individuals to experiment with cocaine. However, more research needs to be done investigating the mechanisms behind these results.

[1] I use the terms 'opioids' and 'prescription painkillers' interchangeably throughout the paper.

[2] For example, illegal drugs are often laced with other substances in order to increase the weight and therefore price. Sometimes, these added substances are harmful or even fatal (Dan Childs and ABC News Medical Unit (2008)). Unfortunately, my data do not identify admissions for acute reactions, so I am unable to test this hypothesis.

3.1 Background

3.1.1 Motivation

In December of 2014, Nebraska and Oklahoma filed a lawsuit with the Supreme Court in response to a 2012 amendment to Colorado's constitution which legalized marijuana in the state (John Ingold (2014)). At the heart of the lawsuit rested the claim that the legalization of marijuana in Colorado led to extensive negative externalities on Nebraska and Oklahoma, two states which share a border with Colorado. The lawsuit claims that "Marijuana flows...into neighboring states, undermining Plaintiff States' own marijuana bans, draining their treasuries, and placing stress on their criminal justice systems." While the lawsuit does not provide any statistical evidence of these allegations, the allegations are consistent with anecdotal evidence from law enforcement officials in Nebraska and Oklahoma, who have noted increases in marijuana-related crime[3].

Early the next year, another lawsuit was brought against Colorado by several groups of law enforcement officials from Colorado, Nebraska, and Kansas (Niraj Chokshi (2015)). This suit consisted of two complaints. First, the groups from Kansas and Nebraska argued that Colorado's marijuana laws caused an excess burden on their states' law enforcement, similar to the first suit. The group from Colorado made a very different complaint: that legalizing a drug which is currently federally illegal unfairly forced them to choose between enforcing state or federal law.

[3]Ultimately, the Supreme Court declined to hear this case.

Both of these cases illustrate the policy relevance of cross-state spillovers from MMLs. While these specific lawsuits were in response to laws legalizing marijuana for recreational use, it is reasonable to expect spillovers from recreational marijuana legalization to follow the same pattern as spillovers from medical marijuana legalization. In fact, it is likely that the effects I observe from MMLs serve as a lower bound for the effects from recreational legalization since recreational marijuana laws would presumably increase the size of the marijuana market more than MMLs. This study focusing on MMLs is also important in light of several states currently considering adopting some type of MML and could also be important for determining federal enforcement policy.

Finally, this paper is important in light of recent research documenting rising mortality rates in the United States stemming from drug abuse. Historically, long run mortality rates have fallen almost monotonically in the US; however, Case and Deaton (2015) show a unique rise in mortality among middle-aged non-Hispanic whites since 1998. They argue that much of this marked reversal in mortality can be explained by increases in drug and alcohol poisonings. Christopher M. Jones, Karin A. Mack and Leonard J. Paulozzi (2013) found that in 2010 about 60 percent of drug overdose deaths were the result of abuse of prescription opioids. The number of opioid related deaths has risen by a factor of four since 1999, and currently exceed the number of fatalities from car accidents (David Powell, Rosalie Liccardo Pacula and Mireille Jacobson (2015)). This dramatic rise has even led the President to refer to opioid abuse as an "epidemic" that "has to be something that is right up there at the top of our radar screen" along with combatting terrorism and strengthening the economy (Obama (2016*b*)). The President has since encouraged Congress to pass a 1.1

billion dollar bill to expand access to treatment and prevent the over prescription of opioids (Barack Obama (2016*a*)). Given that MMLs have the potential to either alleviate (due to substitution away from more dangerous drugs) or exacerbate (due to increased marijuana use) the current drug abuse crisis, empirical evidence of the effects of these laws is vital for policy recommendations.

3.1.2 Legal and Medical Background

Marijuana is currently classified as a Schedule I drug by the United States Controlled Substances Act. This means that the drug is considered to have a high potential for abuse and no currently accepted medical use. Recently, both of these assumptions have become the subject of debate. In light of growing evidence that marijuana can effectively treat chronic pain and muscle spasms as well as nausea and appetite loss (Laura M. Borgelt, Kari L. Franson, Abraham M. Nussbaum and George S. Wang (2013)), the American Medical Association has recommended that marijuana's Schedule I status be changed in order to facilitate additional research, including large-scale clinical trials (H-95.952). This is not an official endorsement of medical marijuana; however, it does signal that the medical community is open to the possibility that marijuana has valid medical uses. While there is evidence suggesting that marijuana can be addictive, rates of addiction for marijuana are among the lowest of illegal drugs, and marijuana users report lower incidence of addiction than alcohol users (Elena M. Kouri and Harrison G. Pope Jr. (2000), James C. Anthony, Lynn A. Warner and Ronald C. Kessler (1994)).

In response to the growing medical literature as well as changing public perception regarding marijuana use, many states have adopted laws legalizing marijuana for medical use. To date 23 states and the District of Columbia have adopted some type of MML. Importantly, there is significant heterogeneity in these MMLs along a number of dimensions including legal allowance of dispensaries, who can purchase medical marijuana, who can grow marijuana and how much they can grow, and the criteria for prescribing marijuana. Table 3.1 summarizes the relevant laws over my sample period. Column (2) shows when each MML state first implemented its law while column (3) indicates which states have loose supply regulations, which I will define more precisely in Section 3.2.

Perhaps the most important legal detail, which I alluded to above, is that despite almost half of the states legalizing medical marijuana, it is still federally illegal. This led to an interesting legal gray area, where individuals buying and selling marijuana in accordance with state law could still be prosecuted under federal law. This uncertain legal status stunted the growth of the marijuana market in states with MMLs. This changed in late 2009, when the Ogden Memo was announced. The Ogden Memo declared that federal resources should not be expended prosecuting those who were in compliance with their state's marijuana laws. This effectively ended federal prosecution of marijuana users and sellers in states with MMLs. As shown in Rosanna Smart (2016), which I discuss in more detail in Section 3.2, this led to rapid growth in the sizes of both the legal and illegal marijuana markets.

3.2 Literature Review

Since the first MML was passed in California in 1996, economists have been interested in the effects of legalizing marijuana. Several papers have examined the effects MMLs have on the states that implement them. Outcomes that economists have studied include the use and abuse of marijuana, alcohol, prescription painkillers, and hard drugs such as heroin and cocaine (Hefei Wen, Jason M. Hockenberry and Janet R. Cummings (2014), Powell, Pacula and Jacobson (2015), Yu-Wei Luke Chu (2015*b*)). Other papers have also studied indirect effects such as fatal car accidents and educational attainment (Smart (2016), Rosalie Liccardo Pacula, Karen E. Ross and Jeanne Ringel (2003)).

While a few early studies looked at cross-sectional comparisons of marijuana use in MML states to marijuana use in non-MML states, this research design proved ineffective given the different levels of marijuana use prior to the MML being adopted. By far the most common strategy in this literature is to use a difference-in-differences framework to compare states that have implemented MMLs to states that have not. Essentially, this involved comparing outcomes in the dark blue states in Figure 3.1 to the light blue states before and after implementation of each state's MML. Early studies with this research design found mixed results. However, these papers neglected the fact that there was substantial heterogeneity in the details of various states' MMLs. Later papers such as Rosalie L. Pacula, David Powell, Paul Heaton and Eric L. Sevigny (2014) and Powell, Pacula and Jacobson (2015) showed that taking into account the specific details of the various states MMLs leads to more consistent results. However, these papers still fail to account for the change in federal enforcement discussed above.

The paper whose methodology I follow most closely is Smart (2016), which makes several contributions to this literature. First, this is the only paper that takes into consideration the change in federal enforcement of the national marijuana ban. Smart collects data on statewide marijuana registration rates (most states with MMLs require users to register) and shows that registration rates only seem to grow in response to the Ogden Memo as opposed to changes in state MMLs. Second, she shows that the spike in registration rates only occurs in states with loose supply regulations. A state is considered a 'loose' state if suppliers were able to provide marijuana to an unlimited number of patients. In states with tighter supply regulations, registration rates do not appear to grow. Throughout my analysis I adopt Smart's definition of loose states. Table 3.1 indicates the states with loose MMLs.

3.2.1 Contribution

All of the papers above study the effects of MMLs in the states that implement them. However, their research designs implicitly assume that the effects of MMLs are confined to the states that adopt them and do not affect other states. This stands in direct contrast to anecdotal evidence presented in the lawsuits discussed in the introduction. Given the ease of interstate travel in the United States, it is entirely plausible that marijuana flows from states where it is legal to states where it is not. This paper's major contribution to this literature is addressing whether marijuana does indeed flow from MML states into neighboring non-MML states, and if so what effects this has on the neighboring states. Even if marijuana does spill over across state borders, it is not ex ante clear whether this is welfare

reducing or not. On the one hand, the fact that marijuana is illegal in the neighboring states indicates that marijuana usage causes some utility loss in those states, assuming the legal status of marijuana is representative of the states' voters' preferences. To the extent that MMLs increase marijuana and other drug use, MMLs will be welfare reducing, at least to the median voter[4]. However, in light of the suggestive medical evidence of the efficacy of medical marijuana, it is possible that MMLs can generate some positive externalities. If MMLs lead to a reduction in abuse of prescription painkillers or substitute for other harmful drugs, MMLs will be welfare increasing. While I do not have the data to conduct a full welfare analysis, I investigate several important effects of MMLs and clearly identify at least one positive and one negative externality.

A second contribution of this paper relates to a problem that has typically been overlooked in the prior MML literature. Many of the states that have adopted MMLs have done so via voter referendum, which makes inference from the difference-in-differences research design problematic. If the laws were implemented in response to higher marijuana usage and changing social attitudes, then it is likely that the difference-in-differences estimation is picking up these changes within the state in addition to the effects of the MML. Essentially, if these MMLs are adopted endogenously, then the difference-in-differences estimators may be biased. This endogeneity is much less likely to be a problem in my research design. The treated states in my analysis are those which border MML states, and it is unlikely that MMLs are adopted in response to changing attitudes in neighboring states[5]. Therefore, in

[4]However, assuming rationality, consuming marijuana is welfare increasing to those who choose to use it.
[5]An argument could be made that there is some spatial correlation in citizens attitudes so that attitudes

addition to measuring spillovers my estimates are likely also a lower bound on the effects of a MML for the adopting state.

3.3 Data and Estimation Strategy

3.3.1 Data

The ideal dataset for my analysis would consist of past and current drug use for everyone in the United States. While these data do not exist, there are several surveys which measure similar information. Perhaps the best data on drug use come from the National Survey of Drug Use and Health (NSDUH). This is a nationally representative survey of drug use in the United States conducted biennially. In addition to detailed demographic information, it asks respondents about current and past drug use for a variety of different types of drugs. Unfortunately, the publicly available data do not contain geographic identifiers, and the restricted version of the data is currently unavailable[6]. Without state identifiers, I am unable to test for cross-state spillovers from MMLs and so will not be able to use this data for my analysis.

Another source of survey data is the National Longitudinal Survey of Youth (NLSY). This data follows a cohort of youth over time and asks participants several questions related

in border states track attitudes in MML states more closely than do attitudes in non-border states. However, the legal challenges to Colorado's laws indicate that these attitudes toward marijuana do not necessarily have a strong spatial correlation.

[6]The NSDUH is administered by the Substance Abuse and Mental Health Services Administration (SAMHSA). When I attempted to apply for the restricted access data I was informed that they were in the middle of changing their data storage and dissemination systems so there was no way to access the data. They do not have an estimated date for when the new system will be finished. I was added to an email list and will be notified when the data become available.

to drug use including whether they have ever used a certain drug and if they currently use the drug. They ask this for several drugs including marijuana and alcohol. In addition to drug use, the data contain a rich set of covariates for each individual in the survey. However, I again encountered the problem that the public use version of the NLSY does not contain geographic identifiers in order to protect the privacy of the survey participants. While I have completed the application for the restricted access data that contain geographic identifiers, I have not yet received the data and cannot use it for this draft[7].

A final source of survey data is the Youth Risk Behavior Survey (YRBS) conducted by the Centers for Disease Control and Prevention (CDC). While the individual-level data is restricted, state-level aggregates are publicly available. This allows me to observe the fraction of youth in each state-year who have ever used alcohol or marijuana, as well as the fraction of youth who currently use alcohol and marijuana. However, there are several problems with this data. First, participation in the survey is voluntary across states, and many states either do not participate at all or participate inconsistently. For example, a state may only report data during one survey wave and not another. Unfortunately, participation rates are poor. A second problem is that the survey is only conducted every two years, which makes it difficult to see the effects of a legal change in a specific year. These data limitations

[7]In order to access the restricted access version of the NLSY, the Bureau of Labor Statistics (BLS) requires that the applicant have a secure way to store the data. This involved finding a non-networked computer that I could store in my office, which took some time. Since I submitted the first draft, the BLS approved my application. However, before I can receive the data, someone with the proper authority from the university will need to sign a contract on my behalf. In order to obtain this signature I first need to obtain IRB approval (for which my application is pending) after which it could take another several weeks to receive the data. I have worked out all of these details with various university personnel, but unfortunately do not have the data for this version of the paper.

make it difficult to estimate effects with any statistical precision[8].

Due to these issues with the survey data, I will instead use data which allows me to measure indirect evidence of cross-state spillovers from MMLs. My primary data set is the Treatment Episodes Data Set (TEDS), which contain data on all drug abuse treatment facilities that receive federal funding. This ultimately ends up covering about 75 percent of all drug abuse treatment admissions. The data contain detailed information about every admission to treatment. Importantly for my analysis, the data list up to three self-reported substances of abuse, in order of importance. For example, someone could enter a treatment facility primarily because of a cocaine addiction, but also use alcohol and marijuana. Another important feature of the data is that it identifies patients who were referred by the criminal justice (CJ) system. This is important if police, prosecutor, or judge behavior responds endogenously to MMLs. For example, in states that border MML states the CJ system may be more or less likely to require a drug user to enter rehab than in other states. For most of my analysis, I exclude all CJ referrals, which accounts for about 20 percent of the data. It is important to keep in mind that these data do not directly measure drug use, but rather drug use that leads to entrance to a treatment facility. However, if MMLs significantly change drug use habits, we may expect changes in the number of people entering treatment for various drugs. The outcome variables that I will use in my regressions are the number of people entering a treatment facility in a state-year for a given drug. The drugs that I examine are alcohol, marijuana, heroin, cocaine, and opioids. My sample spans the years 1992 through 2012. Note that the first recreational marijuana law was passed

[8]The results from this analysis are in an unsubmitted appendix available upon request.

after this, so my analysis will not be confounded by the effects of recreational marijuana laws.

Another data set which I use to investigate drug use is the National Vital Statistics System (NVSS) which contain the universe of deaths in the United States. This allows me to observe the effects of MMLs on relatively rare but important outcomes, deaths from drug abuse. I use this data to construct information about the number of people killed in each state-year from various drug related causes, including alcohol poisonings and prescription painkiller overdoses.

Summary statistics for all of my variables are included in Table 3.2. The unit of observation is the state-year average of admissions or poisonings per 100,000 from 1992 to 2012[9]. Interestingly, admissions for all types of drug abuse are lower in border states than non-border states when looking at the entire sample period (Panel B), although both alcohol and opioid poisonings are slightly higher in border states[10]. However, these differences are to be expected if MMLs are causing spillovers onto border states. Perhaps most interesting is that when I restrict my sample to the period before the passage of the first MML in 1996 (panel A), border and non-border states look very similar. The only noticeable differences are in cocaine and heroin admissions. This is suggestive that MMLs may have contributed to the observed differences in drug related admissions over time. The growth in overall admissions and for specific types of drugs is shown in Figure 3.3. The panels showing overall admissions and admissions for alcohol, marijuana, and opioids are particularly striking. Prior to the

[9]Alcohol and opioid poisoning data are only available from 1999-2012.

[10]Here border state refers to states which border any state which ever implemented a 'loose' MML

implementation of the first MML in 1996, all of these series seem to be evolving in parallel, although they begin trending apart after 1996.

3.3.2 Empirical Framework

The purpose of this paper is to investigate whether MMLs have effects on the states that do not implement them. To test this hypothesis I make the assumption that the states most likely to be affected by another state's MML are those states which share a border with the MML state; that is, I assume that border states are treated and non-border states are untreated. The idea is that spillovers are more likely to occur across shorter distances. For example, since it is less costly to transport goods from Colorado to Kansas versus Colorado to Georgia, I expect Colorado's MML to have larger effects on Kansas than Georgia. This idea is consistent with other papers on cross-state trafficking such as Knight (2013), which shows that illegal guns are more likely to end up close to the source state and Lovenheim (2008) which provides evidence of trafficking of cigarettes from across the border from states with high cigarette taxes to states with lower cigarette taxes.

Given the findings of Smart (2016), I only consider those states with loose supply regulations as MML states[11]. These states are shown graphically in Figure 3.2. Recall that Smart showed that the size of the legal marijuana market did not expand until the Ogden Memo was released, so my initial strategy is to compare changes in outcomes of the border (green) states before and after the Ogden Memo to changes in outcomes of the non-border

[11] In results not shown here, I experiment with using all MML states. Under this specification my regression coefficients tend toward zero and are generally statistically insignificant. This suggests that MMLs with loose regulations are the relevant source of variation in identifying spillovers.

(red) states before and after the Ogden Memo.

The initial estimating equation is therefore

$$y_{st} = \alpha_s + \gamma_t + \phi\ Ogden_t + \delta\ border_s \times Ogden_t + \Gamma X_{st} + \epsilon_{st} \tag{3.1}$$

where s indexes the state and t indexes the year. State and year fixed effects are given by α and γ, respectively. The state fixed effects control for any time-invariant differences in outcomes across states, while the year fixed effects control for national trends. Ogden is an indicator variable that takes on a value of zero before the Ogden Memo and a value of one afterward. Note that the Ogden variable is not separately identifiable from the year fixed effects, so I first run my regressions excluding the year fixed effects and then add in the year effects to more flexibly control for aggregate trends. I include state fixed effects in all specifications given large level differences across states[12]. The state fixed effects are also important given that most border states are in the West, while most non-border states are in the East. Since East or West is a time invariant characteristic of each state, the state fixed effects should control for this[13]. Border is an indicator for whether the state is a border state. In this specification I restrict border to be time invariant; that is, a state that ever bordered a loose state is always considered a border state. I impose this restriction in light

[12]One potential explanation for these level differences is large disparities in funding for treatment facilities across states.

[13]Although the inclusion of state fixed effects should remedy any concerns about internal validity, one may still be worried about external validity, i.e., the results not being generalizable to the Eastern US. In an alternate specification I attempt to address this concern by focusing on the one state in the East which has a loose MML: Michigan. Essentially I repeat the same analysis as described in this section, but I throw out all Western states and compare the states which border Michigan to other non-border Eastern states. I discuss this exercise in more detail in the document 'Specific Responses to Referee Report'.

of Smart's finding that the marijuana market only grew in response to the change in federal policy as opposed changes in state policy. However, in another specification I will test this restriction explicitly. The coefficient of interest, δ, measures the change in y_{st} in the border states before and after the Ogden Memo relative to the change in y_{st} over the same time in the non-border states[14]. I include a vector of covariates X_{st} to control for time-varying state characteristics that may affect the outcome variables. The controls I include are the log of the population and the unemployment rate. The log of the population controls for possible differences due to population density, while the unemployment rate proxies for aggregate economic conditions. Standard errors are clustered at the state level in order to control for possible correlation of the residuals within states (Colin A. Cameron and Douglas L. Miller (2015)).

Since the purpose of this paper is to identify spillover effects rather than the effects of MMLs on implementing states, I drop the loose states from my regressions[15]. Also, since Alaska and Hawaii do not border any states they are excluded as well.

The second specification I use also exploits variation due to the adoption of MMLs by individual states as opposed to just variation arising from the Ogden Memo. The only difference here is that I add in a time varying border coefficient, which allows for border states to begin experiencing effects immediately after a neighboring state implements a loose

[14]No states passed loose MMLs after the Ogden Memo, so I do not have to worry about confounding effects from this.

[15]As a robustness check I drop all MML states (loose and strict) and find very similar results.

MML. For example, rather than always treating Kansas as a border state, it only becomes a border state in 2000 when Colorado first adopted its MML. The estimating equation here is

$$y_{st} = \alpha_s + \gamma_t + \phi\ Ogden_t + \eta\ border_{st} + \delta\ border_{st} \times Ogden_t + \Gamma X_{st} + \epsilon_{st} \tag{3.2}$$

Note that in this specification, I can explicitly test the hypothesis that MMLs have no effects until after the passage of the Ogden Memo by testing the null hypothesis that $\eta = 0$.

Finally, I also estimate a 'naive' model in which I do not take into account the effects of the Ogden Memo. Essentially, this entails estimating equation 3.2 while imposing the restriction that $\phi = \delta = 0$. This model estimates the effects of the adoption of each of the loose states' MMLs on neighboring states using only the variation across states in the timing of adoption, similar to most previous papers studying the effects of MMLs. This allows me to compare the results from my estimation strategy to the previous literature.

3.4 Results

First, I present the results from the estimating equation 3.1 with the total admissions per 100,000 to treatment facilities as the dependent variable in Panel A of Table 3.3. The first row gives the coefficient for the Ogden indicator, while the coefficient of interest is presented in the second row. The first column is the most basic specification and does not include year fixed effects or any control variables. Moving from column (1) to column (2) I add the log of the population as well as the unemployment rate as control variables.

Column (3) adds year fixed effects to more flexibly control for time trends[16]. The last row of the table gives the mean of the dependent variable.

Note that the difference-in-differences estimator is large in magnitude and stays relatively similar across model specifications, although it is only statistically significant at the 10 percent level when all of the controls are included. The coefficient implies that overall admissions to treatment facilities fell by about 68 individuals per 100,000 in border states relative to non-border states after the Ogden Memo, a decrease of about 16 percent. This is consistent with individuals in border states shifting from potentially more addictive drugs toward marijuana given its easier access. Another possible explanation is that marijuana users in border states who would have entered treatment facilities in the absence of the Ogden Memo decided not to enter treatment. One potential explanation for this is that the Ogden Memo may have sent a signal that marijuana use was not as serious of a problem as previously thought. However, when I examine marijuana specifically I find that a reduction in admissions for marijuana users cannot explain the entire reduction in admissions. Therefore, it is possible that this drop in admissions is partially explained by a reduction in addictive drug abuse.

Next, I estimate equation 3.2 for total admissions and present the results in Panel B of Table 3.3. In this table the third row is now the coefficient on the time-varying border co-

[16]In results not shown here, I also estimate models which allow for state-specific linear time trends. However, doing so kills any significant results. One possible explanation for this is that the Ogden Memo does not immediately change the outcome variable, but instead changes it over time. This could cause the time trends to absorb all of the relevant variation.

efficient. Interestingly, the coefficient on the interaction term falls in magnitude significantly, although it is qualitatively similar. When I include all of the controls and fixed effects in column (6), I find that the coefficient for border is large in magnitude and marginally significant, which is consistent with admissions falling not only in response to the Ogden Memo but also in response to individual states implementing MMLs.

Lastly, I estimate the naive model and present the results in Panel C. Note that the border coefficient is quantitatively very similar to the border coefficient in Panel B, although slightly larger in magnitude[17]. This larger coefficient is consistent with the naive regression picking up some of the effects of the Ogden Memo. However, note that the border coefficient does not pick up all of the effects from the Ogden Memo, which may partially explain weaker results in previous papers that only used this border variation.

Next, I present evidence that MMLs are associated with at least one economically and statistically significant positive externality on bordering states: a reduction in prescription drug abuse. Table 3.4 follows the same format as Table 3.3 except the dependent variable is now the number of opioid-related treatment admissions per 100,000. Notice that the coefficient of interest is large in magnitude and statistically significant at the 1 percent level. Once I have added in all of the controls and fixed effects, the coefficient implies MMLs lead to a reduction of opioid-related admissions of 34 per 100,000 (column (3) of Panel A). This

[17]Note that I only include the coefficient from the regression which includes all of the controls and fixed effects. I did this to save space since the pattern of the border coefficient is almost identical to that in Panel B for all of the outcome variables.

suggests that people in chronic pain may substitute away from prescription painkillers as marijuana becomes more accessible, which is consistent with evidence from Powell, Pacula and Jacobson (2015). Interestingly, this reduction in painkiller abuse is taking place across state lines, which is consistent with either growth in the size of the illegal market making marijuana easier to access in neighboring states, or those in chronic pain actually traveling across state lines in order to access medical marijuana. Either way, this may suggest that some opioid users prefer marijuana to opioids, or at least recognize the potential addictive properties of opioids and have chosen to substitute toward marijuana. In Panel B I allow for the border coefficient to vary with time, and find that state-level legal changes prior to the Ogden Memo do lead to a reduction in prescription opioid abuse (column (6)), although the interaction term is still large in magnitude and highly significant. This indicates that while substitution away from opioids began immediately following the implementation of individual states' MMLs, it was accelerated following the Ogden Memo. The border coefficient in column (7) is similar to that in column (6), although a bit larger in magnitude which may be due to it picking up some of the effects of the Ogden Memo.

Given the strong reduction in opioid-related admissions, it seemed reasonable to expect a drop in opioid overdoses in border states. To test for this I used the NVSS data and reran the regressions from equations 3.1 and 3.2 with opioid-related deaths per 100,000 as the dependent variable. Surprisingly, I see no reduction in opioid-related deaths[18]. The coefficient of interest is close to zero and statistically insignificant. It seems that while some

[18]In places where I found zero effects, I reference those results but do not include the tables in order to save space.

opioid users may substitute away from opioids toward marijuana, these were not the same users who would have gone on to overdose on opioids. One possible explanation for this is that the substitution from opioids to marijuana occurred primarily among those who were using opioids for medical reasons as opposed to recreationally and were thus less likely to overdose. Unfortunately, I do not have sufficiently rich data to test this hypothesis[19].

Next, I present the results for alcohol abuse. Since a very large fraction of individuals in the TEDS data lists alcohol as one of their three substances of abuse, my measure only consists of those whose primary substance of abuse is alcohol. The results are given in Table 3.5. The results here are less conclusive. When I make the restriction that there are no effects until after the Ogden Memo, the coefficient on the interaction term is consistently negative, although never significant at conventional levels. These coefficients may imply some substitution away from alcohol towards marijuana. However, when I drop this restriction, I find negative and large coefficients on the border variable, but positive coefficients on the interaction term, although the interaction term is small in magnitude and statistically insignificant. This could indicate a reduction in alcohol abuse in response to neighboring states' MMLs but no response to the Ogden Memo. The border coefficient for the naive model is slightly smaller in magnitude than the border coefficient from equation 3.2. Since the interaction term is positive, this is again consistent with the border coefficient in the naive model picking up some but not all of the effects of the Ogden Memo. The difficulty in identifying effects on alcohol use is consistent with the previous literature which tells a com-

[19]To test for this I would need individual data on current and past drug use. The NSDUH contains all of the needed data, although I do not yet have access to it. The NLSY could be used in principle, except to my knowledge they do not ask participants about opioid use.

plex and at times inconsistent story about the relationship between alcohol and marijuana use.

Although I do not find strong effects for alcohol admissions, I do find an increase in alcohol overdoses. The results in Panel A of Table 3.6 show a statistically significant increases in overdoses in border states after the Ogden Memo. In Panel B the interaction term is very similar in magnitude although only statistically significant at the 10 percent level. The border coefficient is small and statistically insignificant, indicating that there were no effects on alcohol poisonings until after the Ogden Memo. It is surprising that the effects for alcohol poisonings look so much different than the results for alcohol treatment admissions, and this disparity is difficult to reconcile.

My ex ante prediction for marijuana admissions was that there would be an increase in admissions in border states relative to non-border states. However, as shown in Table 3.7, I actually find the opposite. While the point estimates are relatively small in magnitude compared to my other estimates, they are consistently negative, indicating fewer admissions to treatment related to marijuana in border states versus non-border states. There are several potential explanations for this initially surprising result. First, it is important to keep in mind that I do not have data on marijuana usage; I only have data for admissions to treatment. Even if marijuana usage increased in border states as a result of MMLs, this does not necessarily mean that marijuana admissions would increase. For example, it may be that the Ogden Memo sent a signal to marijuana users that the federal government's leniency toward marijuana use was increasing. Given state laws for marijuana use and possession are

typically not very severe, this may have convinced marijuana users not to enter treatment. A related explanation is that many entrants to treatment for marijuana are adolescents who enter treatment at the behest of their parents. If parents interpreted the Ogden Memo as a signal that marijuana use is not as serious of an offense as previously thought, they may decide not to send their child to treatment[20]. Note that for both of these explanations, these signals would have to be stronger in border states than non-border states, which seems plausible given the closer geographic proximity to MML states.

Finally, I investigate the effects of MMLs on hard drug use. I find a somewhat surprising result for cocaine admissions, which I present in Table 3.8. Here I find a positive and statistically significant result, indicating that increased availability of marijuana actually led to an increase in cocaine admissions. Interestingly, when I include the time-varying border variable the coefficient is close to zero and statistically insignificant, implying that the changes only took place after the Ogden Memo. There are several possible explanations of this result. One is the gateway hypothesis, which says that marijuana leads users to experiment with harder drugs either through increasing exposure to criminal networks or by causing them to seek more powerful highs. I am hesitant to adopt the second interpretation for two reasons. First, I am not aware of any other papers which find evidence supporting this mechanism, while several find no effect of increased access to marijuana on hard drug use. Second, it is difficult to explain why I see a positive effect for cocaine but not for any other drugs.

[20] Again, I am unable to test the legitimacy of either of these explanations. The NSDUH includes questions about participants' attitudes toward various drugs, which would be useful to investigate these explanations.

However, note that the gateway hypothesis allowed for two mechanisms by which we may expect an increase in hard drug use. I posit a possible explanation that relies on the first mechanism: an increased exposure to criminal networks. One explanation for why I see an increase in cocaine while other papers do not could relate to the fact that I am looking at border states, not states that actually adopt MMLs. If a state makes it easier to access marijuana legally, then an individual who obtains legal marijuana has not increased his exposure to criminal networks. However, an individual living in a border state who obtains marijuana illegally may very well increase his exposure to criminal networks. It is plausible that papers which estimate the effects of marijuana on hard drugs by looking at states with MMLs do not see anything because they do not observe this increased exposure to criminal networks. However, in my setting exposure to illegal drug markets is much more likely.

Results for heroin admissions are included in Table 3.9. Qualitatively, the results look similar to that of opioids and marijuana, although the coefficients of interest are generally statistically insignificant. In the restricted model the interaction term is consistently negative, although it is relatively small in magnitude and statistically insignificant. However, in the unrestricted model the sign on the interaction term flips once I include all of the controls and year fixed effects. In both the unrestricted and naive models the border coefficient is negative and significant at the five percent level. This pattern of results is consistent with substitution away from heroin in response to neighboring states adopting MMLs but no effects from the Ogden Memo. However, the fact that the interaction term switches signs when I include year fixed effects is somewhat troubling so these results should be viewed

with some caution.

3.4.1 Discussion

In this section I briefly highlight three issues which warrant some extra attention. First, I discuss the plausibility of the identifying assumptions. The fact that the pre-trends in Figure 3.3 seem to evolve in parallel prior to the passage of the first MML in 1996 is encouraging. Before the first MML, there did not seem to be any large differences in the trends for border and non-border states. This lends plausibility to the idea that MMLs were an important factor in determining differences in drug use in border states relative to non-border states. Unfortunately, since all of the loose states adopted MMLs in different years there is no way easy way to visually evaluate whether border states and non-border states would have continued to evolve in parallel had no states adopted MMLs. While it is unclear whether the parallel trends assumption is reasonable when looking at the effects of MMLs upon adoption, it appears very unlikely when considering the effects of the Ogden Memo. With the exception of alcohol admissions, all of the series appear to be trending apart well before the Ogden Memo, which makes inference about the effects of the Ogden Memo difficult. However, given that the Ogden Memo was not issued until over a decade after many states had adopted MMLs, it is not necessarily surprising that border states and non-border states were trending differently[21]. In light of these issues regarding the identifying assumptions, one should use caution in interpreting the results in section 3.4.

[21] In fact, if MMLs had effects before the Ogden Memo one would expect the trends to differ.

Second, in many of my regressions I reject the null hypothesis that MMLs have no effects until after the Ogden Memo, which differs somewhat from Smart (2016). However, this does not necessarily contradict her findings. Smart shows that registration rates only respond in loose states after the Ogden Memo while there are no effects in states with stricter MMLs. However, the fact that registration rates only respond to the change in federal law does not necessarily indicate that there were no changes in the illegal market directly in response to the states' MMLs. Many users may have been hesitant to register prior to the Ogden Memo for fear of prosecution by the federal government, as registering as a medical marijuana user would essentially be an affidavit to breaking federal law. Additionally, even when I allow for the border variable to vary with time, I still see additional effects after the Ogden Memo, which suggests that the Ogden Memo was an important factor in causing these cross-state spillovers.

Finally, it is worth highlighting the concerning fact that not all of the results point in the same direction. For example, there appears to be a reduction in opioid abuse in response to MMLs and the Ogden Memo, but an increase in cocaine abuse following the Ogden Memo and no response to individual states MMLs. This pattern of results is difficult to reconcile. Throughout section 3.4, I speculate as to what causes the results that I observe for each drug. However, given the lack of corroborating evidence these explanations should be viewed with caution. Once I obtain access to the NSDUH and NLSY data I will be able to explore these suggested mechanisms more rigorously.

3.5 Conclusion

In reaction to growing evidence of the efficacy of marijuana in treating several medical ailments, many states have adopted MMLs in spite of federal prohibition. Alleged externalities across state borders have led several states to sue adopting states for damages from increases in drug-related activity. Knowing the extent to which these externalities exist is important both in light of these recent court cases as well as for determining federal enforcement practices. In late 2009 the federal government decided that it would not prosecute marijuana users and sellers who were in compliance with state laws, which led to rapid growth in both the legal and illegal marijuana markets. If the lack of federal enforcement contributes to negative externalities on non-MML states, this may suggest a change in federal enforcement policy. However, if these MMLs lead to positive externalities as well, this may suggest broader liberalization of marijuana laws.

This paper provides the first estimates of externalities on other states from MMLs. Using data from TEDS, I find a reduction in overall drug abuse in states which border MML states relative to non-border states, which suggests drug users substituting toward marijuana from other drugs which are more likely to cause addiction. I find a strong decrease in opioid abuse, consistent with other literature suggesting marijuana can serve as an effective painkiller. I also find some evidence of a decrease in heroin abuse. I find mixed evidence for alcohol abuse. Surprisingly, I find an increase in admissions related to cocaine abuse, which may indicate a growing illegal drug market in border states.

Since I do not have the data to estimate the entire range of effects from MMLs, I

cannot conduct a full welfare analysis. However, my results suggest that MMLs cause both positive and negative externalities on bordering states. More research needs to be done on the relative magnitudes of these externalities before any policy recommendations can be made. In addition, the different patterns I observe for different drugs is difficult to reconcile. I posit several potential explanations, but do not have sufficient data to further investigate these explanations. Further research needs to be conducted in order to explain these different patterns.

Table 3.1: Summary of MMLs from 1996-2012

State	Year of First MML	Loose
Alaska	1998	
Arizona	1996	
California	1996	✓
Colorado	2000	✓
Delaware	2011	
District of Columbia	2010	
Hawaii	2000	
Maine	1999	
Maryland	2011	
Michigan	2008	✓
Montana	2004	✓
Nevada	2001	
New Jersey	2009	
New Mexico	2007	
Oregon	1998	✓
Rhode Island	2007	
Vermont	2004	
Washington	1998	✓

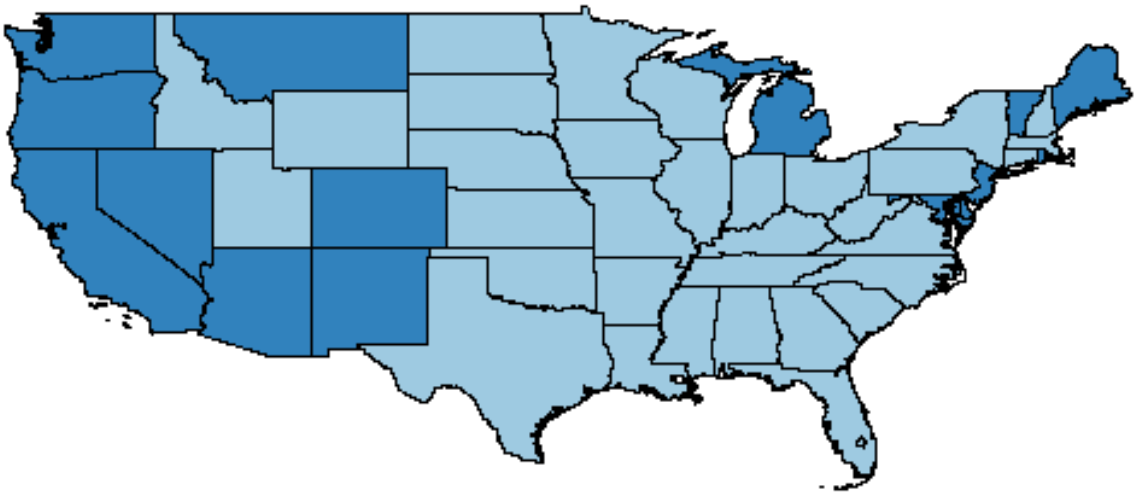
Note: Data on MMLs come from appendix tables from Smart (2016) and Pacula et al. (2014). The second column indicates the first year in which any MML was adopted by the state. A checkmark in the third column indicates that the MML is a 'loose' MML, which means that suppliers were able to provide marijuana to an unlimited number of patients.

Table 3.2: Summary Statistics

	A. Pre-1996		B. Entire sample	
	Non-border	Border	Non-border	Border
Admissions	458.01	417.80	491.98	318.62
Alcohol	252.84	272.52	209.15	142.10
Marijuana	30.31	31.65	53.77	43.35
Cocaine	86.58	42.21	59.28	25.67
Opioids	5.71	4.22	43.85	15.25
Heroin	56.86	30.01	92.59	27.39
Log Population	15.18	14.77	15.32	15.04
Unemployment	6.21	5.40	5.80	5.68
Alcohol Overdoses			3.70	4.90
Opioid Overdoses			4.23	5.46

Note: This table shows summary statistics for all outcome and control variables included in my regressions. The state-year averages for all variables are broken down by border versus non-border states, as well as by time period. Panel A shows the period prior to any MMLs being passed, while panel B shows the entire sample period (1992-2012). In this table border states are those that border a state which ever implemented a 'loose' MML. Data for Alcohol and Opioid poisonings come from the NVSS, data on state population come from the US Census Bureau, and data on state unemployment rates come from the BLS. The admissions and drug related outcomes are measured as the number per 100,000 population.

Figure 3.1: States with MMLs as of 2012



Note: This figure presents a static picture of the legal environment surrounding medical marijuana in 2012. Light blue represents states with no MML. Dark blue states are those with some type of MML. This figure does not distinguish between the specific type of MML. See Table 3.1 for the names of the dark blue states and the year of their first MML.

Table 3.3: TEDS Admissions per 100,000 (Excluding CJ Referrals)

	A. Restricted Model			B. Unrestricted Model			C. Naive Model
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
	Admissions	Admissions	Admissions	Admissions	Admissions	Admissions	Admissions
Ogden	17.98	48.27^{+}		17.98	42.18		
	(18.57)	(25.60)		(18.58)	(25.12)		
Ogden*Border	-68.96*	-70.64*	-67.77^{+}	-40.60	-44.32	-22.77	
	(28.79)	(28.56)	(35.19)	(28.43)	(28.14)	(27.51)	
Border				-56.18	-56.98	-89.33^{+}	-95.23^{+}
				(50.55)	(52.65)	(50.30)	(49.99)
Observations	864	864	864	864	864	864	864
R^2	0.857	0.859	0.867	0.859	0.861	0.872	0.872
Year FE	No	No	Yes	No	No	Yes	Yes
State FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Controls	No	Yes	Yes	No	Yes	Yes	Yes
Mean	425.10	425.10	425.10	425.10	425.10	425.10	425.10

$^{+}$ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$

Note: This table shows the main regression results with the number of treatment admissions per 100,000 (excluding CJ referrals) as the dependent variable. Panel A displays the results from equation 3.1, Panel B displays the results from equation 3.2, and Panel C displays the results from the 'naive' approach, where I do not take into account separate effects from the Ogden Memo (this can be thought of as equation 3.2 with the restriction that $\phi = \delta = 0$). Columns (1) and (4) are the most basic specifications and do not include year fixed effects or any control variables. Columns (2) and (5) add the log of the population and the unemployment rate as control variables, and Columns (3), (6), and (7) include the control variables as well as year fixed effects. State fixed effects are included throughout. Standard errors clustered at the state level are shown in parentheses.

Table 3.4: TEDS Opioid Admissions per 100,000 (Excluding CJ Referrals)

	A. Restricted Model			B. Unrestricted Model			C. Naive Model
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
	Opioids	Opioids	Opioids	Opioids	Opioids	Opioids	Opioids
Ogden	53.71**	44.11**		53.71**	44.07**		
	(10.35)	(11.20)		(10.35)	(11.14)		
Ogden*Border	-38.13**	-40.90**	-33.87**	-42.25**	-40.75**	-24.68**	
	(10.56)	(11.62)	(9.61)	(10.46)	(11.00)	(7.50)	
Border				8.15**	-0.34	-18.24**	-24.64**
				(1.55)	(3.24)	(5.94)	(7.39)
Observations	864	864	864	864	864	864	864
R^2	0.515	0.535	0.658	0.517	0.535	0.667	0.659
Year FE	No	No	Yes	No	No	Yes	Yes
State FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Controls	No	Yes	Yes	No	Yes	Yes	Yes
Mean	24.56	24.56	24.56	24.56	24.56	24.56	24.56

$^{+}$ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$

Note: This table shows the main regression results with the number of opioid related treatment admissions per 100,000 (excluding CJ referrals) as the dependent variable. Panel A displays the results from equation 3.1, Panel B displays the results from equation 3.2, and Panel C displays the results from the 'naive' approach, where I do not take into account separate effects from the Ogden Memo (this can be thought of as equation 3.2 with the restriction that $\phi = \delta = 0$). Columns (1) and (4) are the most basic specifications and do not include year fixed effects or any control variables. Columns (2) and (5) add the log of the population and the unemployment rate as control variables, and Columns (3), (6), and (7) include the control variables as well as year fixed effects. State fixed effects are included throughout. Standard errors clustered at the state level are shown in parentheses.

Table 3.5: TEDS Alcohol Admissions per 100,000 (Excluding CJ Referrals)

	A. Restricted Model			B. Unrestricted Model			C. Naive Model
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
	Alcohol	Alcohol	Alcohol	Alcohol	Alcohol	Alcohol	Alcohol
Ogden	-29.35**	-13.24		-29.35**	-20.96^{+}		
	(9.65)	(12.63)		(9.66)	(10.54)		
Ogden*Border	-17.87	-8.60	-23.97	26.11	24.78	5.88	
	(20.84)	(20.65)	(26.43)	(17.03)	(16.79)	(17.47)	
Border				-87.12^{+}	-72.27	-59.26	-57.74
				(46.46)	(48.76)	(44.02)	(43.94)
Observations	864	864	864	864	864	864	864
R^2	0.789	0.801	0.820	0.808	0.813	0.827	0.827
Year FE	No	No	Yes	No	No	Yes	Yes
State FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Controls	No	Yes	Yes	No	Yes	Yes	Yes
Mean	194.85	194.85	194.85	194.85	194.85	194.85	194.85

$^{+}$ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$

Note: This table shows the main regression results with the number of alcohol related treatment admissions per 100,000 (excluding CJ referrals) as the dependent variable. Panel A displays the results from equation 3.1, Panel B displays the results from equation 3.2, and Panel C displays the results from the 'naive' approach, where I do not take into account separate effects from the Ogden Memo (this can be thought of as equation 3.2 with the restriction that $\phi = \delta = 0$). Columns (1) and (4) are the most basic specifications and do not include year fixed effects or any control variables. Columns (2) and (5) add the log of the population and the unemployment rate as control variables, and Columns (3), (6), and (7) include the control variables as well as year fixed effects. State fixed effects are included throughout. Standard errors clustered at the state level are shown in parentheses.

Table 3.6: Alcohol Deaths per 100,000

	A. Restricted Model			B. Unrestricted Model			C. Naive Model
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
	Deaths	Deaths	Deaths	Deaths	Deaths	Deaths	Deaths
Ogden	-0.53*	0.03		-0.53*	0.03		
	(0.20)	(0.19)		(0.20)	(0.20)		
Ogden*Border	0.27	0.55*	0.45*	0.28	0.52^{+}	0.41^{+}	
	(0.24)	(0.26)	(0.22)	(0.27)	(0.29)	(0.24)	
Border				-0.01	0.10	0.15	0.29
				(0.27)	(0.33)	(0.22)	(0.20)
Observations	585	585	585	585	585	585	585
R^2	0.760	0.797	0.855	0.760	0.797	0.855	0.854
Year FE	No	No	Yes	No	No	Yes	Yes
State FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Controls	No	Yes	Yes	No	Yes	Yes	Yes
Mean	4.06	4.06	4.06	4.06	4.06	4.06	4.06

$^{+}$ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$

Note: This table shows the main regression results with the number of alcohol related deaths per 100,000 as the dependent variable. Panel A displays the results from equation 3.1, Panel B displays the results from equation 3.2, and Panel C displays the results from the 'naive' approach, where I do not take into account separate effects from the Ogden Memo (this can be thought of as equation 3.2 with the restriction that $\phi = \delta = 0$). Columns (1) and (4) are the most basic specifications and do not include year fixed effects or any control variables. Columns (2) and (5) add the log of the population and the unemployment rate as control variables, and Columns (3), (6), and (7) include the control variables as well as year fixed effects. State fixed effects are included throughout. Standard errors clustered at the state level are shown in parentheses.

Table 3.7: TEDS Marijuana Admissions per 100,000 (Excluding CJ Referrals)

	A. Restricted Model			B. Unrestricted Model			C. Naive Model
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
	Marijuana	Marijuana	Marijuana	Marijuana	Marijuana	Marijuana	Marijuana
Ogden	15.09**	12.72*		15.09**	12.45*		
	(4.43)	(5.07)		(4.43)	(5.11)		
Ogden*Border	-14.30*	-16.97**	-12.12*	-16.25*	-15.83*	-6.13	
	(5.88)	(6.20)	(5.94)	(6.36)	(6.46)	(6.10)	
Border				3.86	-2.48	-11.90*	-13.49*
				(4.62)	(5.33)	(5.26)	(5.00)
Observations	864	864	864	864	864	864	864
R^2	0.654	0.680	0.752	0.655	0.680	0.761	0.760
Year FE	No	No	Yes	No	No	Yes	Yes
State FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Controls	No	Yes	Yes	No	Yes	Yes	Yes
Mean	44.09	44.09	44.09	44.09	44.09	44.09	44.09

$^{+}$ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$

Note: This table shows the main regression results with the number of marijuana related treatment admissions per 100,000 (excluding CJ referrals) as the dependent variable. Panel A displays the results from equation 3.1, Panel B displays the results from equation 3.2, and Panel C displays the results from the 'naive' approach, where I do not take into account separate effects from the Ogden Memo (this can be thought of as equation 3.2 with the restriction that $\phi = \delta = 0$). Columns (1) and (4) are the most basic specifications and do not include year fixed effects or any control variables. Columns (2) and (5) add the log of the population and the unemployment rate as control variables, and Columns (3), (6), and (7) include the control variables as well as year fixed effects. State fixed effects are included throughout. Standard errors clustered at the state level are shown in parentheses.

Table 3.8: TEDS Cocaine Admissions per 100,000 (Excluding CJ Referrals)

	A. Restricted Model			B. Unrestricted Model			C. Naive Model
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
	Cocaine	Cocaine	Cocaine	Cocaine	Cocaine	Cocaine	Cocaine
Ogden	-34.78**	-24.62**		-34.78**	-25.04**		
	(4.31)	(6.32)		(4.31)	(6.31)		
Ogden*Border	16.30*	18.39*	16.47*	21.71**	20.19**	17.03**	
	(6.42)	(7.00)	(6.68)	(5.58)	(5.99)	(5.65)	
Border				-10.70**	-3.89	-1.11	3.31
				(3.26)	(3.79)	(4.85)	(5.40)
Observations	864	864	864	864	864	864	864
R^2	0.744	0.756	0.769	0.747	0.757	0.769	0.766
Year FE	No	No	Yes	No	No	Yes	Yes
State FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Controls	No	Yes	Yes	No	Yes	Yes	Yes
Mean	56.82	56.82	56.82	56.82	56.82	56.82	56.82

$^{+}$ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$

Note: This table shows the main regression results with the number of cocaine related treatment admissions per 100,000 (excluding CJ referrals) as the dependent variable. Panel A displays the results from equation 3.1, Panel B displays the results from equation 3.2, and Panel C displays the results from the 'naive' approach, where I do not take into account separate effects from the Ogden Memo (this can be thought of as equation 3.2 with the restriction that $\phi = \delta = 0$). Columns (1) and (4) are the most basic specifications and do not include year fixed effects or any control variables. Columns (2) and (5) add the log of the population and the unemployment rate as control variables, and Columns (3), (6), and (7) include the control variables as well as year fixed effects. State fixed effects are included throughout. Standard errors clustered at the state level are shown in parentheses.

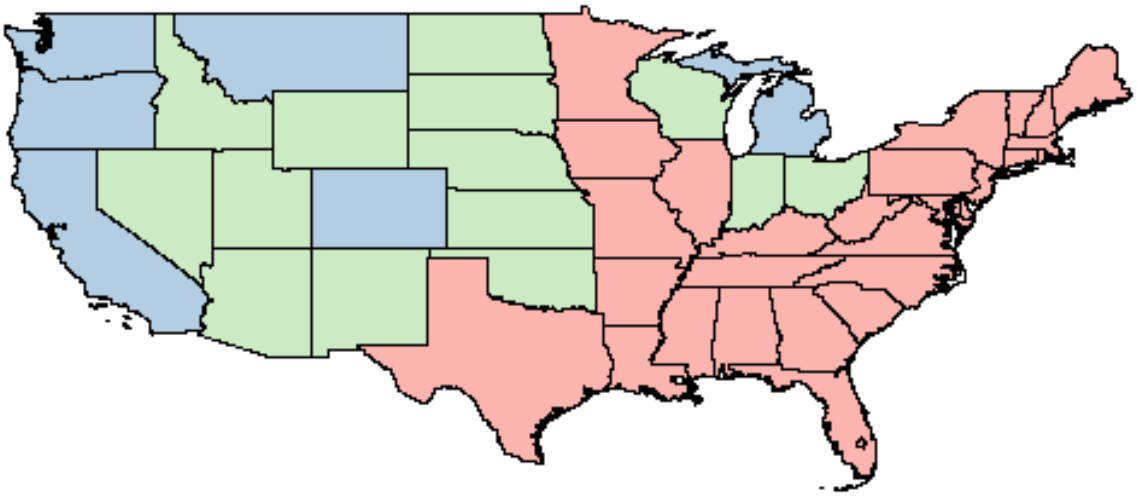
Table 3.9: TEDS Heroin Admissions per 100,000 (Excluding CJ Referrals)

	A. Restricted Model			B. Unrestricted Model			C. Naive Model
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
	Heroin	Heroin	Heroin	Heroin	Heroin	Heroin	Heroin
Ogden	7.63	22.23**		7.63	21.89**		
	(7.44)	(8.22)		(7.45)	(8.11)		
Ogden*Border	-3.00	-8.15	-2.35	-4.51	-6.68	7.70	
	(8.14)	(8.57)	(8.66)	(7.97)	(7.86)	(7.60)	
Border				3.00	-3.18	-19.95*	-17.95*
				(2.87)	(5.75)	(7.60)	(7.97)
Observations	864	864	864	864	864	864	864
R^2	0.897	0.904	0.917	0.897	0.904	0.919	0.919
Year FE	No	No	Yes	No	No	Yes	Yes
State FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Controls	No	Yes	Yes	No	Yes	Yes	Yes
Mean	66.22	66.22	66.22	66.22	66.22	66.22	66.22

$^{+}$ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$

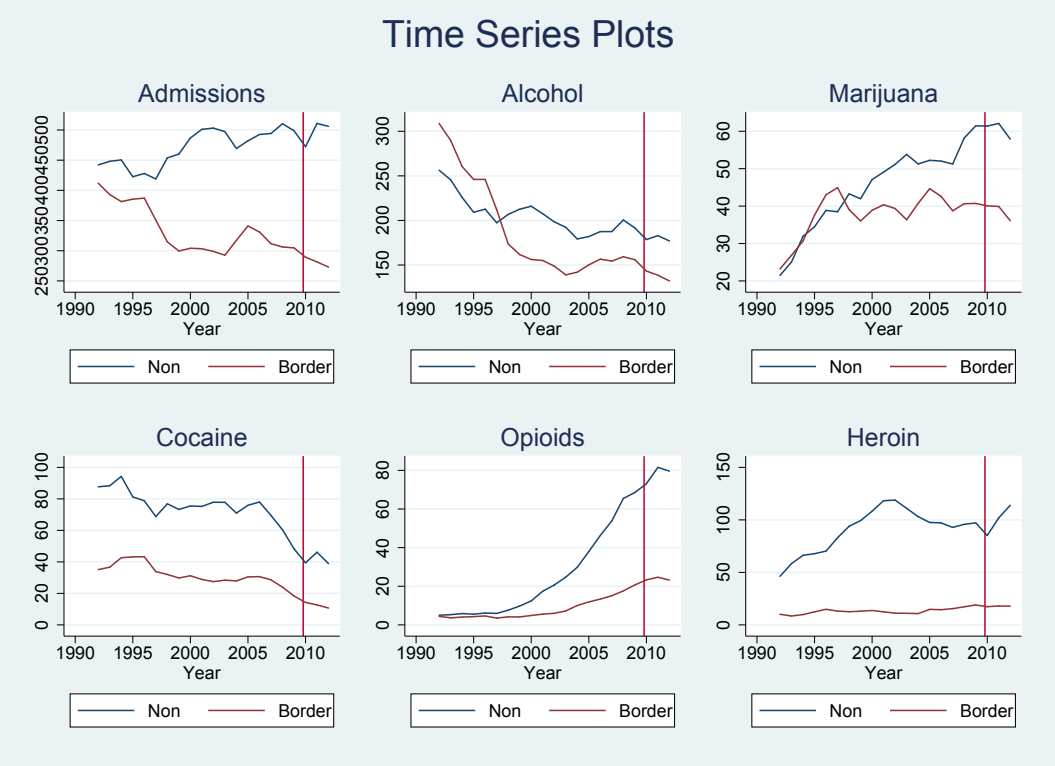
Note: This table shows the main regression results with the number of heroin related treatment admissions per 100,000 (excluding CJ referrals) as the dependent variable. Panel A displays the results from equation 3.1, Panel B displays the results from equation 3.2, and Panel C displays the results from the 'naive' approach, where I do not take into account separate effects from the Ogden Memo (this can be thought of as equation 3.2 with the restriction that $\phi = \delta = 0$). Columns (1) and (4) are the most basic specifications and do not include year fixed effects or any control variables. Columns (2) and (5) add the log of the population and the unemployment rate as control variables, and Columns (3), (6), and (7) include the control variables as well as year fixed effects. State fixed effects are included throughout. Standard errors clustered at the state level are shown in parentheses.

Figure 3.2: Loose, Border, and Non-Border States



Note: This figure summarizes the relevant cross-state variation in MMLs as of 2012. Light blue represents states with loose supply regulations as defined by Smart (2016), green states are border states, and red states are non-border states. See column (3) of Table 3.1 for the names of the light blue states.

Figure 3.3: Evolution of Drug Related Admissions over Time



Note: Time series for all TEDS outcome variables, measured as the number of primary admissions per 100,000. The red lines indicate the average across border states and the blue lines indicate the average across non-border states. In this figure border states are those that border a state which ever implemented a 'loose' MML. The vertical red line represents the date that the Ogden Memo was released.

Appendices

Appendix A

Appendix to Chapter 1

Table A.1: Coefficients for Regressions of ARCOS Opioid Measures on Medicare Part D Measures

	(1) Hydrocodone	(2) Codeine	(3) Morphine	(4) Fentanyl	(5) Methadone	(6) Oxycodone	(7) Hydromorphone
	40.87***	190.4***	135.7***	2.812***	170.8***	109.8***	62.22***
	(34.98)	(18.89)	(30.58)	(20.06)	(10.62)	(34.01)	(32.32)
Observations	883	883	883	882	882	883	882
R^2	0.581	0.288	0.515	0.314	0.114	0.568	0.543
Corr. Coef.	0.76	0.54	0.72	0.56	0.34	0.75	0.74

Note: This table presents the coefficients from regressions of the per capita distribution of each drug from ARCOS on the corresponding measure from Medicare Part D. Data are from 2013, as this is the only pre-period year available in Part D.

Table A.2: Demographic Summary Statistics by Quartile of Hydro_z^{pre}

	1st	2nd	3rd	4th
Log(Population)	12.42	12.26	12.33	12.24
% Male	49.23	49.7	49.68	49.38
% White	78.45	84.53	83.12	82.37
% Black	11.26	7.25	10.29	11.88
% Hispanic	14.49	11.89	13.72	8.46
% Over 65	15.19	15.85	15.69	16.08
% Under 20	24.81	25.51	25.96	25.44

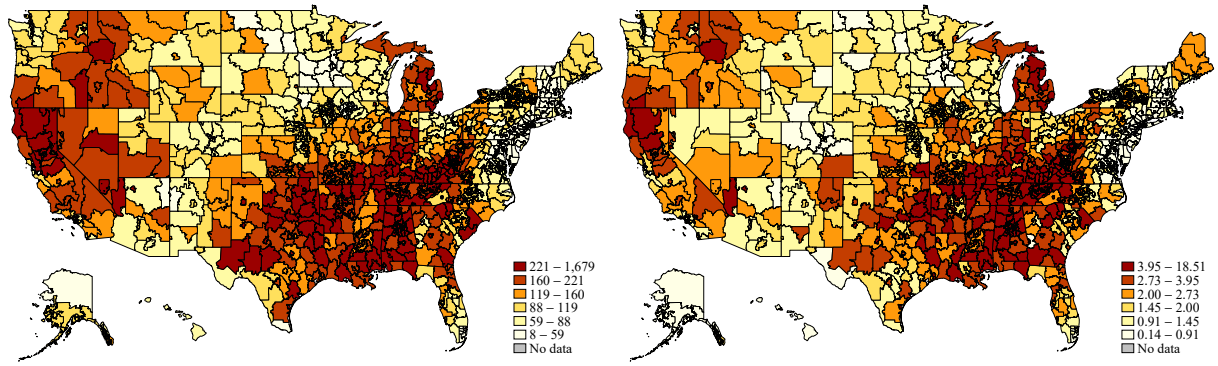
Note: This table shows demographic summary statistics broken down by quartile of the treatment variable. Variables are measured annually and are taken from the Census Bureau.

Table A.3: Placebo Regressions: Impact of One Standard Deviation Increase in Pre-Period Hydrocodone Exposure

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
	Log(Population)	% Male	% White	% Black	% Hispanic	% Over 65	% Under 20
Hydro x Post	-0.00168	-0.00129	-0.00641	0.00301	-0.00516	0.00420	0.00466
	(-0.96)	(-0.44)	(-1.47)	(1.09)	(-1.86)	(1.10)	(1.02)
Observations	6174	6174	6174	6174	6174	6174	6174
Mean	12.29	49.50	82.05	10.24	12.25	15.69	25.43

Note: This table shows θ coefficients from a series of placebo regressions of the form $Y_{zt} = \lambda_z + \psi_t + \sum_Z \phi_Z \cdot 1(z = Z) \cdot t + \theta \cdot 1(t > Oct.'14) \times \text{Hydro}_z^{pre} + \eta X_{zt} + \nu_{zt}$. Dependent variables are measured annually at the zip3 level and are taken from the Census Bureau.

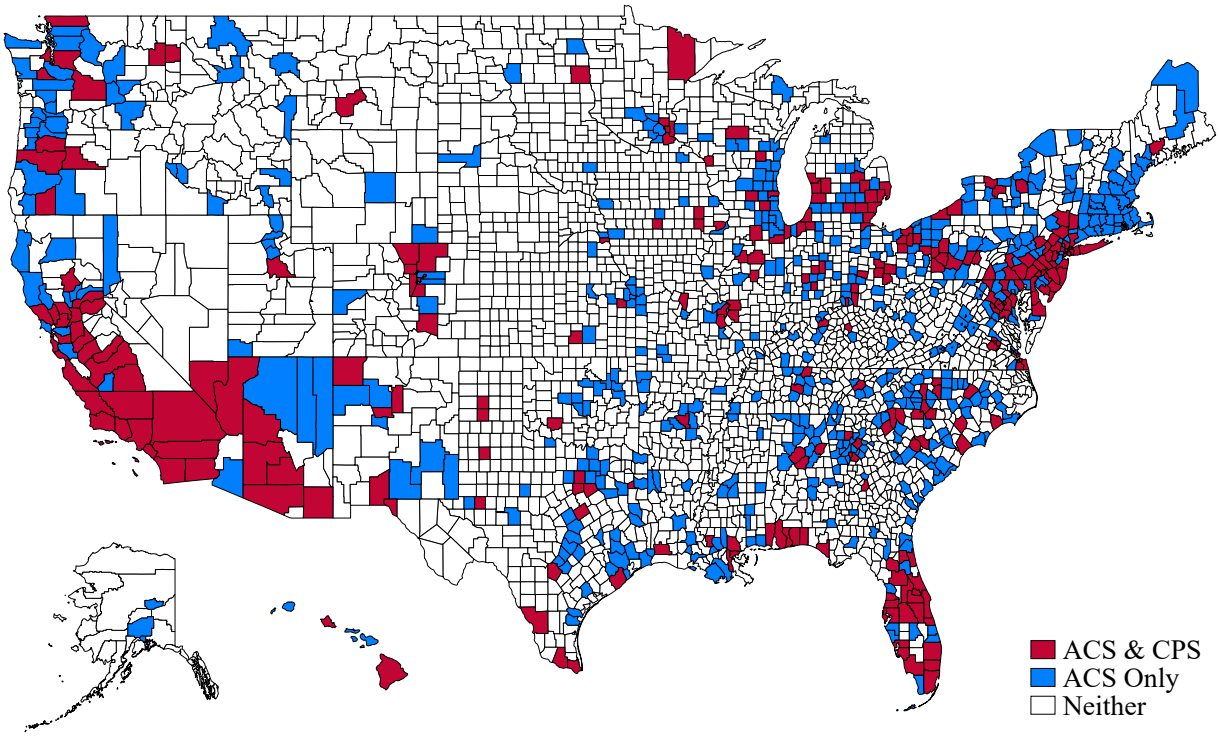
Figure A.1: Geographic Variation in Hydrocodone Distribution, Consumption for 2013



(a) Milligrams Per Person, ARCOS (b) Days Supplied Per Person, Medicare Part D

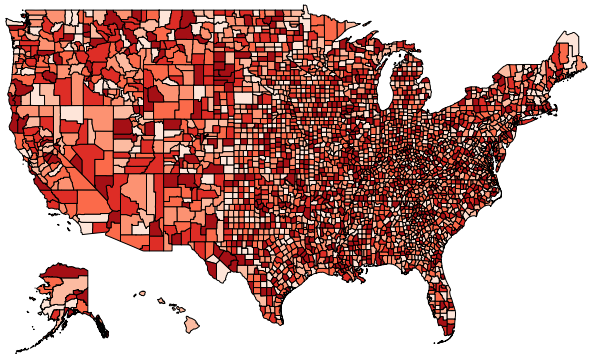
Note: These maps show different measures of the consumption of hydrocodone in ARCOS and Medicare Part D. Panel (A) shows the per capita distribution of hydrocodone in milligrams at the zip3 level in 2013 as reported in ARCOS. Panel (B) shows the per capita number of hydrocodone days supplied in Medicare Part D over the same time frame.

Figure A.2: Counties Identified in the CPS and ACS

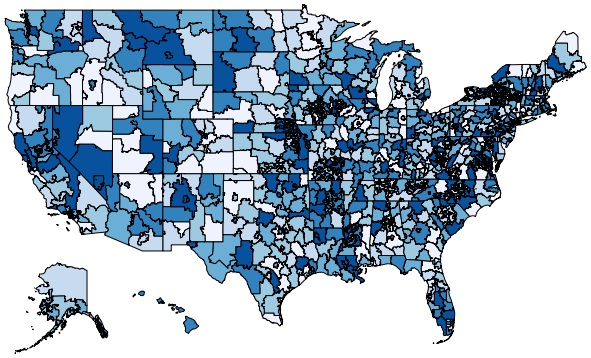


Note: This map illustrates which counties are identified in the ACS and CPS. The counties shaded red are those which are available in the CPS and ACS, while the counties shaded blue are available in the ACS but not CPS. Counties in white are identified in the LAUS, but neither the ACS nor CPS.

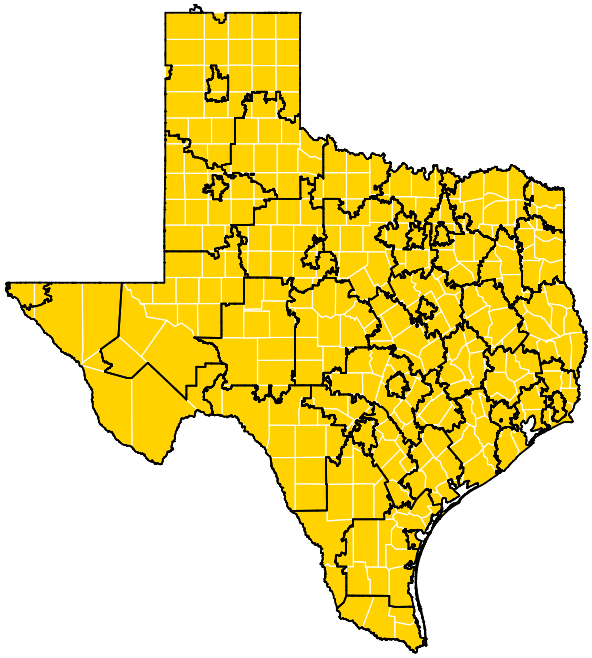
Figure A.3: Zip3 and County Maps



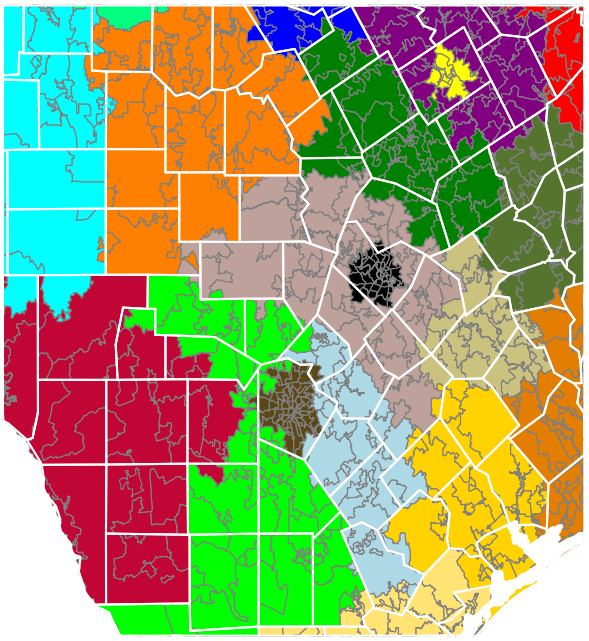
(a) US Counties



(b) US Zip3s



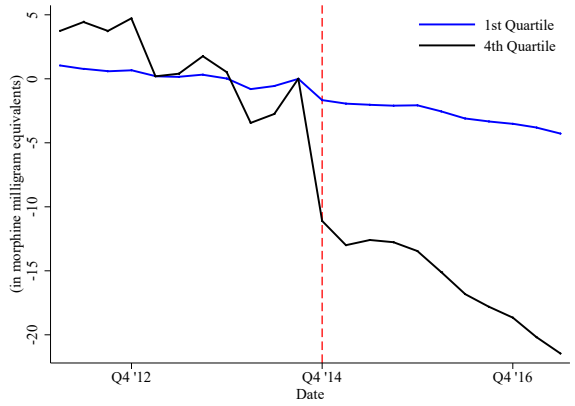
(c) Texas Zip3s and Counties



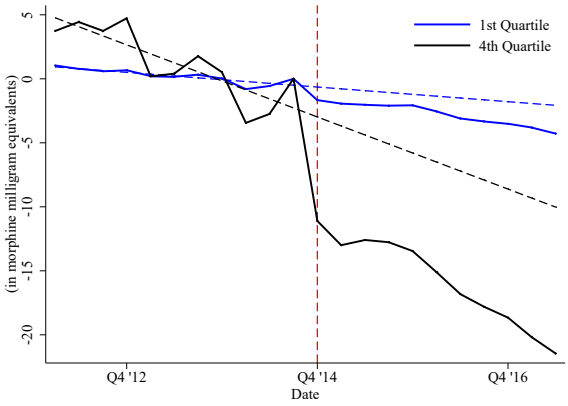
(d) Central Texas Zip5s, Zip3s, and Counties

Note: These maps illustrate the differences between counties, 5-digit zip codes, and 3-digit zip codes. Panel (A) shows counties in varying shades of red, while panel (B) shows zip3s in varying shades of blue. Panel (C) overlays zip3 and county boundaries for the state of Texas, with county boundaries shown in white and zip3 boundaries in black. Panel (D) shows the relationship between 5-digit zip codes (shown in gray), zip3s (different colors), and counties (outlined in white) for the central Texas region.

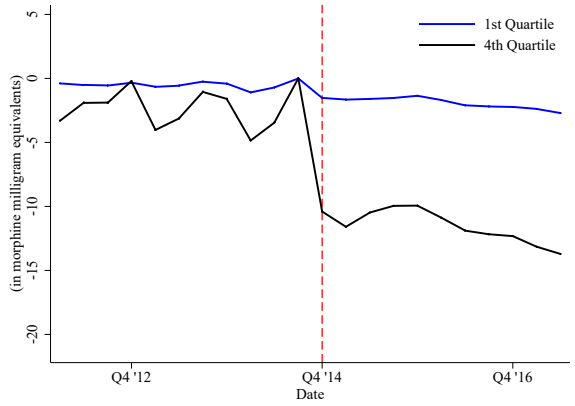
Figure A.4: Hydrocodone Distribution: Dynamics by 1st and 4th Quartiles of Hydro_z^{pre}



(a) Raw Hydro



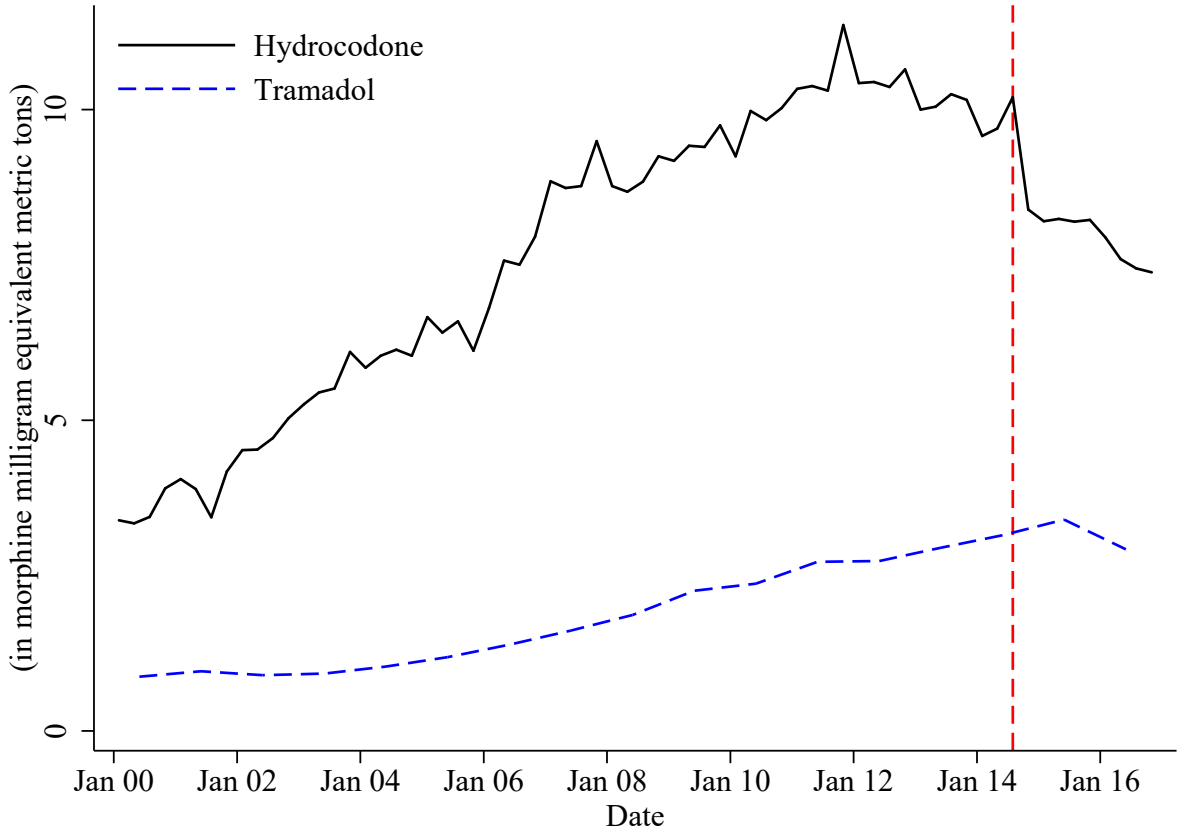
(b) Raw Hydro (with fitted trends)



(c) Hydro Detrended

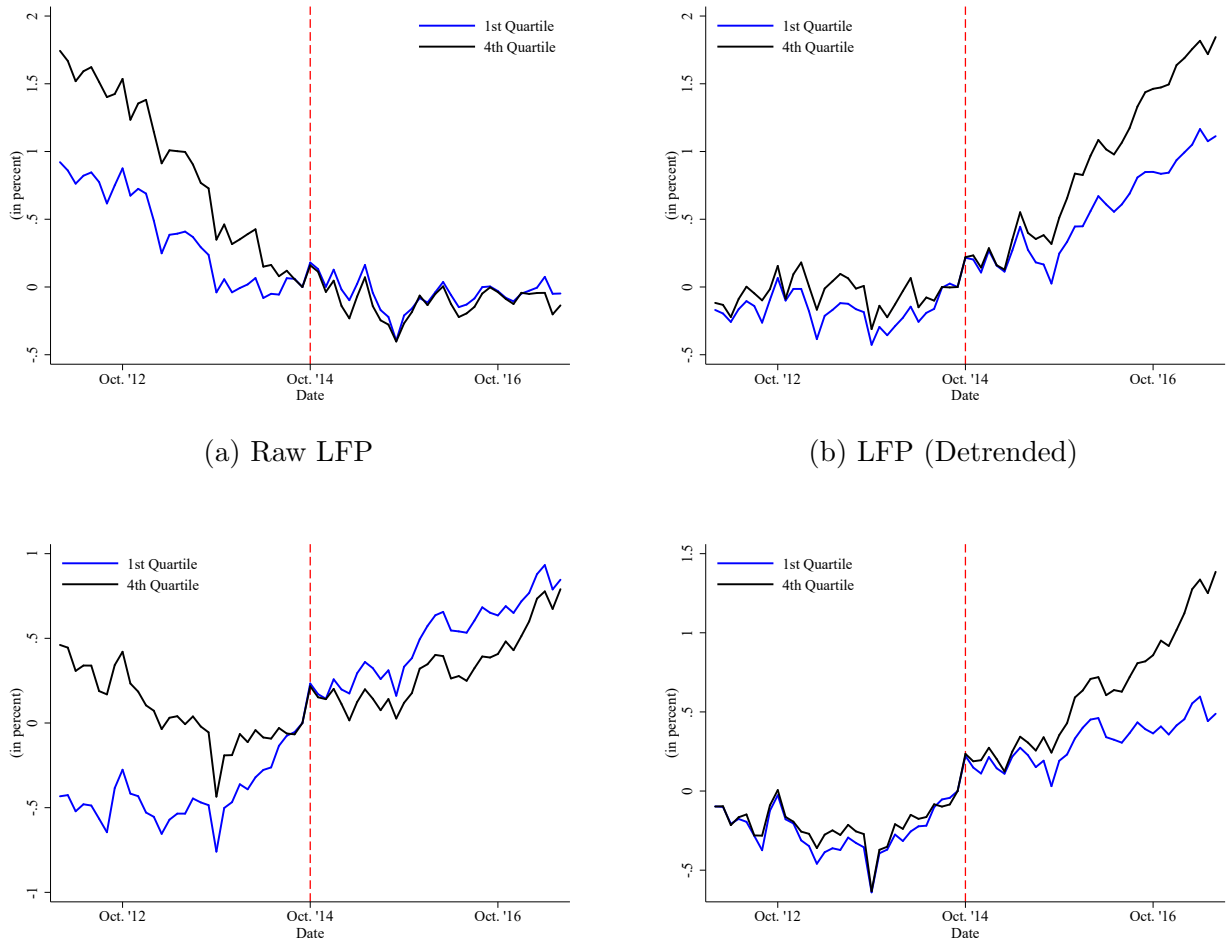
Note: These figures show time series for the distribution of hydrocodone per capita broken down by quartile of Hydro_z^{pre}. The first quartile is shown in blue in each panel while the fourth quartile is shown in black. Panel (A) shows the raw data normalized to zero in the third quarter of 2014. Panel (B) superimposes linear time trends fit based on the pre-period, while Panel (C) shows the data after subtracting out linear trends fitted based on the pre-period, analogous to regression equation 2.

Figure A.5: Tramadol and Hydrocodone Distribution Over Time



Note: This figure shows the quarterly distribution of hydrocodone (black solid line) and Tramadol (blue dashed line) from 2000 to 2016. Data on the distribution of hydrocodone is taken from ARCOS while the Tramadol data are taken from Figure (3) of US Food and Drug Administration (2018) which uses data from IQVIA. The Tramadol line is the annual distribution divided by four (quarterly data were not published).

Figure A.6: Labor Force Participation Rate and Employment-to-Population Ratio: Dynamics by 1st and 4th Quartiles of Hydro_z^{pre}



(a) Raw LFP

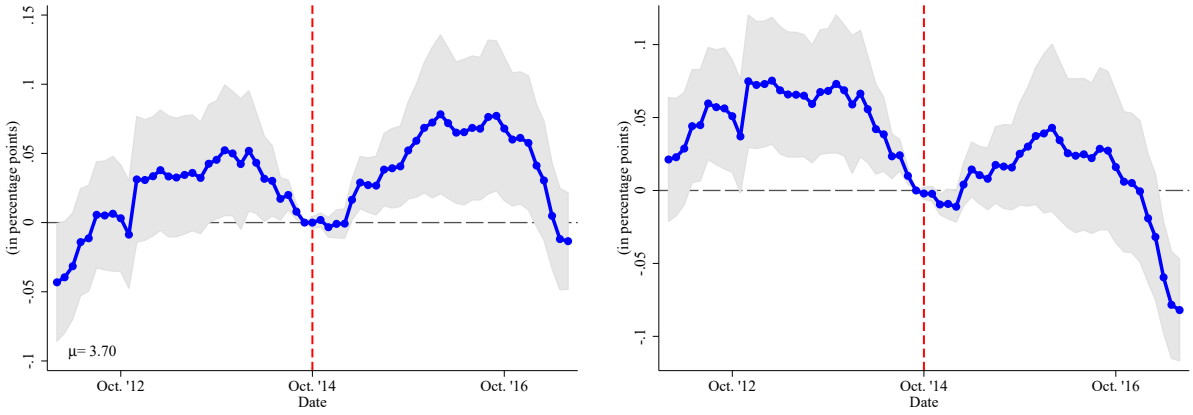
(b) LFP (Detrended)

(c) Raw EPR

(d) EPR (Detrended)

Note: These figures show time series for the LFP rate and EPR broken down by quartile of Hydro_z^{pre}. The first quartile is shown in blue in each panel while the fourth quartile is shown in black. Panels (A) and (B) show the labor force participation rate, while panels (C) and (D) show the employment-to-population ratio. Panels (A) and (C) show the data with September 2014 normalized to zero, while panels (B) and (D) show the data after subtracting out linear trends fit based on the pre-period, analogous to regression equation 2.

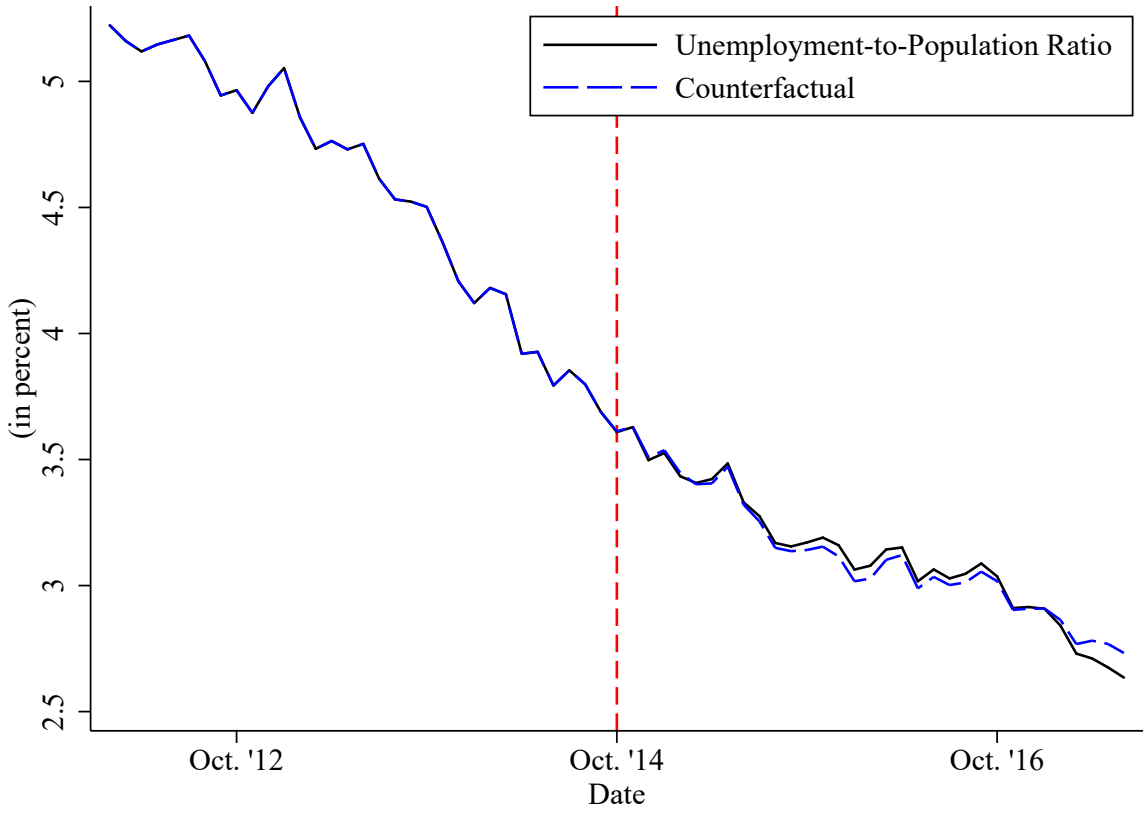
Figure A.7: Unemployment-to-Population Ratio Regression Estimates: Impact of One Standard Deviation Increase in Hydro_z^{pre}



(a) Non-Parametric (equation 1.1) (b) Parametric (equation 1.2)

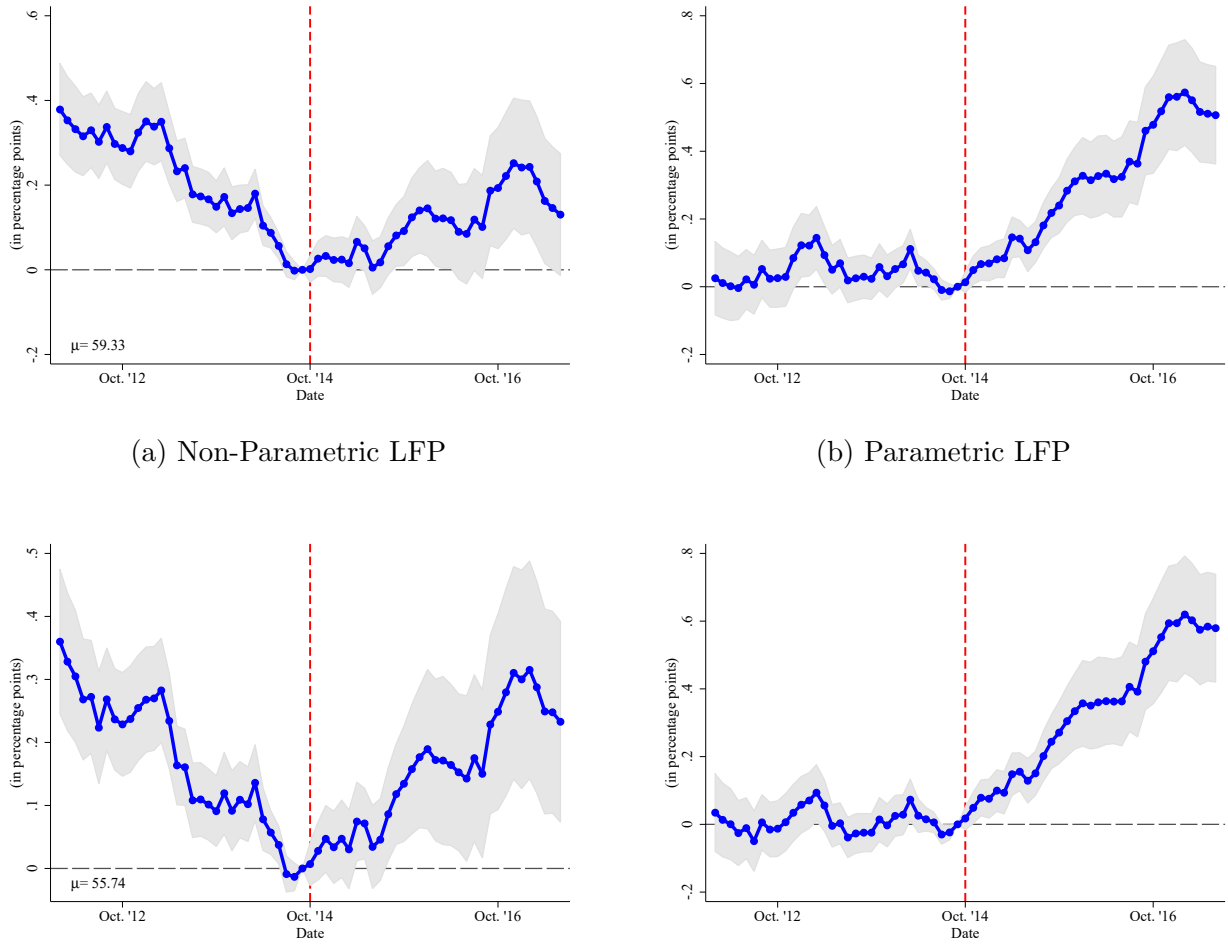
Note: These figures show the coefficients on the $\text{Hydro}_z^{pre}\times$ time interactions from regression equations 1 (panel (A)) and 2 (panel (B)) with the unemployment-to-population ratio as the dependent variable. The dependent variable is measured at the zip3-by-month level. The coefficients can be interpreted as the effect of a one standard deviation increase in pre-period hydrocodone consumption.

Figure A.8: Counterfactual Path of the Unemployment-to-Population Ratio



Note: This figure shows the predicted and counterfactual unemployment-to-population ratio. The counterfactual estimates use the regression coefficients from equation 2, but assume that each zip3 has $\text{Hydro}_z^{pre} = 0$. The black line shows the predicted values with the actual value of Hydro_z^{pre}, while the blue dashed line shows the counterfactual.

Figure A.9: Alternate Treatment Variable: Medicare Part D Hydrocodone Days Supplied



(a) Non-Parametric LFP

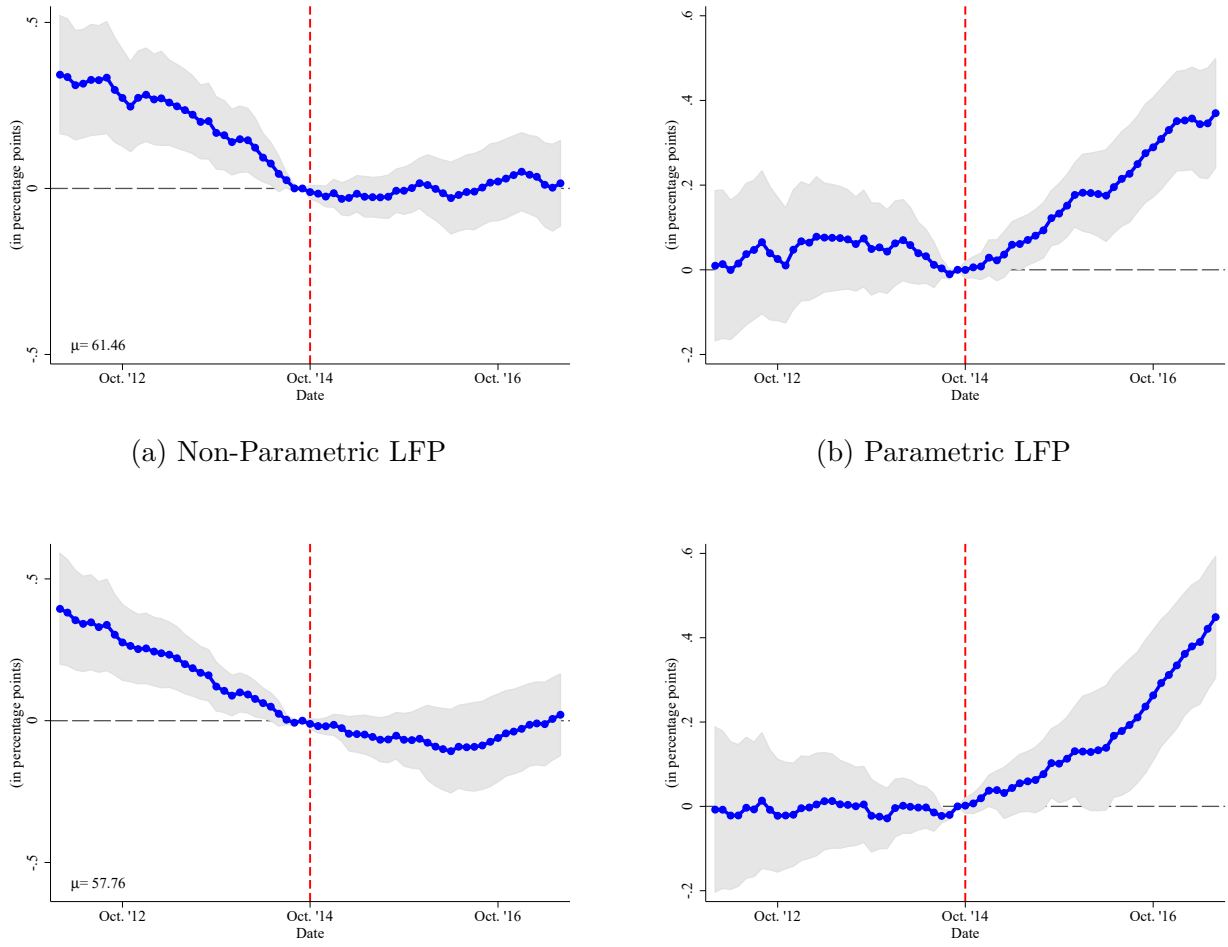
(b) Parametric LFP

(c) Non-Parametric EPR

(d) Parametric EPR

Note: These figures show the coefficients on the $\text{Hydro}_z^{pre} \times$ time interactions from regression equations 1 (panels (A) and (C)) and 2 (panel (B) and (D)). In these regressions the measure of pre-period hydrocodone consumption comes from Medicare Part D as opposed to ARCOS. Panels (A) and (B) show the results for the labor force participation rate, while panels (C) and (D) show the results for the employment-to-population ratio. The dependent variables are measured at the county-by-month level. The coefficients can be interpreted as the effect of a one standard deviation increase in pre-period hydrocodone consumption.

Figure A.10: Regressions Controlling for Other Opioids



(a) Non-Parametric LFP

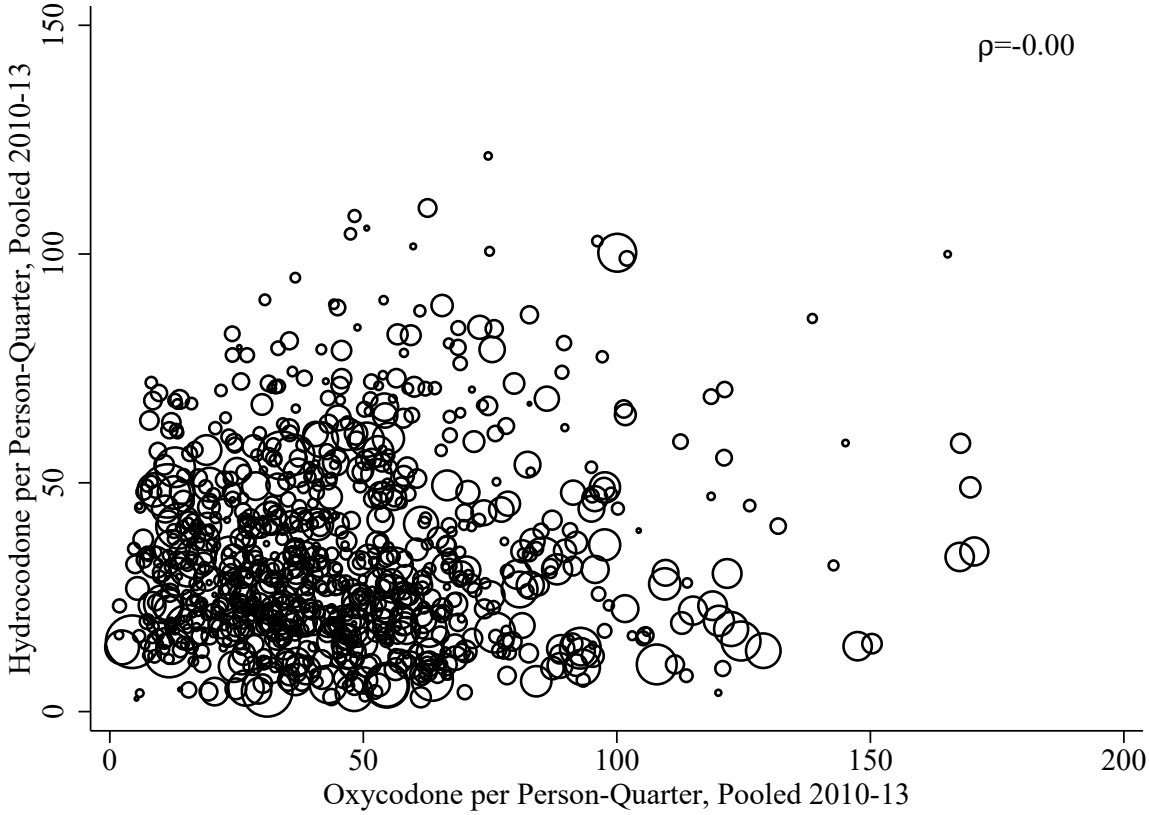
(b) Parametric LFP

(c) Non-Parametric EPR

(d) Parametric EPR

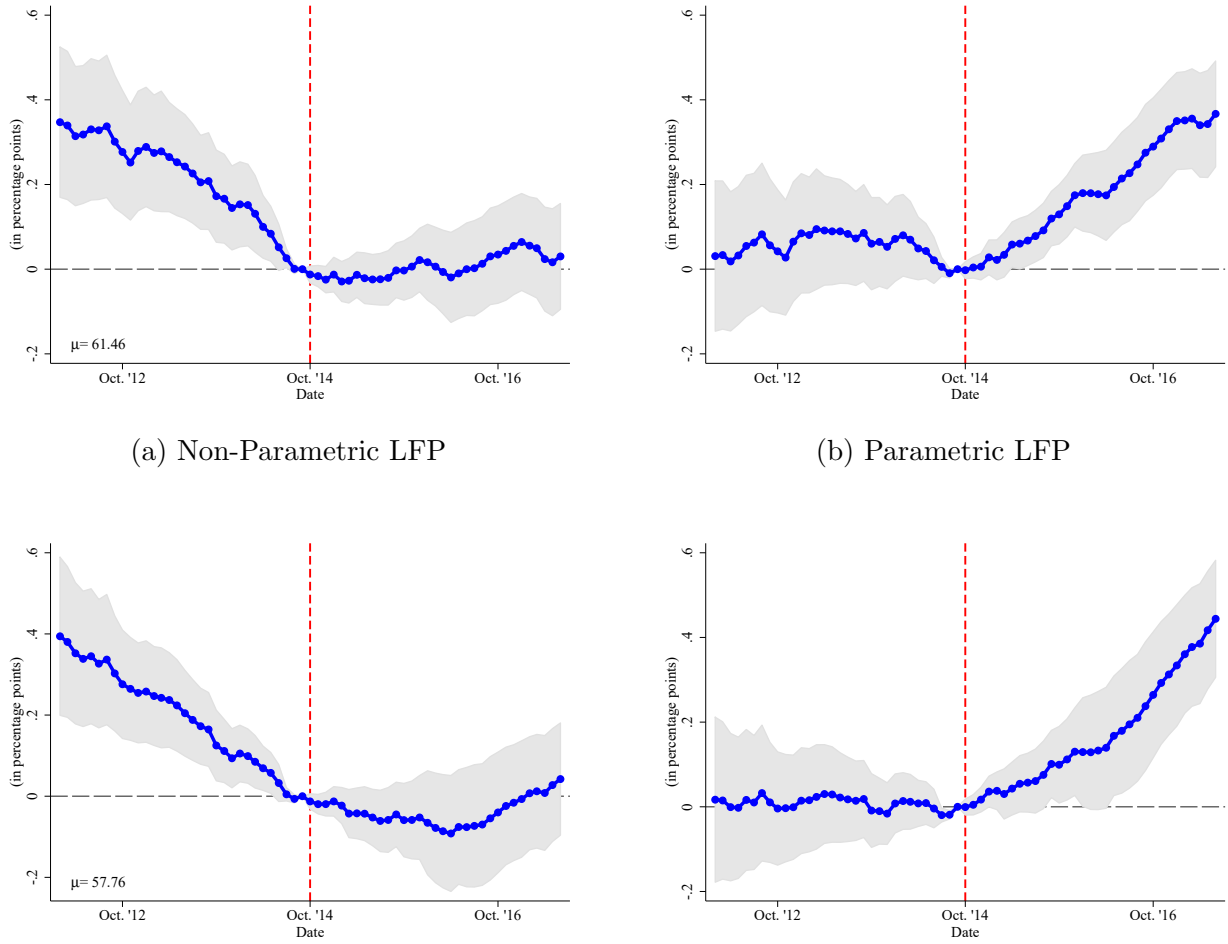
Note: These figures show the coefficients on the $\text{Hydro}_z^{pre} \times$ time interactions from regression equations 1 (panels (A) and (C)) and 2 (panel (B) and (D)). These regressions explicitly control for the interaction of time fixed effects with non-hydrocodone opioids. Panels (A) and (B) show the results for the labor force participation rate, while panels (C) and (D) show the results for the employment-to-population ratio. The dependent variables are measured at the zip3-by-month level. The coefficients can be interpreted as the effect of a one standard deviation increase in pre-period hydrocodone consumption.

Figure A.11: Correlation Between Hydrocodone and Oxycodone Shipments



Note: This figure shows a scatter plot of each zip3's hydrocodone consumption per capita (y-axis) versus its oxycodone consumption per capita (x-axis). Data are pooled from 2010-2013 and exclude zip3s above the 99th percentile in either distribution. The size of each circle represents the relative population size of the zip3.

Figure A.12: Regressions Controlling for Oxycodone Distribution



(a) Non-Parametric LFP

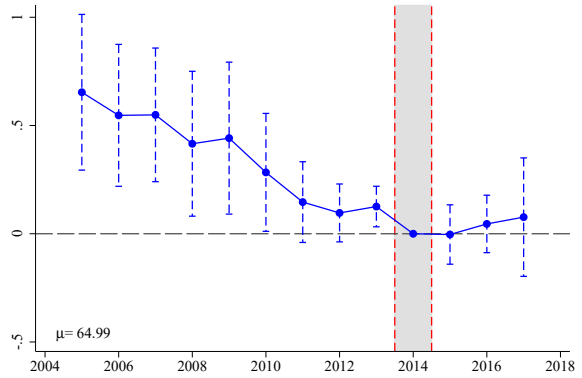
(b) Parametric LFP

(c) Non-Parametric EPR

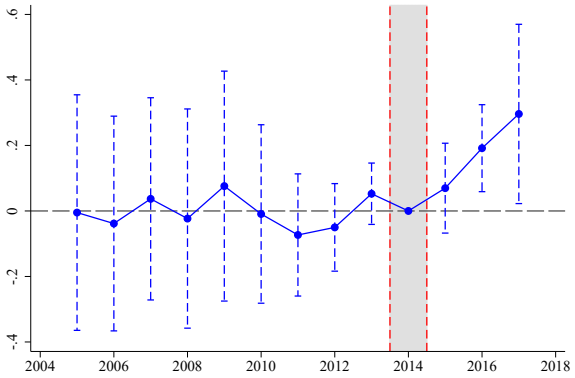
(d) Parametric EPR

Note: These figures show the coefficients on the $\text{Hydro}_z^{pre}\times$ time interactions from regression equations 1 (panels (A) and (C)) and 2 (panel (B) and (D)). These regressions explicitly control for the interaction of time fixed effects with a measure of pre-period consumption of oxycodone. Panels (A) and (B) show the results for the labor force participation rate, while panels (C) and (D) show the results for the employment-to-population ratio. The dependent variables are measured at the zip3-by-month level. The coefficients can be interpreted as the effect of a one standard deviation increase in pre-period hydrocodone consumption.

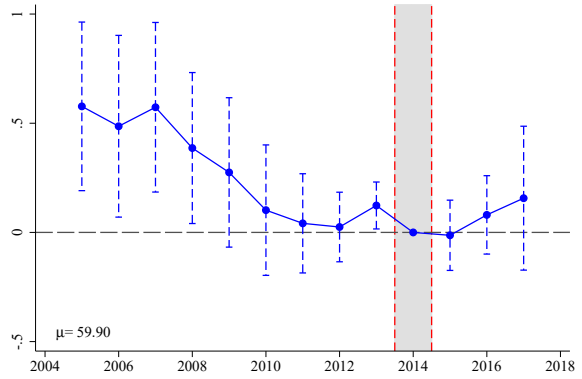
Figure A.13: Labor Force Participation Rate and Employment-to-Population Ratio Regression Estimates Using Data from the ACS: Impact of One Standard Deviation Increase in Hydro_z^{pre}



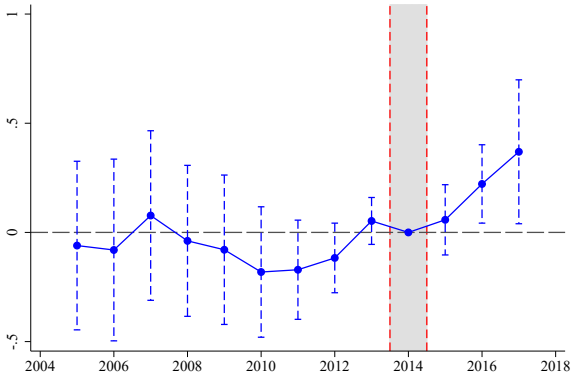
(a) Non-Parametric LFP (equation 1.1)



(b) Parametric LFP (equation 1.2)



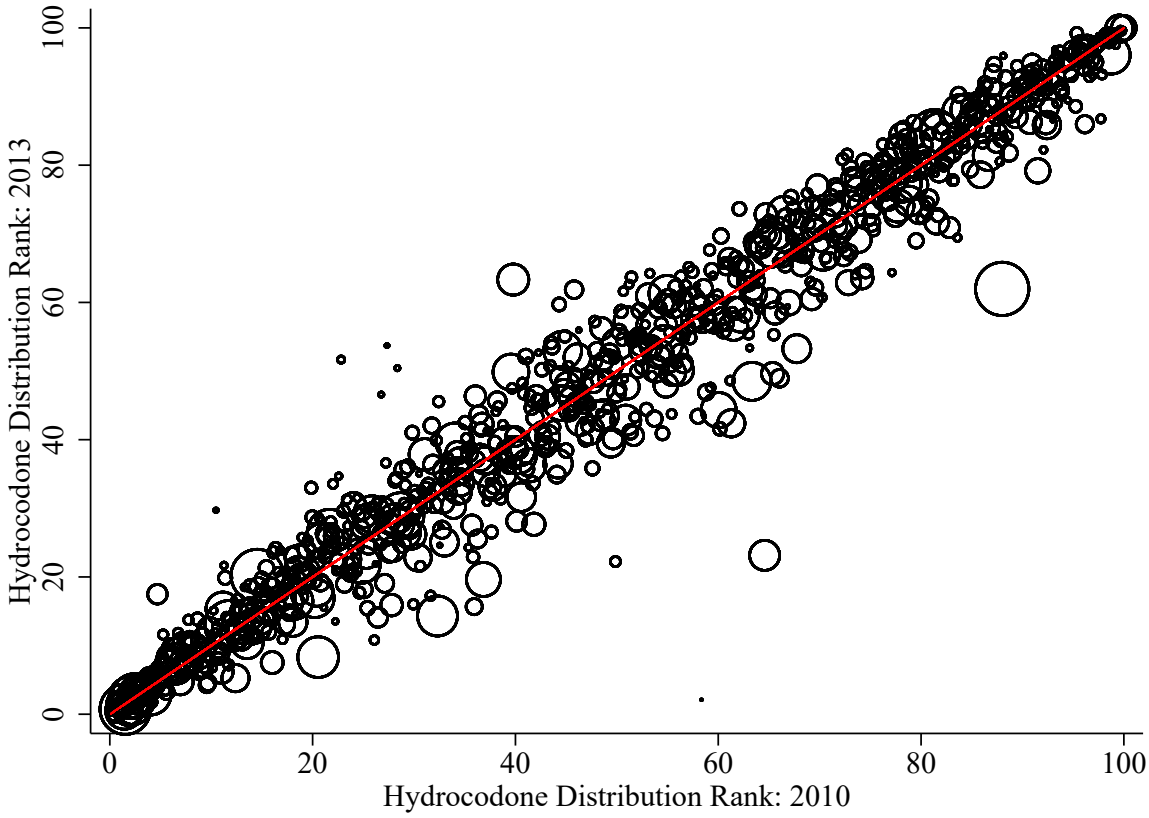
(c) Non-Parametric EPR (equation 1.1)



(d) Parametric EPR (equation 1.2)

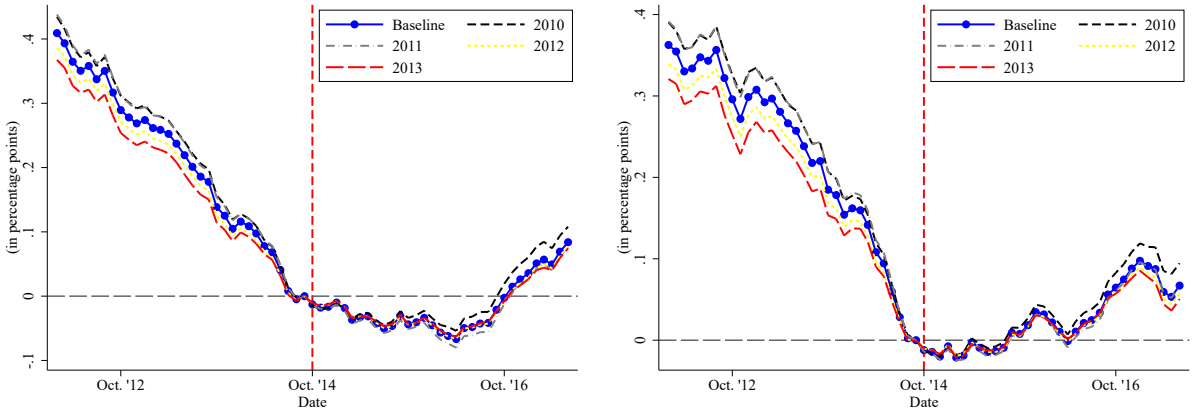
Note: These figures show the coefficients on the $\text{Hydro}_z^{pre}\times$ year interactions from regression equations 1 (panels (A) and (C)) and 2 (panel (B) and (D)). Panels (A) and (B) show the results for the labor force participation rate, while panels (C) and (D) show the results for the employment-to-population ratio. The dependent variables taken from the ACS and are measured at the state-by-year level. The coefficients can be interpreted as the effect of a one standard deviation increase in pre-period hydrocodone consumption.

Figure A.14: Rank in the Hydrocodone Distribution Over Time



Note: This figure shows a scatter plot of each zip3s rank in the hydrocodone distribution in 2010 versus 2013. The rank is normalized between 0 and 100, with 100 indicating the zip3 with the highest per capita consumption of hydrocodone.

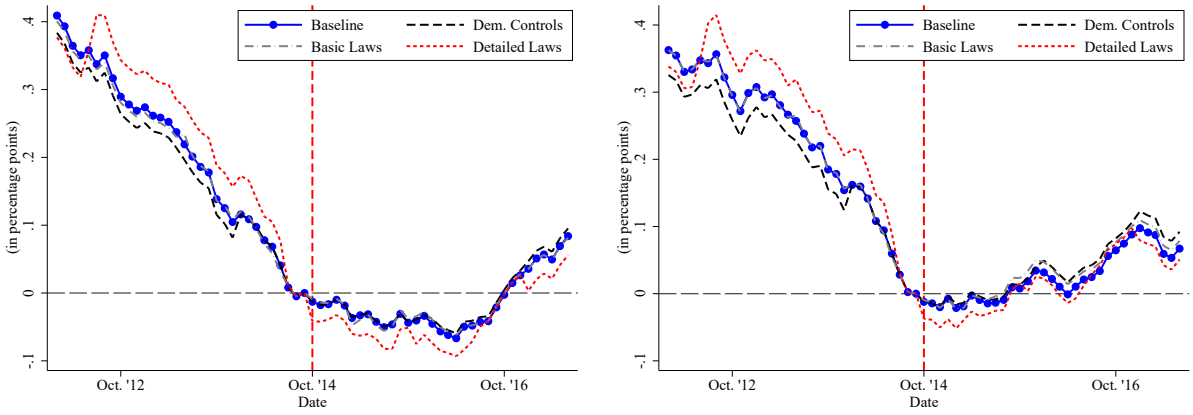
Figure A.15: Alternate Definitions of the Treatment Variable



(a) Employment-to-Population Ratio (b) Labor Force Participation Rate

Note: These figures show the coefficients on the $\text{Hydro}_z^{pre} \times$ time interactions from regression equation 1 with the employment-to-population ratio (panel (A)) and labor force participation rate (panel (B)) as the dependent variables. The blue coefficients correspond to the baseline specification pooling data from 2010-2013 for the treatment variable. The other colors indicate the coefficients defining the treatment variable by the per capita distribution of hydrocodone in a single year. The dependent variable is measured at the zip3-by-month level. The coefficients can be interpreted as the effect of a one standard deviation increase in pre-period hydrocodone consumption.

Figure A.16: Regressions Controlling for Other Laws, Demographics

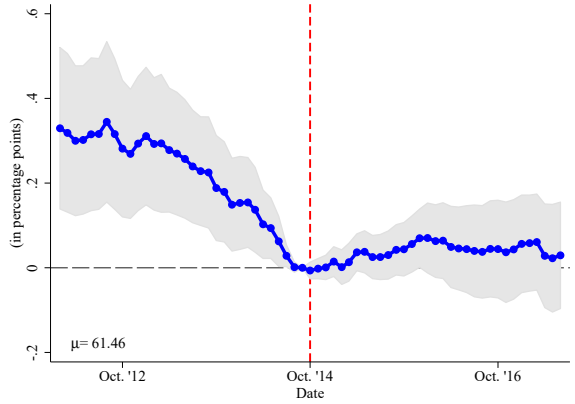


(a) Employment-to-Population Ratio

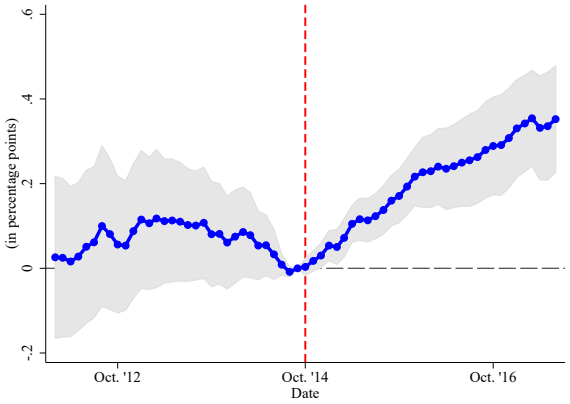
(b) Labor Force Participation Rate

Note: These figures show the coefficients on the $\text{Hydro}_z^{pre} \times$ time interactions from regression equation 1 with the employment-to-population ratio (panel (A)) and labor force participation rate (panel (B)) as the dependent variables. The blue coefficients correspond to the baseline specification. The gray lines show the coefficients when adding in indicators for other laws such as prescription drug monitoring programs, Good Samaritan laws, and Naloxone access laws. The red lines add further indicators with more detailed legal coding. The black lines control for various demographic characteristics of the zip3. The dependent variables are measured at the zip3-by-month level. The coefficients can be interpreted as the effect of a one standard deviation increase in pre-period hydrocodone consumption.

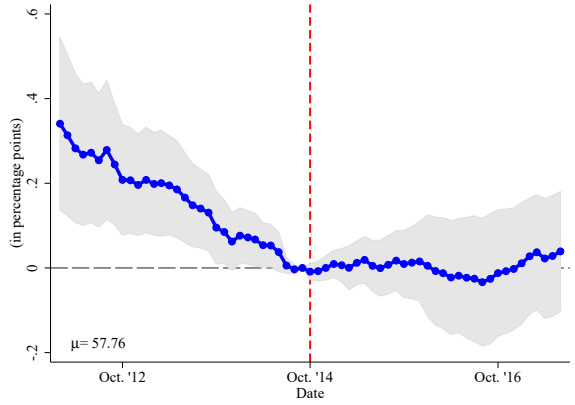
Figure A.17: Labor Force Participation Rate and Employment-to-Population Ratio Regression Estimates with Region-by-Time Fixed Effects: Impact of One Standard Deviation Increase in Hydro_z^{pre}



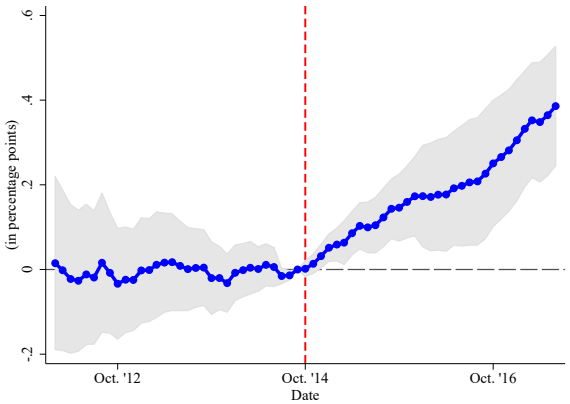
(a) Non-Parametric LFP w/ Region-by-Time FE



(b) Parametric LFP w/ Region-by-Time FE



(c) Non-Parametric EPR w/ Region-by-Time FE



(d) Parametric EPR w/ Region-by-Time FE

Note: These figures show the coefficients on the $\text{Hydro}_z^{pre}\times$ time interactions from regression equations 1 (panels (A) and (C)) and 2 (panels (B) and (D)) with the inclusion of Census region-by-time fixed effects. Panels (A) and (B) show the results for the labor force participation rate, while panels (C) and (D) show the results for the employment-to-population ratio. The dependent variables are measured at the zip3-by-month level. The coefficients can be interpreted as the effect of a one standard deviation increase in pre-period hydrocodone consumption.

Appendix B

Appendix to Chapter 2

B.0.1 Counterfactuals

Taken together, the regression coefficients in Figure 2.4 suggest that a significant share of the aggregate increase in new cases of hepatitis C, as well as the leveling off of new cases of hepatitis B documented in Figure 2.1 can be attributed to the reformulation of OxyContin. In order to quantify this, I use the regression coefficients to predict the counterfactual growth in new cases of hepatitis B and C under the assumption that all states had the same level of OxyContin misuse in the pre-period as the state with the least misuse.[1] That is, I estimate equation 2.1 and then calculate

$$y_{st}^{cf} = \hat{\alpha}_s + \hat{\gamma}_t + \sum_{T \neq 2009} \hat{\beta}_T \cdot \min_s(\text{Oxy Misuse}_s^{pre}) + \hat{\delta} X_{st}, \tag{B.1}$$

where variables with hats are the estimates from equation 2.1. I then graphically show both y_{st}^{cf} as well as the values I actually observe in the data in Figure B.1 for both hepatitis C (left panel) and hepatitis B (right panel). In each sub-figure the solid black line represents the actual number of estimated diagnoses, while the red dashed line represents the counterfactual time trend. Integrating between the black and red lines from 2011 onward gives an estimate

[1] Another candidate counterfactual would be so assume that pre-period OxyContin misuse was equal to zero in all states, as opposed to the minimum in my sample. I chose to report the minimum instead, as assuming misuse equal to zero requires extrapolation well outside any value I actually observe in my sample.

of what might have happened absent the OxyContin reformulation. These estimates are listed in the bottom row of Table B.1, and predict about 76% fewer cases of hepatitis C and 53% fewer cases of hepatitis B in the years since the OxyContin reformulation.

In order to give some sense of the economic magnitude of these effects, I perform a simple back-of-the-envelope calculation in which I estimate the cost associated with treatment for all of the new cases hepatitis C attributable to the reformulation. With the median cost of new hepatitis C cures about $65,000, the cost to cure every new case of hepatitis C attributable to the reformulation since 2011 would be around $6.69 billion dollars. A similar calculation is much more difficult for hepatitis B as there is currently no cure and treatment costs vary widely across individuals.

B.0.2 Robustness

In this section I conduct several tests of the robustness of the main results. First, I examine the sensitivity of the results to an alternative measure of pre-period OxyContin misuse: online searches for OxyContin via Google Trends. A common concern with the NSDUH is that survey respondents are known to underreport certain stigmatized or illegal attitudes and behaviors.[2] For example, in a literature review of survey methodology Roger Tourangeau and Ting Yan (2007) find that among those whose urine tested positive for cocaine or opioids, only 30-70% actually admit to using either substance in surveys. The idea behind using online searches for OxyContin as the treatment variable is not necessarily that users are attempting to purchase drugs via Google, but that relative differences in

[2]To the extent that this underreporting is uniform across states, it would have no effect on the results since the identifying variation comes from relative differences across states, not levels. However, if the severity of underreporting varies across states then the results will be biased.

Google search intensity are correlated with relative differences in actual drug use. Of course, one may be concerned that Internet users may be hesitant to search for this type of sensitive information online. However, Gregory Conti and Edward Sobiesk (2007) find that this sort of online self-censorship does not appear to be very common. In addition, papers by Seth Stephens-Davidowitz (2014) and Scott R Baker and Andrey Fradkin (2017) find Google searches to be more reliable measures than standard surveys in studies examining racial animus and job search. The results from this exercise are shown in columns (3) and (4) of Table 2.2. Comfortingly, the results are both qualitatively and quantitatively similar.[3]

Next, I examine whether the results are robust to the inclusion of additional covariates. In particular, many other policies were enacted around the same time as the reformulation of OxyContin. For example, two recent working papers by Doleac and Mukherjee (2018) and Rees et al. (2017) study the impact of "Naloxone access laws", laws which broaden access to a drug which counteracts the effects of an opioid overdose and remove restrictions which bar laypeople from administering it. Another important policy is the enactment of prescription drug monitoring programs (PDMPs), which are state-run databases which healthcare providers may consult before prescribing or dispensing painkillers in an effort to identify potential abuse or diversion. Early papers examining the impact of these laws typically found no effects (Paulozzi, Kilbourne and Desai, 2011; Joanne E Brady, Hannah Wunsch, Charles DiMaggio, Barbara H Lang, James Giglio and Guohua Li, 2014; Guohua Li, Joanne E Brady, Barbara H Lang, James Giglio, Hannah Wunsch and Charles DiMaggio, 2014), although Buchmueller and Carey (2018) and Dave, Grecu and Saffer (2017) find that

[3]The coefficients are scaled quite differently. The Google Trends index ranges from a maximum value of 100 to a minimum value of 36, as opposed to the NSDUH measure which ranges from 1.15 to 0.26.

PDMPs which explicitly require the prescribing physician to check the PDMP do reduce measures of opioid misuse. It is possible that the regressions are actually picking up the effects of these policies rather than the reformulation of OxyContin. To test for this I re-run the main regressions while including controls for these laws[4]. Results from these regressions are shown in columns (5) and (6) of Table 2.2 and indicate that the inclusion of these laws do not significantly affect the results.

Finally, I consider a battery of placebo tests in an attempt to rule out alternate explanations for this paper's findings. One potential concern is the possibility that states with higher levels of OxyContin misuse in the pre-period began more intensive hepatitis testing coincident, but unrelated to the reformulation of OxyContin. If this was the case, we may also expect to see an increase in hepatitis A diagnoses in these states. This would cast doubt on the results as hepatitis A is typically spread from drinking contaminated water as opposed to needle sharing and should not be affected by an increase in heroin use. Figure B.4 shows the regression coefficients with the rate of hepatitis A diagnoses as the outcome variable, which are also reported numerically in column (7) of Table 2.2. The pre-trends are somewhat noisy and do not appear to satisfy the parallel trends assumption, which makes the figure difficult to interpret. However, the pattern of coefficients does not show an obvious increase in hepatitis A, which suggests that the results are not simply driven by changes in hepatitis testing.[5]

Another possible explanation behind the increase in heroin deaths is that states with

[4]PDMP laws are taken from the Prescription Drug Abuse Policy System (available here: http://www.pdaps.org/). Naloxone access laws are taken from Doleac and Mukherjee (2018).

[5]The p-value indicates that the post coefficients are jointly significant; however, this is seemingly a result of choosing 2009 as the base year.

higher levels of pre-period OxyContin misuse are states which are more prone to drug abuse in general and it was some other shock in 2010 which is driving the results. Similarly, it could be the case that residents of these states are more risk-loving and all risky behavior in these states increased for reasons unrelated to the reformulation of OxyContin. While it is difficult to rule this out completely, I provide some evidence against this explanation by examining cocaine deaths in Figure B.5 (also shown in column (8) of Table 2.2). The figure shows no differential increase in cocaine deaths in states with higher OxyContin misuse, which is reassuring since one would generally expect OxyContin users to switch toward a closer substitute such as heroin.[6]

As I final placebo test, I examine whether the hepatitis results could be explained by an increase in blood-borne diseases not necessarily related to injection drug use. While HIV can be spread via needle sharing, the most common transmission mechanism by far is sexual contact. Valdiserri et al. (2014) report that HIV is less likely to be transmitted via a single needle stick than hepatitis C, and HIV is unable to survive as long outside the body (e.g., on contaminated surfaces) as hepatitis C. Consistent with this, only 5-8% of new HIV infections were due to injection drug use in 2014.[7] Therefore, while it is still possible that the reformulation of OxyContin could affect the spread of HIV, it is less likely than with hepatitis B or C. Figure B.6 displays the regression coefficients from equation 2.1 with new diagnoses of HIV as the outcome variable (column (9) of Table 2.2). The figure shows no increase in HIV, although since HIV data is only available from 2008 onward it is difficult

[6]Cocaine is a stimulant, not an opioid.

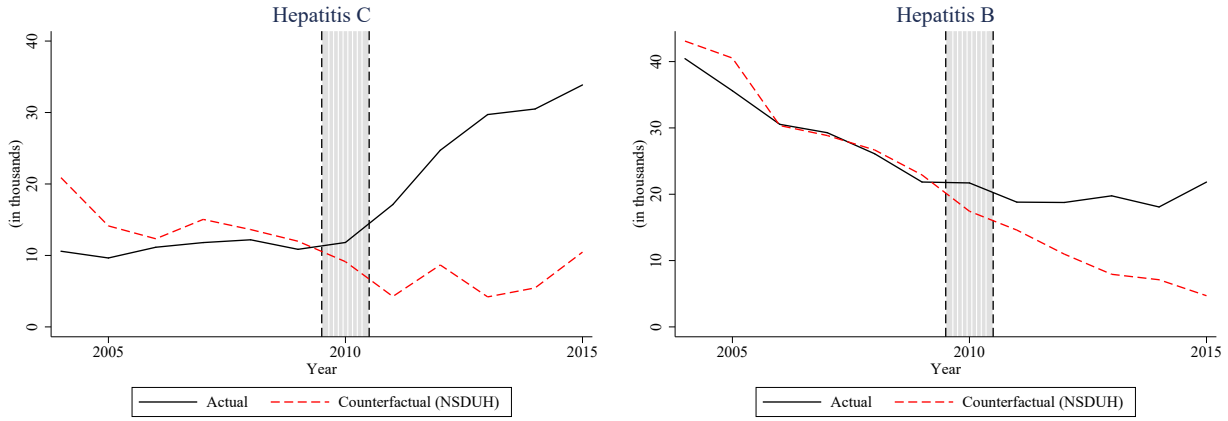
[7]About 70% were the result of male-to-male sexual contact, with about 23% the result of male-to-female sexual contact (https://www.cdc.gov/hiv/basics/statistics.html).

to determine the plausibility of the parallel trends assumption.[8] However, the combination of rising rates of hepatitis B and C and no detectable change in HIV is consistent with the results being driven by an increase in injection drug use caused by the reformulation of OxyContin.

Taken together these robustness tests support a causal interpretation of the papers' main results. The results are qualitatively and quantitatively similar regardless of the measure of pre-period OxyContin misuse and are largely unaffected by other policies implemented around the same time as the reformulation such as PDMPs or Naloxone access laws. There is no obvious increase in hepatitis A, indicating that the results are not driven by a change in overall hepatitis testing. Furthermore, the results do not appear to be driven by an increase in drug use more generally, as indicated by the cocaine findings. Finally, the increase in blood-borne diseases is concentrated among the diseases more commonly spread via injection drug use as opposed to sexually.

[8]Prior to the availability of highly active antiretroviral therapy (HAART), the CDC did not track HIV separately from AIDS since the progression from HIV to AIDS was fairly rapid. However, with increased accessibility to HAART it became necessary to measure the two separately as progression from HIV to AIDS is now much less predictable. A uniform reporting system was not adopted by all 50 states until 2008.

Figure B.1: Counterfactual Growth in Hepatitis B and C Transmissions



Note: This figure shows actual and counterfactual new cases of hepatitis C (left) and hepatitis B (right). The counterfactual estimates use the regression coefficients from equation 2.1, but assume that every state had OxyContin misuse equal to the state with the least misuse. The black line shows actual deaths/cases, while the red dashed line shows the estimated counterfactual number of deaths/cases.

Table B.1: Counterfactual Hepatitis B and C Diagnoses in the Absence of OxyContin Reformulation

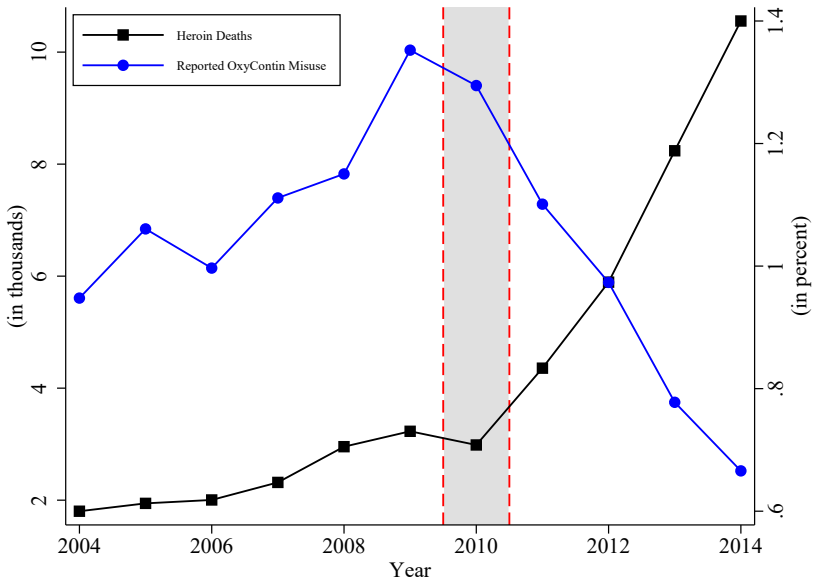
	Hepatitis C	Hepatitis B
Actual No.	135,914	97,258
Predicted No.	124,223	95,773
Counterfactual No.	33,055	45,321
% Fewer Under CF	76%	53%

Note: This table shows actual and counterfactual new cases of hepatitis B and C from 2011-2015. The counterfactual estimates use the regression coefficients from equation 2.1, but assume that every state had OxyContin misuse equal to the state with the least misuse. The first row reports actual deaths/diagnoses, while the second row reports the predicted number from equation 2.1. The third row reports the counterfactual number. The last row shows the % fewer cases under the counterfactual scenario $(1 - \frac{\text{counterfactual}}{\text{actual}})$.

Figure B.2: Demonstration of Abuse-Deterrent Properties of OxyContin Reformulation

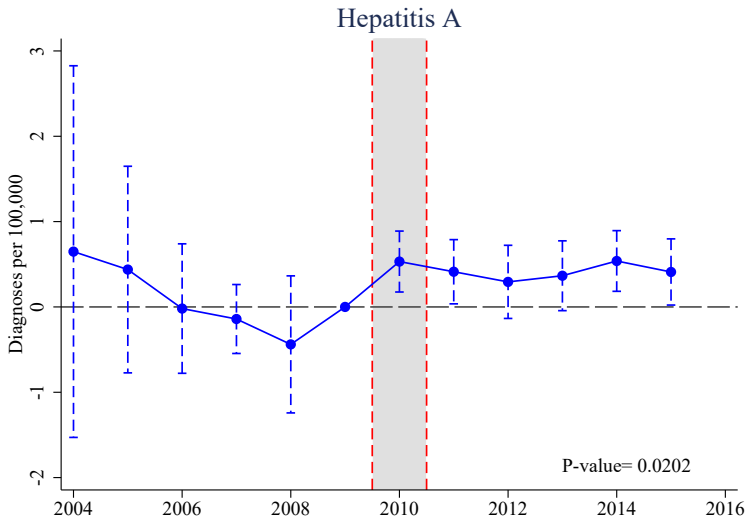
Note: This figure demonstrates the abuse-deterrent properties of the reformulated version of OxyContin. The left column shows the original formulation while the right shows the reformulated version. The first row displays the pills side-by-side. The second row shows an attempt to crush each pill with a blunt object. While the original grinds into a fine powder which could be snorted, the new formulation does not. The third row shows each pill after being put through a coffee grinder. Still, the new formulation does not break down into a powder. The last row shows the crushed pill mixed with water. While the original formulation dissolves into a liquid which can be drawn into a syringe, the new formulation turns to a gel which cannot be injected (Opiate Addiction and Treatment Resource, 2013).

Figure B.3: Fraction of NSDUH Respondents Reporting OxyContin Misuse; Heroin Overdose Deaths



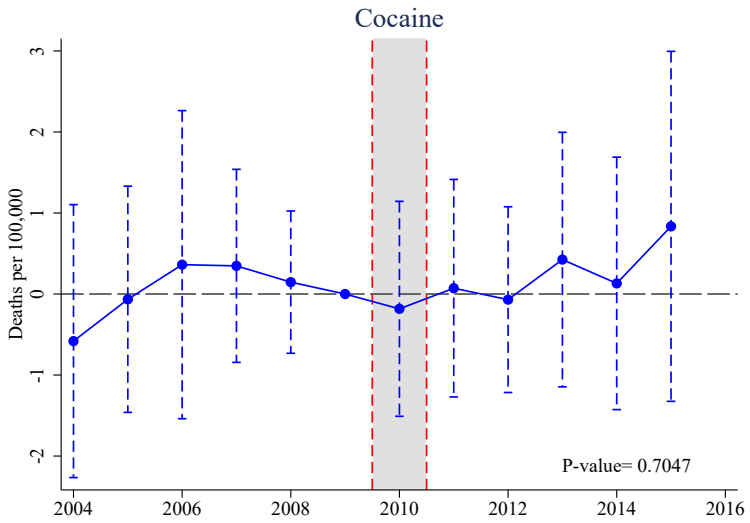
Note: This figure shows the fraction of respondents reporting non-medical OxyContin use during the past year for the 2004-05, 2006-07, 2008-09, 2010-11, 2012-2013, and 2014-15 waves of the NSDUH in blue, as well as the annual number of heroin overdose deaths in black. The left y-axis corresponds to the number of heroin overdose deaths and is measured in thousands, while the right y-axis corresponds to the fraction of NSDUH respondents reporting OxyContin misuse and is measured in percent. The shaded region indicates the year that OxyContin was reformulated.

Figure B.4: Hepatitis A Transmissions: Impact of One Percentage Point Increase in Pre-period OxyContin Misuse



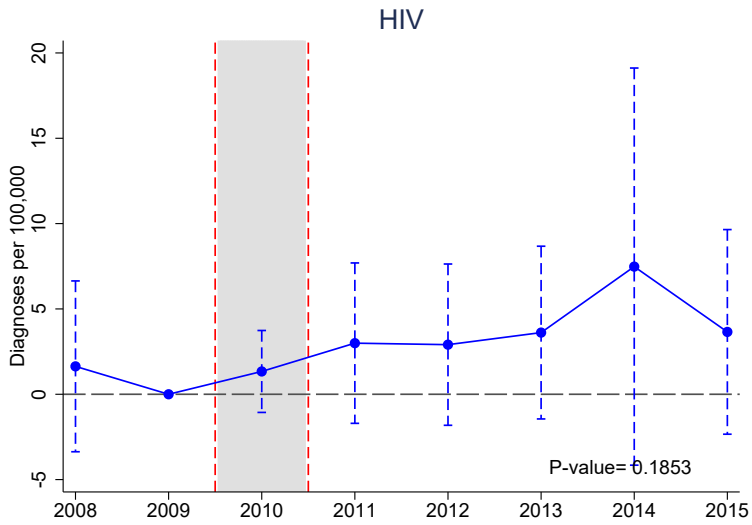
Note: This figure shows coefficients on Oxy Misuse$_s^{pre}$ × year interactions from regression equation 2.1 for the number of hepatitis A diagnoses per 100,000. The coefficients can be interpreted as the effect of a one percentage point increase in pre-period OxyContin misuse. Dependent variable is measured at the state-year level.

Figure B.5: Cocaine Overdose Deaths: Impact of One Percentage Point Increase in Pre-period OxyContin Misuse



Note: This figure shows coefficients on Oxy Misuse$_s^{pre}\times$ year interactions from regression equation 2.1 for the number of cocaine overdose deaths per 100,000. The coefficients can be interpreted as the effect of a one percentage point increase in pre-period OxyContin misuse. Dependent variable is measured at the state-year level.

Figure B.6: New HIV Diagnoses: Impact of One Percentage Point Increase in Pre-period OxyContin Misuse



Note: This figure shows coefficients on Oxy Misuse$_s^{pre}\times$ year interactions from regression equation 2.1 for the number HIV diagnoses per 100,000. The coefficients can be interpreted as the effect of a one percentage point increase in pre-period OxyContin misuse. Dependent variable is measured at the state-year level.

Table B.2: States Ordered in Terms of OxyContin Misuse from 2004-2009

State	% Reported Misuse	Rank	State	% Reported Misuse	Rank
Rhode Island	1.15	1	Pennsylvania	0.65	27
West Virginia	1.13	2	Arizona	0.62	28
Utah	1.04	3	South Carolina	0.60	29
Wisconsin	0.98	4	Louisiana	0.60	30
Massachusetts	0.97	5	Kansas	0.59	31
Kentucky	0.97	6	Virginia	0.57	32
Montana	0.96	7	Ohio	0.57	33
Indiana	0.96	8	North Carolina	0.56	34
Nevada	0.95	9	Colorado	0.54	35
Alaska	0.94	10	New Jersey	0.53	36
Oklahoma	0.90	11	New York	0.53	37
Maine	0.86	12	Maryland	0.52	38
New Mexico	0.81	13	Alabama	0.52	39
New Hampshire	0.81	14	Hawaii	0.51	40
Vermont	0.81	15	Michigan	0.51	41
Tennessee	0.81	16	District of Columbia	0.48	42
Missouri	0.79	17	Minnesota	0.47	43
Idaho	0.79	18	Georgia	0.39	44
Wyoming	0.77	19	Nebraska	0.39	45
Washington	0.77	20	Mississippi	0.37	46
Oregon	0.76	21	California	0.30	47
North Dakota	0.75	22	Texas	0.29	48
Connecticut	0.72	23	Iowa	0.27	49
Florida	0.71	24	South Dakota	0.26	50
Arkansas	0.71	25	Illinois	0.26	51
Delaware	0.66	26			

Summary Statistics	
Mean	0.57
Standard Deviation	0.22
25th Percentile	0.30
75th Percentile	0.71

Note: This table displays each state in descending order of pre-period OxyContin misuse. The table reports the fraction of NSDUH respondents indicating past year OxyContin misuse in the pre-period. Each state's rank in terms of reported OxyContin misuse is listed in the columns labeled 'Rank'. Summary statistics for the measure are included in the bottom left panel. Summary statistics are weighted by population.

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