Origins of the Opioid Crisis and Its Enduring Impacts*

Abby Alpert†
University of Pennsylvania and NBER

William N. Evans
University of Notre Dame and NBER

Ethan M.J. Lieber
University of Notre Dame and NBER

David Powell
RAND

First Version: November 2018
This Version: July 2019

ABSTRACT

Although overdoses involving opioids have increased dramatically since the 1990's, leading to the worst drug overdose epidemic in U.S. history, there is little empirical evidence on the initial causes. In this paper, we examine the role of the 1996 introduction and marketing of OxyContin as a potential leading cause of the opioid crisis. We leverage information about cross-state variation in OxyContin's early marketing obtained from recently-unsealed court documents involving Purdue Pharma. These documents reveal that state-based triplicate prescription programs posed a major obstacle to sales of OxyContin and suggest that less marketing was targeted to these states. We find that the supply of OxyContin was over 50 percent lower in "triplicate states" in the years immediately after the launch. Prior to OxyContin's launch, triplicate states had higher rates of overdose deaths on average, but shortly after the launch of OxyContin, this relationship had flipped and the triplicate states saw substantially slower growth in overdose deaths, continuing even twenty years after OxyContin's introduction. Our results suggest a leading role of OxyContin in explaining the rise in overdoses since the mid-1990's.

Keywords: opioid crisis, physician detailing, geographic variation in opioid mortality
JEL classification: I12, I18, J11

---

* We thank seminar and conference participants at the Midwest Health Economics Conference, University of Southern California, Tulane University, iHEA, and RAND for helpful feedback. For help obtaining some of the unsealed court case documents, we also thank Caitlin Esch and Marketplace, Nicholas Weilhammer in the Office of Public Records for the Office of the Attorney General of Florida, and La Dona Jensen in the Office of the Attorney General of Washington.
† Corresponding author: The Wharton School, University of Pennsylvania, 3641 Locust Walk, Philadelphia, PA 19104 (email: alpertab@wharton.upenn.edu)

1 Introduction

Over the last two decades, there has been a staggering increase in mortality from drug overdoses in the U.S. which has reached epidemic proportions. The basics of the problem are summarized in Figure 1. Between 1983 and 2017, the drug overdose death rate increased by a factor of eight with a noticeable inflection point in the late 1990s. Deaths involving opioids are the primary cause of the increase. The opioid death rate increased by a factor of 28 compared to a factor of 3 for non-opioid drug overdose deaths. Opioids account for 75 percent of the increase in drug overdoses and, by 2017, represent two-thirds of all drug overdose deaths. Opioid overdoses claimed the lives of 47,600 people in 2017[1] and almost 400,000 since 1999,[2] about the same number of U.S. soldiers that died in World War II (DeBruyne, 2018). The opioid crisis has contributed to a three-year decline in life expectancy, the longest sustained period of decline since 1915.[3]

There are many hypotheses about what caused the opioid crisis. Case and Deaton (2015, 2017) suggest that demand factors played an important role as worsening cultural and economic conditions have sparked a surge in "deaths of despair": suicides, alcohol poisonings, and drug overdoses including opioids.[4] Alternative hypotheses, though not mutually exclusive, consider the role of supply factors given the dramatic increase in opioid access due to changes in physician attitudes and practice patterns (Jones et al., 2018). Beginning in the 1990's, doctors began to treat pain more aggressively with opioids, following widespread concerns that pain had been "under-treated" (Morgan, 1985; WHO, 1986; Melzack, 1990). The American Pain Society launched an influential campaign declaring pain as the "fifth vital sign" and, in response, the Joint Commission on Accreditation of Healthcare Organizations revised its guidelines in 2001 requiring that doctors assess pain along with other vitals during medical visits (Phillips, 2000). In 1998, a major national treatment guideline was revised to recommend more liberal use of opioids for chronic pain.[5] Finally, another potential supply-side mechanism was the introduction of OxyContin in 1996. The aggressive marketing by its manufacturer, Purdue Pharma, has also

[1] https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates
[2] https://www.cdc.gov/drugoverdose/epidemic/index.html
[3] https://www.bmj.com/content/363/bmj.k5118
[4] Motivated by this hypothesis, recent studies have explored the association of local economic conditions and drug overdose deaths with mixed results (Hollingsworth et al., 2017; Ruhm, 2018; Pierce and Schott, 2016).
[5] The Federation of State Medical Boards Model Pain Policy was rewritten in 1998 to encourage use of opioids for non-cancer pain: "the Board recognizes that controlled substances including opioid analgesics may be essential in the treatment of acute pain due to trauma or surgery and chronic pain, whether due to cancer or non-cancer origins."

been implicated as a central cause of the opioid crisis (Kolodny et al., 2015).[6] Despite the discussion of these hypotheses throughout the literature, there is surprisingly little systematic empirical evidence on any individual factor's importance.

In this paper, we provide the first quasi-experimental evidence on the causes of the opioid crisis.[7] We focus on isolating the impacts of the introduction of OxyContin in 1996 and find that it played a leading role. OxyContin is a prescription opioid pain reliever whose active ingredient, oxycodone, has been in use in the U.S. since the early 1900s. OxyContin's key technological innovation was a sustained release formulation that stores a high concentration of the active ingredient to provide 12 hours of continuous pain relief. However, the sustained release aspect of OxyContin is contingent on taking the pill whole. Crushing or dissolving the pill allowed users to access the high dosage of oxycodone all at once, producing an intense high. Concerns about widespread abuse of OxyContin were reported as early as 2000 (GAO, 2003) and OxyContin became one of the leading drugs of abuse by 2004 (Cicero et al., 2005). OxyContin's role in the opioid crisis can be partially understood by observing the effects of the removal of the original formulation and its replacement by an abuse-deterrent version in 2010. After the reformulation, opioid overdoses declined but heroin overdoses increased dramatically as people substituted from OxyContin to heroin (Alpert et al., 2018; Evans et al., 2019). While these prior studies showed that OxyContin played a major role in explaining overdose trends for the later waves of the opioid epidemic after 2010, in this paper, we study the effects of OxyContin's introduction.

Studying OxyContin's introduction is challenging because the drug was launched nationwide. This makes it difficult to isolate OxyContin's effects from other concurrent changes and secular trends. To circumvent this issue, we exploit geographic variation in exposure to OxyContin's introduction due to a previously unexplored state policy that substantially limited OxyContin's entry and marketing in select states. We leverage recently unsealed information

[6] As of June 2019, 48 states and 500 cities have filed lawsuits against Purdue Pharma for its deceptive marketing practices claiming that they have contributed to the opioid crisis (https://www.vanityfair.com/news/2019/06/david-sackler-pleads-his-case-on-the-opioid-epidemic).

[7] Ruhm (2018) studies whether opioid supply or economic conditions since 2000 are more predictive of changes in opioid overdose rates. This test also addresses the main drivers of the opioid crisis, though the paper notes the difficulties in finding exogenous variation in these possible mechanisms. Other studies have tested whether shocks to opioid access, such as through prescriptions to family members (Khan et al., 2019) or physician prescribing patterns (Barnett et al., 2017), predict long-term use of opioids or overdoses. This research is also relevant to the general question about the role of supply versus demand factors in the ongoing opioid crisis.

from multiple settled lawsuits involving Purdue Pharma, the manufacturer of OxyContin, that outline the manufacturer's internal strategies around the introduction of OxyContin, including the official launch plan, focus group research, and annual budgets. These documents reveal that Purdue Pharma viewed "triplicate prescription programs" (an early version of Prescription Drug Monitoring Programs) as significant barriers to entry for OxyContin and suggested that they should not target marketing to these states since the returns from doing so would be low.

Triplicate prescription programs were early systems designed to control diversion and misuse of controlled substances and were adopted decades prior to OxyContin's launch. In states with triplicate programs, the prescriber is mandated to use state-issued triplicate prescription forms when prescribing Schedule II controlled substances, which include many prescription opioids. The triplicate copies of the form were retained by the prescriber, pharmacist, and the state's prescription drug monitoring agency. Discussions of triplicate programs appear dozens of times in internal documents concerning the launch and promotion of OxyContin. These documents discuss how doctors in triplicate states rarely used Schedule II opioids like oxycodone to treat non-cancer pain because "writing triplicate prescriptions was more trouble than others" and providers "did not want to give the Government an excuse to monitor their activities" (Groups Plus, 1995). These barriers led to the recommendation that "the product [OxyContin] should only be positioned to physicians in non-triplicate states" (Groups Plus, 1995). Purdue Pharma does not express concern over any other state policy or type of monitoring system.

Using a difference-in-differences framework, we take advantage of the variation in OxyContin supply caused by the triplicate policies to trace out overdose trends in states with triplicate programs (henceforth "triplicate states") relative to states without these programs ("non-triplicate states"). We consider the non-triplicate states more exposed to OxyContin's introduction because the barriers to entry were lower and there was more initial marketing targeted to these states. Indeed, we find that non-triplicate states had more than twice the amount of OxyContin supply per capita than triplicate states after its launch. Meanwhile, the supply of other types of opioids unaffected by triplicate policies such as hydrocodone (primarily a Schedule III controlled substance) were nearly identical across triplicate and non-triplicate states.

We then turn to estimating OxyContin's impacts on the time-path of opioid overdose death rates over the short and long run using variation from the triplicate policies. For the decade

prior to OxyContin's introduction, triplicate and non-triplicate states had similar trends in opioid death rates; though, non-triplicate states had lower levels of opioid deaths per capita. Yet, shortly after the launch of OxyContin, the trends diverged causing the non-triplicate states to have higher opioid death rates than triplicate states. Non-triplicate states experienced substantially faster growth in opioid deaths, a trend that continued even twenty years after OxyContin's introduction. Additionally, we find significantly higher rates of OxyContin misuse and a disproportionate rise in substance abuse treatment admissions for opioids in non-triplicate states. Our estimates imply that not having a triplicate program in 1996 increased cumulative overdose death rates by over 40% through 2017. The vastly different trajectories in overdose death rates between triplicate and non-triplicate states after 1996 are not explained by differential pre-existing trends, systematic adoption of other opioid policies, state characteristics such as population size, or availability of substance abuse treatment.

This research contributes to our understanding of what drove the opioid crisis. We show that the introduction of OxyContin explains a substantial portion of the opioid overdose deaths over the last two decades. Although triplicate programs were discontinued in the years after OxyContin's launch, their initial deterrence of OxyContin promotion and adoption had long-term effects on overdoses in these states, dramatically decreasing overdose rates even today. The triplicate states we study, spread throughout the U.S., currently have some of the lowest overdose rates in the country. Our work, therefore, also speaks to the substantial geographic variation in opioid overdose deaths. Within small regions of the country, there are widely varying overdose rates and this variation is difficult to explain based on demographics, economic conditions, and current policies. Our results suggest the importance of initial conditions—particularly the policy landscape at the beginning of the epidemic— in inducing variation in overdose rates even years later.

Finally, our results speak to the potentially harmful consequences of pharmaceutical promotion for controlled substances. While triplicate programs themselves may have independently discouraged OxyContin adoption, our evidence also suggests that the relative lack of marketing in these states played an important role in reducing exposure to the drug. When triplicate states are compared to other states with similar prescribing practices or even states which had just recently eliminated their triplicate programs prior to 1996, they still have

uniquely low overdose rate growth. We discuss how this evidence is consistent with marketing practices playing a crucial role.

The remainder of the paper proceeds as follows. We provide additional background in Section 2. Section 3 introduces the data while Section 4 discusses the empirical strategy. We present the results in Section 5. In Section 6, we provide evidence on the roles of the triplicate programs and Purdue Pharma's marketing. Section 7 concludes.

2 Background

2.1 OxyContin's Launch and Promotional Activities

OxyContin was approved by the Food and Drug Administration (FDA) in 1995 and introduced to the market in January 1996 by Purdue Pharma. It is a brand-name prescription drug used for the treatment of moderate to severe pain. Its main active ingredient is oxycodone—a semi-synthetic opioid similar to morphine—which is classified as a Schedule II controlled substance, meaning that it has high potential for abuse.

OxyContin was approved just as Purdue Pharma's patent for MS Contin—a long-acting form of morphine used for treating severe cancer pain— was set to expire. As Purdue Pharma noted in their launch plan, "one of the major strategies in launching OxyContin will be to replace all prescriptions for MS Contin." However, Purdue Pharma did not only set their sights on treating late-stage cancer pain with OxyContin. They also aimed to treat patients in the earlier stages of cancer (positioning it as "the opioid to start with and to stay with") and to expand treatment beyond cancer to the much larger market for non-malignant pain. At the time of the launch, these other types of pain would have been typically treated (if at all) with non-opioid painkillers (e.g., Tylenol) or short-acting combination oxycodone products (e.g., Percocet, Tylox, and Percodan) and hydrocodone products (e.g., Vicodin or Lortab) that include acetaminophen or aspirin. OxyContin was a stronger opioid than the combination oxycodone products because it was a pure concentration of oxycodone and contained more of the active ingredient.[8] It was also a stronger opioid than the hydrocodone combination products, which were classified as Schedule III controlled substances at the time given their slightly lower abuse potential.

[8] The strength of the combination oxycodone and hydrocodone products is limited by the maximum safe dosage of acetaminophen (which can cause liver failure at high dosages). In contrast, OxyContin is made of pure oxycodone, so there is no ceiling dosage and dosages can be more readily escalated (GAO, 2003).

Many believed that OxyContin would be *less* addictive than other opioids because of its long-acting formulation. In fact, the original FDA-approved product label for OxyContin included the statement that, "delayed absorption as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug." However, users learned that they could defeat OxyContin's controlled-release delivery system by crushing or dissolving the pill, allowing them to access the entire store of oxycodone all at once. OxyContin soon became one of the leading drugs of abuse, surpassing all other forms of oxycodone and hydrocodone combined (Cicero et al., 2005).

That OxyContin would be safer than other opioid drugs became a central tenet of the initial marketing strategy. Additionally, marketing materials included misleading claims based on research (e.g., Porter and Jack, 1980) that the risk of addiction was "much less than one percent" and some materials failed to include any information about its addiction potential (Van Zee, 2009). These claims were important for convincing doctors—who for decades had been extremely cautious about prescribing opioids— to switch from less potent opioid products to OxyContin and to expand the use of strong oxycodone products for types of pain previously untreated by these drugs such as non-cancer chronic pain. To achieve growth for non-cancer chronic pain, Purdue Pharma also targeted primary care physicians, although this raised concerns given their limited experience and training in pain management. From 1997 to 2002, OxyContin prescriptions increased at a faster rate for non-cancer pain than for cancer pain (GAO, 2003).

In 2001, the FDA product label for OxyContin was revised to remove the incorrect statements about its abuse liability and add a black box safety warning. However, the indication was also changed from covering patients "where use of an opioid analgesic is appropriate for more than a few days" to patients who require "a continuous around-the-clock analgesic for an extended period of time." Internal documents show that Purdue Pharma viewed the new label as a way to expand its market for chronic pain:

> "The action by the FDA to clarify the OxyContin Tablets labeling has created enormous opportunities. In effect, the FDA has expanded the indication for OxyContin Tablets to any patient with moderate or severe around-the-clock persistent pain, provided that the pain is moderate to severe, and expected to be for an extended duration. This broad labeling is likely to never again be available for an opioid seeking FDA approval." (Purdue Pharma, 2002, p. 1-47)

Purdue Pharma pursued an aggressive campaign to promote OxyContin, dedicating most of its sales resources to it, expanding its sales force considerably, and spending $200 million in 2001 alone for OxyContin marketing (Goldenheim, 2002). Purdue Pharma's promotional spending was unprecedented for an opioid drug. They spent 6-12 times more on promotional efforts for OxyContin in each of its first six years (1996-2001) than they had spent for promotion of MS Contin in its first six years (1984-1989) and that Janssen Pharmaceutical Products spent for promotion of Duragesic, one of OxyContin's competitors (GAO, 2003). They employed an enormous sales force to promote the drug to doctors which doubled in size between 1996 and 2002.[9] Additionally, Purdue Pharma promoted OxyContin heavily through a variety of other channels such as sponsoring pain-related educational programs and conferences,[10] distributing coupons and gifts,[11] and advertising in medical journals. These marketing efforts likely contributed to OxyContin's blockbuster success. Revenue from OxyContin sales skyrocketed over this time period, debuting at $48 million in 1996 and growing to $1.1 billion in 2000 (Van Zee, 2009) and $3.1 billion in 2010 (IMS, 2011). However, the aggressive marketing of OxyContin concerned the federal government and eventually led to a multi-state lawsuit against Purdue Pharma. In 2007, Purdue Pharma agreed to pay over $600 million in fines because of misleading advertising that minimized the risks of OxyContin.

While we consider 1996 as the beginning of the treated period throughout our analysis, OxyContin's prevalence and promotion expanded considerably over the first several years. In addition, higher-dosage tablets were separately introduced to market over time. It is difficult to attribute changes in outcomes to any specific promotional activity, new tablet introduction, or labeling change, but we will recognize the potential for a delayed and escalating effect in the early years. We adopt an approach which flexibly maps out changing effects over time.

2.2 Identifying Variation in Exposure to OxyContin

[9] In 1996, Purdue Pharma employed 318 sales representatives themselves and contracted with an additional 300 through a co-promotion deal with Abbott Laboratories. This number increased to 1,067 in 2002 (GAO, 2003).
[10] Purdue funded more than 20,000 pain-related educational programs from 1996-2002 (GAO, 2003). They also provided significant amounts of funding to several medical societies such as the American Pain Society and JCAHO, organizations which recommended more aggressive diagnosis and treatment of pain.
[11] As noted in the GAO report (2003), "according to DEA, Purdue's use of branded promotional items to market OxyContin was unprecedented among schedule II opioids, and was an indicator of Purdue's aggressive and inappropriate marketing of OxyContin."

This study exploits previously unexplored geographic variation in OxyContin's initial promotion and supply to identify its impact on overdose mortality. To understand the marketing strategies of Purdue Pharma around the launch of OxyContin, we made Freedom of Information Act (FOIA) requests to Florida, Washington, and West Virginia to obtain recently unsealed documents from early state court cases involving Purdue Pharma. Among these documents, we obtained the official launch plan of OxyContin, the focus group research conducted prior to the launch, and annual itemized budgets for OxyContin from 1996-2000. Examples of these records are shown in Figure A1. We also combined this information with court filings available online from Massachusetts.[12]

These documents reveal that Purdue Pharma would have difficulty penetrating markets that had enacted a state policy known as "triplicate prescription programs" (an early version of a prescription drug monitoring program or PDMP). Purdue Pharma viewed these programs as significant barriers to entry for OxyContin and it was suggested that they should not target marketing to these states.

A. What are Triplicate Prescription Programs?

Triplicate prescription programs aimed to reduce the diversion and misuse of controlled substances. In states with these programs, doctors were mandated to use state-issued triplicate prescription forms when prescribing Schedule II controlled substances (including certain opioids). Triplicate forms have three copies. The physician is required to maintain one copy for their records. The patient is given two copies to give to the pharmacy; the pharmacy keeps one and sends the third copy to the state prescription monitoring program.

At the time of OxyContin's launch there were five states with active triplicate programs (California, Idaho, Illinois, New York, and Texas), and these states had implemented their programs decades before OxyContin's launch. New York implemented the first (non-triplicate) prescription drug monitoring program in 1918, requiring a doctor prescribing certain quantities of heroin, cocaine, morphine, opium, or codeine to use prescription forms issued by the state health department (PDMP TTAC, 2018). New York transitioned to a triplicate program in 1972, which ended in 2001 when it was replaced by an electronic PDMP.[13]

[12] https://www.documentcloud.org/documents/5715954-Massachusetts-AGO-Amended-Complaint-2019-01-31.html, last accessed July 22, 2019

[13] This end date was confirmed in a personal correspondence with the New York Bureau of Narcotic Enforcement.

California adopted the first triplicate program in 1939 (Joranson et al., 2002) due to concerns of the growing diversion of opium-based pharmaceuticals (Simoni-Wastila and Toler, n.d.). California was also the last state in the country with a triplicate program, ending the program in 2004. California, like other states, adopted an electronic system to work in tandem with the triplicate prescription forms before eliminating the triplicate requirement. Illinois enacted its triplicate program in 1961, ending in 2000 when it was replaced by an electronic system.[14] Idaho adopted its program in 1967, switching to a duplicate program in 1997 (Joranson et al., 2002; Fishman et al., 2004).[15] Texas adopted a triplicate system in 1981 (Gage, 1982), converting to an electronic system in 1999.[16]

There is a small academic literature on the effects of triplicate programs. Survey evidence suggests that physicians intentionally avoided prescribing Schedule II drugs in response to multiple copy prescriptions programs (MCPPs) (Anness et al., 1995), which includes both triplicate and duplicate programs. Physicians in states with MCPPs appear to substitute Schedule II analgesics for less potent drugs (Wastila and Bishop, 1996). The literature has found that triplicate programs in particular led to especially large reductions in prescribing of drugs subject to the policy (Simoni-Wastila et al., 2004; Hartzema et al., 1992; Weintraub et al., 1991; Sigler et al., 1984).

There are two main reasons given in the triplicate literature and Purdue Pharma research for why triplicate programs would be a major deterrent for opioid prescribing. First, physicians in triplicate states were concerned about government oversight of their prescribing behavior. In a survey conducted after the implementation of the Texas program, it was found that physicians were generally supportive of the triplicate program but that potential review of prescriptions by the state narcotics division made physicians nervous (Berina et al., 1985). Although electronic monitoring programs also involved government insight, relative to electronic systems, "It was felt that paper forms, tangible reminders of such scrutiny when handled by the prescribing physician and dispensing pharmacist, would have a greater effect on reduced prescribing and dispensing than would an electronic system that remained largely invisible to health care practitioners" (Simoni-Wastila and Toler, n.d.).

[14] See footnote 85 of https://www.isms.org/opioidplan/, last accessed May 20, 2019
[15] Also see https://legislature.idaho.gov/wp-content/uploads/OPE/Reports/r9901.pdf, last accessed May 20, 2019
[16] See https://www.pharmacy.texas.gov/DPS.asp, last accessed March 10, 2019

Second, the hassle cost to the physician of triplicate programs were hypothesized to be especially large. Purdue Pharma's focus group research confirms this: "Writing triplicate prescriptions was more trouble than others, due to the details of the forms and the various people that need to be copied to them" (Groups Plus, 1995, p. 24).[17] Placing the burden specifically on the prescriber, not the pharmacist, suggests a key reason for why these programs are found in the literature to have substantial effects on prescriptions while evidence is more mixed for modern electronic monitoring programs. Also, triplicate programs required the prescriber to store their copy of the prescription for several years, an additional hassle cost unique to triplicate programs. In contrast, duplicate and single-copy programs did not require physicians to keep a copy, reducing the hassle and salience of those programs.

B. Purdue Pharma's Views on Triplicate States

Purdue Pharma's internal focus group and survey research emphasized that physicians in triplicate prescription programs would be less willing to prescribe OxyContin given its designation as a Schedule II substance.[18] The reports concluded that "there was a positive reaction to OxyContin among physicians in the non-triplicate states." (Groups Plus, 1995, p. 3)

However, doctors in triplicate states had a much more negative reaction:

> "The PCP's and surgeons in the non-triplicate state (New Jersey) indicated very high likelihood of using OxyContin for selective treatment of non-cancer related pain, and the rheumatologists in Connecticut also felt it had a place in their practice. However, the doctors in the triplicate states were not enthusiastic about the product at all, with only a couple indicating they would ever use it, and then in very infrequent situations." (Groups Plus, p. 43).

[17] The full quote is: "The triplicate laws seem to have a dramatic effect on the product usage behavior of the physicians. Specifically, the groups in Texas revealed almost no use of the Class II narcotics for treatment of non-cancer pain for the following two key reasons: The doctors did not want to provide the Government with any ammunition to question their medical protocols relative to pain management. The mere thought of the government questioning their judgement created a high level of anxiety in the focus group room among doctors. Writing triplicate prescriptions was more trouble than others, due to the details of the forms and the various people that need to be copied on them. To the extent that they can avoid this extra effort, they will try to follow alternative protocols."

[18] There were two separate focus group analyses. In one, physicians from New Jersey, Connecticut, and Texas were surveyed. In the other, physicians attending the American College of Osteopathic Family Physicians meeting in Orlando were surveyed. In the results from this latter research, physicians are divided into whether they practiced in triplicate and non-triplicate states and most of the results are stratified by triplicate status, suggesting the importance of this designation to Purdue Pharma.

The lack of enthusiasm for OxyContin by doctors in triplicate states relative to non-triplicate states is repeated dozens of times throughout the documents.[19] Based on this research, Purdue Pharma's launch plan acknowledges that "these regulations create a barrier when positioning OxyContin."

The focus group study concludes that while "there seems to be a definite opportunity for OxyContin as a medication for treatment of severe non-cancer pain among doctors in non-triplicate states. More work might have to be done to determine if the product is viable in triplicate states; however, the preliminary evidence is not encouraging." (Groups Plus, 1995, p. 4). Since there would be lower returns to promoting OxyContin in triplicate states, they recommended that "the product [OxyContin] should only be positioned to physicians in non-triplicate states" (Groups Plus, 1995, p. 55). Further they noted that "among the physicians in this triplicate state who do use Class II narcotics in the treatment of non-cancer pain, our research suggests the absolute number of prescriptions they would write each year is very small, and probably would not be sufficient to justify any separate marketing effort." The statements made in these internal documents strongly suggest that Purdue Pharma would initially target less marketing to triplicate states because of their lower expected returns. While we do not have complete information on Purdue Pharma's marketing strategy, we find that this hypothesis is borne out in the data as the triplicate states had among the lowest adoption of OxyContin in the country.

Finally, it appears that Purdue Pharma invested heavily in lobbying for the repeal of triplicate state policies. The clearest evidence of this is from the 1999 budget plan that includes a $750,000 line item to fund a "Program to impact the regulatory environment for opioid prescribing in triplicate states" (Purdue Pharma, 1999). In the following year's budget plan of 2000, they again included $750,000 to fund a "Regulatory Environment Program," which may have also been related to triplicate programs. There are also earlier mentions of triplicate

[19] In other representative examples from the focus group research: "the impact of the triplicate laws was particularly significant when one realizes that the most common narcotic used by the surgeons and PCP's in New Jersey was Percocet/Percodan, whereas in Texas [a triplicate state], this was a product/class of drugs prescribed by most doctors less than five times per year...if at all." and "the overall reactions to OxyContin were very mixed. The most positive were the PCP's and surgeons in New Jersey who viewed this to be an important innovation relative to the treatment of noncancer pain, and definitely would incorporate the product into their medication protocols. The physicians in the triplicate state did not respond positively to the drug, since it is a Class II narcotic which would require triplicate prescriptions. Therefore, only a few would ever use the product, and for them it would be on a very infrequent basis."

programs beginning with the launch plan in 1996 which earmarked $200,000 to fund a "Triplicate States Congress" and the 1998 budget plan earmarked $150,000 for "Opioid Prescribing Regulatory Guidelines CME program," which is described as providing "physicians with an understanding of improving trends in regulation of opioid use in non-cancer pain and how to effectively prescribe within those regulations," possibly prompted by the discontinuation of triplicate programs in some states around that time.

C. Classifying "Treated" States

Our empirical strategy will compare OxyContin exposure and fatal overdose trends in triplicate and non-triplicate states. We consider the non-triplicate states to be more exposed to OxyContin's introduction because the barriers to entry were lower and there was more initial marketing targeted to these states. We define "triplicate states" as states with active triplicate programs at the time of OxyContin's launch in 1996: California, Idaho, Illinois, New York, and Texas. All other states are classified as "non-triplicate states." The enactment and end years of the programs for the triplicate states are listed in the top row of Table 1. It is unclear whether and how quickly Purdue Pharma responded to states transitioning away from triplicate programs. Idaho's program ended in 1997, shortly after OxyContin's introduction. The other triplicate states all ended their programs by 2004, replacing them with electronic programs. Therefore, our results will speak to the long-run effects of the *initial* targeting of Purdue Pharma's marketing.

"Triplicate states" are mentioned regularly in the Purdue documents and some of the states that had triplicate programs, such as Texas, California, and New York are mentioned specifically (Groups Plus, 1995). However, there is never any mention in the Purdue Pharma documents of other existing state policies such as electronic, duplicate, or single-copy monitoring programs, which suggests that they viewed triplicate programs as an especially important barrier to OxyContin prescribing.

Two other states (Indiana and Michigan) had triplicate programs which were discontinued in 1994.[20,21] We do not consider these states as "triplicate states" because they

[20] In addition, Washington adopted a triplicate program but due to limited funding, triplicate forms were required only for physicians disciplined for drug-related violations (Simoni-Wastila and Tompkins, 2001; Fishman et al., 2004).

[21] Indiana's triplicate program began in 1987, but it was replaced by an electronic and single-copy program in 1994 (Joranson et al., 2002). Michigan enacted a triplicate program in 1988, but it also ended in 1994 (Joranson et al.,

were not likely viewed by Purdue Pharma as such at the time of the launch. Purdue Pharma's primary concerns with the monitoring and hassles associated with triplicate programs would no longer be present in these states. While we cannot be certain in knowing exactly how Purdue Pharma treated the former-triplicate states since we do not observe the full marketing strategy, to the extent that they also received less marketing, our results will be attenuated.[22]

3 Data

Our analysis uses data from several sources. We primarily rely on data on fatal overdoses and different measures of opioid supply and prescribing.

3.1 Mortality Data

To generate our primary outcomes, we use the National Vital Statistics System (NVSS) Multiple Cause of Death mortality files – the census of deaths in the U.S. – to study annual overdose deaths for 1983 to 2017.[23] We use restricted geocoded data to access state identifiers. We follow the coding used by the Centers for Disease Control (CDC) to categorize deaths as opiate-related. The 1983-1998 data use ICD-9 codes to categorize causes of deaths while the 1999-2017 data use ICD-10 codes. The CDC reports that the transition from ICD-9 to ICD-10 resulted in a small increase in poisoning-related deaths (not necessarily drug poisonings) of 2% (Warner et al., 2011). For most of our analysis, we will assume that our time fixed-effects will account for this transition, but we will also address this assumption below. The coding change in 1999 is explored more in Appendix Figure A2. We observe an increase in the overdose rate in 1999, though we observe comparable increases in other time periods as well when there were not coding changes. The 1999 increase is larger for opioid-related overdoses but, again, not

2002). Also discussed here: https://www.legislature.mi.gov/documents/2001-2002/billanalysis/Senate/htm/2001-SFA-0660-E.htm, last accessed March 10, 2019.

[22] Purdue Pharma referred to "nine triplicate states" in one instance when discussing retail pharmacy distribution. Since this statement was factually inaccurate at the time (there were five states with triplicate programs), we cannot be certain which set of states were being referenced. It is possible that they meant the nine states with paper-based monitoring systems (including duplicate and single-copy programs), since this statement appears in the context of pharmacists' concerns about the "voluminous paperwork" required for Class II opioids in these states, which would be a consideration with any paper-based system. To the degree that Purdue was also concerned about other paper-based programs (although these were never mentioned directly anywhere in the documents) and also marketed less in these states, our results will be attenuated. That said, the main focus of the discussion was always on triplicate programs and the burdens for the physician and this would apply only to states with active triplicate programs.

[23] We begin in 1983 because the 1981 and 1982 files do not include all deaths. Instead, in selected states, only half of deaths in those areas were included and they were included twice. This feature is not necessarily problematic, but we chose to start our sample with the 1983 data given that this already provides a lengthy pre-period.

uniquely large relative to other annual changes. Given concerns over missing opioid designations on death certificates even in recent years (e.g., Ruhm, 2018), there is value in studying the broad set of overdoses which should be robust to substance-specific classification errors. We present results using both measures.

For 1983-1998, we define drug poisonings as deaths involving underlying cause of death ICD-9 codes E850-E858, E950.0-E950.5, E962.0, or E980.0-E980.5.[24] When we study opioid-related overdoses, we will use deaths involving E850.0, E850.1, E850.2, or N965.0 (Alexander et al., 2018; Green et al., 2017).

For the 1999-2017 data, we code deaths as drug overdoses using the ICD-10 external cause of injury codes X40-X44, X60-64, X85, or Y10-Y14 (Warner et al., 2011). We use drug identification codes, which provide information about the substances found in the body at death, to specify opioid-related overdoses: T40.0-T40.4 and T40.6.[25] When describing the types of opioid deaths during this time period, we will also report disaggregated measures. Deaths with codes T40.1 indicates poisoning by heroin, T40.2 for natural and semisynthetic opioids (e.g., OxyContin), and T40.4 for synthetic opioids excluding methadone (e.g., fentanyl). It is difficult to create specific drug overdose measures which can be linked across the entire time period given differences in ICD-9 and ICD-10 codes[26] so we will only study overdoses by opioid type for 1999-2017 while highlighting the important caveat that this analysis does not include the pre-OxyContin period.

3.2 Opioid Supply

We will also study opioid supply measures using data on the legal supply of opioids at the state-level from the Drug Enforcement Agency's (DEA) Automation of Reports and Consolidated Orders System (ARCOS). The Controlled Substance Act of 1970 requires all manufacturers and distributors to report their transactions and deliveries of all Scheduled II-V substances to the Attorney General. ARCOS is the system that monitors and records the flows of

[24] See Table 2 of https://www.cdc.gov/drugoverdose/pdf/pdo_guide_to_icd-9-cm_and_icd-10_codes-a.pdf, last accessed November 29, 2018

[25] Linking opioid overdoses across ICD-9 and ICD-10 codes in this manner is recommended in Table 3 of https://www.cdc.gov/drugoverdose/pdf/pdo_guide_to_icd-9-cm_and_icd-10_codes-a.pdf. One exception is our use of T40.6. The inclusion of this code does not change our results meaningfully. We show this in the Appendix.

[26] For example, while E850.0 is sometimes labelled as "heroin" (or heroin and opium) when using ICD-9 codes, we find a 29% decline in heroin mortality between 1998 and 1999 using this coding (the estimated decline is similar if we include opium deaths in 1999).

these controlled substances as they move from manufacturers to retail distributors. ARCOS records the distribution of substances and does not necessarily reflect prescriptions. In the public data, only the active ingredients are reported so we observe the distribution of oxycodone by state, but not OxyContin specifically. These data are available online for 2000-2017,[27] and we were able to collect earlier data for 1997-1999 using the WayBack Machine.[28] Because of this paper's specific interest in OxyContin, we made a FOIA request for OxyContin distribution specifically and received these data for 2000-2016.[29]

We will also provide information on hydrocodone distribution. Hydrocodone (e.g., Vicodin) is a clinical substitute for oxycodone and is also commonly abused, although it is primarily classified as a Schedule III substance and generally not subject to triplicate state program rules. We report all ARCOS measures in morphine equivalent doses (60 morphine milligram equivalents).

Unfortunately, it is difficult to obtain measures of opioid prescriptions around 1996.[30] To provide evidence about pre-2000 OxyContin prescription variation, we use quarterly Medicaid State Drug Utilization Data (SDUD) for 1991-2005,[31] which lists outpatient drugs paid by Medicaid agencies by quarter and state.[32] We aggregate all SDUD analyses to the annual level given concerns about uneven reporting across quarters in these data. While the Medicaid population is non-representative, we consider prescriptions among this group as a potentially useful proxy for state prescribing behavior while also representing an important population disproportionately affected by the opioid crisis (e.g., CDC, 2009; Sharp and Melnik, 2015; Whitmire and Adams, 2010; Fernandes et al., 2015). Opioid Medicaid prescriptions are highly-correlated with the opioid supply measures in the ARCOS data. Annual Medicaid OxyContin

[27] The data are found here: https://www.deadiversion.usdoj.gov/arcos/retail_drug_summary/, last accessed November 30, 2018.
[28] https://web.archive.org/web/20030220041015/https://www.deadiversion.usdoj.gov/arcos/retail_drug_summary/
[29] Our request for pre-2000 OxyContin data was denied, and we were told that these years of data are unavailable.
[30] Many of the data aggregators which researchers often purchase prescription drug claims data from (e.g., IQVIA) do not maintain state-specific records for the 1990s or early 2000s.
[31] We end the sample in 2005 due to the introduction of Medicare Part D.
[32] While recent version of SDUD suppress the number of prescriptions for a given NDC-state-quarter when that number is smaller than 10, we rely on an earlier version of the data downloaded before this suppression was implemented.

prescriptions per 1,000 beneficiaries[33] and per capita OxyContin supply (ARCOS) in 2000 – the first year available – have a correlation coefficient of 0.66.

We also used a restricted version of the Medical Panel Expenditure Survey (MEPS), accessed through the AHRQ Data Facility. The MEPS is a nationally-representative survey of households and their medical providers, including medical and pharmaceutical claims. We constructed per capita OxyContin prescriptions for 1996-2016. While state identifiers are available in the AHRQ Data Facility, the MEPS is not representative at the state-level, but our results are similar with and without the MEPS survey weights. Per capita OxyContin prescriptions in the 2000 MEPS have a cross-sectional (N=51) correlation with the 2000 ARCOS of 0.53.

All population measures are estimates generated by the Surveillance, Epidemiology, and End Results Program (SEER). We will also control for some demographics constructed using SEER data. In addition, we control for the fraction of the population with a college degree, which was created using Current Population Survey data (Ruggles et al., 2018).

3.3 Summary Statistics

In Table 1, we present summary statistics for 1991-1995, representing the pre-period for our difference-in-differences estimates, separately for each triplicate state as well as aggregated means by triplicate status. Strikingly, overdose rates are higher on average in the triplicate states before OxyContin's introduction, including overdoses involving opioids. With the exception of Idaho, each triplicate state had an opioid-related overdose rate above the median. Some of these differences can be explained by disproportionately higher rates of cocaine overdoses in triplicate states. When overdoses involving cocaine are eliminated, the differences between triplicate and non-triplicate states shrink. Demographically, triplicate states were less white (by 2.8 percentage points) and had a higher fraction of people with college degrees. They also had a smaller fraction of the 25-59 age group working (by 3 percentage points).

Appendix Table A1 ranks states based on their oxycodone prescribing behavior using 1991-1995 Medicaid oxycodone prescriptions per 1,000 beneficiaries. Triplicate states have some of the lowest oxycodone prescribing rates in the country prior to OxyContin's introduction.

[33] We scaled the number of prescriptions by the number of Medicaid beneficiaries using data from the University of Kentucky Center for Poverty Research (University of Kentucky Center for Poverty Research, 2018).

4 Empirical Strategy

We compare outcomes in non-triplicate states relative to triplicate states before and after the launch of OxyContin in a difference-in-differences framework. We rely primarily on event-study models due to their transparency and because the timing of the effect is of interest. We report the differential change in overdoses for non-triplicate states relative to triplicate states given that non-triplicate states were more "exposed" to the introduction of OxyContin. Our primary specification is

$$y_{st} = \alpha_s + \gamma_t + 1(\text{Non-Triplicate})_s \times \beta_t + \varepsilon_{st}, \quad (1)$$

where y_{st} represents quarterly overdoses per 100,000 people in state s in quarter t. This specification includes state (α_s) and quarter (γ_t) fixed effects. We normalize the β_t coefficient for the fourth quarter of 1995 to equal zero. We will present population weighted and unweighted regression results – our baseline results are weighted. We present the estimates of β_t along with 95% confidence intervals graphically.

We will also present difference-in-differences estimates using more aggregated time intervals for the purposes of summarizing the event study results. The excluded category in this specification is 1991-1995. We estimate three separate "post" effects to permit some heterogeneity while still providing more aggregated effects. The first post-OxyContin time period is 1996-2000. This period represents the introduction of OxyContin and the launch of different dosages as well as the ramp up of marketing by Purdue Pharma. We also estimate a separate effect for 2001-2010, corresponding to the "first wave" of the opioid crisis. Finally, we estimate a separate effect for 2011-2017, representing the second and third waves of the opioid crisis. In general, as the more flexible quarterly event studies will show, our results are not sensitive to the choice of time periods to aggregate. The specification is

$$\begin{aligned} y_{st} = \alpha_s + \gamma_t + \delta_1 \times 1(\text{Non-Triplicate})_s \times 1(1996 \leq Year \leq 2000)_s \quad (2) \\ + \delta_2 \times 1(\text{Non-Triplicate})_s \times 1(2001 \leq Year \leq 2010)_s \\ + \delta_3 \times 1(\text{Non-Triplicate})_s \times 1(2011 \leq Year \leq 2017)_s + \boldsymbol{X}'_{st}\theta + \varepsilon_{st}. \end{aligned}$$

Our controls include the fraction of the population that is white, the fraction ages 25-44, and the fraction with at least a college degree.[34] We interact these covariates with year

[34] While the specification operates at the quarter level, these covariates only vary annually.

indicators, permitting them to have differential effects in each year.[35] We do not include some of the typical controls often included in models of opioid overdoses, including policy variables (e.g., PDMPs, medical marijuana laws, etc.) and economic condition proxies. A motivation of this paper is to understand the initial conditions of the opioid crisis, which has potentially affected a wide range of outcomes. We remain agnostic about the breadth of effects and choose not to control for these types of covariates in our main specification given that these covariates may also be outcomes. However, we will show that our results are robust to conditioning on subsequent policy adoption.

In addition, we have some outcome variables for which the data first becomes available after 1996. Despite the lack of a pre-period, it will be useful to analyze the cross-sectional levels and trajectories of these outcomes. For these outcomes, we plot the non-normalized differences in the outcomes between triplicate and non-triplicate states, implemented by excluding state fixed effects.

Because we have a limited number of untreated states, traditional cluster covariance estimators are likely to produce standard error estimates which are too small (Conley and Taber, 2011). For this reason, we use a wild bootstrap method at the state-level.[36] When there are a small number of clusters, Webb (2013) points out that there will be too few unique t-statistics produced by a wild bootstrap using Rademacher weights to generate meaningful p-values. In a difference-in-differences framework, a related problem occurs when there are a small number of untreated (or treated) units relative to the total number of units.[37] Webb (2013) introduces a 6-point distribution to use with the wild bootstrap for a few clusters to generate more independent t-statistics, and this distribution is beneficial in the difference-in-differences context for similar reasons.[38] Given p-values for a range of null hypotheses, we construct and report 95% confidence intervals. The 95% confidence intervals will not be symmetric using this approach. [39]

[35] Recent work has suggested that this type of flexibility is necessary in difference-in-differences analyses (Jaeger et al., 2018).
[36] Specifically, we use the approach in which a null hypothesis is imposed and then a t-statistic is compared to distribution of placebo t-statistic (this is method 13 on page 418 of Cameron et al. 2008).
[37] In this case, the bootstrapped t-statistics are all within the neighborhood of a finite number of values. This issue is discussed in the case of one treated (or untreated) unit in MacKinnon and Webb (2018).
[38] When the number of treated or untreated units is especially small, then other techniques are likely necessary such as a permutation-type test, though these approaches often require additional assumptions. With five untreated clusters, however, and a 6-point distribution, this approach produces adequate independent variation in the bootstrapped t-statistics.
[39] We use the boottest package in Stata (Roodman et al., 2018) to implement this procedure.

Alternative methods, such as wild bootstrap with Rademacher weights or traditional "clustered" standard errors, provide tighter confidence intervals than those reported. In robustness tests, we will show traditional standard errors in Appendix Table A2.

5 Results

Our analysis begins by studying the differences in OxyContin exposure across triplicate and non-triplicate states. Given large differences in the supply of OxyContin between the two sets of states, we then estimate the impact of this differential initial exposure to OxyContin on trends in fatal overdoses in the short and long run. We also investigate alternative explanations for these trends including differential policy adoption and substance abuse treatment access, supply of other opioids, and state characteristics such as population size. Finally, we explore mechanisms for the differential initial exposure to OxyContin.

5.1 Effects of Triplicate Status on OxyContin Exposure

In Figure 2, we first show that non-triplicate states were more exposed to the introduction of OxyContin as measured by OxyContin distribution and prescriptions per capita. We begin by presenting trends for the supply of OxyContin using ARCOS data, the most comprehensive supply measure available. Panel A of Figure 2 shows the trend in quarterly OxyContin supply for triplicate and non-triplicate states, measured in morphine equivalent doses per capita, for the available years of data 2000-2016. Panel B shows the difference in means between the two sets of states and 95% confidence intervals. By 2000, non-triplicate states had two and a half times the amount of OxyContin supply per capita than triplicate states. These differences persisted through 2017 and were statistically significant in almost every quarter.

As complementary measures of OxyContin exposure, we use two other data sources that enable us to observe OxyContin prescriptions for earlier years. Panel C shows trends for Medicaid OxyContin prescriptions per 1,000 beneficiaries from 1996-2005. Panel D plots OxyContin prescriptions per 1,000 using the restricted-access MEPS for 1996-2016. In both datasets, we observe higher rates of OxyContin prescriptions in non-triplicate states that begin as early as 1996 in the Medicaid data and 1997 in MEPS (there are no observations for OxyContin in the 1996 MEPS[40]). Overall, OxyContin prescribing increases rapidly during the first several

[40] The 1996 MEPS is relatively small since it contains only half the number of panels as the other years, which may partially explain the lack of OxyContin in the data.

years after its launch, however, there is a striking reduction in total OxyContin prescriptions in 2005-2006, revealing some important dynamics in early OxyContin sales and promotion.[41] OxyContin prescribing decreases again after its abuse-deterrent version is released in 2010. However, non-triplicate states continue to experience differential exposure to OxyContin throughout these downturns.

Using the Medicaid data, we further examine how the initial "adoption" of OxyContin varied across states by triplicate status. Panel A of Appendix Figure A3 shows the number of prescriptions per 1,000 beneficiaries in 1996 across all states. The triplicate states largely cluster near the bottom of the distribution. Four of the triplicate states (CA, IL, NY, TX) are among the five states with the lowest number of OxyContin prescriptions per capita in 1996, although Idaho is an exception with higher prescribing.[42] We cannot report state-specific figures from the restricted-use MEPS, but Panel B replicates this distribution using the first available quarter of ARCOS data in 2000. The pattern is similar with four of the triplicate states positioned among the lowest six states in the distribution. This shows that triplicate states were some of the lowest OxyContin adopters in the country.

5.2 Exposure to Other Opioids in Triplicate and Non-Triplicate States

We next examine whether there are differences in the supply of other prescription opioids across triplicate and non-triplicate states that could also contribute to differences in overdose rates. We use the ARCOS data to compare the supply of oxycodone with hydrocodone, a clinical substitute which is also commonly abused. Most hydrocodone products during this time period were classified as Schedule III controlled substances and would be unaffected by triplicate programs. These trends are shown in Figure 3 starting in 1997, the earliest year of data available. Hydrocodone supply is nearly identical in triplicate and non-triplicate states over the

[41] One likely explanation for this decline is the end of a copromotion agreement with Abbott Laboratories. Abbott provided at least 300 sales representatives through this agreement to sell OxyContin (GAO, 2003), initialing doubling Purdue Pharma's sales force, and a company executive documented in 1997 that 25% of OxyContin prescription were written by "Abbott MD's." This agreement with Abbott ended just around the time that we see the dramatic drop in OxyContin supply (https://www.statnews.com/2016/09/22/abbott-oxycontin-crusade/, last accessed May 8, 2019) as Purdue Pharma decided not to renew this relationship given early reports about OxyContin abuse and the federal government's concerns over these reports. In April 2008, Purdue Pharma began to increase its sales force again (p. 72 in Commonwealth of Massachusetts, 2019).

[42] This exception may reflect that Idaho was in the process of replacing its triplicate program at the time. We do not have complete information about Purdue Pharma's marketing targets so it is unclear whether they anticipated this legislative change and adjusted their promotional activities in response.

entire 1997-2017 time period. Meanwhile there are large differences in oxycodone supply between triplicate and non-triplicate states.

The difference in oxycodone supply between the two sets of states exceeds the difference observed for OxyContin alone in Figure 2 and grows over time, suggesting possible spillovers of OxyContin's promotion on the use of other oxycodone products. This would be consistent with Purdue Pharma's marketing strategies that aimed to promote the use of strong oxycodone products for non-chronic pain to doctors who were initially less comfortable using these products.

In Table 2, we present regression estimates for ARCOS measures of the supply of OxyContin, oxycodone, and hydrocodone. These estimates represent the differences in outcomes between non-triplicate and triplicate states for each time period. OxyContin supply is significantly greater in non-triplicate states in each time period (the 1997-2000 estimate for OxyContin refers only to 2000 due to data availability), though we observe evidence of convergence over time. We estimate sizable differences in oxycodone supply that are statistically significant and growing from the initial period observed in the data to the last period. We do not observe significant differences in hydrocodone at any point in time.

5.3 Effects of OxyContin Exposure on Fatal Overdoses

Next, we examine whether the differential exposure to OxyContin led to differences in overdose deaths over time. Figure 4 presents these results graphically, separately for overall overdoses and opioid overdoses. Panel A shows trends in fatal overdoses per 100,000 people for triplicate and non-triplicate states. During the decade prior to OxyContin's introduction, non-triplicate states had lower rates of overdose deaths than triplicate states,[43] but shortly after the launch of OxyContin this relationship flipped. Non-triplicate states experienced substantial growth in overdose deaths that started immediately after OxyContin's introduction and accelerated throughout the early 2000s. Meanwhile, triplicate states experienced little growth in overdose deaths for several years (until about 2002). Prior to OxyContin's introduction, these two sets of states generally had similar trends.

[43] These differences may be partially due to the crack epidemic of the early 1990s which was more concentrated in urban areas. We discuss the effect of cocaine overdoses on these pre-1996 trends in greater detail in Section 5.4.

Panel B presents the coefficients from estimating the event-study specification in equation (1) and 95% confidence intervals. The coefficients are all statistically insignificant prior to OxyContin's launch which indicates that there were no differences in trends across triplicate and non-triplicate states. However, by 1999, these trends begin to diverge as overdose deaths increased rapidly in non-triplicate states relative to triplicate states. The differential quarterly effect becomes statistically significant in 2003 and continues through 2017. Although, as we will show below, a joint test that the 1996-1998 estimate is equal to 1991-1995 can be rejected at the 5% level. It is not surprising that the largest effects on overdoses are delayed given the relatively low level of sales in the earliest years, expansions in promotion over time, and the FDA's relabeling in 2001 that expanded opportunities for greater marketing for chronic use.

The patterns are similar for opioid-related overdose deaths in Panels C and D of Figure 4. The event study estimates are generally smaller in magnitude because of the smaller baseline mean relative to total overdoses. The event studies for total overdose and opioid overdoses are also similar without population-weights or when we condition on time-varying covariates.[44]

To summarize the magnitude of these effects, in Table 3, we present difference-in-differences estimates from equation (2). Appendix Table A2 provides the same estimates but with traditional (non-bootstrapped) clustered standard errors. We present results for overall overdoses and opioid overdoses separately but find similar patterns.[45] In Column 1 of Table 3, we present unweighted estimates. Relative to the baseline 1991-1995 period, non-triplicate states experienced a relative increase in total overdose deaths of 0.311 per 100,000 in the earliest years of the launch (1996-2000). This effect is statistically significant at the 1% level. By 2011-2017, the relative increase grew to 1.562 fatal overdoses per 100,000. In Column 2, we present weighted estimates. The point estimates are larger in magnitude. Non-triplicates experienced a differential rise in overdoses of 0.331 per 100,000 for 1996-2000. We estimate that the "counterfactual" overdose rate of non-triplicates during this time period would have been 1.029 (per 100,000) if they had been triplicate states, implying that the increase in overdoses represents

[44] See Figure A4 for the unweighted event study estimates. Figure A5 replicates Figure 4 but conditions on time-varying covariates. Figure A6 replicates Figure A4 while conditioning on time-varying covariates.

[45] As discussed above, given difficulties in coding opioid-related deaths, we suspect that opioid overdoses were not consistently coded over time and that the broader overdose category includes some additional opioid-related deaths. For this reason, we favor the broader measure of overdoses, especially when studying early overdose trends.

a 32% increase (0.331/1.029).[46] This difference grows to 1.976 by 2011-2017, representing a 78% increase for non-triplicate states. Column 3 shows that the estimates are robust to including time-varying covariates. In Column 4, we include Census region-time interactions to account for geographic differences in overdose rate growth. The results are generally similar. For opioid-related overdoses in the bottom panel of Table 3, the 1996-2000 estimate implies a 42% increase for non-triplicate states; the 2011-2017 estimate implies that non-triplicate status more than doubled the opioid overdose rate. Thus, proportionally, we find larger effects for opioid-related overdoses than total overdoses.

5.4 State-Specific Results

We also study heterogeneity in the overdose rate changes across states to determine whether these changes are common across triplicate states or driven by a single outlier state. In Figure 5, we analyze changes in overdose rates for each triplicate state separately relative to the changes experienced by all of their neighboring states. We graph the change in the overdose rate for the ten years after OxyContin's launch (1996-2005) relative to the ten years before (1986-1995). We find that for four out of the five triplicate states, the triplicate state had the smallest growth rate relative to all of their bordering states[47] and the one exception – Illinois – had the second-to-lowest growth rate. This pattern is not specific to the chosen set of years. Figure A7 repeats this exercise but uses the most recent 10 years of data (2008-2017) as the post-period.

Figure A8 shows the placement of the triplicate states relative to all other states in the country. The triplicate states are clustered close to the bottom of the distribution of overdose changes. The remarkable consistency of low overdose growth across the triplicate states and relative to other states in their regions strongly suggests that it was the triplicate program and not other state characteristics which drove the relatively slow growth in these states, though we explore alternative explanations further in the next section

[46] The counterfactual rate is the overdose rate of the non-triplicate states minus the estimated effect of "non-triplicate" in that time period. This represents the overdose rate that would have been observed had the non-triplicate states continued to follow the growth rate of the triplicate states.

[47] While Idaho had a relatively high OxyContin adoption rate, many of its neighbors did too, suggesting meaningful regional differences. For Idaho, this high rate of adoption did not translate into a high growth rate in overdoses, which might suggest simply a high demand for legitimate uses of the product which have different consequences than marketing-driven adoption of the drug. Other explanations are also possible.

5.5 Robustness Tests

In this section, we explore the robustness of our findings. These robustness tests are presented in Table 4. We will also present complementary figures throughout this section. We focus our discussion on overall overdoses, but find generally similar results for opioid overdoses. Column 1 repeats the main baseline estimate (Column 2 of Table 3).

5.5.1 Non-Opioid Overdoses

We begin by considering whether other types of overdoses, specifically cocaine, may be confounding our analysis. We focus on cocaine because the pre-period coincides with the end of the crack epidemic and we observe a differential spike in cocaine overdoses in the triplicate states prior to OxyContin's introduction (see Appendix Figure A9). Column 2 of Table 4 excludes overdoses involving cocaine. While the estimates decrease in magnitude, this is due to the smaller baseline mean. In proportional terms, the results are similar to the main results. We still observe statistically significant growth in non-triplicate states in each post-period. The event studies are also similar when we exclude overdoses involving cocaine (see Appendix Figure A10).[48]

5.5.2 Population Size

It is notable that four of the triplicate states are the largest states in the country. One concern is that states with large populations (and more urban cities) would have experienced systematically different trends in overdose deaths independent of their triplicate status. To test for this possibility, we compare triplicate states to the largest non-triplicate states.

In Column 3 of Table 4, we select the four largest non-triplicate states in terms of 1990 population size (Florida, Pennsylvania, Ohio, and Michigan) as comparison states for the four largest triplicate states and Idaho. We replicate our difference-in-differences analyses with these select states. The estimates are generally similar to the main estimates. Despite the additional noise due to the much smaller sample size, the estimates remain statistically different from zero. These results suggest that systematic difference in population sizes are not driving our results.

[48] In addition, our original coding included T40.6 ("other and unspecified narcotics") as opioids for the ICD-10 years (1999-2017). In Appendix Figure A11, we drop overdoses which involve T40.6 and *not* T40.0-T40.4. The results are similar.

Though not shown here, this result is also robust to including additional large population states in the comparison group and to controlling for 1990 population interacted with a full set of year indicators.

5.5.3 Adoption of Other Policies

Another concern is whether triplicate states followed different policy paths which addressed opioid misuse more effectively than those in non-triplicate states. Given that the triplicate states were the earliest adopters of PDMPs, they may have also implemented other mechanisms which reduced opioid access or potentially were at the frontier of reducing prescription drug abuse in the years following OxyContin's introduction. In Column 4 of Table 4, we compare triplicate states to states with other types of PDMPs in 1996—electronic PDMPs and duplicate programs. These programs were not mentioned in Purdue Pharma documents, yet if we believe that some states are simply "ahead of the curve" in moderating opioid misuse, then we would expect that states with electronic PDMPs and duplicate programs would also experience slower growth in overdoses. However, the estimates actually *increase* when we use this sample, suggesting that triplicate states experienced uniquely small changes in overdose growth even relative to states with other types of PDMPs.[49]

As a complementary approach, in Column 5 of Table 4, we replicate our main analysis for the full sample of states while controlling for a set of policy variables: indicators for whether the state has any PDMP, "must access" PDMP, pain clinic regulations, medical marijuana laws, and legal/operational medical marijuana dispensaries. Again, the results are similar, implying that triplicate and non-triplicate states did not adopt systematically different policies post-1996 which can explain the discrepancy in the growth rate of overdoses.

We also explicitly test whether triplicate and non-triplicate states had differential adoption of stronger PDMP features following OxyContin's introduction (e.g., mandatory use, timely reporting, etc). Pardo (2017) [50] introduces an index of PDMP strength for 1999-2015, aggregating several different PDMP dimensions together and validating the metric by showing that increases in PDMP strength are related to reductions in opioid-related overdose rates. In Appendix Figure A12 (Panel A), we show differences in PDMP strength (equal to 0 for states

[49] Results are similar if we drop the duplicate states and use only electronic PDMP states as the comparison group.
[50] We thank Bryce Pardo for sharing his data.

without a PDMP) for non-triplicate states relative to triplicate states. Unsurprisingly, triplicate states have stronger PDMPs in the early years of the sample. However, we see that PDMP strength begins to converge in 2004 while we do not observe convergence in overdose rates. In Panel B, we select on states that had any type of PDMP as of 1996 (the same set of states used in the analysis in Column 4 of Table 4) and compare triplicate states to states with the other types of PDMPs. Supporting our earlier assumptions, there is little difference in how PDMP strength evolved between these two groups of states. Yet we found much larger overdose growth in non-triplicate states.

We also test for initial differences in substance abuse treatment access between triplicate and non-triplicate states. States with more access to substance abuse treatment may have stymied rising overdose rates following OxyContin's introduction. We use the 1997 Uniform Facility Data Set (UFDS), a predecessor to the N-SSATS which records all known private and public substance abuse treatment facilities. We use this metric, scaled by population, as a measure of access to treatment.[51] The 1997 UFDS is the first year available from SAHMSA so we assume that treatment facilities did not open or close immediately due to differential OxyContin exposure. In 1997, non-triplicate states had 3.938 treatment facilities per 100,000; triplicate states had 4.000. These rates are nearly-identical, and the difference is statistically insignificant (p-value=0.94).

5.5.4 ICD-9 to ICD-10 Coding Changes

Finally, in Column 6 of Table 4, we limit the sample to 1991-1998, which precedes the switch from ICD-9 to ICD-10 codes. We continue to find statistically significant growth in overdoses (at the 5% level) in non-triplicate states suggesting that the coding change is not confounding our analysis. The effects are not statistically significant for opioid-specific overdoses, which is consistent with the difficulties in creating a consistent series for opioid-specific deaths around the coding change.

[51] More information about the UFDS can be found here: https://www.datafiles.samhsa.gov/study/uniform-facility-data-set-us-ufds-1997-nid13557, last accessed May 9, 2019.

5.6 Alternative Inference Methods

In Appendix B, we replicate our results using synthetic control methods. We estimate similar overdose growth differences as our main OLS estimates.

5.7 Alternative Outcomes

5.7.1 Non-Mortality Outcomes

Fatal overdoses are an extreme outcome of OxyContin use. We are also interested in understanding non-fatal harms resulting from OxyContin's introduction. In Appendix Figure A13, we show trends in opioid misuse rates in triplicate and non-triplicate states using the National Study of Drug Use and Health (NSDUH) from 2004-2012.[52] In Panel A, we first compare cross-sectional differences in self-reported rates of OxyContin misuse. We find large and statistically significant differences in OxyContin misuse rates across triplicate and non-triplicate states. Non-triplicate states have about twice as much OxyContin misuse as triplicate states. However, in Panel B, for pain reliever misuse (excluding OxyContin) we do not observe meaningful or statistically significant differences. This set of results is consistent with the difference in overdose rates being primarily attributable to OxyContin.[53]

As a complementary measure, in Appendix Figure A14, we examine differences in substance abuse treatment admissions for opioids using the Treatment Episode Data Set (TEDS). The TEDS includes all admissions into treatment facilities receiving public funding.[54] The results are consistent with the fatal overdose findings. Non-triplicates states experienced sharper growth in substance abuse treatment admissions for opioids after OxyContin's introduction. These results help corroborate the mortality findings while also providing evidence that OxyContin exposure affected less extreme measures of substance use.

[52] The NSDUH is a nationally representative household survey of individuals ages 12 and older and is the largest annual survey collecting information on substance use in the U.S. State-level metrics are publicly reported in two year waves. For more information, please consult Section II.A of Alpert et al. (2018).
[53] These measures are self-reported and, thus, likely prone to some reporting error. NSDUH uses techniques designed to elicit accurate and honest answers from respondents. These methods – such as showing pictures of OxyContin – reduces concerns that the "OxyContin misuse" measure reflects misuse of other types of oxycodone.
[54] While TEDS is often used in substance use research, there are concerns about underreporting of admissions. Some states may not report in each year or may not report admissions in the same manner over time (SAMHSA, 2013). Our assumption is that triplicate states did not systematically change reporting (relative to non-triplicate states) behavior around 1996. We tested this assumption explicitly by replicating the analysis for other substances (e.g., marijuana, alcohol) and do not observe a similar pattern, suggesting that reporting issues are not driving the results.

5.7.2 Heroin and Fentanyl Overdoses

We also present evidence about the type of opioid involved in fatal overdoses from 1999-2017. The specific type of opioid involved in overdose deaths is not reliably coded before 1999. Appendix Figure A15 shows differences across triplicate and non-triplicate states for natural and semisynthetic opioids (e.g., oxycodone and hydrocodone), heroin, and synthetic opioids (e.g., fentanyl). The results show that, prior to 2010, the difference in overdose mortality between triplicate and non-triplicate states is mainly limited to natural and semisynthetic opioids, the category which includes OxyContin. Heroin overdose trends are nearly-identical across the two sets of states before 2010. Synthetic opioid trends are similar prior to 2014.

Interestingly, we observe a large relative increase in heroin-related overdoses in non-triplicate states starting in 2011, although this difference is not statistically significant. This is qualitatively consistent with the findings in Alpert et al. (2018) that areas with high rates of OxyContin misuse—which we showed in the above section was related to triplicate status—experienced faster growth in heroin overdoses beginning after an abuse-deterrent version of OxyContin was introduced in 2010. Similarly, Evans et al. (2019) found that states with more oxycodone supply experienced faster growth in heroin overdoses after OxyContin's reformulation. We also find that sharp differences in synthetic opioid overdose death rates emerged in 2014, which is consistent with reformulation leading to substitution to heroin and the delayed entry of fentanyl into the United States heroin supply (Ciccarone, 2017).

The timing of these differential drug-specific trends suggests that the introduction of OxyContin had long-term effects on drug overdose patterns through each wave of the opioid crisis. As the opioid crisis transitioned first to heroin and then to synthetic opioids such as illicit fentanyl, the states that were less exposed to OxyContin 15-20 years prior were also less affected by these transitions. The causal link to OxyContin's introduction is supported by previous research which has shown that these transitions were primarily induced by exposure to OxyContin interacted with reformulation.

5.7.3 Deaths of Despair

Explaining growth in fatal overdoses is a central theme of the "deaths of despair" hypothesis discussed in Case and Deaton (2015, 2017). This hypothesis suggests that we would

have observed an increase in mortality even in the absence of a rise in opioid supply due to cultural and economic factors. In this section, we study other non-opioid deaths of despair – specifically, suicides (excluding overdoses) and alcohol poisonings. For alcohol poisonings, we end the analysis in 2006 given a change in coding of alcohol-related deaths in 2007.[55]

Figure A16 presents the event study estimates. We observe little evidence, especially of the same magnitudes and significance as the overdose effects, of differential rises in suicide rates or alcohol poisoning rates. Suicides appear to trend slightly upward in the non-triplicate states relative to the triplicate states beginning in the pre-period and continuing through the end of the sample period. Alcohol poisonings exhibit little evidence of any pattern until a small differential decline around 2006. Overall, we find no evidence that other deaths of despair follow the same patterns as overdose deaths, suggesting the differential supply and access to opioids played a crucial role in the opioid crisis. Moreover, the lack of a *decline* in suicides and alcohol poisonings suggests that opioid overdoses were not substitutes for these types of deaths.

6 Mechanisms

The evidence above shows that non-triplicate states were more exposed to the introduction of OxyContin, leading to a large and enduring increase in overdose rates. In this section, we explore two possible mechanisms for what drove the substantial differential growth of OxyContin exposure in non-triplicate states. First, the triplicate programs themselves may have independently thwarted widespread OxyContin adoption. Second, since internal documents suggest that Purdue Pharma did not initially position OxyContin in triplicate states, this lack of marketing may have reduced OxyContin exposure. It is inherently difficult to disentangle these two mechanisms because the recommendations to not promote OxyContin in triplicate states were partially based on the belief that triplicate programs created a prescribing culture which would involve very little adoption of oxycodone products.

In this section, we conduct two tests to provide evidence on these mechanisms. In the first test, we compare triplicate states to other states that had similarly low prescribing of oxycodone prior to 1996. We will find that triplicate states are unique in terms of their low

[55] Alternatively, we could rely on time fixed effects to account for this change and assume there should not have been a differential effect of this change on our measure of alcohol poisonings. When we replicate our analysis using this approach, there is still little evidence of any differential effects.

overdose rate trends and exposure to OxyContin even when compared to states with similar oxycodone prescribing habits. In a second test, we compare the five triplicate states to two former triplicate states that had discontinued their programs prior to 1996. Again, we will find that the five triplicate states experienced uniquely different overdose patterns. This supports the role of Purdue Pharma's marketing rather than cultural factors (i.e., entrenched prescribing habits) in explaining OxyContin exposure and mortality patterns.

First, we replicate the main event study analysis but limit the sample to the triplicate states and the five non-triplicate states with the lowest oxycodone prescribing rates[56] in the 1991-1995 Medicaid data (as previously listed in Appendix Table 1). Figure 6 shows these event study estimates. For both OxyContin supply (Panel A) and overdose rates (Panel B), the estimates are remarkably similar to the main results of the paper. We have also operationalized this test in alternative ways such as estimating the main event study for all states while controlling for a linear index of the 1991-1995 Medicaid prescribing rate interacted with time indicators, and the estimates are not meaningfully affected.

Next, we test for whether there were differential effects for two former triplicate states – Michigan and Indiana – which had triplicate programs prior to OxyContin's introduction but had eliminated them by 1994. These former triplicate states serve as useful counterfactuals since they would have similar prescribing habits as the five triplicate states (indeed, they were also among the lowest prescribers of oxycodone prior to 1996 as shown in Appendix Table A1), yet it is possible that they were not spared from Purdue Pharma's marketing since they did not have active triplicate programs at the time of OxyContin's launch. Although we do not observe the full OxyContin promotional strategy, the Purdue Pharma documents never mention former triplicate states directly and seemed most concerned with the monitoring and hassles associated with active triplicate programs. Nevertheless, there is uncertainty about how Purdue Pharma treated former triplicate states, so this analysis jointly tests for whether Purdue Pharma avoided marketing to former triplicate states.

In Appendix Figure A17, we estimate our main event study specification comparing the five triplicate states to all other non-triplicate states, but permit the former triplicates to have

[56] This metric is highly-correlated with oxycodone prescriptions divided by oxycodone plus hydrocodone prescriptions, and the results are similar when using this metric. This alternative metric has the advantage of accounting for differences in opioid prescribing more generally, but we do not find that it matters empirically.

different effects than the never-triplicates. In Panel A, we present the differences in OxyContin supply between triplicate states and either former triplicates or never triplicates (confidence intervals are suppressed). The former triplicates adopted OxyContin at a substantially higher rate than the triplicate states, although at a lower rate than the never triplicates (the difference is 0.10 morphine equivalent doses per capita in former triplicates versus 0.14 in never triplicates in 2000q1). Additionally, Appendix Figure A3 (discussed earlier) showed that the former triplicate states adopted OxyContin at about the median rate.[57] Overall, the former triplicates appear more like the never triplicates than the triplicate states in terms of OxyContin exposure. In terms of overdoses, Panel B presents the coefficients for the former triplicates and the never triplicates. The former triplicates and never triplicates experienced similar overdose trajectories relative to triplicate states.

We draw two conclusions from these tests. First, prescribing culture alone cannot explain the lack of OxyContin adoption by triplicate states, since states with similarly low levels of oxycodone prescribing as triplicate states had much higher rates of OxyContin adoption and overdoses. Second, states that had recently discontinued triplicate programs adopted OxyContin and experienced subsequent rises in overdoses of similar magnitude as other non-triplicate states. Our five triplicate states, however, continued to experience relatively low rates of OxyContin use and reduced overdose rates even after eliminating their own triplicate programs in the late 1990s and early 2000s, suggesting that the 1996 triplicate states were differentially treated compared to the former triplicate states. A potential explanation for these differences between triplicate and former triplicate states is marketing that was differentially targeted to non-triplicate states at the time of OxyContin's launch.

However, why were there strong enduring effects even after these triplicate programs were eliminated? One explanation relates to the serial correlation in Purdue Pharma's detailing strategy. Internal Purdue Pharma documents suggest that their strategy was to call and visit the top OxyContin prescribers, and this behavior continued (and even became more frequent) until 2018. The early budget plans annually dictated that the sales force target calls to the top 1 to 3 (depending on the year) deciles of physicians in terms of past prescribing behavior. The recently-filed Massachusetts case against Purdue Pharma includes additional evidence from

[57] Indiana is closer to the bottom of the distribution when we use Medicaid prescriptions specifically, but both are near the middle of the distribution using the ARCOS metric.

internal communications discussing this targeting behavior and how it extended even until 2018.[58] This type of behavior would generate serial correlation in OxyContin prescribing given differential initial exposure.

While we have been unable to obtain data on state-level physician detailing behavior from the 1990s to study these differences directly, we can study payments to physicians from Purdue Pharma in 2013-2016 using the Open Payments Data as a measure of persistent differences in detailing. This database reports payments to physicians for meals, travel, gifts, etc. regarding promotion of specific drugs. We calculate the total payments to physicians per 100,000 people over these years for OxyContin. Figure A18 (Panel A) shows that there are large (and statistically significant) differences between triplicate and non-triplicate states. Non-triplicate states receive 44-71% more payments per capita than triplicates states in each year. As an alternative metric, we can scale the OxyContin-specific payments by total payments to account for state-level differences in promotional activities. Though not shown, the gap grows substantially when using this metric. In Panel B, we estimate separate effects for the former-triplicate states. Again, the former-triplicates are more similar to the never-triplicate states than the five triplicate states.

This evidence is consistent with greater initial marketing by Purdue Pharma in non-triplicate states, leading to higher rates of prescribing which, in turn, led Purdue Pharma to target those places more in later years. It is otherwise difficult to explain why the triplicate states as of 1996 experienced such enduringly low rates of overdose growth, but states that had eliminated their programs just two years prior experienced trends almost identical to never-triplicate states. If triplicate programs themselves had such enduring effects, then we would expect to observe similar effects for the former triplicate states as well.

One open question is why Purdue Pharma would dedicate significant resources to eliminating triplicate programs and then not make a major detailing push in those states when those programs were eliminated. Unfortunately, there are limits to our ability to discern Purdue Pharma's promotional strategies. However, the evidence in this section is consistent with Purdue Pharma's initial physician detailing driving some of the persistent differences across states. The

[58] "McKinsey recommended doubling down on Purdue Pharma's strategy of targeting high prescribers for even more sales calls…" (p. 212 of Commonwealth of Massachusetts, 2019)

evidence of triplicate programs independently inducing differential and enduring prescribing of OxyContin is less well supported.

7 Discussion and Conclusion

Despite the importance of the opioid crisis and the desire to understand its origins, there is little empirical work exploring its initial causes. We study the effects of the introduction of OxyContin in 1996, exploiting early variation in its promotion based on existing state policies, triplicate prescription programs. These state policies were adopted decades earlier and became outdated soon after OxyContin's launch. However, their initial deterrence of OxyContin promotion and use had long-term effects on overdoses in these states, dramatically decreasing overdose rates even today.

Our results imply dramatic differences throughout the opioid crisis due to differences in initial policy conditions. States with more exposure to OxyContin's introduction experienced higher growth in overdoses in almost every quarter since 1996. Our estimates show that non-triplicate states experienced 44% higher growth in overdose death rates from 1996-2017 (63% for opioid overdose death rates) than they would have if they had been triplicate states. On average, in each quarter, non-triplicate states had 1.00 additional overdose death per 100,000 people.

While no part of the United States was unaffected by OxyContin, our estimates allow us to linearly extrapolate to what the national overdose death rate would have been in the absence of OxyContin's introduction. To do so, we first calculate the difference in initial "exposure" to OxyContin between triplicate and non-triplicate states. To measure initial exposure, we use the first quarter of ARCOS data; this difference was 0.18 morphine equivalent doses (MEDs) per capita. The national average at that time was 0.23 per capita MEDs. Thus, while we estimate a reduction of 1.00 overdose deaths per 100,000 due to an exposure difference of 0.18 MEDs, we can linearly extrapolate that reduced exposure by 0.23 MEDs nationally (i.e., moving from the national average exposure to zero MEDs) would have decreased overdose deaths by 1.28 per 100,000 ((0.23/0.18)*1.00). The actual average quarterly increase in overdose deaths is 1.69 per 100,000 relative to the pre-1996 baseline. Thus, OxyContin explains 1.28 out of the 1.69 overdoses per 100,000 above baseline, or 76% of the rise in the overdose rate since 1996. A similar calculation implies that OxyContin explains 89% of the rise in opioid-related overdoses.

These calculations are quite far out of sample since no state had zero OxyContin exposure, so they should be interpreted with caution. Also, these estimates capture both the direct and indirect consequences of initial exposure to OxyContin, including spillovers of OxyContin promotion to other opioid drugs and transitions to heroin and fentanyl in the later waves of the epidemic. It is clear that states that initially had high exposure to OxyContin evolved very differently than states with low initial exposure. This is consistent with OxyContin's introduction playing a major role in igniting the opioid crisis.

Finally, the evidence suggests that Purdue Pharma's local marketing tactics played an important role in explaining this growth. When triplicate states are compared to other states with similar oxycodone prescribing rates or even states which had just recently eliminated their triplicate programs, they still have uniquely low overdose rate growth. This suggests that it is less likely that triplicate programs independently influenced OxyContin adoption by reducing prescriber-level exposure to oxycodone products. Instead, the evidence is more consistent with differences in local marketing and serial correlation induced by Purdue Pharma's marketing techniques. Overall, we find strong evidence that the marketing practices of OxyContin interacted with state-level policy conditions led to dramatically reduced overdose rates in triplicate states. By deterring OxyContin's widespread introduction in 1996, triplicate programs appear to have protected states against the long-term overdose trends experienced by many other states.

References

Abadie, Alberto, Alexis Diamond, and Jens Hainmueller, "Synthetic control methods for comparative case studies: Estimating the effect of California's tobacco control program," *Journal of the American Statistical Association*, 2010, *105* (490), 493-505.

_ , _ and _ , "Comparative politics and the synthetic control method," *American Journal of Political Science*, 2015, *59* (2), 495-510.

_ and Javier Gardeazabal, "The economic costs of conflict: A case study of the Basque Country," *American Economic Review*, 2003, *93* (1), 113-132.

Alexander, Monica J, Mathew V Kiang, and Magali Barbieri, "Trends in black and white opioid mortality in the United States, 1979-2015," *Epidemiology (Cambridge, Mass.)*, 2018, *29* (5), 707.

Alpert, Abby, David Powell, and Rosalie Liccardo Pacula, "Supply-side drug policy in the presence of substitutes: Evidence from the introduction of abuse-deterrent opioids," *American Economic Journal: Economic Policy*, 2018, *10* (4), 1-35.

Anness, Bridgit A, Cynthia J Willey, and Albert H Taubman, "Physician attitudes toward the Rhode Island duplicate prescription law and self-reported prescribing practices for Schedule II medications," *Clinical research and regulatory affairs*, 1995, *12* (4), 283-306.

Barnett et al. "Opioid-Prescribing Patterns of Emergency Physicians and Risk of Long-Term Use," NEJM. 2017.

Berina, Leslie F., Brock G. Guernsey, James A. Hokanson, William H. Doutre, and Lonnie E. Fuller, "Physician perception of a triplicate prescription law." *American Journal of Health-System Pharmacy,* 1985, 42(4), 857-860.

Cameron, A Colin, Jonah B Gelbach, and Douglas L Miller, "Bootstrap-based improvements for inference with clustered errors," *The Review of Economics and Statistics*, 2008, *90* (3), 414-427.

Case, Anne and Angus Deaton, "Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century," *Proceedings of the National Academy of Sciences*, 2015, *112* (49), 15078-15083.

_ and _ , "Mortality and morbidity in the 21st century," *Brookings papers on economic activity*, 2017, *2017*, 397.

Centers for Disease Control and Prevention (CDC). Overdose deaths involving prescription opioids among Medicaid enrollees-Washington, 2004-2007. *MMWR: Morbidity and Mortality Weekly Report*, 2009, *58*(42), 1171-1175.

Ciccarone, D. Fentanyl in the US heroin supply: a rapidly changing risk environment. *The International journal on drug policy*. 2017. *46*, pp.107-111.

Cicero, Theodore J., et al. "Trends in Abuse of OxyContin® and Other Opioid Analgesics in the United States: 2002-2004," *The Journal of Pain.* 2005.

Cicero, Theodore J and Matthew S Ellis, "Abuse-deterrent formulations and the prescription opioid abuse epidemic in the United States: Lessons learned from OxyContin," *JAMA Psychiatry*, 2015, *72* (5), 424-430.

_ , James A Inciardi, and Alvaro Muñoz, "Trends in abuse of OxyContin and other opioid analgesics in the United States: 2002-2004," *The Journal of Pain*, 2005, *6* (10), 662-672.

Conley, Timothy G and Christopher R Taber, "Inference with 'difference in differences' with a small number of policy changes," *The Review of Economics and Statistics*, 2011, *93* (1), 113-125.

DeBruyne, N. "American War and Military Operations Casualties: Lists and Statistics." Congressional Research Service. 2018.

Department of Health and Human Services, "Multiple Copy Prescription Programs: State Experiences," Technical Report 1992.

Evans, William N, Ethan Lieber, and Patrick Power, "How the Reformulation of OxyContin Ignited the Heroin Epidemic," Review of Economics and Statistics. 2018. 101(1):1-15.

Fernandes, Jessie C., David Campana, Todd S. Harwell, and Steven D. Helgerson. "High mortality rate of unintentional poisoning due to prescription opioids in adults enrolled in Medicaid compared to those not enrolled in Medicaid in Montana." *Drug and Alcohol Dependence*, 2015, 153, 346-349

Fishman, Scott M, Jennifer S Papazian, Susana Gonzalez, Paul S Riches, and Aaron Gilson, "Regulating opioid prescribing through prescription monitoring programs: Balancing drug diversion and treatment of pain," *Pain Medicine*, 2004, *5* (3), 309-324.

Fujimoto, Darlene, "Regulatory issues in pain management," *Clinics in Geriatric Medicine*, 2001, *17* (3), 537-551.

Gage, TW, "Drug substitution and triplicate prescription forms," *Texas Dental Journal*, 1982, *99* (1), 16.

GAO, *Prescription Drugs: OxyContin Abuse and Diversion and Efforts to Address the Problem: Report to Congressional Requesters*, DIANE Publishing, 2003.

Goldenheim, Paul, "OxyContin: Balancing risks and benefits," in "Hearing of the Committee on Health, Education, Labor, and Pensions, United States Senate" 2002.

Green, C. et al.,"Assessing the accuracy of opioid overdose and poisoning codes in diagnostic information from electronic health records, claims data and death records." *Pharmacoepidemiology & Drug Safety.* 2017.

Groups Plus, "Purdue Pharma Company Focus Group Research & Findings Oxycontin for Non-Cancer Pain Management," Technical Report 1995.

Hartzema, Abraham G, Miquel S Porta, Hugh H Tilson, Sergio G Zullich, Thaddeus H Grasela Jr, Jill B Fiedler-Kelly, and Francis M Gengo, "Impact of triplicate prescription program on psychotropic prescribing patterns in long-term care facilities," *Annals of Pharmacotherapy*, 1992, *26* (4), 539-546.

Hollingsworth, Alex, Christopher J Ruhm, and Kosali Simon, "Macroeconomic conditions and opioid abuse," *Journal of Health Economics*, 2017, *56*, 222-233.

IMS Institute for Healthcare Informatics, "The use of medicines in the United States: Review of 2010," 2011.

INCB, "Report of the International Narcotics Control Board for 2008," *New York: United Nations*, 2009.

Jaeger, David A, Theodore J Joyce, and Robert Kaestner, "A Cautionary Tale of Evaluating Identifying Assumptions: Did Reality TV Really Cause a Decline in Teenage Childbearing?" *Journal of Business & Economic Statistics*, 2018, pp. 1-10.

Jones M. et al. "A Brief History of the Opioid Epidemic and Strategies for Pain Medicine," *Pain and Therapy.* 2018. 7(1): 13-21.

Joranson, David E, Grant M Carrow, Karen M Ryan, Linda Schaefer, Aaron M Gilson, Patricia Good, John Eadie, Susan Peine, and June L Dahl, "Pain management and prescription monitoring," *Journal of Pain and Symptom Management*, 2002, *23* (3), 231-238.

Khan, N. et al. "Association of Opioid Overdose With Opioid Prescriptions to Family Members," JAMA Internal Medicine. 2019.

Kolodny, Andrew, David T Courtwright, Catherine S Hwang, Peter Kreiner, John L Eadie, Thomas W Clark, and G Caleb Alexander, "The prescription opioid and heroin crisis: A public health approach to an epidemic of addiction," *Annual Review of Public Health*, 2015, *36*, 559-574.

MacKinnon, J. and M. Webb, "The wild bootstrap for few (treated) clusters," *The Econometrics Journal.* 2018. 21, 114-135.

Max, Mitchell B, Marilee Donovan, Christine A Miaskowski, Sandra E Ward, Debra Gordon, Marilyn Bookbinder, Charles S Cleeland, Nessa Coyle, Margaret Kiss, Howard T Thaler et al., "Quality improvement guidelines for the treatment of acute pain and cancer pain," *JAMA*, 1995, *274* (23), 1874-1880.

Melzack R. "The tragedy of needless pain." Scientific American.1990;262(2):27–33.

Morgan JP. "American opiophobia: customary underutilization of opioid analgesics." Adv AlcoholSubst Abuse. 1985;5:163–73.

Pardo, Bryce, "Do more robust prescription drug monitoring programs reduce prescription opioid overdose?" Addiction, 2017, 112(10): 1773-1783

Paulozzi, Leonard J, "Opioid analgesic involvement in drug abuse deaths in American metropolitan areas," *American Journal of Public Health*, 2006, *96* (10), 1755-1757.

PDMP TTACB, "History of Prescription Drug Monitoring Programs," March 2018. http://www.pdmpassist.org/pdf/PDMP_admin/TAG_History_PDMPs_final_20180314.pdf, last accessed November 11, 2018.

Phillips, Donald M, "JCAHO pain management standards are unveiled," *JAMA*, 2000, *284* (4), 428-429.

Pierce, Justin and Peter Schott. "Trade Liberalization and Mortality: Evidence from U.S. Counties." *NBER Working Paper No.* 22849. 2016.

Porter J, Jick H. "Addiction rare in patients treated with narcotics." NEJM. 1980;302(2):123.

Purdue Pharma, "OxyContin Launch Plan," Technical Report 1995.

_ , "1997 Budget Plan," Technical Report 1997.

_ , "1998 Budget Plan," Technical Report 1998.

_ , "1999 Budget Plan," Technical Report 1999.

_ , "2001 Budget Plan," Technical Report 2001.

_ , "2002 Budget Plan," Technical Report 2002.

Roodman, David Malin, James G MacKinnon, Morten Ørregaard Nielsen, and Matthew Webb, "Fast and Wild: Bootstrap Inference in Stata using Boottest," Technical Report, Queen's Economics Department Working Paper 2018.

Ruggles, Steven, Sarah Flood, Ronald Goeken, Josiah Grover, Erin Meyer, Jose Pacas, and Matthew Sobek, "IPUMS USA: Version 8.0 [dataset]," 2018.

Ruhm, Christopher J, "Corrected US opioid-involved drug poisoning deaths and mortality rates, 1999–2015." *Addiction*, 2018, 113 (7), 1339-1344.

Ruhm, Christopher J, "Deaths of despair or drug problems?," Technical Report, National Bureau of Economic Research 2018.

Seth, P, L Scholl, RA Rudd, and S Bacon, "Increases and Geographic Variations in Overdose Deaths Involving Opioids, Cocaine, and Psychostimulants with Abuse Potential - United States, 2015-2016," *MMWR Morb Mortal Wkly Rep. ePub*, 2018, *29.*

Sharp, Mark J., and Thomas A. Melnik. "Poisoning deaths involving opioid analgesics—New York State, 2003–2012." *MMWR. Morbidity and Mortality Weekly Report*, 2015, 64 (14): 377.

Sigler, KA, BG Guernsey, NB Ingrim, AS Buesing, JA Hokanson, E Galvan, and WH Doutre, "Effect of a triplicate prescription law on prescribing of Schedule II drugs," *American Journal of Health-System Pharmacy*, 1984, *41* (1), 108-111.

Simoni-Wastila, Linda and Wendy Toler, "State-Issued Prescription Forms," n.d. https://cdn.ymaws.com/www.safestates.org/resource/resmgr/imported/Simoni%20Wastila.pdf, last accessed March 11, 2019.

Simoni-Wastila, Linda and Christopher Tompkins, "Balancing diversion control and medical necessity: The case of prescription drugs with abuse potential," *Substance Use & Misuse*, 2001, *36* (9-10), 1275-1296.

_ , Dennis Ross-Degnan, Connie Mah, Xiaoming Gao, Jeffrey Brown, Leon E Cosler, Thomas Fanning, Peter Gallagher, Carl Salzman, and Stephen B Soumerai, "A retrospective data analysis of the impact of the New York triplicate prescription program on benzodiazepine use in Medicaid patients with chronic psychiatric and neurologic disorders," *Clinical Therapeutics*, 2004, *26* (2), 322-336.

Smith, Nathan, Silvia S. Martins, June Kim, Ariadne Rivera-Aguirre, David S. Fink, Alvaro Castillo-Carniglia, Stephen G. Henry et al, "A typology of prescription drug monitoring programs: a latent transition analysis of the evolution of programs from 1999 to 2016." *Addiction*, 2019, 114(2): 248-258.

Strategic Business Research, Inc., "OxyContin: Quantative Research," Technical Report 1996.

Substance Abuse and Mental Health Services (SAMHSA) Center for Behavioral Health Statistics and Quality, "Treatment Episode Data Set (TEDS): 2001-2011. State Admissions to Substance Abuse Treatment Services," 2013.

University of Kentucky Center for Poverty Research, "UKCPR National Welfare Data, 1980-2017," 2018.

Warner, Margaret, Li Hui Chen, Diane M Makuc, Robert N Anderson, and Arialdi M Miniño, "Drug poisoning deaths in the United States, 1980-2008," *NCHS data brief*, 2011, (81), 1-8.

Wastila, Linda J and Christine Bishop, "The influence of multiple copy prescription programs on analgesic utilization," *Journal of Pharmaceutical Care in Pain & Symptom Control*, 1996, *4* (3), 3-19.

Webb, Matthew D, "Reworking wild bootstrap based inference for clustered errors," Technical Report, Queen's Economics Department Working Paper 2013.

Weintraub, Michael, Satesh Singh, Louise Byrne, Kumar Maharaj, and Laurence Guttmacher, "Consequences of the 1989 New York State triplicate benzodiazepine prescription regulations," *JAMA*, 1991, *266* (17), 2392-2397.

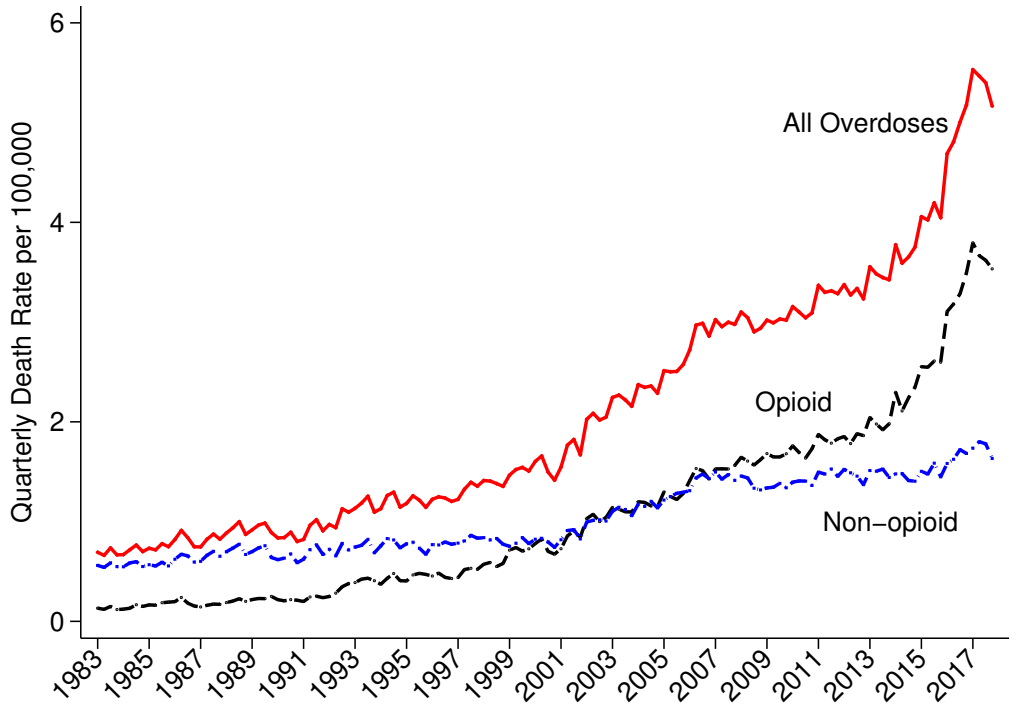
Whitmire, J. Timothy, and Glenda Waslaski Adams, "Unintentional overdose deaths in the North Carolina Medicaid population: prevalence, prescription drug use, and medical care services." Center for Health Statistics, 2010. https://schs.dph.ncdhhs.gov/schs/pdf/schs_162_web_081310.pdf, last accessed March 11, 2019

World Health Organization, "Cancer Pain Relief," 1986.

Zee, Art Van, "The promotion and marketing of OxyContin: Commercial triumph, public health tragedy," *American Journal of Public Health*, 2009, *99* (2), 221-227.

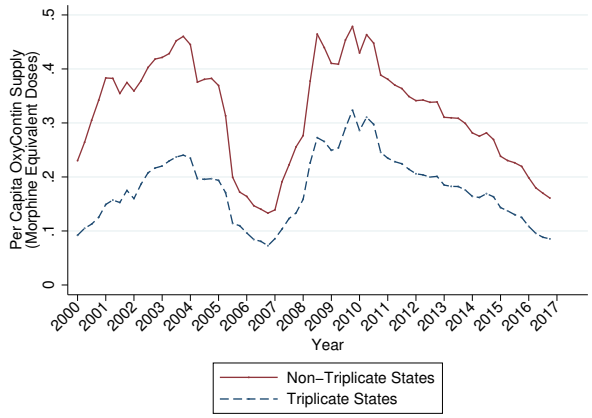
Figures

Figure 1: Trends in National Overdose Death Rates

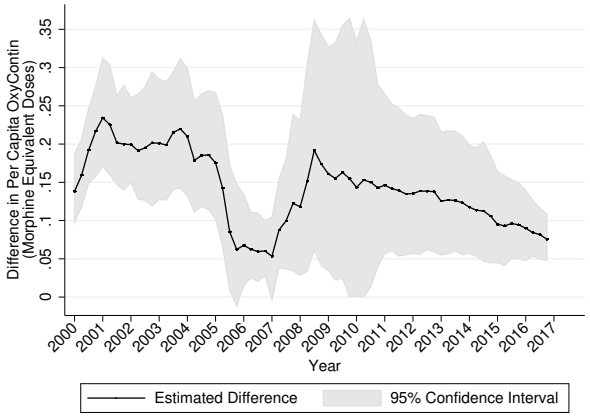


Notes: These data use NVSS mortality data. ICD codes are reported in the text.

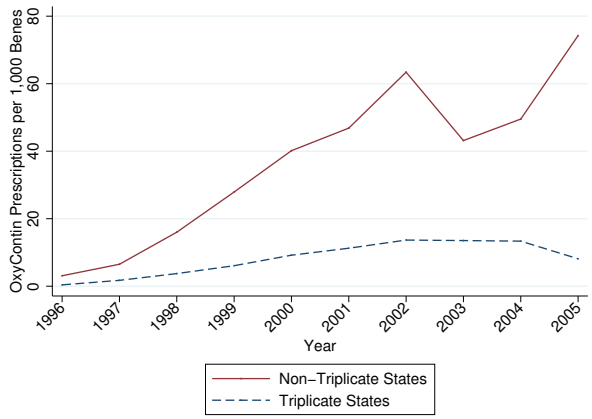
Figure 2: OxyContin Supply



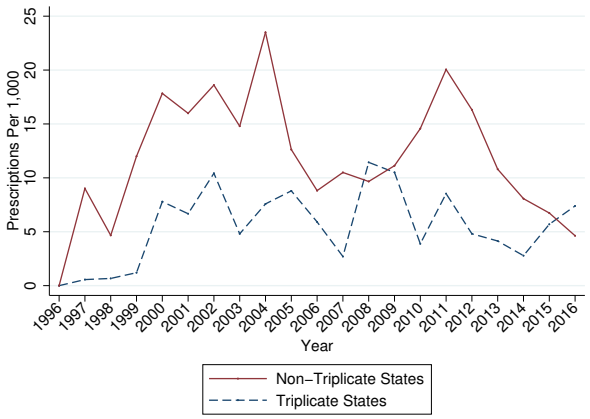
A: ARCOS Supply



B: Estimated Differences



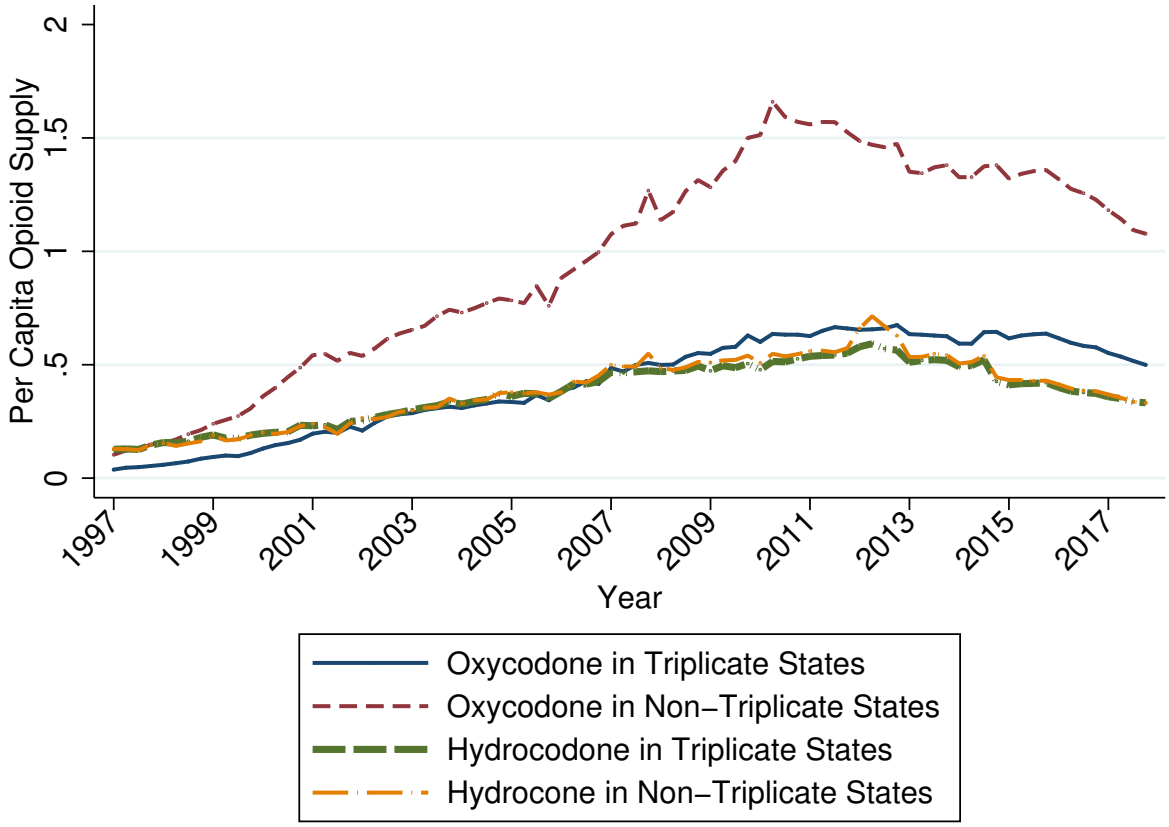
C: Medicaid Prescriptions



D: MEPS Prescriptions

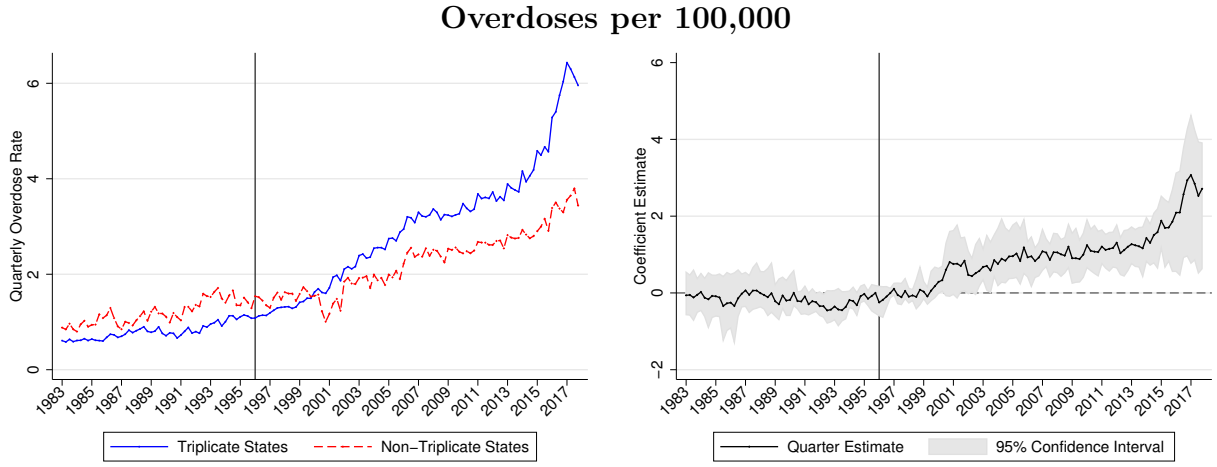
Notes: In Panel A, we use ARCOS data and construct morphine equivalent doses per capita. OxyContin data are only available for 2000-2016. Panel B reports estimates from a regression which includes quarter fixed effects. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. In Panel C, we report the number of prescriptions per 1,000 beneficiaries from the Medicaid SDUD. In Panel D, we report the number of prescriptions per 1,000 people using the MEPS. We use the MEPS survey weights to calculate the means.

Figure 3: Oxycodone and Hydrocodone Supply



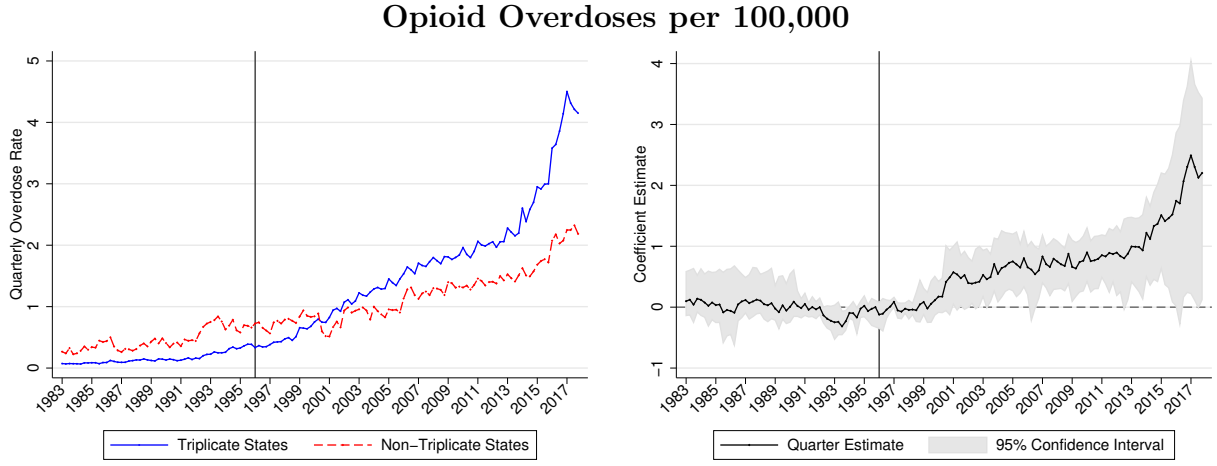
Notes: We use ARCOS data to construct morphine equivalent doses per capita by substance.

Figure 4: Overdose Death Rates



A: Triplicate and Non-Triplicate States

B: Event Study

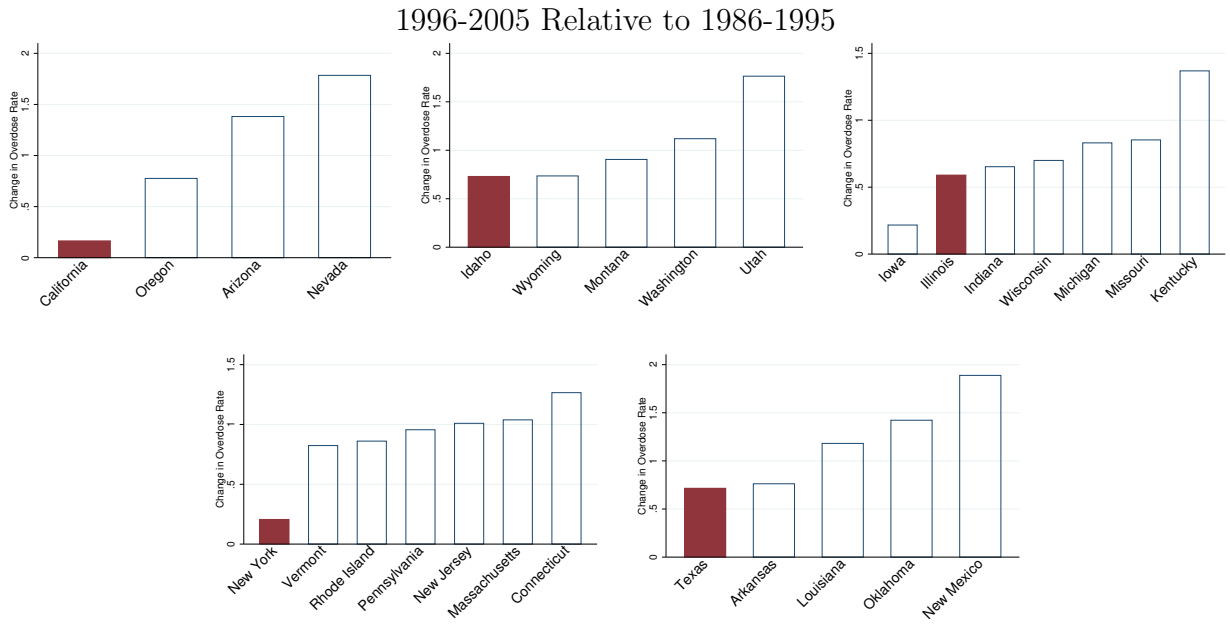


C: Triplicate and Non-Triplicate States

D: Event Study

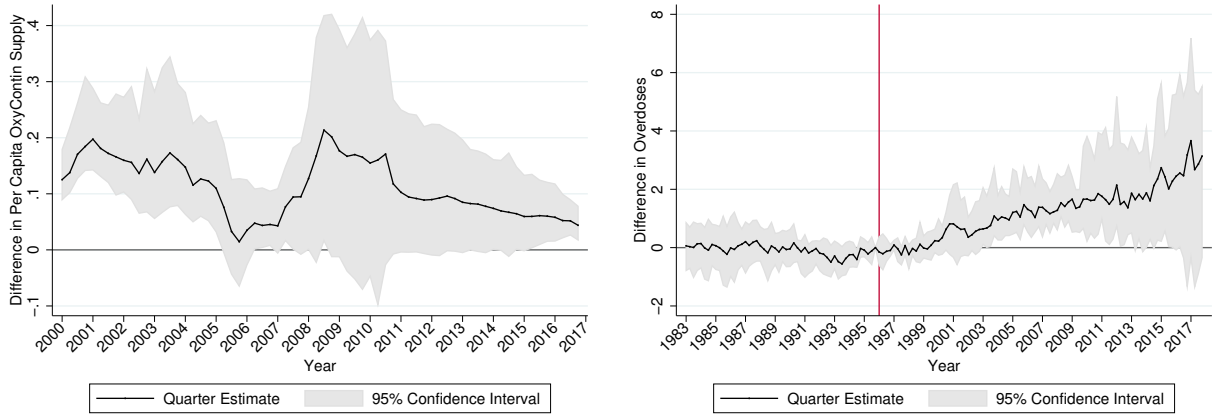
Notes: We use geocoded NVSS data to construct overdoses and opioid overdoses per 100,000. See text for exact ICD codes used in each period. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in the final quarter of 1995. Weighted by population.

Figure 5: Overdose Rate Changes For Each Triplicate States, Compared to Neighboring States



Notes: We construct the change in the overdose rate (per 100,000) for 1996-2005 relative to 1986-1995. We plot this change for each triplicate state relative to its neighboring states.

Figure 6: Comparing Outcomes Based on 1991-1995 Medicaid Oxycodone Prescribing



A: OxyContin Supply B: Overdoses per 100,000

Notes: We compare "low oxycodone" non-triplicate states in terms of oxycodone Medicaid prescriptions per 1,000 beneficiaries before 1996 to triplicate states. The estimates above are robust to other breakdowns based on 1991-1995 Medicaid oxycodone prescriptions per 1,000 beneficiaries. Figure A relies on ARCOS data for 2000-2016. Figure B uses mortality data for 1983-2017. All specifications include state and time fixed effects. Confidence intervals are generated by a wild bootstrap using Webb (2013) weights.

Tables

Table 1: Summary Statistics for 1991-1995

Statistics for 1991-1995	California	Idaho	Illinois	New York	Texas	Triplicate	Non-Triplicate
Triplicate Program							
First Year	1939	1967	1961	1972	1981		
Last Year	2004	1997	2000	2001	1999		
Annual Overdose Rate							
Overdoses per 100,000	7.10	2.92	4.58	6.14	3.86	5.72	3.86
Overdose Rate Rank	3	30	16	9	20	–	–
Overdoses (excluding cocaine) per 100,000	5.65	2.74	2.74	2.78	2.73	3.88	3.15
Overdose (excluding cocaine) Rate Rank	4	23	21	20	24	–	–
Opioid Overdoses per 100,000	2.95	0.47	2.27	3.82	0.77	2.52	1.00
Opioid Overdose Rate Rank	5	34	10	2	21	–	–
Demographics							
% White	80.5%	97.2%	81.6%	77.2%	85.2%	81.2%	84.0%
% Ages 25-44	34.1%	29.5%	32.3%	32.4%	32.8%	33.1%	31.8%
% College Degree	26.3%	21.6%	27.3%	28.2%	23.7%	26.2%	24.4%
Economic Conditions							
% Working (Ages 25-59)	74.3%	79.7%	78.8%	73.3%	78.2%	75.7%	78.6%

Table 2: Opioid Supply (ARCOS)

Non-Triplicate ×	OxyContin (1)	Oxycodone (2)	Hydrocodone (3)
$1997 - 2000^{\dagger}$	0.177***	0.159***	-0.004
	[0.132, 0.230]	[0.117, 0.201]	[-0.068, 0.082]
$2001 - 2010$	0.154***	0.565***	0.013
	[0.079, 0.251]	[0.319, 0.869]	[-0.138, 0.173]
$2011 - 2017^{\dagger}$	0.115***	0.737***	0.025
	[0.054, 0.195]	[0.243, 1.130]	[-0.143, 0.279]
Mean	0.276	0.808	0.389
N	3,468	4,284	4,284

Notes: ***Significance 1%, **Significance 5%, *Significance 10%. Estimated specifications include quarter fixed effects. The reported coefficients refer to the interaction of the given time period and an indicator for whether the state had a triplicate program in 1996. The outcome is the per capita morphine equivalent doses of the substance listed. 95% confidence intervals reported in brackets are estimated by wild bootstrap. Regressions are population-weighted.

† OxyContin data only cover 2000-2016 and, therefore, the 1997-2000 category only refers to 2000; the 2011-2017 refers to 2011-2016.

Table 3: Overdose Death Rate

Non-Triplicate ×	Overdoses per 100,000 (1)	(2)	(3)	(4)
1996-2000	0.311***	0.331***	0.347***	0.341**
	[0.117, 0.592]	[0.115, 0.638]	[0.103, 0.562]	[0.101, 0.640]
2001-2010	0.939**	1.141***	1.037***	0.849***
	[0.401, 1.586]	[0.560, 1.643]	[0.628, 1.362]	[0.397, 1.252]
2011-2017	1.562**	1.976***	1.260***	1.636***
	[0.765, 2.370]	[1.018, 2.591]	[0.630, 1.998]	[0.912, 2.286]
Weighted	No	Yes	Yes	Yes
Covariates	No	No	Yes	Yes
Region-Time Dummies	No	No	No	Yes
Mean (1991-1995)	0.968	1.109	1.109	1.109
N	4,968	4,968	4,968	4,968
Non-Triplicate ×	Opioid Overdoses per 100,000 (5)	(6)	(7)	(8)
1996-2000	0.175**	0.158**	0.184**	0.184*
	[0.040, 0.419]	[0.029, 0.418]	[0.022, 0.360]	[-0.016, 0.397]
2001-2010	0.669***	0.748***	0.722***	0.512**
	[0.297, 1.118]	[0.307, 1.109]	[0.299, 1.151]	[0.025, 0.994]
2011-2017	1.283**	1.486***	0.909**	1.069***
	[0.381, 2.165]	[0.473, 2.176]	[0.133, 1.822]	[0.252, 1.737]
Weighted	No	Yes	Yes	Yes
Covariates	No	No	Yes	Yes
Region-Time Dummies	No	No	No	Yes
Mean (1991-1995)	0.293	0.369	0.369	0.369
N	4,968	4,968	4,968	4,968

Notes: ***Significance 1%, **Significance 5%, *Significance 10%. The reported coefficients refer to the interaction of the given time period and an indicator for whether the state did not have a triplicate program in 1996. Estimates are relative to pre-period 1991-1995. 95% confidence intervals reported in brackets are estimated by wild bootstrap. All models include state and quarter fixed effects. Covariates include the fraction white, fraction with college degree, and fraction ages 25-44. These covariates are interacted with year indicators.

Table 4: Robustness Tests

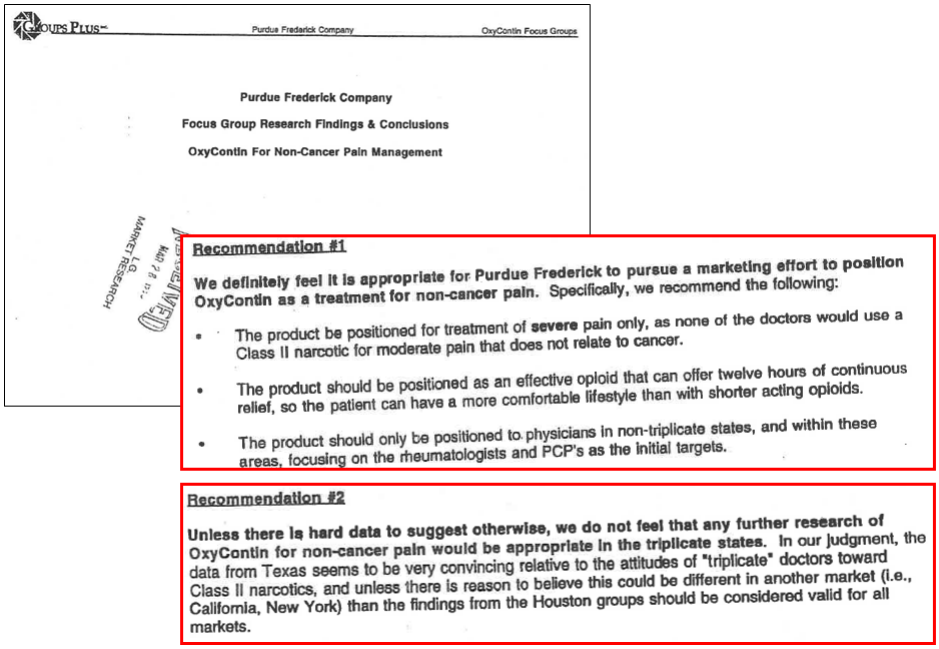
	Baseline Results	Exclude Overdoses with Cocaine	Select on Population Size	Select on PDMP States in 1996	Control for Policy Variables	1991-1998 Only
Panel A: Overdoses per 100,000						
Non-Triplicate ×	(1)	(2)	(3)	(4)	(5)	(6)
1996-2000	0.331***	0.158**	0.325**	0.368***	0.303***	0.189**
	[0.115, 0.638]	[0.020, 0.407]	[0.043, 0.573]	[0.108, 0.651]	[0.075, 0.547]	[0.034, 0.395]
2001-2010	1.141***	0.748***	1.404***	1.468***	0.869***	–
	[0.560, 1.643]	[0.297, 1.105]	[0.551, 2.110]	[0.516, 1.150]	[0.125, 1.156]	
2011-2017	1.976***	1.486***	2.860***	2.482***	1.248***	–
	[1.018, 2.591]	[0.421, 2.223]	[1.323, 4.549]	[0.727, 1.819]	[0.292, 2.034]	
Mean 1991-1995	1.109	0.969	1.283	1.305	1.109	1.109
N	4,968	4,968	972	1,836	4,968	1,632
Panel B: Opioid Overdoses per 100,000						
	Baseline Results	Exclude Overdoses with Cocaine	Select on Population Size	Select on PDMP States in 1996	Control for Policy Variables	1991-1998 Only
Non-Triplicate ×						
1996-2000	0.158**	0.072**	0.124	0.221**	0.151*	0.067
	[0.029, 0.418]	[0.000, 0.176]	[-0.060, 0.352]	[0.017, 0.483]	[-0.010, 0.389]	[-0.044, 0.245]
2001-2010	0.748***	0.559***	0.726**	1.075***	0.533***	–
	[0.307, 1.109]	[0.279, 0.793]	[0.046, 1.276]	[0.198, 0.866]	[0.125, 1.156]	
2011-2017	1.486***	1.171***	1.918**	1.977***	0.891***	–
	[0.473, 2.176]	[0.342, 1.740]	[0.515, 4.094]	[0.316, 1.529]	[0.292, 2.034]	
Mean 1991-1995	0.369	0.392	0.470	0.544	0.369	0.369
N	4,968	4,968	972	1,836	4,968	1,632

Notes: ***Significance 1%, **Significance 5%, *Significance 10%. Outcome is overdoses per 100,000 unless otherwise specified. The reported coefficients refer to the interaction of the given time period and an indicator for whether the state did not have a triplicate program in 1996. Estimates are relative to pre-period 1991-1995. 95% confidence intervals reported in brackets are estimated by wild bootstrap. All models include state and quarter fixed effects. Column (1) excludes overdoses also involving cocaine. Column (2) selects on the four non-triplicate states with the largest population in 1990 along with the four largest triplicate states. Column (3) selects on states with some form of PDMP (triplicate, duplicate, electronic) in 1996. Column (4) includes policy controls for PDMPs, "must access" PDMPs, pain clinic regulation, medical marijuana laws, and operational/legal medical marijuana dispensaries. Column (5) only uses years 1991-1998 such that the only reported estimate refers to the differential increase in opioid overdoses for 1996-1998. In 1991-1998, only ICD-9 codes are used to categorize deaths.

Appendix A

Appendix Figures

Figure A1: Example of Purdue Pharma Focus Group Recommendations



OUPS PLUS+ Purdue Fredarick Company OxyContin Focus Groups

Purdue Frederick Company

Focus Group Research Findings & Conclusions

OxyContin For Non-Cancer Pain Management

Recommendation #1

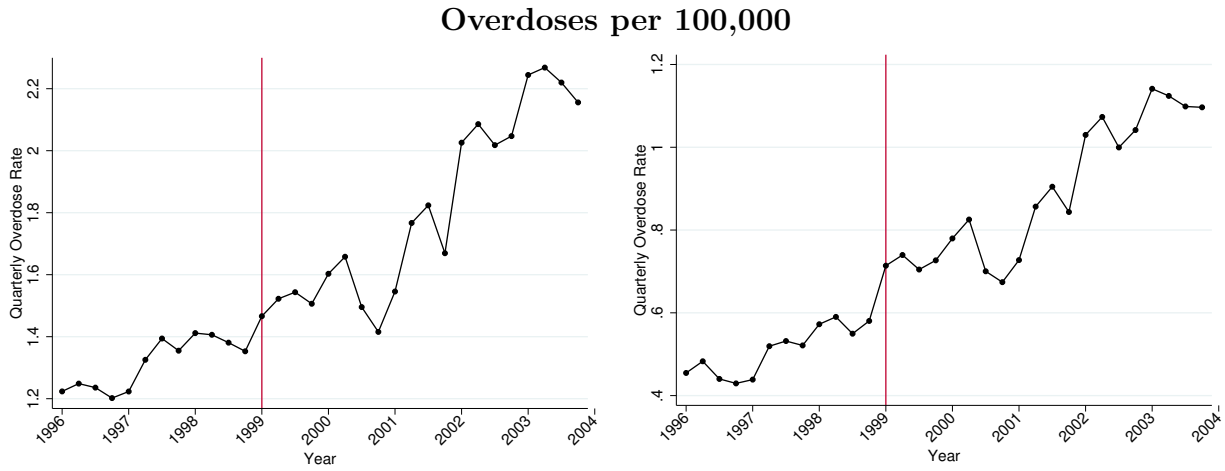
We definitely feel it is appropriate for Purdue Frederick to pursue a marketing effort to position OxyContin as a treatment for non-cancer pain. Specifically, we recommend the following:

- The product be positioned for treatment of **severe** pain only, as none of the doctors would use a Class II narcotic for moderate pain that does not relate to cancer.
- The product should be positioned as an effective opioid that can offer twelve hours of continuous relief, so the patient can have a more comfortable lifestyle than with shorter acting opioids.
- The product should only be positioned to physicians in non-triplicate states, and within these areas, focusing on the rheumatologists and PCP's as the initial targets.

Recommendation #2

Unless there is hard data to suggest otherwise, we do not feel that any further research of OxyContin for non-cancer pain would be appropriate in the triplicate states. In our judgment, the data from Texas seems to be very convincing relative to the attitudes of "triplicate" doctors toward Class II narcotics, and unless there is reason to believe this could be different in another market (i.e., California, New York) than the findings from the Houston groups should be considered valid for all markets.

Figure A2: ICD Code Change in 1999



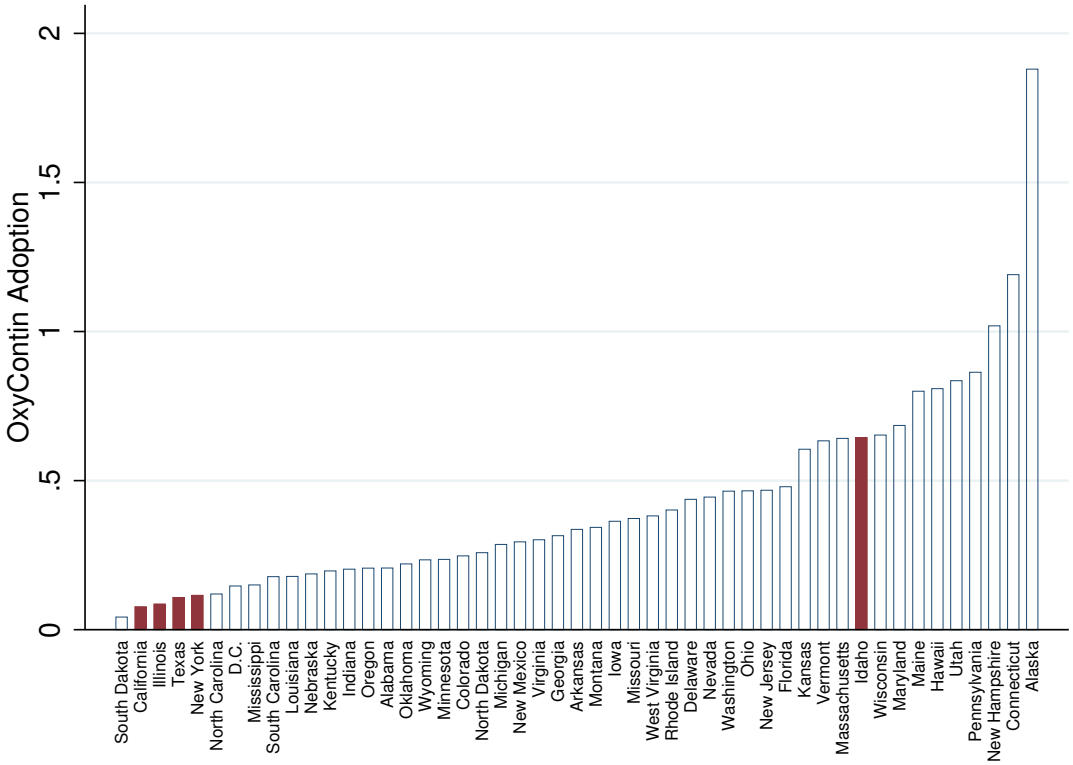
A: All Overdoses

B: Opioid Overdoses

Notes: We use geocoded NVSS data to construct overdoses per 100,000. These figures study the transition from ICD-9 to ICD-10 codes in 1999.

Figure A3: OxyContin Adoption by State

(a) Medicaid OxyContin Prescriptions per 1,000 Benes in 1996



(b) ARCOS Per Capita OxyContin Morphine Equivalent Doses in 2000q1

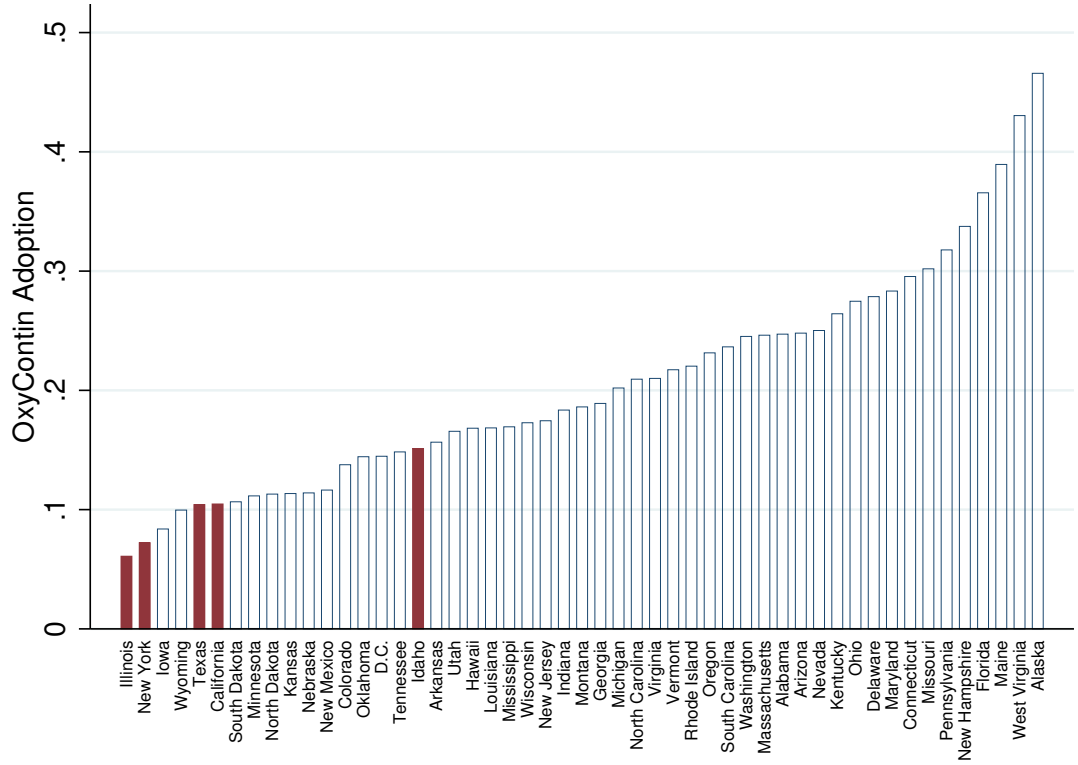
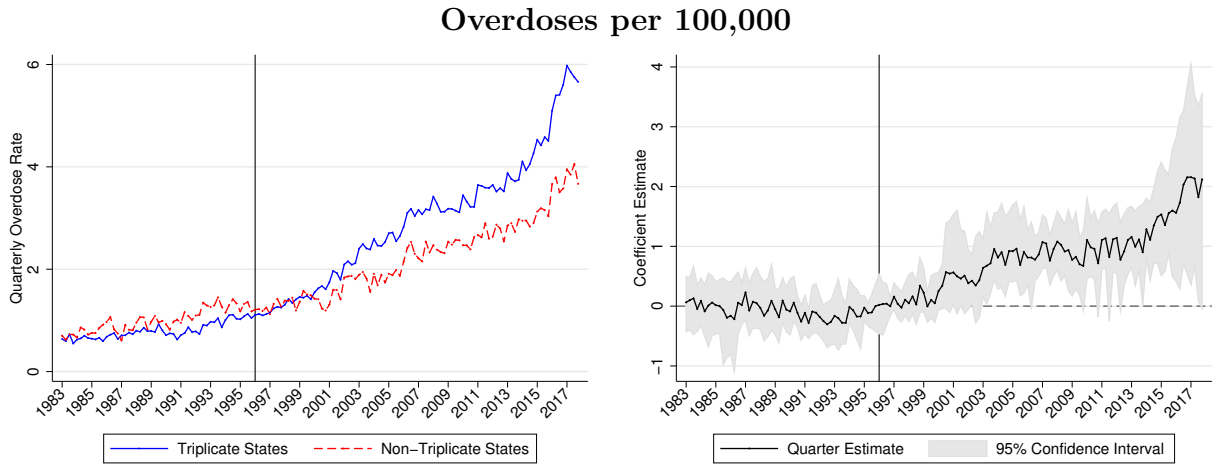
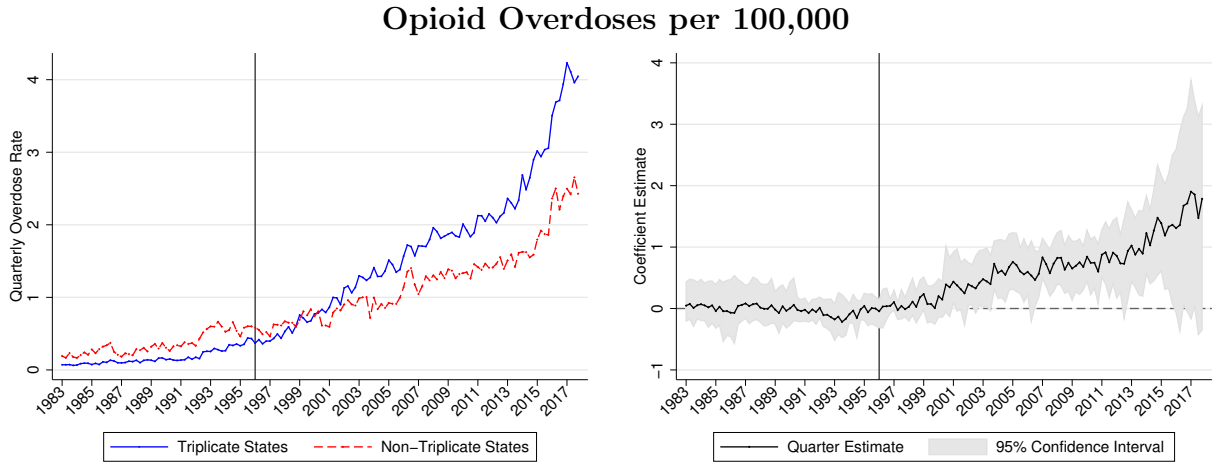


Figure A4: Overdose Rates – Unweighted



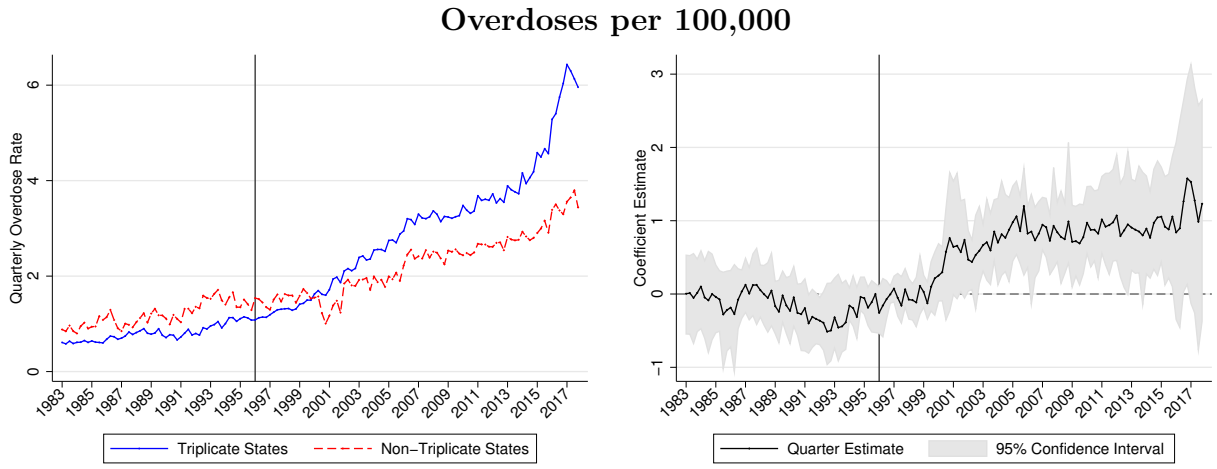
A: Triplicate and Non-Triplicate State Means B: Event Study Results



C: Triplicate and Non-Triplicate State Means D: Event Study Results

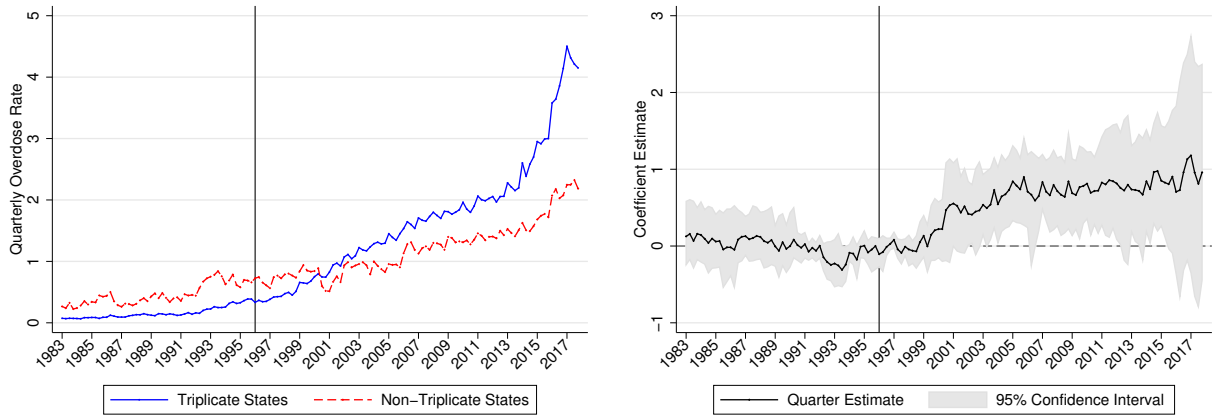
Notes: We use geocoded NVSS data to construct overdoses and opioid overdoses per 100,000. See text for exact ICD codes used in each period. Panels B and D report event study estimates from a regression which includes state and quarter fixed effects. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in the final quarter of 1995.

Figure A5: Overdose Rates – Weighted by Population, With Covariates



A: Triplicate and Non-Triplicate States

B: Event Study Results

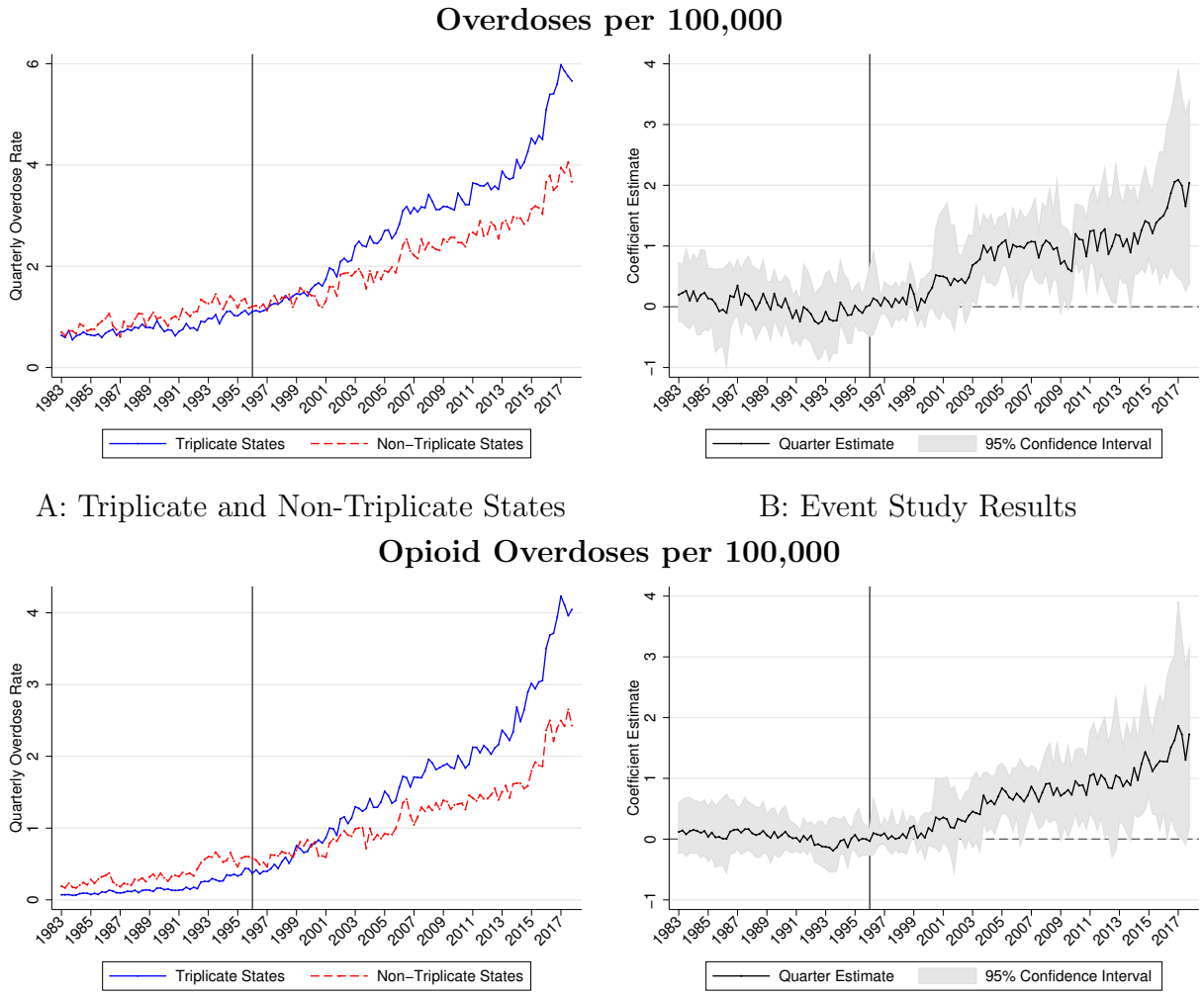


C: Triplicate and Non-Triplicate States

D: Event Study Results

Notes: We use geocoded NVSS data to construct overdoses and opioid overdoses per 100,000. See text for exact ICD codes used in each period. Panels B and D report event study estimates from a regression which includes state and quarter fixed effects as well as the fraction white, fraction with college degree, and fraction ages 25-44. The latter covariates are interacted with year indicators. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in the final quarter of 1995.

Figure A6: Overdose Rates – Unweighted, With Covariates



A: Triplicate and Non-Triplicate States

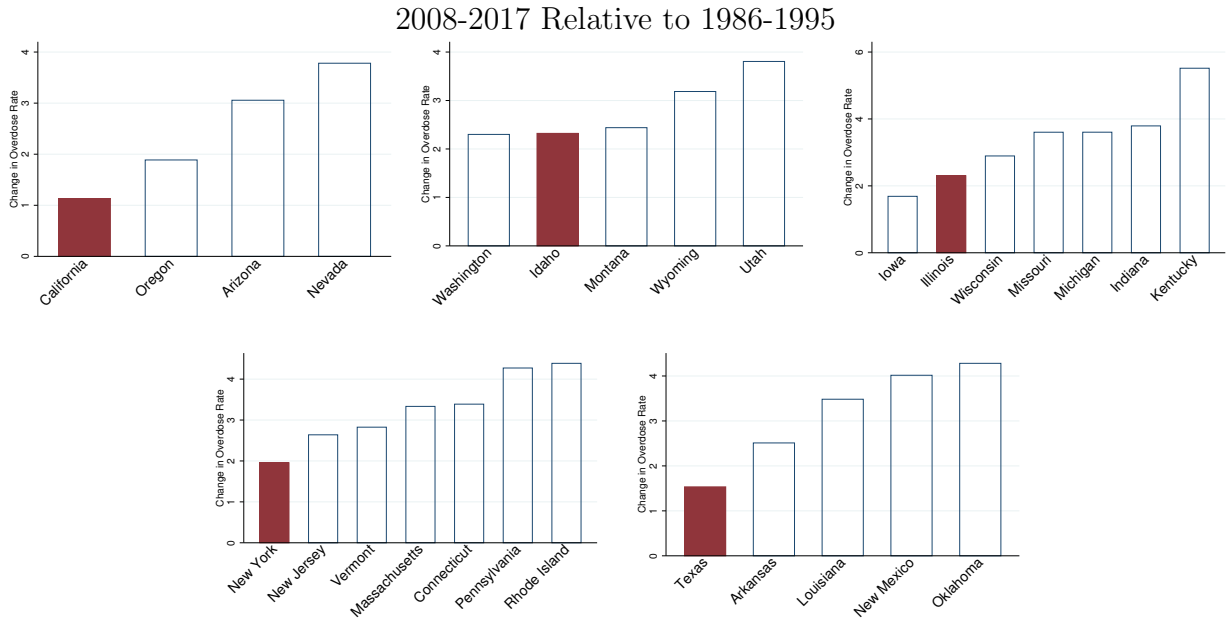
B: Event Study Results

C: Triplicate and Non-Triplicate States

D: Event Study Results

Notes: We use geocoded NVSS data to construct overdoses and opioid overdoses per 100,000. See text for exact ICD codes used in each period. Panels B and D report event study estimates from a regression which includes state and quarter fixed effects as well as the fraction white, fraction with college degree, and fraction ages 25-44. The latter covariates are interacted with year indicators. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in the final quarter of 1995.

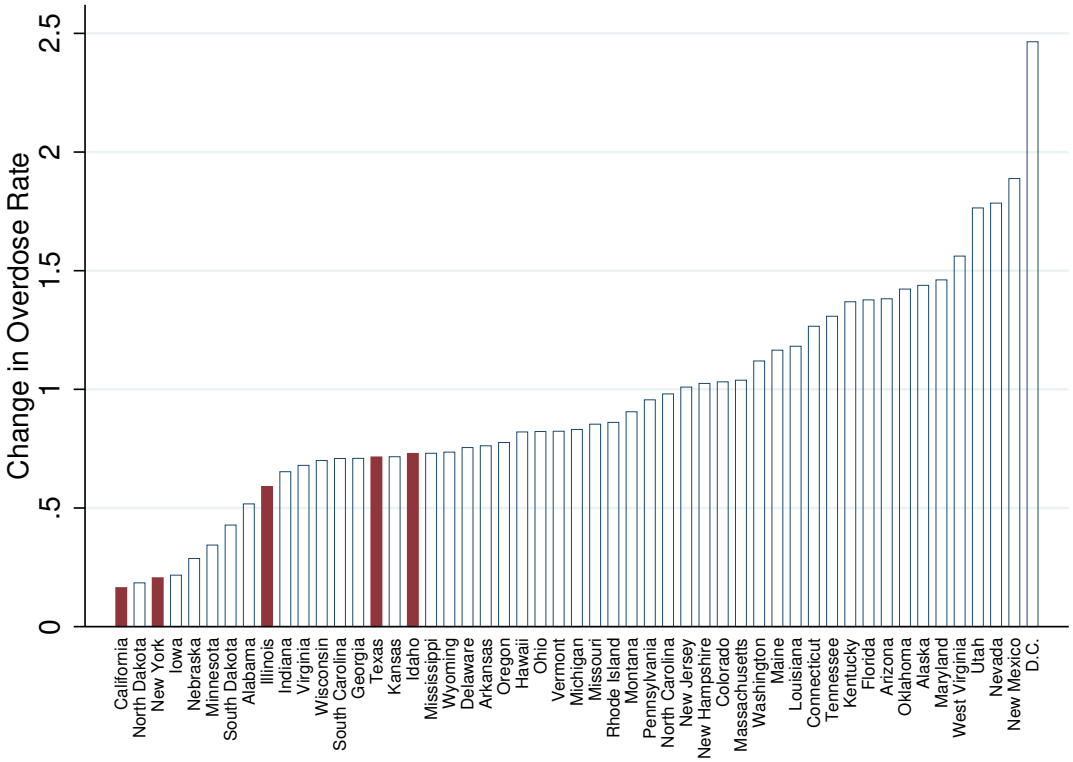
Figure A7: Overdose Rate Changes For Each Triplicate States, Compared to Neighboring States



Notes: We construct the change in the overdose rate (per 100,000) for 2008-2017 relative to 1986-1995. We plot this change for each triplicate state relative to its neighboring states.

Figure A8: Overdose Rate Changes by State

(a) 1996-2005 Relative to 1986-1995



(b) 2008-2017 Relative to 1986-1995

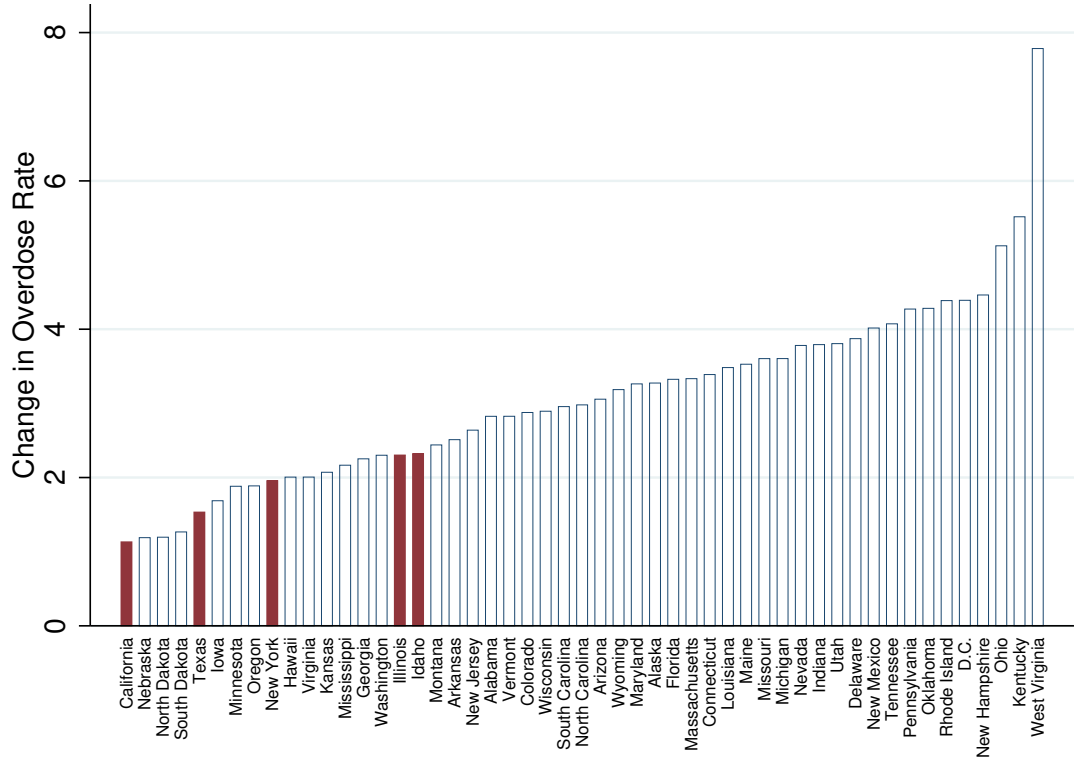
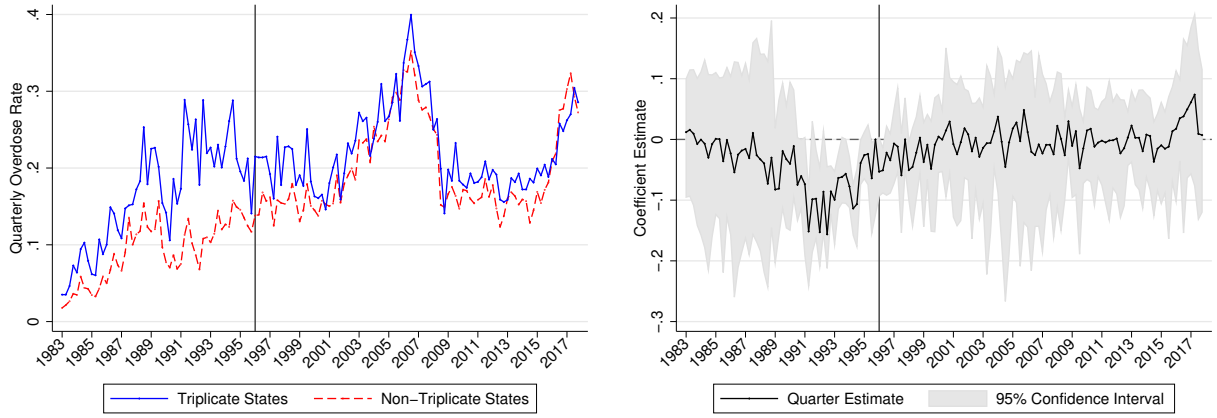


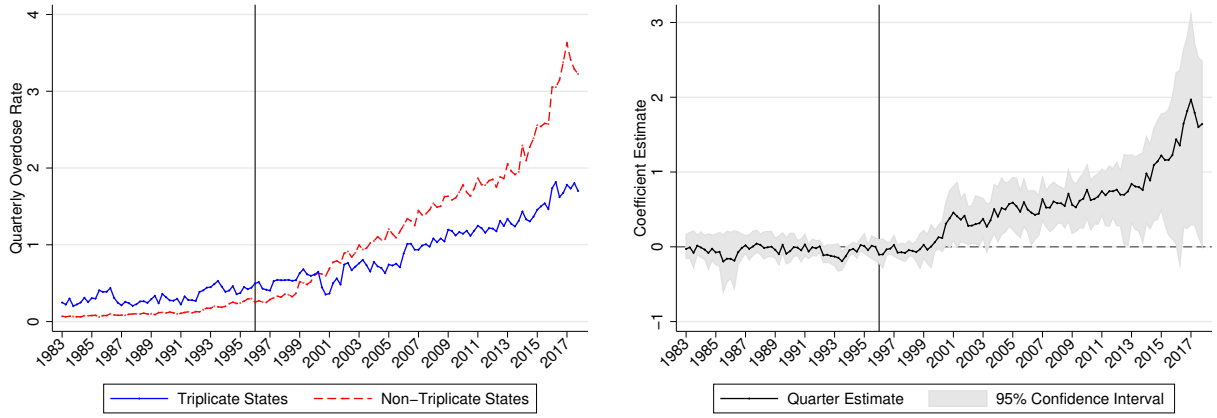
Figure A9: Cocaine Overdose Rates, Excluding Opioids



A: Triplicate and Non-Triplicate State Means B: Event Study Results

Notes: We use geocoded NVSS data to construct cocaine overdoses (excluding opioids) per 100,000. Panel B reports event study estimates from a regression which includes state and quarter fixed effects. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in the final quarter of 1995.

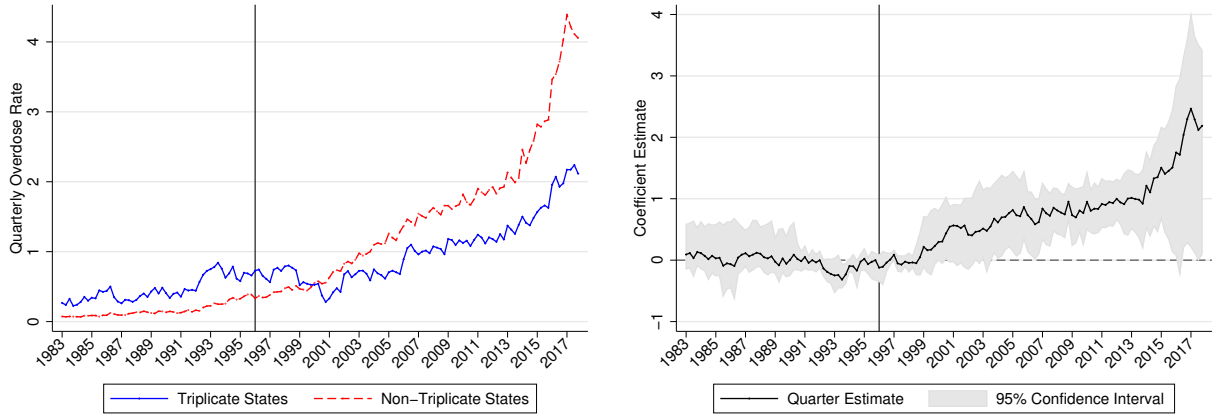
Figure A10: Opioid Overdose Rates Excluding Cocaine



A: Triplicate and Non-Triplicate State Means B: Event Study Results

Notes: We use geocoded NVSS data to construct opioid overdoses per 100,000. We exclude overdoses also involving cocaine. See text for exact ICD codes used in each period. Panel B reports event study estimates from a regression which includes state and quarter fixed effects. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in the final quarter of 1995.

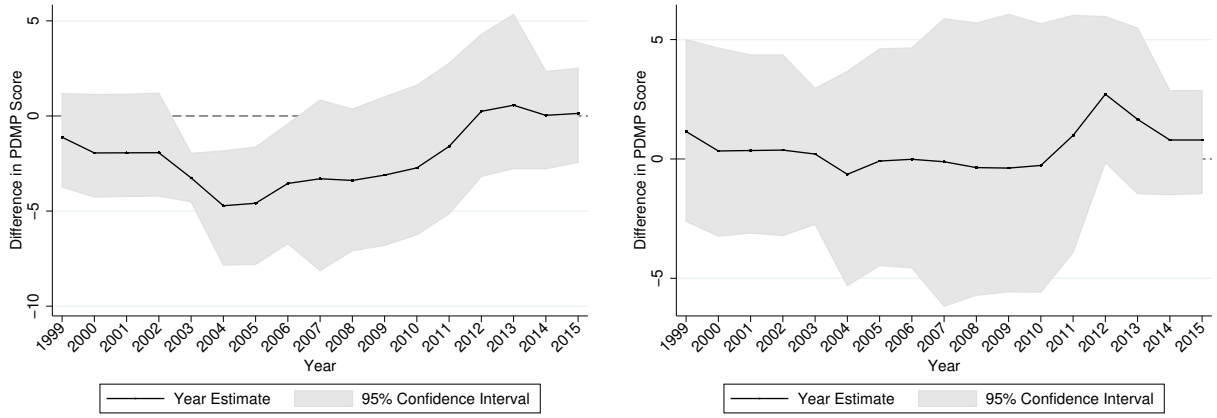
Figure A11: Opioid Overdose Rates, Excluding Unspecified Category



A: Triplicate and Non-Triplicate State Means B: Event Study Results

Notes: We use geocoded NVSS data to construct opioid overdoses, excluding those which *only* have T40.6 coded, per 100,000. Panel B reports event study estimates from a regression which includes state and quarter fixed effects. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in the final quarter of 1995.

Figure A12: Comparing PDMP Strength

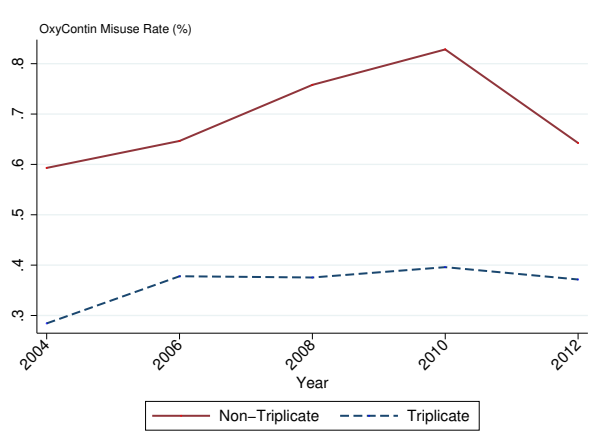


A: All States

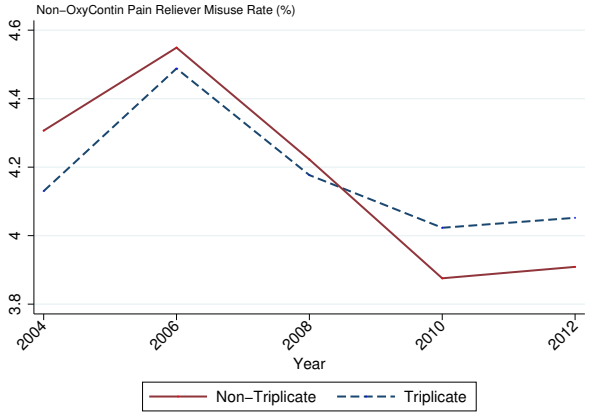
B: States with PDMPs in 1996

Notes: Each estimate represents the cross-sectional difference in the outcome variable, comparing non-triplicate states relative to triplicate states. 95% confidence intervals generated using wild bootstrap clustered by state using Webb (2013) weights. The outcome is the Pardo (2017) index of PDMP robustness. Pardo (2017) sets this index to zero for states without PDMPs.

Figure A13: Non-Medical Use Rates



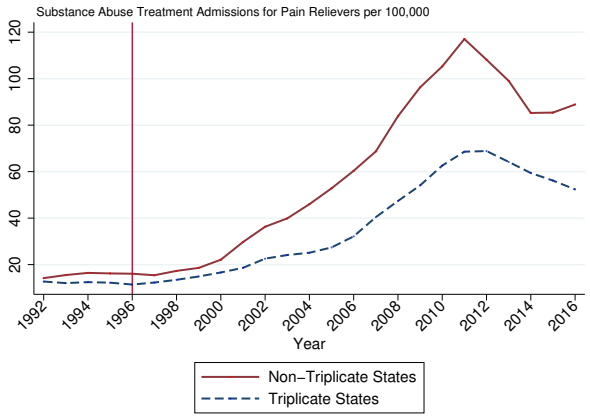
A: OxyContin Misuse per 100



B: Pain Reliever (Excluding OxyContin) Misuse per 100

Notes: Misuse rates are calculated from the National Survey on Drug Use and Health using the years available. Each year refers to a wave such that "2004" refers to 2004-2005, "2006" refers to 2006-2007, etc.

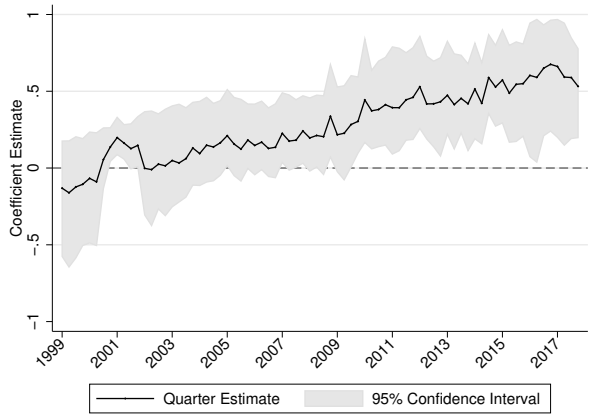
Figure A14: Opioid-Related Substance Abuse Treatment Admissions



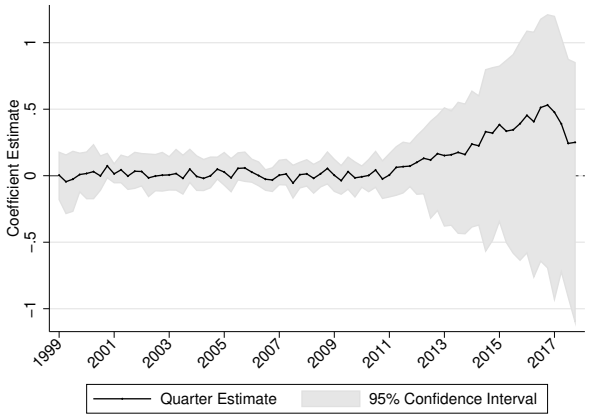
Pain Reliever Substance Abuse Treatment Admissions per 100,000

Notes: Substance abuse treatment admissions are calculated using the Treatment Episode Data Set.

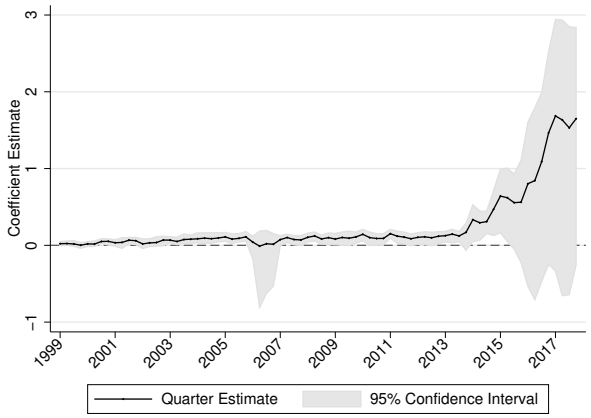
Figure A15: Overdose Rate Differences by Type of Opioid for 1999-2017



A: Natural and Semisynthetic Opioids (T40.2)



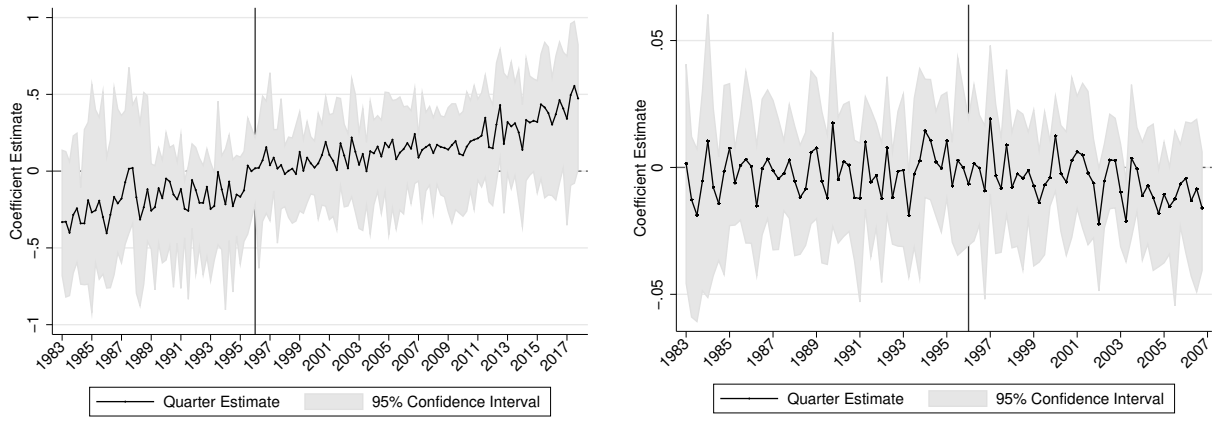
B: Heroin (T40.1)



C: Synthetic Opioids (T40.4)

Notes: We use geocoded NVSS data to construct overdoses per 100,000 for the reported opioid types (see text for additional information). We show estimates from a regression which includes quarter fixed effects and non-triplicate indicators interacted with quarter estimates. 95% confidence intervals are generated using a clustered (at state) wild bootstrap.

Figure A16: Other Deaths of Despair

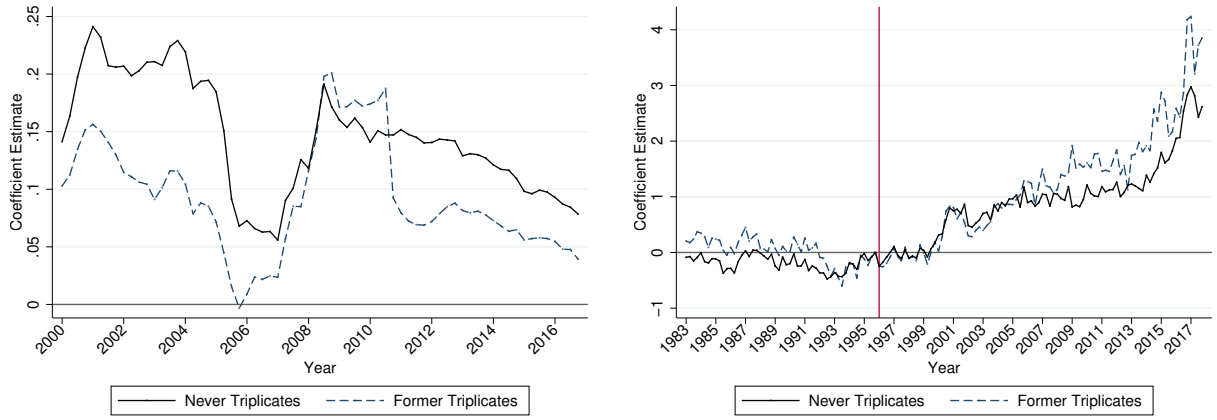


A: Suicides

B: Alcohol Poisonings

Notes: We use geocoded NVSS data to construct alcohol poisoning and suicides (excluding those involving opioids) per 100,000. These figures report event study estimates from a regression which includes state and quarter fixed effects. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in the final quarter of 1995. Alcohol poisoning series ends in 2006 because of a coding change in 2007 which makes it difficult to create a consistent time series.

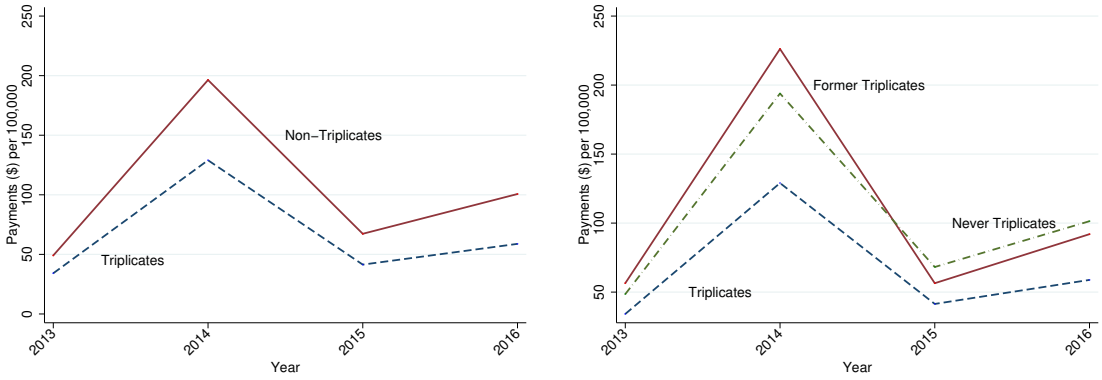
Figure A17: Comparing Former Triplicates States to Triplicate States



OxyContin Supply | Overdoses per 100,000

Notes: We estimate our primary event study using the triplicate states as controls and estimating effects separately for never-triplicate states and former-triplicate states.

Figure A18: Payments to Physicians



Notes: We used Open Payments Data to calculate total payments and gifts made to physicians regarding OxyContin. The outcomes correspond to August 2013 – December 2016.

Appendix Tables

Table A1: State Oxycodone Prescribing Prevalence, 1991-1995

State	Medicaid Prescriptions per 1000 Benes (1991-1995)
TEXAS	**1.68**
ILLINOIS	**2.73**
CALIFORNIA	**7.61**
KENTUCKY	8.03
MICHIGAN	*10.15*
NEW YORK	**11.19**
IDAHO	**19.18**
WASHINGTON	20.13
INDIANA	*20.60*
RHODE ISLAND	21.97
SOUTH DAKOTA	22.43
ARKANSAS	25.87
MINNESOTA	26.95
MISSISSIPPI	27.84
IOWA	30.26
OKLAHOMA	30.40
NORTH DAKOTA	30.90
NEBRASKA	36.27
ALABAMA	36.33
SOUTH CAROLINA	38.62
DISTRICT OF COLUMBIA	39.77
KANSAS	39.91
GEORGIA	40.61
MISSOURI	41.20
WEST VIRGINIA	42.73
OREGON	43.86
FLORIDA	44.15
TENNESSEE	44.19
NORTH CAROLINA	44.57
OHIO	45.07
LOUISIANA	45.27
WYOMING	51.82
WISCONSIN	56.44
VIRGINIA	61.33
COLORADO	62.07
NEVADA	62.78
NEW JERSEY	65.51
NEW MEXICO	67.83
PENNSYLVANIA	69.93
HAWAII	71.89
DELAWARE	74.42
MONTANA	76.13
UTAH	91.30
ALASKA	93.21
MARYLAND	97.37
MAINE	111.52
NEW HAMPSHIRE	125.88
VERMONT	131.13
MASSACHUSETTS	131.45
CONNECTICUT	133.59
ARIZONA	(no data)

Notes: This table sorts states by Medicaid oxycodone prescriptions per 1,000 beneficiaries for 1991-1995. Triplicate states as of 1996 are bolded; former triplicate states are italicized.

Table A2: Overdoses – Clustered (not bootstrapped) Confidence Intervals

		Overdoses per 100,000		
Non-Triplicate ×	(1)	(2)	(3)	(4)
1996-2000	0.311***	0.331***	0.347***	0.341***
	[0.127, 0.496]	[0.159, 0.503]	[0.162, 0.532]	[0.151, 0.530]
2001-2010	0.939***	1.141***	1.037***	0.849***
	[0.486, 1.393]	[0.720, 1.563]	[0.741, 1.332]	[0.533, 1.165]
2011-2017	1.562***	1.976***	1.260***	1.636***
	[0.919, 2.205]	[1.347, 2.605]	[0.746, 1.774]	[1.099, 2.174]
Weighted	No	Yes	Yes	Yes
Covariates	No	No	Yes	Yes
Region-Time Dummies	No	No	No	Yes
N	4,968	4,968	4,968	4,968
		Opioid Overdoses per 100,000		
Non-Triplicate ×	(5)	(6)	(7)	(8)
1996-2000	0.175**	0.158**	0.184**	0.184**
	[0.039, 0.312]	[0.018, 0.297]	[0.040, 0.327]	[0.036, 0.331]
2001-2010	0.669***	0.748***	0.722***	0.512***
	[0.335, 1.002]	[0.427, 1.069]	[0.390, 1.055]	[0.153, 0.871]
2011-2017	1.283***	1.486***	0.909***	1.069***
	[0.605, 1.961]	[0.770, 2.203]	[0.288, 1.530]	[0.484, 1.655]
Weighted	No	Yes	Yes	Yes
Covariates	No	No	Yes	Yes
Region-Time Dummies	No	No	No	Yes
N	4,968	4,968	4,968	4,968

Notes: ***Significance 1%, **Significance 5%, *Significance 10%. This table replicates Table 3 while reporting traditional clustered 95% confidence intervals instead of those generated by a wild bootstrap. The reported coefficients refer to the interaction of the given time period and an indicator for whether the state did not have a triplicate program in 1996. Estimates are relative to pre-period 1991-1995. All models include state and quarter fixed effects. Covariates include the fraction white, fraction with college degree, and fraction ages 25-44. These covariates are interacted with year indicators.

B. Synthetic Control Estimates

While we observed little evidence of pre-existing trends in our results, the triplicate states did begin with higher levels of overdoses. One way to address differences in pre-treatment levels is to construct synthetic controls for each treated state using the synthetic control method (Abadie and Gardeazabal, 2003; Abadie et al., 2010, 2015). Here, we estimate synthetic controls for each triplicate state using non-triplicate states as potential components of the synthetic controls.[1] Thus, the "treatment" is triplicate state status in 1996 (unlike the prior analyses where the treatment was non-triplicate state status in 1996) since it makes more sense to use the 46 non-triplicate states to construct synthetic controls for the 5 triplicate states than vice versa. We then present the negative of the average weighted difference in the triplicate states relative to their synthetic controls, where the weights are the inverse of the variance in the pre-treatment period. This approach upweights states with more appropriate synthetic controls.[2] The negative sign makes the estimates comparable to those presented throughout the paper.

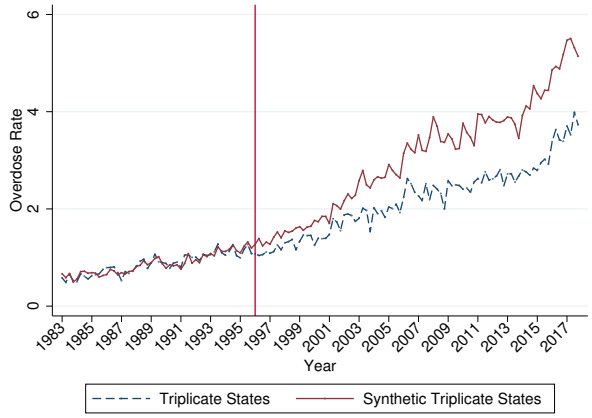
The results are shown in Figure B1.[3] We estimate similar overdose reductions as our main estimates. These estimates are summarized for our three aggregate time periods in Table B1. For inference, we use a permutation test, randomly-assigning triplicate status to non-triplicate states and then reporting the rank of the main estimate to the 999 placebo estimates. The estimates are similar to the difference-in-differences estimates and generally statistically significant at the 1% level. These results suggest that our main estimates are not driven by initial differences in overdose rates between the triplicate and non-triplicate states.

[1] Given that we have a relatively long pre-period consisting of 52 quarters, we are less concerned about overfitting in this context and construct the synthetic controls based on the value of the outcome in each quarter in the pre-period.

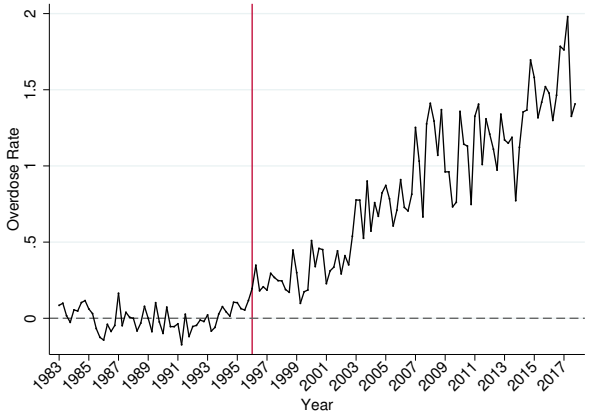
[2] We also present the time series overdose rates for the triplicate and synthetic triplicate states, using these same weights. Thus, the time series trends will not match those shown earlier in the paper.

[3] The synthetic control weights are shown in Table B2.

Figure B1: Synthetic Control Results: Overdoses

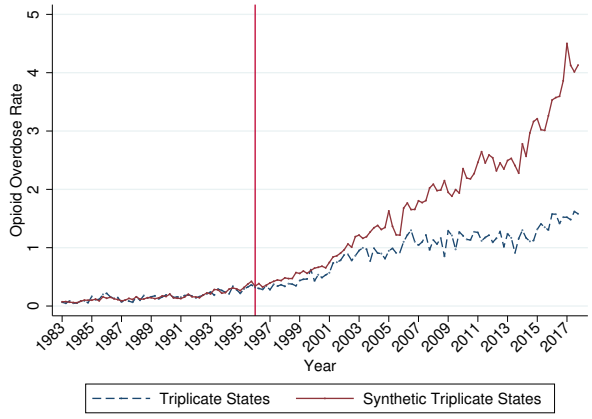


A: Triplicate and Synthetic Triplicate States

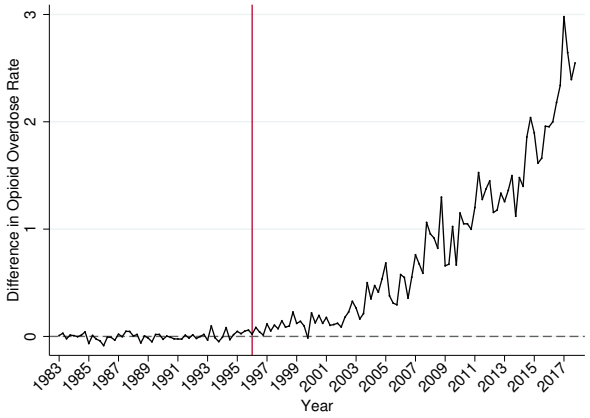


B: Difference

Synthetic Control Results: Opioid Overdoses



A: Triplicate and Synthetic Triplicate States



B: Difference

Notes: We construct a synthetic control for each triplicate state. We then take a weighted (by the "fit" of the synthetic control before 1996) average of the triplicate states and a weighted average of the synthetic control. The difference is shown in Panel B. See Table B2 for the synthetic control weights.

Table B1: Synthetic Control Results

Non-Triplicate ×	Overdoses per 100,000	Opioid Overdoses per 100,000
1996-2000	0.275	0.104
	[1/1000]	[149/1000]
2001-2010	0.800	0.558
	[1/1000]	[8/1000]
2011-2017	1.351	1.738
	[2/1000]	[1/1000]

Notes: We estimated synthetic controls for each triplicate state and report the weighted average of the synthetic controls (which are non-triplicates) minus the triplicate states. The weights are the inverse of the variance before 1996. This approach considers the triplicate states as "treated" given that it would be difficult to construct synthetic controls for each non-triplicate state using only the 5 triplicate states. Below each estimate, we report the rank of that estimate relative to the 999 placebo estimates and the main estimate itself, produced by randomly-assigning states to "triplicate" status and repeating the entire strategy.

Table B2: Synthetic Control Weights

State	Overdoses					Opioid Overdoses				
	CALIFORNIA	IDAHO	ILLINOIS	NEW YORK	TEXAS	CALIFORNIA	IDAHO	ILLINOIS	NEW YORK	TEXAS
ALABAMA	0	0	0	0	0	0	0.49	0	0	0
ALASKA	0	0	0.075	0	0.071	0	0	0	0	0
ARIZONA	0	0	0	0	0	0	0	0.044	0	0
ARKANSAS	0	0	0	0	0.121	0	0.083	0	0	0
COLORADO	0	0	0	0	0	0	0	0	0	0
CONNECTICUT	0	0	0	0.285	0	0	0	0	0.103	0
DELAWARE	0	0.06	0.006	0	0	0	0	0	0	0
DISTRICT OF COLUMBIA	0.184	0	0.023	0	0	0	0	0	0	0
FLORIDA	0	0	0.082	0	0	0	0	0	0	0
GEORGIA	0	0	0	0	0	0	0	0	0.006	0
HAWAII	0	0	0	0	0	0	0	0	0	0
INDIANA	0	0	0	0	0.042	0	0	0	0	0.192
IOWA	0	0.227	0	0	0.095	0	0.042	0	0	0
KANSAS	0	0	0	0	0	0	0	0	0	0
KENTUCKY	0	0	0	0	0	0	0	0	0	0.124
LOUISIANA	0	0	0	0	0	0	0	0	0	0
MAINE	0	0	0	0	0	0	0	0	0	0
MARYLAND	0	0.082	0.061	0	0	0	0	0	0	0
MASSACHUSETTS	0	0	0	0	0	0	0	0	0.086	0
MICHIGAN	0	0	0	0	0	0	0	0	0	0
MINNESOTA	0	0	0	0	0	0	0	0	0	0.062
MISSISSIPPI	0	0	0	0	0.069	0	0	0	0.118	0
MISSOURI	0	0	0	0	0	0	0	0	0	0.109
MONTANA	0	0	0	0	0.036	0	0.167	0	0	0
NEBRASKA	0	0.273	0.132	0.051	0.053	0	0	0	0	0.048
NEVADA	0.562	0	0	0	0	0.386	0.066	0	0	0.076
NEW HAMPSHIRE	0	0	0	0	0.069	0	0	0	0	0.038
NEW JERSEY	0	0.07	0	0	0	0	0.009	0	0	0
NEW MEXICO	0.091	0	0.147	0.346	0.121	0	0	0.021	0.475	0
NORTH CAROLINA	0	0.036	0.032	0	0.002	0	0	0	0	0
NORTH DAKOTA	0	0	0	0	0	0	0	0	0	0.012
OHIO	0	0	0	0	0	0	0	0	0	0
OKLAHOMA	0	0	0	0.121	0.008	0	0	0	0	0
OREGON	0.163	0	0.15	0	0.057	0	0	0.049	0	0.07
PENNSYLVANIA	0	0	0	0	0.065	0	0	0	0	0.049
RHODE ISLAND	0	0	0	0	0	0	0	0	0	0
SOUTH CAROLINA	0	0	0	0	0.142	0	0	0	0	0.094
SOUTH DAKOTA	0	0	0	0	0.022	0	0	0	0	0
TENNESSEE	0	0	0.034	0	0	0	0	0	0	0
UTAH	0	0	0.092	0	0	0	0	0.199	0.099	0
VERMONT	0	0	0.043	0	0	0	0	0	0.053	0
VIRGINIA	0	0.247	0	0	0	0	0	0.206	0	0
WASHINGTON	0	0	0	0	0	0.614	0	0.465	0	0
WEST VIRGINIA	0	0	0.124	0.057	0	0	0.086	0	0	0.089
WISCONSIN	0	0	0	0	0	0	0	0	0	0
WYOMING	0	0.006	0	0.141	0.027	0	0.057	0.016	0.06	0.037
"Fit" Weight	0.112	0.304	1.226	0.342	1.952	0.189	3.165	0.866	0.689	12.641

Notes: This table reports the weights assigned to the state in the row to construct a synthetic control for the triplicate state listed in the column header. Each column adds to one. The last row reports the overall "fit" weight which is used to aggregate the 5 triplicate estimates together based on the strength of the synthetic control fit (the inverse of the sum of the squares of the difference between the outcome and the synthetic outcome in the pre-period).