ORIGINS OF THE OPIOID CRISIS AND ITS ENDURING IMPACTS*

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Overdose deaths involving opioids have increased dramatically since the 1990s, leading to the worst drug overdose epidemic in U.S. history, but there is limited empirical evidence about 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 cross-state variation in exposure to OxyContin's introduction due to a state policy that substantially limited OxyContin's early entry and marketing in select states. Recently-unsealed court documents involving Purdue Pharma show that state-based triplicate prescription programs posed a major obstacle to sales of OxyContin and suggest that less marketing was targeted to states with these programs. We find that OxyContin distribution was more than 50% lower in "triplicate states" in the years after OxyContin's launch. While triplicate states had higher rates of overdose deaths prior to 1996, this relationship flipped shortly after the launch and triplicate states saw substantially slower growth in overdose deaths, continuing even twenty years after OxyContin's introduction. Our results show that the introduction and marketing of OxyContin explain a substantial share of overdose deaths over the last two decades.

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1 Introduction

Over the last two decades, there has been a staggering increase in mortality from drug overdoses in the United States. Between 1983 and 2017, the drug overdose death rate increased by a factor of eight, with a dramatic increase beginning in the 1990s (Figure I). Overdose deaths involving opioids account for 75% of the growth and, by 2017, two-thirds of all drug overdose deaths were related to opioids.[1] Overdoses involving opioids claimed the lives of 47,600 people in 2017 (Scholl et al., 2019) and almost 500,000 since 1999 (CDC, 2021), about the same number of U.S. soldiers who died in World War II (DeBruyne, 2018). This massive rise in opioid deaths has contributed to the longest sustained decline in life expectancy since 1915 (Dyer, 2018).

There are many hypotheses about the initial causes of the opioid crisis. Case and Deaton (2015, 2017) suggest that demand factors played an important role as worsening cultural and economic conditions may have sparked a surge in "deaths of despair": suicides, alcohol-related mortality, and drug overdoses. Empirical tests have found mixed evidence on the role of economic conditions in driving drug misuse and overdoses (e.g., Ruhm, 2019a; Pierce and Schott, 2020; Venkataramani et al., 2020). Alternative hypotheses, though not mutually exclusive, consider the role of supply factors. Beginning in the 1990s, changing attitudes and new treatment guidelines encouraged doctors to treat pain more aggressively with opioids (Quinones, 2015; Jones et al., 2018).[2] Additionally, in 1996, Purdue Pharma launched its drug OxyContin, a prescription opioid pain reliever that quickly became one of the leading drugs of abuse in the U.S. (Cicero, Inciardi, and Muñoz, 2005).

[1] Some of these overdoses may involve non-opioid drugs in addition to opioids. Ruhm (2019b) documents the recent rise in non-opioid overdose death rates.

[2] 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 (JCAHO) revised its guidelines in 2001, requiring that doctors assess pain along with other vitals during medical visits (Phillips, 2000).

Despite the discussion of these supply-side hypotheses throughout the literature, there is surprisingly little empirical evidence on any individual factor's importance. Ruhm (2019a) finds that increased access to opioids overall, rather than economic conditions, was a major driver of growth in overdose rates since 1999. Powell, Pacula, and Taylor (2020) show that increased opioid access through Medicare led to higher rates of opioid diversion and overdose deaths.[3] Existing research is relevant to understanding the role of supply versus demand factors in driving the ongoing crisis; however, none of these studies isolate the causes of the initial rise in overdose deaths in the 1990s.

In this paper, we provide the first quasi-experimental evidence on the initial causes of the opioid crisis, which is commonly dated as beginning in the 1990s.[4] We examine the role of the introduction and marketing of OxyContin as a potential leading cause, exploring its impacts on drug overdose deaths over the two decades since its launch. The aggressive and deceptive marketing of OxyContin has been the subject of enormous public and scholarly discussion (e.g., Van Zee, 2009; Kolodny et al., 2015; Quinones, 2015) and thousands of lawsuits from state and local governments, which have implicated OxyContin as "the taproot of the opioid epidemic."[5] However, defenders of OxyContin argue that numerous other suppliers of opioids and the behaviors of physicians and patients have played a larger role (Mclean, 2019).[6]

[3] In addition, Finkelstein, Gentzkow, and Williams (2018) find that place-specific factors are important determinants of opioid abuse rather than individual-level factors; however, their study design does not allow them to separate out the relative importance of local economic and cultural conditions from opioid access.
[4] The CDC marks the first wave of the crisis as beginning in the 1990s (https://www.cdc.gov/drugoverdose/epidemic/index.html, last accessed December 1, 2020). Maclean et al. (2020) date the first wave beginning in the mid-1990s.
[5] See the 2019 New York complaint: https://ag.ny.gov/sites/default/files/oag_opioid_lawsuit.pdf
[6] For example, an attorney for Purdue Pharma argues that the opioid epidemic "is not caused by Purdue's sale of its legal, FDA-regulated medications, but rather by doctors who wrote improper prescriptions and/or by third parties who caused persons without valid and medically necessary prescriptions to get opioid medications or illegal street drugs. Purdue has no control over those persons" (Satterfield, 2018).

Since OxyContin was launched nationwide, it is difficult to isolate its effects from other concurrent changes to prescribing practice patterns, opioid availability, and demand. We address this issue by exploiting 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 obtained information on the importance of this state policy from recently-unsealed court documents that we collected from multiple settled lawsuits involving Purdue Pharma. These documents provide an unprecedented look at the manufacturer's internal marketing strategies around the introduction of OxyContin. They reveal that Purdue Pharma viewed state-based "triplicate prescription programs," an unusually stringent early prescription drug monitoring program, as a significant barrier to prescribing OxyContin. They suggest that the company did not target marketing to states with triplicate programs given the lower expected returns. For example, Purdue Pharma's focus group research found that "doctors in the triplicate states were not enthusiastic about the product [OxyContin] at all, with only a couple indicating they would ever use it, and then in very infrequent situations" and recommended that "the product should only be positioned to physicians in non-triplicate states" (Groups Plus, 1995).

Using a difference-in-differences framework, we take advantage of the variation in OxyContin use induced by these triplicate policies to study drug 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 to be more exposed to OxyContin's introduction because the barriers to prescribing were lower and more initial marketing was targeted to these states. Indeed, we find that OxyContin distribution was more than twice as high in non-triplicate states in the years after the launch.

Given this variation in exposure to OxyContin's introduction, we estimate OxyContin's impact on drug overdose deaths over the short and long run. Prior to OxyContin's launch, the two groups of states had similar trends in drug overdose death rates. These trends diverged shortly after the launch, with drug overdose deaths increasing much more rapidly in non-triplicate states, a trend that continued even twenty years later. This differential growth is driven by drug overdoses involving prescription opioids until 2010. After 2010, when the original formulation of OxyContin was replaced with an abuse-deterrent version, large differences in deaths involving heroin and fentanyl emerged. This is consistent with prior evidence that areas with high rates of OxyContin misuse experienced differential transitions to illicit opioids as people substituted from OxyContin to heroin (Alpert, Powell, and Pacula, 2018; Evans, Lieber, and Power, 2019).

Overall, our estimates imply that non-triplicate states would have had an average of 34% fewer drug overdose deaths and 45% fewer opioid overdose deaths from 1996 to 2017 if they had been triplicate states at the time of OxyContin's launch. Our results are not explained by other opioid policies, economic shocks, or differences in urbanicity and population size. We do not find similar patterns in the use of prescription opioids not covered by triplicate programs or other "deaths of despair." It is statistically rare to observe effect sizes of a similar magnitude as our main estimates when we randomly assign triplicate status to other states.

This research contributes to our understanding of what initially sparked the opioid crisis. We find that the introduction and marketing of OxyContin explain a substantial share of 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 had long-term effects on overdose deaths in these states, dramatically decreasing overdose death rates

even today. The triplicate states currently have some of the lowest overdose death rates in the country. Our work therefore also speaks to the importance of early regulations in explaining current geographic variation in overdose deaths.

While triplicate programs themselves may have discouraged OxyContin adoption, the enduring mortality differences across states even after triplicate programs had ended suggest that persistent marketing practices played a more central role. We evaluate the role of marketing relative to the independent long-term effects of triplicate programs by studying "former triplicate states" that had eliminated their triplicate programs just prior to OxyContin's launch. Former triplicate states experienced high rates of OxyContin adoption and overdose mortality growth similar to states that never had triplicate programs, suggesting minimal legacy effects of triplicate programs themselves. Instead, the lack of OxyContin marketing in triplicate states appears to explain the persistent low growth in overdose deaths.

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 and discuss mechanisms in Section 5. In Section 6, we consider alternative explanations for the observed differential overdose trends. Section 7 concludes. All appendix material can be found in the Online Appendix.

2 Background

2.1 OxyContin's Launch and Promotional Activities

In this section, we provide a brief background on OxyContin and its promotion (see Appendix Section B for a more detailed history). OxyContin is a long-acting formulation of oxycodone, a morphine-like drug, produced by Purdue Pharma. Given its high potential for

abuse, it is classified as a Schedule II controlled substance. The Food and Drug Administration (FDA) approved OxyContin in 1995 and the drug was introduced to the market in January 1996. OxyContin's key technological innovation was its sustained-release formulation that uses a high concentration of the active ingredient to provide 12 hours of continuous pain relief. However, crushing or dissolving the pill allowed users to access the high dosage of oxycodone all at once, producing an intense high. The high potency of OxyContin made it one of the leading drugs of abuse in the U.S. (Cicero, Inciardi, and Muñoz, 2005) and concerns about widespread abuse of this drug were being reported by 2000 (GAO, 2003).

Purdue Pharma launched an aggressive advertising campaign for OxyContin which was unprecedented for an opioid in terms of the promotional spending (GAO, 2003) and the type of physicians being targeted. They targeted marketing to primary care physicians to promote the drug for non-cancer chronic pain— a previously untapped market for opioids.[7] Such physician detailing has been shown to be effective at increasing prescribing (Agha and Zeltzer, forthcoming; Carey, Lieber, and Miller, 2021).[8] Indeed, OxyContin prescriptions increased at a faster rate for non-cancer pain than for cancer pain from 1997 to 2002 (GAO, 2003). The initial marketing strategy also centered on false claims that the drug had low abuse potential and was safer than other opioid drugs.[9] The original FDA product label for OxyContin included the

[7] Purdue Pharma also promoted OxyContin through a variety of other channels such as sponsoring pain-related educational programs and conferences, distributing coupons and gifts, and advertising in medical journals.
[8] Purdue Pharma conducted internal research showing that its promotional activities were effective. From Commonwealth of Massachusetts (2019): "The effectiveness of the sales visits was corroborated by an outside consulting firm: McKinsey confirmed that Purdue's sales visits generated opioid prescriptions" (p. 137); "Purdue knew its sales push drove patients to higher doses…Purdue's business plans emphasized that 'OxyContin is promotional sensitive, specifically with the higher doses, and recent research findings reinforce the value of sales calls'" (p. 19); "Director Richard Sackler testified that the sales representatives were the main way that Purdue promoted its opioids. He testified that the key to getting doctors to prescribe and keep prescribing Purdue opioids was regular visits from the sales force" (p. 50).
[9] For example, marketing materials relied heavily on a 100-word letter to the editor (Porter and Jick, 1980) to support the claim that the risk of addiction among opioid users was "much less than one percent."

statement that "delayed absorption as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug," which became a cornerstone of the initial marketing campaign.

Overall, these marketing efforts contributed to OxyContin's blockbuster success. Revenue from OxyContin sales skyrocketed from $48 million in 1996 to $1.1 billion in 2000 (Van Zee, 2009) and $3.1 billion in 2010 (IMS, 2011). The marketing of OxyContin eventually concerned local and state governments. In 2007, Purdue Pharma paid fines over $600 million for misleading advertising. In 2020, another lawsuit resulted in an $8.3 billion settlement.

2.2 Geographic Variation in Exposure to OxyContin's Introduction

This study exploits previously unexplored geographic variation in OxyContin's introduction and initial marketing. To understand how OxyContin was marketed, we made Freedom of Information Act (FOIA) requests to obtain recently unsealed documents in Florida, Washington, and West Virginia from investigations and settled court cases involving Purdue Pharma.[10] Among these documents, we obtained the launch plan for OxyContin, the focus group research conducted prior to the launch (see Figure A1), and annual itemized budgets for OxyContin from 1996 to 2002. These documents revealed that Purdue Pharma would have difficulty penetrating markets that had enacted a state policy known as a "triplicate prescription program" and suggested that it would target less marketing to these states.

2.2.1 What Are Triplicate Prescription Programs?

Triplicate prescription programs were among the earliest prescription drug monitoring programs enacted to reduce the diversion and misuse of controlled substances. Triplicate programs mandated that doctors use state-issued triplicate prescription forms when prescribing

[10] The documents come from three main sources. In November 2001, the Florida Attorney General opened an investigation into Purdue Pharma's marketing tactics. The investigation was closed about a year later. Purdue Pharma paid the state of Florida a $2 million settlement. We also received documents from the State of Washington v. Purdue Pharma L.P. et al. (filed September 2017) and State of West Virginia v. Purdue Pharma et al. (filed June 11, 2001, settled in 2004).

Schedule II controlled substances (which includes many opioids). The physician was required to maintain one copy of the triplicate form for their records. The patient was given two copies to give to the pharmacy; the pharmacy kept one and sent the third copy to the state drug monitoring agency. States kept a database of the forms to monitor and investigate prescribing irregularities.

The academic literature on triplicate programs finds that such programs led to dramatic reductions in the 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 for these reductions. First, physicians in triplicate states were concerned about government oversight of their prescribing behavior (Berina et al., 1985). As Purdue Pharma observed in its focus group research: "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" (Groups Plus, 1995, p. 24). Although electronic monitoring programs also involved government oversight, 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., p. 3).

Second, triplicate programs imposed large hassle costs on physicians. According to Purdue Pharma's research: "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. To the extent that they [physicians] can avoid this extra effort, they will try to follow alternative protocols" (Groups Plus, 1995, p. 24). Placing this burden specifically on the prescriber rather than on the pharmacist suggests a key reason for why triplicate programs are found to have substantial

effects on prescriptions, while some modern electronic Prescription Drug Monitoring Programs (particularly, non-mandate PDMPs) have more muted effects.[11]

At the time of OxyContin's launch in 1996, five states had active triplicate programs: California, Idaho, Illinois, New York, and Texas.[12] The enactment and end years of the triplicate programs are listed in Table A1.[13] These triplicate programs were adopted decades before OxyContin's launch. California adopted the first triplicate program in 1939 (Joranson et al., 2002); other states adopted the program between 1961 and 1988. Indiana and Michigan also had triplicate programs, but they ended their programs two years before OxyContin's launch.[14]

The triplicate states all discontinued their programs by 2004. Therefore, our analysis speaks to the long-run effects of the *initial* targeting of Purdue Pharma's marketing due to triplicate status during the launch. The discontinuation of these programs provides an opportunity to isolate long-term persistent effects of marketing from the direct effects of having a triplicate program. In addition, we separate the legacy effects of triplicate programs from the

[11] Must-access PDMPs have been shown to reduce opioid prescribing, while non-mandate PDMPs have muted effects (Buchmueller and Carey, 2018). Notably, similar to triplicate programs, must-access PDMPs impose a hassle cost on the prescriber, which can explain a large share of the prescribing reduction from these programs (Alpert, Jacobson, and Dykstra, 2020). The hassle costs were even higher for the triplicate programs, which may explain their large deterrent effects. Doctors needed to purchase the triplicate forms and store the written prescriptions for years. In 2001, only 57.6% of physicians in California requested triplicate prescription forms, implying that the other 42.4% were not even capable of prescribing Schedule II opioids (Fishman et al., 2004).

[12] In one instance in the internal documents we reviewed, there is an incorrect reference to "nine triplicate states" when discussing retail pharmacy distribution. It is possible they were referring to the nine states with paper-based monitoring systems (including duplicate and single-copy programs), because this statement appears in the context of pharmacists' concerns about the "voluminous paperwork" required in these states, which would be a consideration with any paper-based system. To the degree that Purdue Pharma was also concerned about other paper-based programs and also marketed less in these states, our results will be attenuated.

[13] Idaho adopted its program in 1967, switching to a duplicate program in 1997 (Joranson et al., 2002; Fishman et al., 2004, see also: https://legislature.idaho.gov/wp-content/uploads/OPE/Reports/r9901.pdf). Illinois enacted its triplicate program in 1961, converting to an electronic system in 2000 (see https://www.isms.org/opioidplan/). New York enacted a triplicate program in 1972 (Joranson et al., 2002), which ended in 2001 (NY Bureau of Narcotic Enforcement, personal communication, May 3, 2019). Texas adopted a triplicate system in 1982 (Sigler, 1984), converting to an electronic system in 1999 (see https://www.pharmacy.texas.gov/DPS.asp).

[14] 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 ended in 1994 (Joranson et al., 2002). Washington also adopted a triplicate program, but because of limited funding, triplicate forms were required only for physicians disciplined for drug-related violations (Simoni-Wastila and Tompkins, 2001; Fishman et al., 2004).

marketing effects induced by OxyContin's launch by separately analyzing the two former triplicate states (Indiana and Michigan), which repealed their triplicate programs prior to 1996.[15]

2.2.2 Purdue Pharma's Marketing in Triplicate and Non-Triplicate States

Triplicate programs are mentioned repeatedly in Purdue Pharma's internal documents given concerns borne out in their pre-market research that physicians in triplicate states would be less willing to prescribe OxyContin. Purdue Pharma found that "physicians in the triplicate state did not respond positively to the drug [OxyContin], 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" (Groups Plus, 1995, p. 36).[16]

Based on this research, the launch plan acknowledges that "these regulations create a barrier when positioning OxyContin" (OxyContin Launch Plan, 1995, p. 4). They recommended that "the product should only be positioned to physicians in non-triplicate states" (Groups Plus, 1995, p. 55). Further they noted that "our research suggests the absolute number of prescriptions they [physicians in triplicate states] would write each year is very small, and probably would not be sufficient to justify any separate marketing effort" (Groups Plus, 1995, p. 49).[17]

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[15] We include these two "former triplicate states" in the set of non-triplicate states. Purdue Pharma's internal documents refer to states that have triplicate programs, which would exclude states that had discontinued their triplicate programs prior to the launch. There is no mention of former triplicate states in the Purdue Pharma documents and we assume they received similar marketing as other non-triplicate states.

[16] Other representative examples: "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 [a non-triplicate state] 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" (Groups Plus, 1996, p. 24); "Targeting will be a key element to the success of OxyContin…Unfortunately, physicians in triplicate states are going to be harder to convince since they use less CII medications" (Strategic Business Research, 1996, p. 7); "These triplicate state physicians are far less likely to use an oxycodone product... Only 14% mentioned the use of oxycodone products for moderately severe pain, whereas almost three times this number of the non-triplicate physicians (37%) utilize this class of opioid." (Strategic Business Research, 1996, p. 13)

[17] Purdue Pharma appears to have lobbied for the repeal of triplicate policies. For example, the 1999 budget plan includes a $750,000 line-item to fund a "Program to impact the regulatory environment for opioid prescribing in triplicate states" (Purdue Pharma Budget Plan, 1999, pg. 68).

While we do not have data that breaks down Purdue Pharma's initial marketing spending by state to confirm this strategy directly, we examined their marketing in 2013-2016 using the CMS Open Payments database as a measure of persistent differences in marketing. These data report payments made from pharmaceutical manufacturers to physicians related to the promotion of specific drugs, including payments for meals, travel, and gifts. Figure II shows that non-triplicate states received 44-71% more payments per capita for OxyContin than triplicate states in each year (see Panel A).[18] As an alternative metric, we scaled OxyContin payments by total payments (across all drugs) to account for state-level differences in marketing (see Panel B). The gap between triplicates and non-triplicates grows wider when using this metric.

The persistence of the initial targeting based on triplicate status is consistent with the marketing strategy discussed in the internal documents. Early budget plans for Purdue Pharma dictated that the sales force target calls to the top deciles of physicians in terms of past prescribing volumes; more recent documents show that this targeting strategy continued through 2018.[19] Thus, if triplicate states initially received less marketing and this resulted in lower prescribing, these states would continue to receive less marketing in future periods as well. This evidence supports our empirical design of studying the long-term effects of OxyContin's launch based on whether a state initially had a triplicate program.

3 Data

3.1 Mortality Data

We use a restricted-use version of the National Vital Statistics System (NVSS) Multiple Cause of Death mortality files from 1983 to 2017 that contains state and county of residence

[18] The evidence of promotional activities for opioids responding to state-level PDMPs is consistent with findings in Nguyen, Bradford, and Simon (2019) about more recent adoption of mandatory access PDMPs in the 2010s.
[19] For example, "McKinsey recommended doubling down on Purdue Pharma's strategy of targeting high prescribers for even more sales calls…" (p. 212 of Commonwealth of Massachusetts, 2018).

identifiers.[20] These data represent a census of deaths in the U.S. The 1983-1998 data use ICD-9 codes to categorize causes of deaths while the 1999-2017 data use ICD-10 codes. We follow the coding used by the Centers for Disease Control (CDC) to categorize deaths as drug and opioid-related across both sets of classification systems.[21] 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).[22] Our time fixed effects account for this transition given that we would not expect systematically different effects of the coding change across states.

Given concerns over missing opioid designations on death certificates for drug-related overdoses (e.g., Ruhm, 2018), we favor using a broader measure of total drug overdose deaths in most of our analysis which should be robust to substance-specific classification errors (Venkataramani and Chatterjee, 2019). However, we also present results for opioid-related overdose deaths. In addition, we study disaggregated measures of drug overdose deaths by type of opioid from 1999 to 2017, including heroin (T40.1), natural and semisynthetic opioids (T40.2) such as OxyContin, and synthetic opioids (T40.4) such as fentanyl.[23]

3.2 Opioid Distribution, Prescriptions, and Misuse

[20] We begin in 1983 because the 1981 and 1982 files do not include all deaths. In select states, only half of deaths were included, and they were included twice.

[21] 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 (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.). When we study opioid-related overdoses, we will use deaths involving E850.0, E850.1, E850.2, or N965.0 (Alexander, Kiang, and Barbieri, 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 to specify opioid-related overdoses: T40.0-T40.4 and T40.6. 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, which we will show in the Appendix.

[22] In Figure A2, we explore this coding change by examining the national trend in drug overdose deaths around 1999. While we observe an increase in 1999, it is comparable to increases in other time periods. The 1999 increase is larger for opioid-related overdose deaths but not uniquely large relative to other annual changes.

[23] The specific type of opioid is not reliably coded before 1999 in a manner that can be linked to 1999-2017 data.

We use state-level data on the legal supply of opioids from the Drug Enforcement Agency's (DEA) Automation of Reports and Consolidated Orders System (ARCOS). Manufacturers and distributors are required to report their transactions and deliveries of all Schedules I and II substances, all narcotic Schedule III substances, and a number of Schedule IV-V substances to the Attorney General. This includes all oxycodone and hydrocodone products.[24] We analyze data available online for 2000-2017, and we collected earlier data for 1997-1999 using the WayBack Machine.[25] In the public data, only active ingredients are reported, so we observe oxycodone but not OxyContin.[26] Because of our specific interest in OxyContin, we made a FOIA request for OxyContin distribution specifically and received these data for 2000-2016. We report all ARCOS measures in morphine equivalent doses (MEDs), defined as 60 morphine milligram equivalents.

As complementary measures, we also use Medicaid State Drug Utilization Data (SDUD) for 1996-2005, which reports the number of Medicaid prescriptions by National Drug Code (NDC), quarter, and state.[27] While the Medicaid population is non-representative, prescriptions among this group are both a potentially useful proxy for state prescribing behavior and represent an important population disproportionately affected by the opioid crisis (Sharp and Melnik,

[24] Distribution of controlled substances from online or mail-order pharmacies is included in the ARCOS data but cannot be separately identified. These distributions will be attributed to the location of the supplier, which may add some measurement error (MEPS/Medicaid reports prescriptions by state of residence). This could attenuate our ARCOS estimates because the use of online pharmacies is more likely in the non-triplicate states given higher levels of OxyContin prescribing. However, this bias is likely to be small, because the use of online pharmacies for opioids was limited. When online pharmacies were first introduced in 1999, there was limited internet access (Stergachis, 2001) and, over time, state and federal laws effectively banned opioid sales online (GAO, 2000).

[25] ARCOS data is available from https://www.deadiversion.usdoj.gov/arcos/retail_drug_summary/(last accessed November 30, 2018). Archived data is available from: https://web.archive.org/web/20030220041015/https://www.deadiversion.usdoj.gov/arcos/retail_drug_summary/

[26] The public ARCOS data do not report all scheduled substances for each state-quarter, especially for the 1997-2001 time period, which raises concerns about comparability over time. However, oxycodone and hydrocodone—the focus of our study—are reported in all years and states. Moreover, in the figures below we do not observe any evidence of unusual year-to-year jumps which would suggest inconsistent reporting for these substances.

[27] We end the sample in 2005 because of the introduction of Medicare Part D. We select on state-years reporting in all four quarters (over 94% of state-years). While a recent version suppresses data with fewer than 10 prescriptions, we rely on an earlier version of the data that is unsuppressed.

2015). Additionally, we use a restricted version of the Medical Expenditure Panel Survey (MEPS) with state identifiers, accessed through the AHRQ Data Facility, for 1996-2016. The MEPS is a nationally representative survey of households, including pharmaceutical claims.

Finally, we study self-reported rates of opioid misuse in the past year for OxyContin and all other pain relievers (excluding OxyContin) using the National Survey of Drug Use and Health (NSDUH) for 2004-2013.[28] OxyContin misuse is first available in 2004 and is reported in two-year waves. The NSDUH is a nationally representative survey of individuals ages 12 and older and is the largest survey collecting information on substance use in the U.S.[29]

3.3 Summary Statistics

In Table A1, we present summary statistics for 1991-1995, representing the pre-OxyContin period, separately for each triplicate state and aggregated means by triplicate status. Drug overdose and opioid-related overdose death rates are higher on average in the triplicate states before OxyContin's introduction. Some of these differences can be explained by disproportionately higher rates of cocaine-related deaths in triplicate states. When overdoses involving cocaine are eliminated, the differences between triplicate and non-triplicate states shrink. With respect to demographic characteristics, triplicate states have larger populations, and a larger share of the population is Hispanic.[30] Age and education distributions are similar.

4 Empirical Strategy

[28] NSDUH defines "misuse" as taking medication that "was not prescribed for you or that you took only for the experience or feeling they caused."
[29] For more information on these data, see Section II.A of Alpert, Powell, and Pacula (2018).
[30] Demographic information comes from Medicare SEER population data for 1990-2017 and Census data for 1983-1989 since SEER only includes population by ethnicity beginning in 1990. The education variables are calculated using the Annual Social and Economic Supplement of the Current Population Study (Ruggles et al., 2018).

To estimate the impact of OxyContin's introduction, we use a difference-in-differences framework that compares outcomes in non-triplicate states relative to triplicate states before and after the launch of OxyContin. We rely on event study models because of their transparency and because the timing of the effect is of interest. We report the differential change in overdose death rates for non-triplicate states relative to triplicate states given that non-triplicate states were more "exposed" to the introduction of OxyContin. The event study specification is:

$$(1) \qquad y_{st} = \alpha_s + \gamma_t + \sum_{k=1983}^{2017} \beta_k \times 1(\text{Non-Triplicate})_s \times 1(\text{t} = k) + \varepsilon_{st},$$

where y_{st} represents annual drug overdose deaths per 100,000 people in state s in year t. This specification includes state (α_s) and year (γ_t) fixed effects. $1(\text{Non-Triplicate})_s$ is an indicator based on the initial triplicate status of the state in 1996, and it is interacted with a full set of year fixed effects. The non-triplicate indicator is fixed over the entire time period so the estimates refer to the effects of initial triplicate status. We present the estimates of β_k along with 95% confidence intervals graphically, normalizing β_{1995} to equal zero. Our main results are population-weighted. We also summarize the results using a more parsimonious difference-in-differences specification:

$$\begin{aligned}(2) \qquad y_{st} = \alpha_s + \gamma_t &+ \delta_1 \times 1(\text{Non-Triplicate})_s \times 1(1996 \le t \le 2000)_s \\ &+ \delta_2 \times 1(\text{Non-Triplicate})_s \times 1(2001 \le t \le 2010)_s \\ &+ \delta_3 \times 1(\text{Non-Triplicate})_s \times 1(2011 \le t \le 2017)_s + \varepsilon_{st},\end{aligned}$$

The excluded category is 1991-1995 as we limit the sample to 1991-2017 for the difference-in-differences analyses.[31] We estimate three separate "post" effects to permit some heterogeneity while still providing more aggregated effects. The first post-OxyContin effect (δ_1) is for the time period 1996-2000, representing the introduction of OxyContin, the launch of different

[31] We condensed the pre-period to 5-years (from the full 13 years available) to provide a more meaningful comparison with the post-periods. As can be seen in the event study results, the estimates are not sensitive to different choices for the pre-period.

dosages, and the initial ramp-up of marketing. We also estimate an effect for 2001-2010 (δ_2), corresponding to the "first wave" of the opioid crisis when most deaths are from prescription opioids. Finally, we estimate a separate effect for 2011-2017 (δ_3), representing the second and third waves of the crisis when deaths from heroin and fentanyl became more prominent.

We also present estimates for both equations including covariates. Our baseline controls include the fraction of the population that is White non-Hispanic, Black non-Hispanic, Hispanic, the fraction ages 25-44, 45-64, 65+, the fraction with a college degree, and log population.

Because we have a small number of untreated states, traditional cluster covariance estimators produce standard error estimates that are too small (Brewer, Crossley, and Joyce, 2018). We use a restricted wild cluster bootstrap method at the state level to account for within-state dependence in all models, relying on a 6-point weight distribution as suggested by Webb (2014) when there are few clusters. Given p-values for a range of null hypotheses, we construct and report 95% confidence intervals, which will not be symmetric using this approach.[32] In the Appendix, we show that traditional "clustered" standard errors produce much smaller confidence intervals. We also conduct permutation tests, discussed in Section 6.2.2.

5 Results

Our analysis begins by documenting large differences in OxyContin use across triplicate and non-triplicate states. We then estimate the impact of these differences on drug overdose deaths over the short and long run and explore the mechanisms for persistent mortality effects.

5.1 Effects of Triplicate Status on OxyContin Use

We first show that non-triplicate states were more exposed to the introduction of OxyContin as measured by OxyContin distribution per capita in the ARCOS data. Panel A of

[32] We use the boottest package in Stata (Roodman et al., 2019) to implement this procedure.

Figure III shows the raw trends for OxyContin distribution per capita and Panel B shows the differences between non-triplicate and triplicate states with 95% confidence intervals. In 2000, there is over 2.5 times more OxyContin distribution per capita in non-triplicate states compared to triplicate states. These large and statistically significant differences persist through 2016.

In Figure A3, we study two complementary data sources that allow us to observe OxyContin prescriptions for earlier years. Panel A shows trends for Medicaid OxyContin prescriptions per 1,000 beneficiaries for 1996-2005. Panel B shows OxyContin prescriptions per 1,000 people using the MEPS for 1996-2016. We again observe much higher rates of OxyContin prescriptions in non-triplicate states. OxyContin prescribing increases rapidly for several years after its launch; however, there is a reduction in OxyContin prescriptions in 2005-2006.[33] OxyContin prescribing decreases again after Purdue Pharma replaced the original formulation with an abuse-deterrent version in 2010. However, non-triplicate states continue to experience additional OxyContin use throughout these downturns.

We also examine patterns of initial "adoption" of OxyContin. In Figure A4, we show the distribution of OxyContin supply per capita across states using the earliest years of Medicaid and ARCOS data. For both measures, the triplicate states cluster close to 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.[34] The pattern is similar in the ARCOS data. Triplicate states initially had some of the lowest rates of OxyContin adoption.

[33] This decline is due to a patent dispute between Purdue Pharma and two generic manufacturers (Endo and Teva) that temporarily introduced generic versions of OxyContin in 2004 and 2005 (Bailey et al., 2006). These generic versions were subsequently pulled from the market by March 2007 because they had infringed on Purdue's patents. During this short window of time when generics were available, some branded OxyContin prescriptions would have been filled with equivalent generics—a direct spillover effect of Purdue's marketing. While Panel A of Figure III shows only branded OxyContin, Panel B shows all oxycodone prescriptions which include both generic and branded versions and suggests that reductions in branded OxyContin were offset by increases in generic versions.

[34] Idaho is an exception. This may reflect that Idaho was in the process of replacing its triplicate program. We do not know whether Purdue Pharma anticipated this legislative change and adjusted its promotional activities.

5.2 Effects of Triplicate Status on Use of Other Opioids

Next, we examine differences in the use of other prescription opioids across triplicate and non-triplicate states that could potentially contribute to differences in overdose death trends. Using ARCOS data, Panel C of Figure III shows raw trends in oxycodone and hydrocodone distribution in MEDs, which adjusts for their potency. Hydrocodone (e.g., Vicodin) is a substitute for oxycodone, but it was primarily classified as a Schedule III drug and would not be subject to triplicate programs which cover Schedule II drugs.[35] Panel D plots differences between the two sets of states for each of these opioid drugs along with 95% confidence intervals. Remarkably, per-capita hydrocodone distribution is nearly identical in triplicate and non-triplicate states over the entire time period. However, there are large and statistically significant differences in oxycodone distribution between triplicate and non-triplicate states. Finding differences in oxycodone, but not hydrocodone, suggests that these differences are caused by triplicate status.

As shown in Figure III, the differences in oxycodone distribution (Panel D) exceed the differences observed for OxyContin alone (Panel B) and grow over time; this growth suggests spillovers of OxyContin's promotion on the use of other oxycodone products (e.g., combination products such as Percocet). We observe evidence of spillovers to other types of oxycodone studying prescriptions in Medicaid (our only data set with pre-1996 prescriptions). We provide event study estimates in Figure A5. The outcome is Medicaid oxycodone prescriptions, excluding OxyContin, per 1000 beneficiaries. We observe no difference across states before 1996. After 1996, non-triplicate states increased their oxycodone prescriptions and this effect persists through the end of the sample period. Such spillovers are likely generated by Purdue Pharma's marketing strategies that aimed to expand the opioid market by normalizing the use of

[35] On October 6, 2014, hydrocodone combinations were switched from Schedule III to Schedule II.

strong opioids for non-cancer chronic pain and creating the message that opioids carry a low risk of addiction (Van Zee, 2009).[36] Moreover, individuals introduced to OxyContin will often transition to using other opioids, especially similar products containing oxycodone.[37]

Finally, in Figure A6, we show trends in the rates of *misuse* of OxyContin versus all other pain relievers using the NSDUH for 2004-2013. There are large differences in OxyContin misuse (Panel A) across triplicate and non-triplicate states, but no meaningful differences in the misuse of other pain relievers excluding OxyContin (Panel B). Taken together, the above results are consistent with any differences in overdose rates being primarily attributable to OxyContin.

5.3 Effects of OxyContin Use on Drug Overdose Deaths

5.3.1 Overall Results

Next, we examine whether this differential OxyContin use led to differences in drug overdose deaths over time. In Figure IV, we show raw trends in drug overdose death rates for triplicate and non-triplicate states. We also show coefficients and 95% confidence intervals from estimating the event study specification in equation (1). As evident in Panel A, the trends in overdose death rates were similar across the two sets of states prior to the introduction of OxyContin. Triplicate states had higher overdose rates initially, but this flips within a few years after the launch. Non-triplicate states see rapid growth in overdose deaths, while the trend for triplicate states is much flatter. The corresponding event study estimates, shown in Panel B, are close to zero and largely statistically insignificant prior to 1996, but then the estimates diverge

[36] Purdue Pharma's objective in the early years was: "To convince health care professional (physicians, nurses, pharmacists, and managed health care professionals) to aggressively treat both non-cancer pain and cancer pain. The positive use of opioids, and OxyContin Tablets in particular, will be emphasized" (Purdue Pharma, 1999, p. 44).
[37] First, patients using OxyContin for chronic pain often also receive short-acting oxycodone for short episodes of "breakthrough" pain (Fishbain, 2008). Second, short-acting oxycodone can be used to taper opioid use when discontinuing OxyContin (Berna, Kulich, and Rathmell, 2015). Third, individuals abusing OxyContin may turn to close substitutes whenever they are unable to access OxyContin. For example, Cicero and Ellis (2015) showed that abusers of OxyContin were most likely to switch to other oxycodone products when the supply of abusable OxyContin was restricted. Thus, it is not surprising to observe large spillovers to other oxycodone products.

and become statistically significant.[38] The event study estimate for 1997 indicates that overdose deaths in non-triplicate states increased by 0.28 deaths per 100,000 compared to triplicate states. These effects increase to a statistically significant 2.20 deaths per 100,000 in 2002 and 11.32 deaths per 100,000 by 2017.[39] It is not surprising that these mortality effects are delayed, given the expansions in OxyContin promotion and sales over time and the FDA's relabeling in 2001 that expanded its market for chronic use.[40] Additionally, it would take time for a person to transition from an initial prescription for OxyContin to dependence and an overdose.[41]

We find similar patterns for opioid-related deaths in Panels C and D of Figure IV, demonstrating that the overall drug overdose effects are largely driven by opioids. The event study estimates are similar without population-weights or when we condition on covariates (see Figure A7). The results are also robust to adding Census Region-year interactions to account for geographic differences in overdose rate growth (see Figure A8).

To quantify the magnitude of these effects, in Table I, we present difference-in-differences estimates for the three post-periods from equation (2).[42] In Column 1, we present unweighted estimates. In Column 2, we present population-weighted estimates, which are slightly larger. Relative to the baseline period, we estimate that non-triplicate states experienced an additional 1.3 overdose deaths per 100,000 people in the earliest years after the launch (1996-2000), which is statistically significant at the 1% level. The "counterfactual" fatal overdose rate

[38] Although the individual event-study estimates do not become statistically significant until after 2001, a joint test (Table I) shows that the pooled 1996-2000 estimate is statistically significant relative to the 1991-1995 pre-period.
[39] Notably, we do not observe a large differential jump in the event study coefficients in 1999 when the switch to ICD-10 codes occurred, suggesting that the rise is not a data artifact.
[40] Purdue Pharma doubled its sales reps from 1996 to 2001 (Table 1, GAO 2003) and tripled marketing spending (Figure 1, GAO 2003). Prescriptions increased from 316,786 in 1996 to 7.2 million in 2001 (Table 2, GAO 2003).
[41] For example, a study of injection drug users shows a median of 7.7 years between initiation of injecting and death (Evans et al., 2012). Another study finds an average of 4 years between initiation and death (Guarino et al., 2018).
[42] Alternatively, in Table A2, we present averages of the event study year-specific estimates for the three aggregated time periods. These results are similar to those estimated from equation (2).

for non-triplicates during this time period was 4.2 per 100,000, implying a 31% increase.[43] The estimated effect grows to 4.5 in 2001-2010, representing a 68% increase, and 7.8 in 2011-2017, a 76% increase over the counterfactual. Column 3 shows that the estimates are robust to including time-varying covariates. Column 4 shows robustness to Census Region-year interactions.

The bottom panel of Table I shows the results for opioid-related overdose deaths. The patterns are similar. The 1996-2000 estimate in Column 2 implies a 40% increase for non-triplicate states and the 2011-2017 estimate indicates an increase over 100%.

5.3.2 State-Specific Results

We also examine the mortality effects for each state separately. In Figure V, we compare the growth in overdose death rates for each triplicate state with its bordering neighbor states for the 10 years before and after OxyContin's introduction. Figure A9 repeats this exercise but uses the most recent 10 years. In almost every case, the triplicate state had the lowest growth in drug overdose rates compared to its neighbors.[44] Thus, the overall results are not driven by a single outlier triplicate state experiencing uniquely low growth in overdose deaths. Instead, we observe this pattern for all triplicate states. This suggests that it was the triplicate program, not other characteristics of the states or regions, that drove the uniquely low mortality growth rates.

5.3.3 Heroin and Fentanyl Overdose Deaths

We next examine trends in overdose deaths by the type of opioid. Figure A10 shows cross-sectional annual differences in opioid-related overdose deaths for natural and semisynthetic opioids, heroin, and synthetic opioids for 1999-2017. Prior to 2010, the only meaningful

[43] The counterfactual is the overdose rate of the non-triplicate states minus the estimated coefficient on the non-triplicate indicator in that time period. The "counterfactual" fatal overdose rate in non-triplicate states (had they been triplicate states) is 4.166 (= 5.456–1.290), with an implied percentage increase of 1.290/4.166=0.31.

[44] While Idaho had a higher OxyContin adoption rate than other triplicate states, many of its neighbors did too, suggesting meaningful regional differences. For Idaho, this higher rate of adoption did not translate into a high growth rate in overdoses, which might suggest a high demand for legitimate uses of the product in this state.

difference in overdose mortality between triplicate and non-triplicate states was for natural and semisynthetic opioids, the category which includes OxyContin. After 2010, we observe a large relative increase in heroin-related fatal overdoses in non-triplicate states, although the differences are not statistically significant. We also find that sharp differences in synthetic opioid overdose death rates emerged in 2014. These patterns are consistent with the main hypothesis of this paper, combined with the earlier findings in Alpert, Powell, and Pacula (2018) and Evans, Lieber, and Power (2019). In 2010, Purdue Pharma introduced an abuse-deterrent version of OxyContin, and the original formulation was discontinued. This earlier work showed that states more exposed to OxyContin (measured by having high pre-reformulation rates of OxyContin misuse) experienced much faster growth in heroin deaths after 2010 as people substituted from OxyContin to heroin. These states later saw faster growth in synthetic opioid deaths (Powell and Pacula, 2021) when fentanyl became mixed with the United States heroin supply (Ciccarone, 2017; Pardo et al., 2019). The timing of these drug-specific trends shows that the introduction of OxyContin affected drug overdose deaths through each wave of the opioid crisis. States less exposed to OxyContin's introduction were also, as predicted by the prior studies, less affected by transitions to illicit drugs after OxyContin's reformulation in later years of the opioid crisis.

5.4 Mechanisms

5.4.1 Effects of Triplicate Programs or Marketing?

We consider two possible mechanisms for the lower OxyContin use and overdose death rates in triplicate states. First, triplicate programs themselves and the prescribing culture that developed from them may have independently protected states against OxyContin adoption and overdose growth, even after these programs were discontinued. Second, these effects could be due to the lack of initial OxyContin marketing targeted to triplicate states.

We conducted two tests to disentangle these mechanisms. In the first test, we compare triplicate states to two former triplicate states—Michigan and Indiana—that had discontinued their triplicate programs in 1994, prior to OxyContin's launch. These former triplicate states serve as a useful counterfactual because they show the long-term effects of having a triplicate program, independent of marketing effects.[45] In Figure VI, we re-estimate our main results while permitting different effects for two groups of non-triplicate states: (1) former triplicate states and (2) never-triplicate states. Using the five triplicate states as the comparison group, Panel A shows estimates of cross-sectional differences in OxyContin distribution for former triplicate states and never-triplicate states relative to triplicate states. Panel B estimates our main event study for drug overdose death rates, allowing separate coefficients for former triplicate and never-triplicate states. These figures show that triplicate states had much lower rates of OxyContin use compared to former triplicate states that eliminated their programs just two years before OxyContin's launch.[46] Triplicate programs also experienced persistently lower overdose rate growth relative to the former triplicate states. In fact, former triplicate states had nearly identical overdose trends as states that never had triplicate programs. Thus, the triplicate programs themselves do not appear to explain the enduringly low overdose rates since triplicate programs are only predictive of low overdose rate growth if they were in effect in 1996, when Purdue Pharma targeted its marketing based on triplicate status. This evidence points to marketing practices as the main driver of the overdose trends.[47]

[45] Using CMS Open Payments Data for 2013-16, Figure A11 (comparable to Figure II) shows that former triplicate states have rates of OxyContin promotion that are close to never-triplicate states. This suggests that Purdue Pharma did not avoid marketing to former triplicate states and viewed them in a similar way as other non-triplicate states.
[46] Compared to states that never had triplicate programs, former triplicate states had lower mean OxyContin distribution rates but similar median distribution rates (see Figure A12).
[47] One alternative explanation for this pattern is that former triplicate states had triplicate programs for shorter time periods than triplicate states. Reduced exposure to the program may have lessened the persistence of any developed prescribing culture. However, Indiana and Michigan had similar oxycodone prescribing rates as the five triplicate states even in 1995 after eliminating their programs (Table A3); this suggests that the triplicate programs induced

In the second test in Figure A13, we compare triplicate states to five non-triplicate states that had similar initial prescribing cultures. Specifically, we select states with the lowest oxycodone prescribing rates in 1991-1995 (see Table A4 for list of states). For both OxyContin distribution (Panel A) and overdose death rates (Panel B), the estimates are similar to the main results. Triplicate states used OxyContin at much lower rates and had lower overdose growth compared to non-triplicate states that initially had similar prescribing habits. These results are difficult to explain by entrenched prescribing culture, further supporting the marketing channel.

5.4.2 Persistence in Marketing Effects

The persistent differences in OxyContin use and overdose deaths following the elimination of all triplicate programs by 2004 are consistent with serial correlation in Purdue Pharma's marketing practices. As discussed in Section 2, the company's strategy was to target sales force visits to the top deciles of physicians based on past prescribing volume.[48] Thus, given initial differences in marketing and the resulting higher prescribing in non-triplicate states, non-triplicate states would, in turn, continue to receive more marketing in future years (as shown previously in Figure II) and higher prescribing would persist. Absent these marketing differences, it is difficult to explain why the triplicate states as of 1996 experienced such enduringly low overdose growth after eliminating their own triplicate programs, but states that had discontinued their programs just two years prior to the launch experienced overdose trends almost identical to states that never had triplicate programs.

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low oxycodone prescribing habits even in that shorter time period. Moreover, Texas, which adopted its program in the same decade as Indiana and Michigan, experienced much lower overdose death growth than these states.

[48] Purdue Pharma's early budget plans regularly highlight the plan to target the top 1 to 3 deciles of doctors based on past prescribing behavior. This is echoed in their more recent internal communications as well: "Purdue ranked the prescribers based on their aggregate opioid prescriptions in deciles from numbers 1 through 10, with 10 being the highest. From 2010 to 2013, Purdue instructed its sales force to primarily focus on the top three deciles of prescribers. The purpose of focusing the sales force on these highest deciles of prescribers was to cause an even higher volume of prescriptions to be written by them" (DOJ Settlement Agreement, 2020, pg. 8 of Addendum A).

It also does not appear that Purdue Pharma significantly increased marketing to triplicate states after their programs were eliminated. In Figure A14, we plot estimates from an event study examining Medicaid prescriptions around triplicate repeal dates.[49] We observe a downward trend over time, consistent with the general separation between non-triplicate and triplicate states due to marketing, but no independent effect of triplicate repeal. While this does not rule out subsequent targeting of marketing to the triplicate states, it suggests that there was not a dramatic increase in marketing intensity. The CMS Open Payments data shows that there is still a large gap in marketing across triplicate and non-triplicate states that has continued to the present day. The likely reason for this is that Purdue Pharma's marketing strategy was to target the highest prescribers which, given earlier targeting, were predominantly in non-triplicate states.[50] Additionally, even if marketing did increase after repeal, it would likely be less effective than during the initial campaign, which could also explain the low demand response.[51]

6. Robustness Tests

In this section, we explore alternative explanations for our findings and test the robustness of our results. The main set of robustness tests for drug overdose deaths are presented in Table II (see Table A5 for opioid-related overdose deaths).

6.1 Alternative Explanations

6.1.1 Population Size

[49] We use Medicaid prescriptions so we can include all triplicate states in the analysis. The ARCOS OxyContin data are available beginning in 2000, so we do not have a sufficient pre-period for all states.
[50] When the program was repealed, doctors in triplicate states would have much lower OxyContin prescribing and would likely generate a lower return from marketing than targeting existing high prescribers in non-triplicate states.
[51] By the early 2000s when triplicate programs were being repealed, there was greater knowledge of OxyContin abuse and scrutiny of the misleading advertising practices had increased. Also, the misleading claim on the FDA label had been removed. As a result, Purdue Pharma may have scaled back its claims that OxyContin had lower abuse potential than other opioids, making it more difficult to convince doctors to switch to their product.

It is notable that four of the triplicate states are among the largest states in the country. One concern is that states with large populations may have experienced different trends in overdose deaths independent of their triplicate status. In Column 2 of Table II, we select the four largest non-triplicate states (FL, PA, OH, and MI) as comparison states for the four largest triplicate states.[52] The estimates are larger than the main estimates, indicating that triplicate states have uniquely low overdose growth, even compared to the largest non-triplicate states.

A related concern is that the triplicate states are more urban than non-triplicate states. In Panel A of Figure A15, we replicate our event study at the county level with county fixed effects, selecting only on urban counties (826 counties).[53] In Panel B, we further select counties with the largest population size: "central counties of metro areas of 1 million population or more" (175 counties).[54] The patterns are remarkably similar to our main results, showing that triplicate status predicts large differences in overdose deaths among the largest metropolitan areas in the country.

6.1.2 Adoption of Other Policies

Triplicate states were some of the earliest adopters of drug monitoring programs and were potentially at the frontier of reducing prescription drug abuse in the years following OxyContin's introduction. If triplicate states followed different policy paths that addressed opioid misuse more effectively than the policies in non-triplicate states, this could be confounding our results. In Column 3 of Table II, we examine drug overdose death rates in triplicate states compared to states with other types of PDMPs in 1996—electronic PDMPs and duplicate programs (Horwitz et al., 2018). States with other types of monitoring programs might also be "ahead of the curve" in moderating opioid misuse and we would expect them to

[52] We use 1990 population size. We exclude Idaho from this analysis, though results are similar if we include it.
[53] We use the 1993 categorization by the Office of Management and Budget which divides counties into metropolitan ("urban") and non-metropolitan ("rural").
[54] We use the 1993 categorization defined by the Department of Agriculture's Economic Research Service.

experience slower growth in overdose death rates. However, the estimates *increase* when we select on this sample of states. As a complementary approach, in Column 4, we replicate the difference-in-differences analysis for the full sample of states while controlling for a set of opioid-related policy variables.[55] Again, the results are similar implying that triplicate states did not adopt systematically different opioid policies post-1996.[56]

6.1.3 Deaths of Despair

The "deaths of despair" hypothesis discussed in Case and Deaton (2015, 2017) suggests that we would have observed an increase in mortality even in the absence of a rise in opioid supply because of worsening cultural and economic factors. In this section, we study other types of deaths of despair: suicides (excluding overdoses) and alcohol-related liver deaths. Figure A17 presents the event study estimates for these outcomes by triplicate status. Suicides trend 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 (Panel A). Alcohol-related liver deaths also exhibit pre-existing trends that continue throughout the period (Panel B). We present de-trended event studies in Panels C and D. Overall, we find little evidence that other deaths of despair follow the same patterns as drug overdose deaths across triplicate and non-triplicate states, suggesting that there is not a confounding underlying factor that is common across these causes of death. This shows that OxyContin played a crucial independent role in the opioid crisis.

[55] We include three indicators for PDMPs from the RAND/USC Schaeffer OPTIC PDMP (2021) data base: enactment of a PDMP; enactment of a modern, electronic system; and adoption of a "must access" provision. In addition, we also include indicators for pain clinic regulations, medical marijuana laws, and legal/operational medical marijuana dispensaries. We code dates for pain clinic regulations using the Prescription Drug Abuse Policy System (PDAPS). Data on marijuana laws and dispensaries are from the RAND Marijuana Policy database (see Powell, Pacula, and Jacobson (2018) and Williams, Pacula, and Smart (2019)).

[56] Additionally, we test for differences in PDMP strength over time across triplicate and non-triplicate states using an index introduced in Pardo (2017) that aggregates together several different PDMP dimensions (e.g., mandatory use, timely reporting, etc.). Figure A16 shows differences in PDMP strength for non-triplicate states relative to triplicate states, selecting on states that had any type of PDMP as of 1996. There is little difference in how PDMP strength evolved between triplicate and non-triplicate states, yet we found much larger growth in fatal overdoses in non-triplicate states relative to these other PDMP states (Table II, Column 3).

Moreover, the lack of a *decline* in suicides and alcohol-related liver mortality suggests that fatal opioid overdoses were not substitutes for these types of deaths.

6.1.4 Additional Alternative Explanations

We conducted numerous additional robustness tests that are discussed in detail in Appendix C. Our results are unchanged if we account for changes in economic conditions by controlling for the unemployment rate or for economic shocks using Bartik-type instruments. The results are also unaffected if we exclude fatal overdoses involving unspecified narcotics. Finally, we implement a "leave-one-out" analysis where we exclude each state in turn. The findings of this paper are not driven by a single triplicate or non-triplicate state.

6.2 Parallel Trends Assumption

In this section, we further evaluate the "parallel trends" assumption in our main analysis and consider the robustness of the results to possible violations of this assumption.

6.2.1 Synthetic Controls

First, we use a synthetic control approach (Abadie, Diamond, and Hainmueller, 2010, 2015) to account for systematic differences in pre-treatment outcomes. We discuss details of the implementation in Appendix D. Table D1 presents estimates for our three post-periods. The estimates are close to our main difference-in-differences estimates and statistically significant at the 1% level. For example, when we population-weight the state-specific estimates (Column 2), we estimate that non-triplicate states experienced a differential increase in overdoses per 100,000 of 2.1 in 1996-2000, 5.1 in 2001-2010, and 6.9 in 2011-2017. The similarity between the main estimates and the synthetic control estimates suggests that the main results are not driven by any pre-existing differences in levels or trends between triplicate and non-triplicate states. Figure D1

presents the results graphically. We observe little evidence of pre-treatment differences between the triplicate states and their synthetic counterfactuals.

We also compare 10-year overdose death rate growth in each triplicate state to its synthetic control state in a manner similar to Figure V (see Figure D2). Each triplicate state had much lower growth than its corresponding synthetic control.

6.2.2 Permutation Test

Second, we consider the uniqueness of the post-OxyContin overdose rate trends for triplicate states. We conduct a permutation-like test where we randomly assign triplicate status to five non-triplicate states and then estimate placebo effects for each of our three post periods. We discuss this procedure further in Appendix E. We present a histogram representing the distribution of placebo estimates in Figure E1 and the distribution of t-statistics (recommended in MacKinnon and Webb, 2020) in Figure E2.

Comparing our main estimates to the placebo estimates, we never observe differences in overdose rates between triplicate and non-triplicate states as large as our actual estimated effects. Our main estimates are outliers, ranking first in the placebo distribution for each time period. In fact, it is impossible to find *any* combination of five non-triplicate states that experienced the same low rate of overdose rate growth as the triplicate states in each of our three post periods.

We also study whether the triplicate states had uniquely low overdose rate growth prior to 1996. We randomly assign triplicate status to five non-triplicate states and estimate the differential growth in overdoses between 1991 and 1995. As shown in Figure E3, the estimates for the actual triplicate states are in the middle of this placebo distribution. Combined with the results of the previous permutation tests, this implies that even if we selected non-triplicate states

in which the pre-trend was similar to the pre-trend for triplicate states, triplicate states still have uniquely low growth in overdose deaths over the entire post-period.

6.2.3 Impact of Cocaine Deaths on Trends

Third, in Figure A18, we exclude overdoses involving cocaine to evaluate the impact of the crack epidemic on pre-1996 trends. The differences between triplicate and non-triplicate states in the pre-period become even smaller, but the post-1996 effects remain. Conversely, as a placebo test, we show event study results for cocaine overdose rates alone in Figure A19. We do not observe a comparable post-treatment upward trend, suggesting that this rise was unique to overdoses involving opioids.

6.2.4 Deviations from Parallel Trends

Finally, we test the sensitivity of our estimates to deviations from the parallel trend assumption using the method of Rambachan and Roth (2020).[57] This approach relaxes the parallel trends assumption by imposing inequality constraints that permit deviations from pre-existing (treatment-specific) linear trends in the post-period. Specifically, if non-triplicates states experience differential annual linear growth prior to treatment equal to θ, then the inequality constraints permit post-treatment differential annual secular growth between $\theta - M$ and $\theta + M$. In Figure A21, we plot confidence intervals for the three aggregated post-periods for different values of M.[58] The estimates in all time periods are statistically different from zero when including a treatment-group specific linear trend (M=0) and even when permitting annual deviations from a linear trend by as much as 0.015.

To interpret these magnitudes, Rambachan and Roth (2020) recommend benchmarking the results to outcome patterns in non-treated units. This practice relates to our permutation test.

[57] In Figure A20 we show event studies adjusting for state-specific trends. We estimate a linear trend for each state prior to 1996 and project it into the post-period. The estimates are similar with or without state-specific trends.
[58] Estimates are averages of the event study coefficients for the 3 time periods, as in Rambachan and Roth (2020).

We replicate Figure A21 but assign placebo triplicate status to the five non-triplicate states with the *lowest* overdose rate growth. This exercise is designed to find the highest placebo values of M for the three post-periods in which it is still possible to statistically reject zero overdose rate growth for non-triplicate states. In Figure A22, we show that the maximum values of *M* for which it is possible to reject zero are *smaller* than those observed in Figure A21 for the true triplicate states. This evidence suggests that it would be extremely rare for the relative trend shift observed for triplicate states to occur randomly.

7 Conclusion

Despite the importance of the opioid crisis, there is little empirical work exploring its initial causes. This study demonstrates the importance of the introduction and marketing of OxyContin in 1996 as a key driver of the opioid crisis. We show this by exploiting early variation in OxyContin's promotion and market entry due to state triplicate prescription programs. Our results imply striking differences throughout the opioid crisis stemming from variation in these initial conditions. States with more exposure to OxyContin's introduction experienced higher growth in overdose deaths in every year since its launch in 1996. Our estimates (from Figure IV) show that non-triplicate states would have experienced 4.21 fewer drug overdose deaths per 100,000 on average from 1996 to 2017 if they had been triplicate states and 3.16 fewer opioid overdose deaths per 100,000. Over this time period, non-triplicate states had an average of 12.32 fatal overdoses per 100,000 annually and 6.98 of those involved opioids. This implies that if non-triplicate states had the same initial exposure to OxyContin's introduction as triplicate states, they would have had 34% fewer drug overdose deaths and 45% fewer opioid overdose deaths on average from 1996 to 2017.

We use our results to provide a back-of-the-envelope calculation of how much of the *growth* in drug overdose deaths can be accounted for by the introduction and marketing of OxyContin. This exercise is explained in detail in Appendix F. Figure F1 shows the estimated counterfactual national overdose death rate trend in the absence of OxyContin. This extrapolation exercise suggests that the introduction of OxyContin explains 79% of the rise in the overdose death rate since 1996. In the absence of OxyContin, overdose death rate levels would be substantially lower and unlikely to rise to the level of an opioid "crisis." In fact, the estimated counterfactual overdose rate does not rise above the 1995 overdose death rate until 2006. We conduct a similar extrapolation exercise for *all-cause* mortality focusing on non-Hispanic Whites ages 45-54, a population highlighted in Case and Deaton (2015) as experiencing the largest reversal in mortality trends after 1998. For this population, we estimate that OxyContin's introduction can explain about one-third of the rise in all-cause mortality since 1998.

Our estimates capture both the direct and indirect consequences of initial exposure to OxyContin's introduction, including spillovers of OxyContin promotion to other opioid drugs and transitions to heroin and fentanyl in the later waves of the epidemic. They also internalize downstream indirect effects of OxyContin's introduction on the behaviors of other entities in the supply chain— distributors, pharmacies, and doctors—which may have further amplified OxyContin's effects. Our findings do not rule out the possibility that economic and cultural factors also contributed to a meaningful share of the rise in drug-related mortality. Also, while these results quantify the harms associated with OxyContin use, our analysis does not speak to the potential benefits of improved opioid access through the introduction of OxyContin. Opioids may be effective pain management tools in some cases, and we do not attempt to estimate the gains from pain reduction stemming from OxyContin's launch.

Finally, the evidence in this paper suggests that Purdue Pharma's marketing practices, in particular, played an important role in explaining growth in drug overdose rates. When triplicate states are compared to states that had just recently eliminated their triplicate programs or other states with similar prior oxycodone prescribing rates, they still have uniquely low overdose death rate growth. This suggests that it was not the triplicate programs themselves that independently influenced OxyContin adoption. Instead, the evidence is more consistent with the idea that differences in marketing led to persistent differences in overdose death rate growth. Overall, we find strong evidence that the marketing practices for OxyContin interacted with state-level policy conditions led to dramatically reduced overdose death rates in triplicate states. Even though triplicate programs are now obsolete, by deterring OxyContin's widespread introduction in 1996, triplicate programs protected some states against the long-term fatal overdose trends experienced by most other states.

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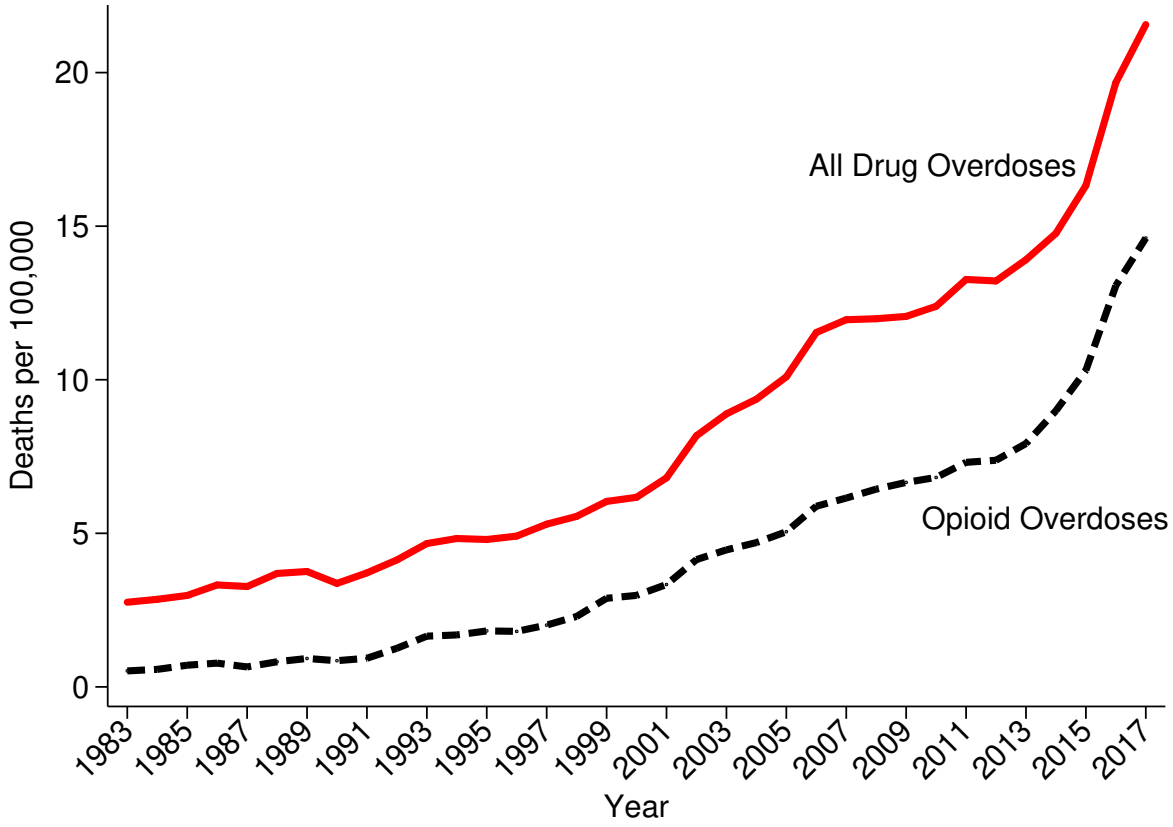
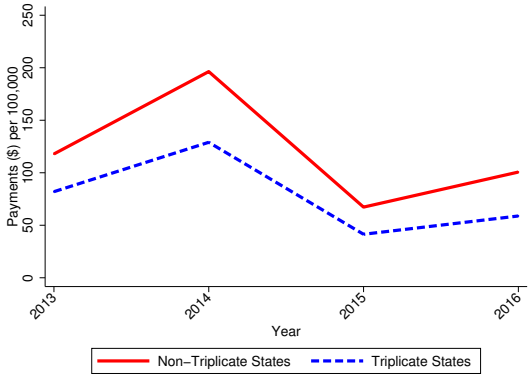
Figures

FIGURE I
National Drug Overdose Death Rates

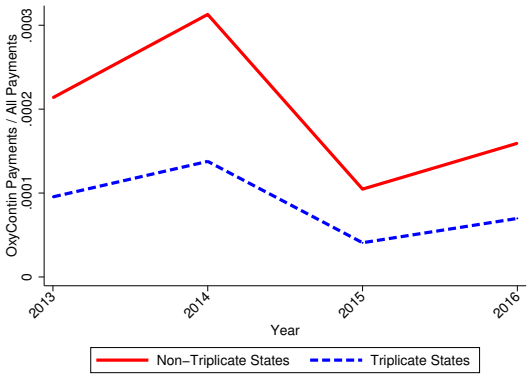


Notes: We use geocoded NVSS data to construct all drug overdose and opioid overdose deaths per 100,000. See Section 3.1 for ICD codes used in each period. Opioid overdoses are defined as overdoses which report opioid involvement (including natural/semi-synthetic opioids, methadone, heroin, and synthetic opioids). These overdoses may or may not also include non-opioid substances.

FIGURE II
OxyContin Promotional Payments to Physicians



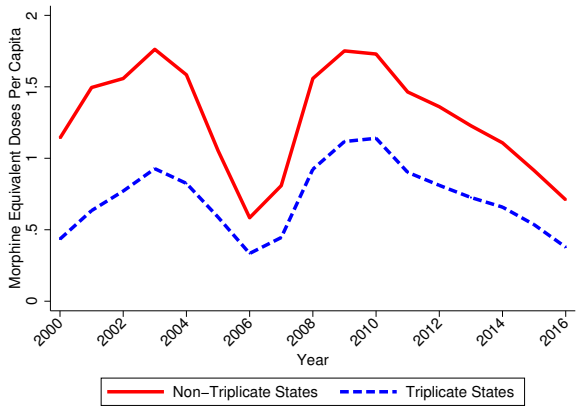
A. OxyContin Spending per 100,000



B. OxyContin Spending / Total Spending

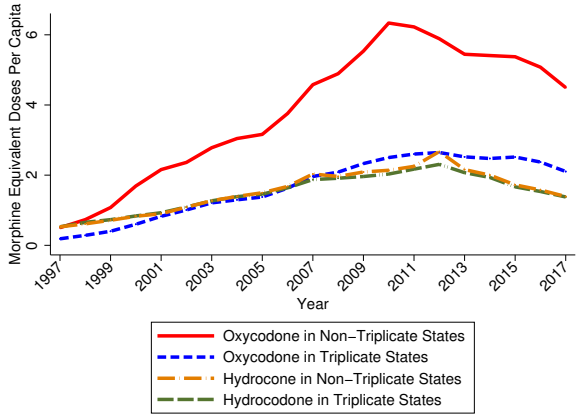
Notes: We used CMS Open Payments Data to calculate total payments and gifts made to physicians regarding OxyContin (presented in nominal dollars). In Panel A, we scaled this measure by population. In Panel B, we scaled this measure by total promotional spending (across all drugs). The outcomes correspond to August 2013 – December 2016. Because the 2013 data only cover a partial year, we annualize the rate in that year.

FIGURE III
Differences in Opioid Distribution by Triplicate Status

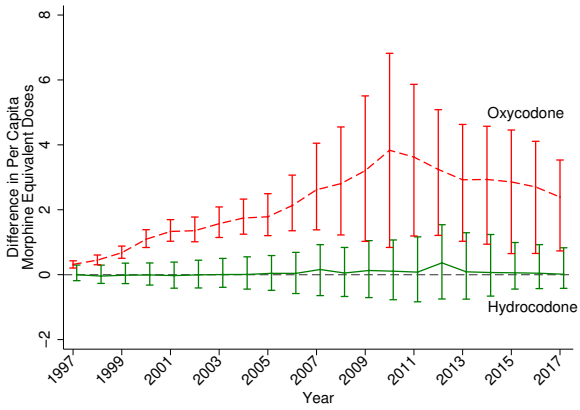


A: Trends in OxyContin Distribution

B: OxyContin (Differences)



C: Trends in Oxycodone and Hydrocodone Distribution

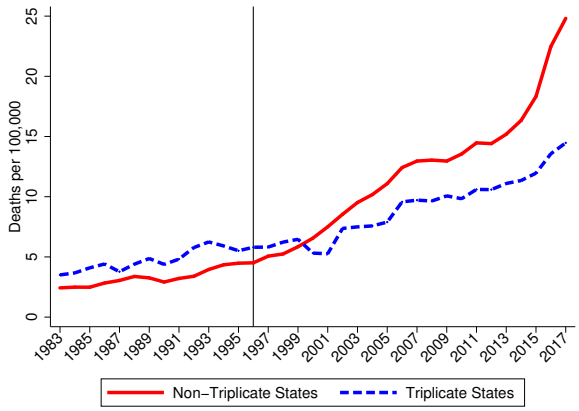


D: Oxycodone and Hydrocodone (Differences)

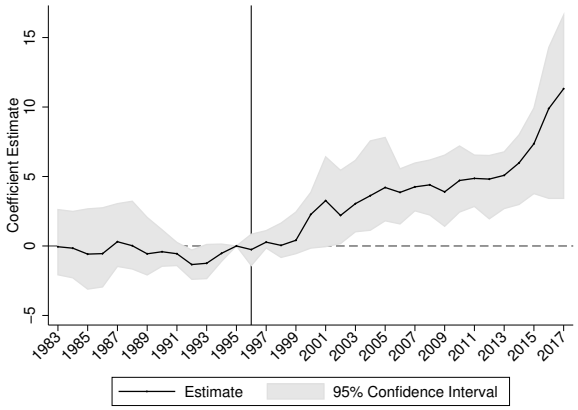
Notes: We use ARCOS data, converted to morphine equivalent doses. Panel A shows raw (per capita) means for OxyContin. Panel C shows raw (per capita) means for oxycodone and hydrocodone in separate trend lines. Estimates in Panels B and D represent cross-sectional differences corresponding to Panels A and C, respectively. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. All figures are population-weighted.

FIGURE IV
Drug Overdose Death Rates by Triplicate Status

All Drug Overdose Deaths

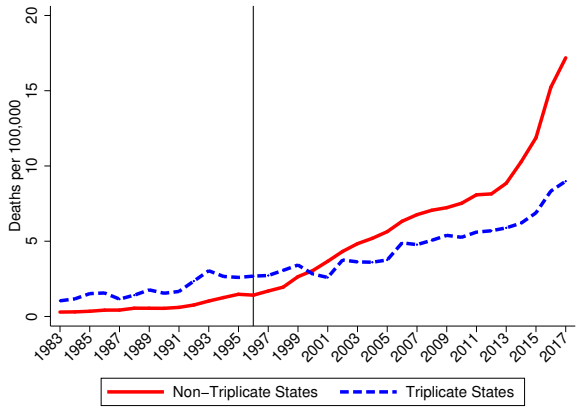


A: Time Series

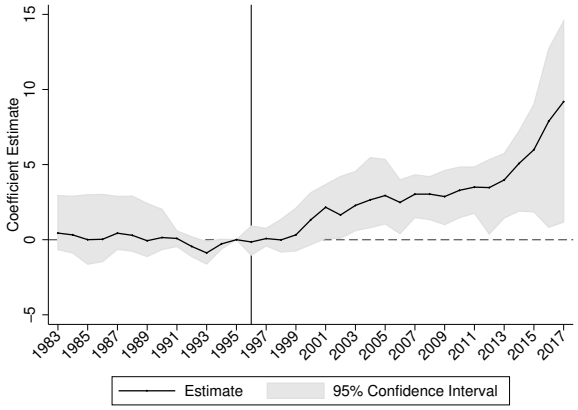


B: Event Study

Opioid Overdose Deaths



C: Time Series

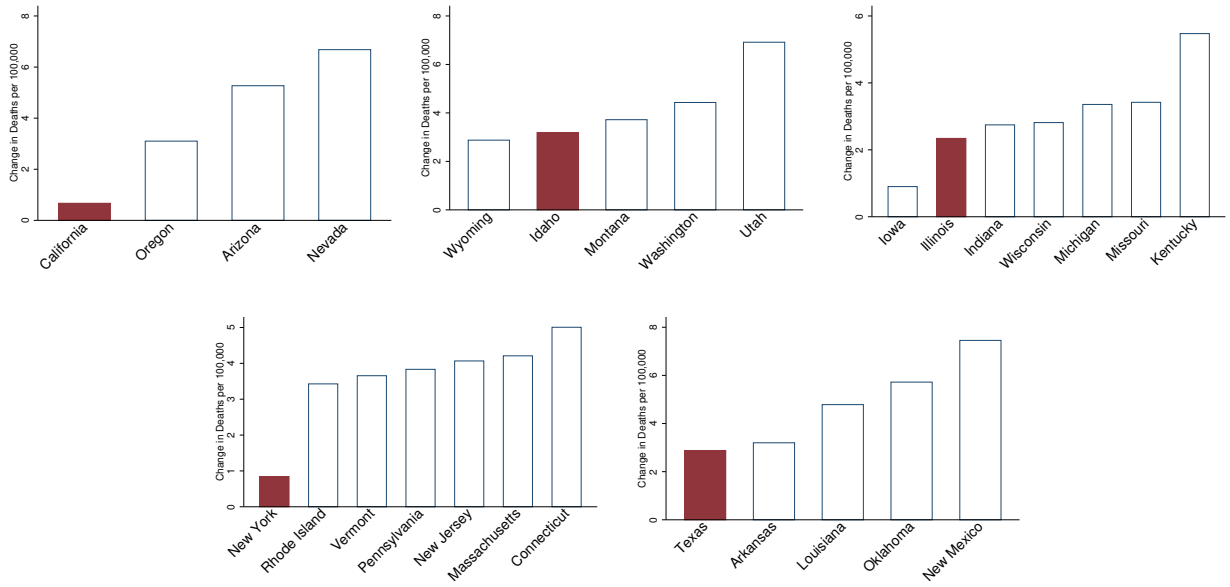


D: Event Study

Notes: We use geocoded NVSS data to construct all drug overdose and opioid overdose deaths per 100,000. See Section 3.1 for exact ICD codes used in each period. Event study models include state and year fixed effects. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in 1995. Weighted by population.

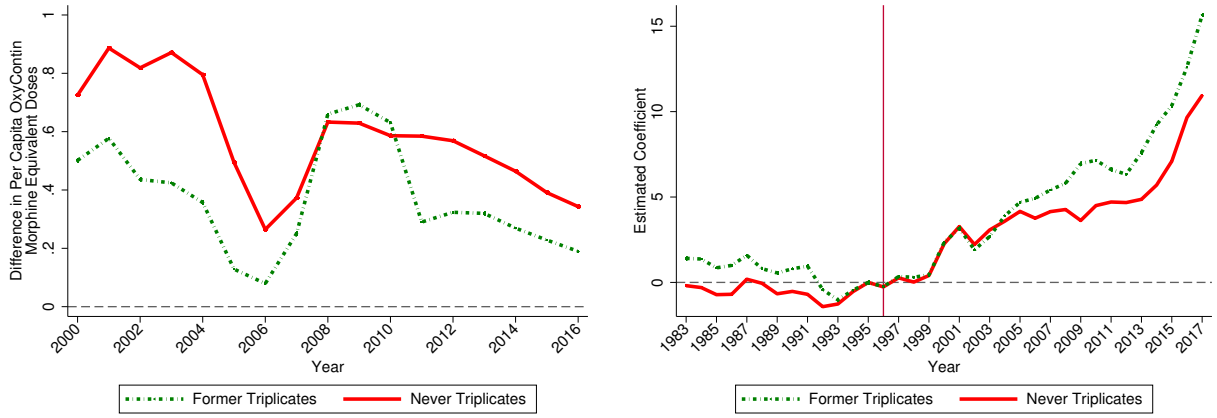
FIGURE V
Drug Overdose Death Rate Changes: Triplicate States vs. Bordering States

1996-2005 Relative to 1986-1995



Notes: We construct the change in all drug overdose deaths per 100,000 for 1996-2005 relative to 1986-1995. We plot this change for each triplicate state relative to its bordering states.

FIGURE VI
Former Triplicate States: OxyContin Distribution and Drug Overdose Deaths



A: OxyContin Distribution (Differences) B: Drug Overdose Deaths (Event Study)

Notes: Panel A estimates the annual differences in OxyContin morphine equivalent doses per capita between never-triplicate and triplicate states as well as the annual differences between former-triplicate and triplicate states. Panel B estimates our main event study for all drug overdoses per 100,000 (as in Figure IV) using the triplicate states as the comparison group, allowing separate coefficients for never-triplicate states and former-triplicate states. The event study model estimated in Panel B includes state and year fixed effects. Regressions are population-weighted.

Tables

TABLE I
Difference-in-Differences Estimates: Drug Overdose Death Rate

	Panel A: All Drug Overdose Deaths per 100,000			
Non-Triplicate ×	(1)	(2)	(3)	(4)
1996-2000	1.173**	1.290***	1.267**	1.229**
	[0.390, 2.374]	[0.421, 2.449]	[0.062, 2.274]	[0.017, 2.483]
2001-2010	3.667**	4.488***	3.561***	3.232**
	[1.521, 6.210]	[2.201, 6.395]	[1.321, 5.687]	[1.011, 5.318]
2011-2017	6.061**	7.806***	5.240***	4.714***
	[2.812, 9.371]	[4.023, 10.439]	[3.213, 7.274]	[1.811, 7.253]
Joint P-Value	0.016	0.000	0.001	0.015
Weighted	No	Yes	Yes	Yes
Covariates	No	No	Yes	Yes
Region-Time Dummies	No	No	No	Yes
Mean 1991-1995	3.890	4.436	4.436	4.436
N	1,377	1,377	1,377	1,377
	Panel B: Opioid Overdose Deaths per 100,000			
Non-Triplicate ×	(5)	(6)	(7)	(8)
1996-2000	0.634**	0.620**	0.725	0.821*
	[0.083, 1.573]	[0.112, 1.614]	[-0.244, 1.621]	[-0.189, 1.761]
2001-2010	2.614**	2.940***	2.081**	2.271**
	[1.115, 4.382]	[1.232, 4.249]	[0.151, 4.192]	[0.297, 4.402]
2011-2017	5.002**	5.899***	3.334***	3.284**
	[1.480, 8.292]	[1.764, 8.895]	[1.415, 5.613]	[0.703, 6.012]
Joint P-Value	0.039	0.010	0.034	0.118
Weighted	No	Yes	Yes	Yes
Covariates	No	No	Yes	Yes
Region-Time Dummies	No	No	No	Yes
Mean 1991-1995	1.189	1.476	1.476	1.476
N	1,377	1,377	1,377	1,377

Notes: ***Significance 1%, **Significance 5%, *Significance 10%. Outcome is all drug overdose deaths or opioid overdose deaths per 100,000. 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 clustered (by state) wild bootstrap. All models include state and year fixed effects. Covariates include the fraction non-Hispanic White, fraction non-Hispanic Black, fraction Hispanic, log of population, fraction with college degree, fraction ages 25-44, fraction ages 45-64, and fraction ages 65+. "Joint P-Value" refers to the p-value from a joint hypothesis test that all three non-triplicate post effects are equal to zero and is also estimated using a restricted wild bootstrap.

TABLE II
Robustness Tests: Drug Overdose Death Rate

Non-Triplicate ×	Baseline Results	Select on Population Size	Select on PDMP States in 1996	Control for Policy Variables
	(1)	(2)	(3)	(4)
1996-2000	1.267**	2.919**	2.163	1.348**
	[0.062, 2.274]	[0.452, 5.067]	[-0.978, 4.828]	[0.176, 2.453]
2001-2010	3.561***	5.543***	5.869*	3.628***
	[1.321, 5.687]	[2.671, 8.591]	[-0.711, 11.369]	[1.671, 5.322]
2011-2017	5.240***	6.045**	9.299***	5.808***
	[3.213, 7.274]	[0.535, 12.242]	[3.528, 14.946]	[3.528, 8.030]
Joint P-Value	0.001	0.073	0.005	0.000
Mean 1991-1995	4.436	5.090	5.294	4.436
N	1,377	216	405	1,377

Notes: ***Significance 1%, **Significance 5%, *Significance 10%. Outcome is all drug overdose deaths per 100,000. 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 clustered (by state) wild bootstrap. All models include state and year fixed effects and time-varying covariates (see Table I for details). Column (1) repeats the Column (3) results from Table I. Column (2) selects on the four non-triplicate states with the largest populations 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 (any PDMP, electronic PDMP, "must access" PDMPs), pain clinic regulation, medical marijuana laws, and operational/legal medical marijuana dispensaries. "Joint P-Value" refers to the p-value from a joint hypothesis test that all three non-triplicate post effects are equal to zero and is also estimated using a restricted wild bootstrap.

Origins of the Opioid Crisis and Its Enduring Impacts: Appendix Materials

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August 2021

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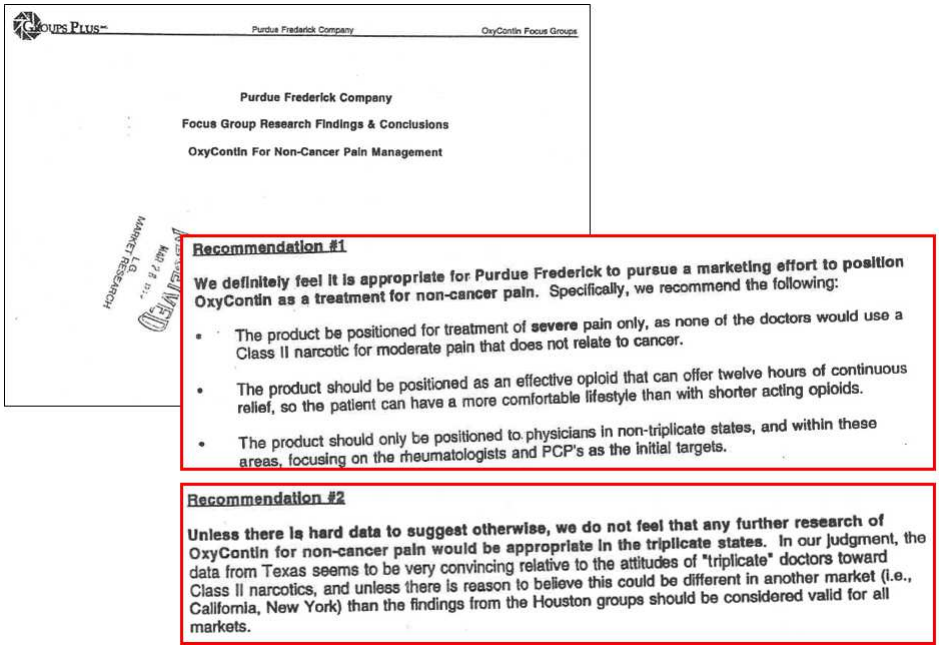
Appendix Figures

Figure A1: Example of Purdue Pharma Focus Group Recommendations



Purdue Fredarick Company — OxyContin Focus Groups

Purdue Frederick Company

Focus Group Research Findings & Conclusions

OxyContin For Non-Cancer Pain Management

Recommendation #1

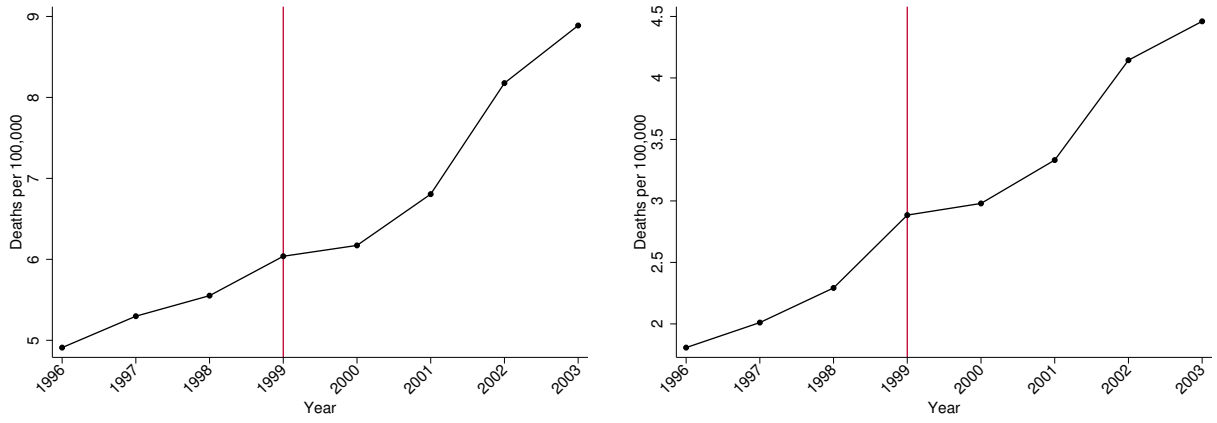
We definitely feel it is appropriate for Purdue Frederick to pursue a marketing effort to position OxyContin as a treatment for non-cancer pain. Specifically, we recommend the following:

- 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.

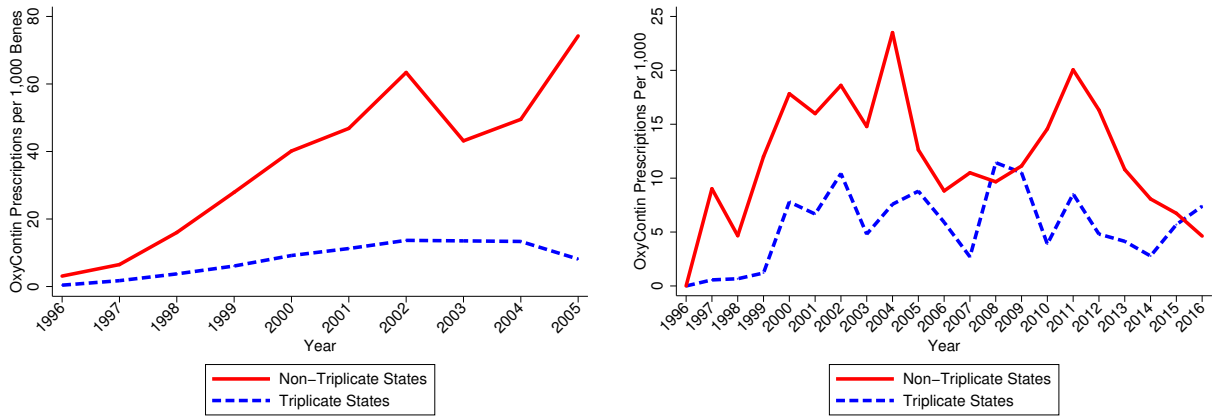
Figure A2: ICD Code Change in 1999



A: All Drug Overdose Deaths per 100,000 B: Opioid Overdose Deaths per 100,000

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

Figure A3: OxyContin Prescriptions by Triplicate State Status

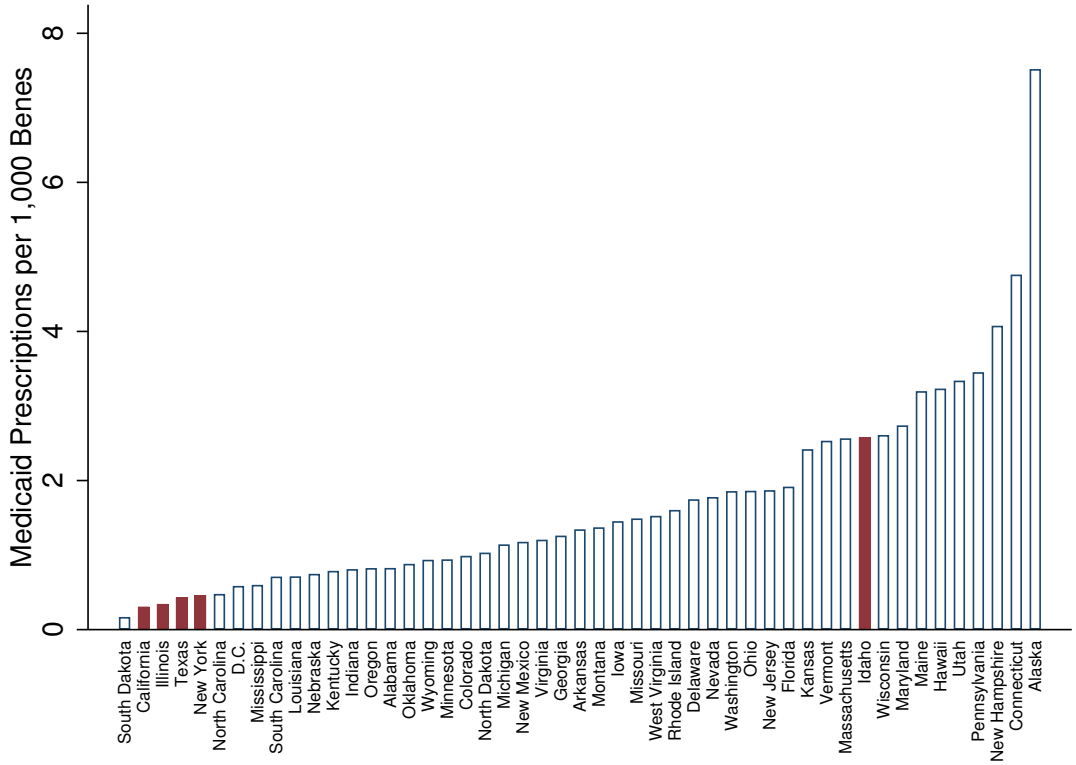


A: OxyContin Prescriptions (Medicaid) B: OxyContin Prescriptions (MEPS)

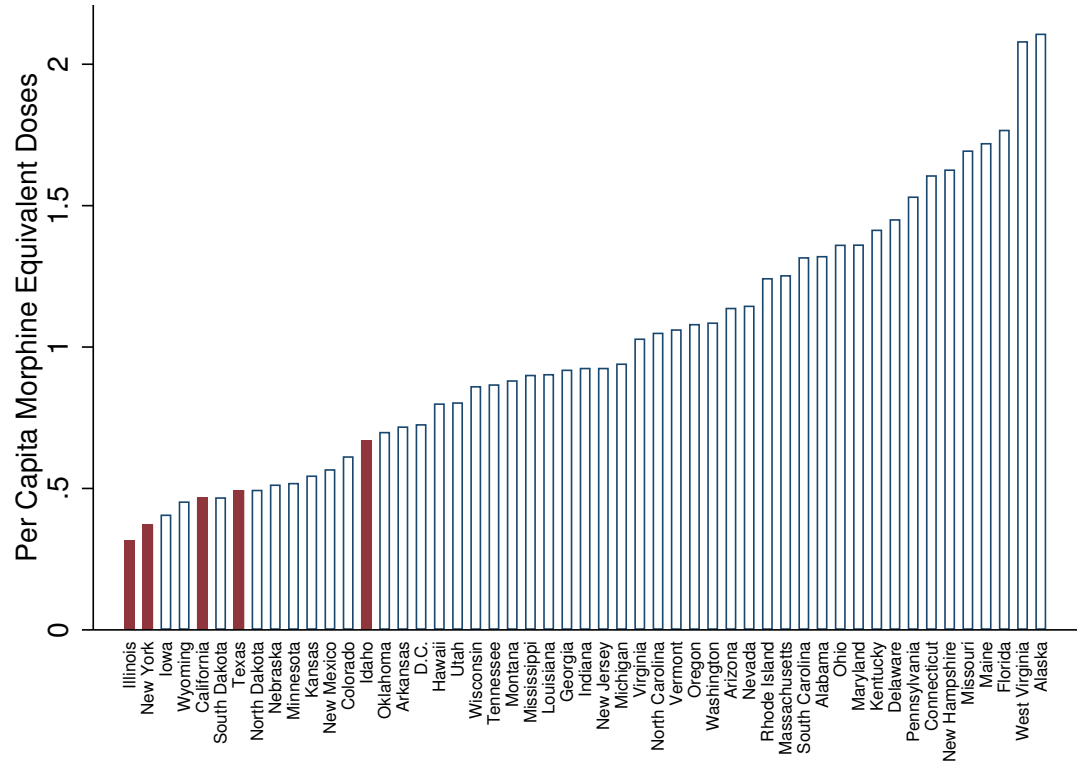
Notes: In Panel A, we report the number of prescriptions per 1,000 beneficiaries from the Medicaid SDUD. We end this time series in 2005 due to the introduction of Medicare Part D. In Panel B, we report the number of prescriptions per 1,000 people in the MEPS. We use the MEPS survey weights. There are no OxyContin prescriptions in the 1996 MEPS. The 1996 MEPS has the smallest number of individuals, households, and prescriptions of all the MEPS samples given that it was the first year of the survey. This reduced size combined with the limited national exposure to OxyContin in 1996 is consistent with not finding any OxyContin prescriptions in the 1996 data.

Figure A4: OxyContin Adoption by State

A. Medicaid OxyContin Prescriptions per 1,000 Benes in 1996

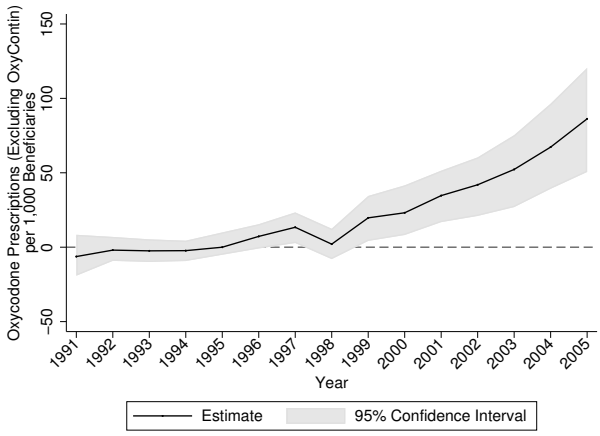


B. ARCOS Per Capita OxyContin Morphine Equivalent Doses in 2000



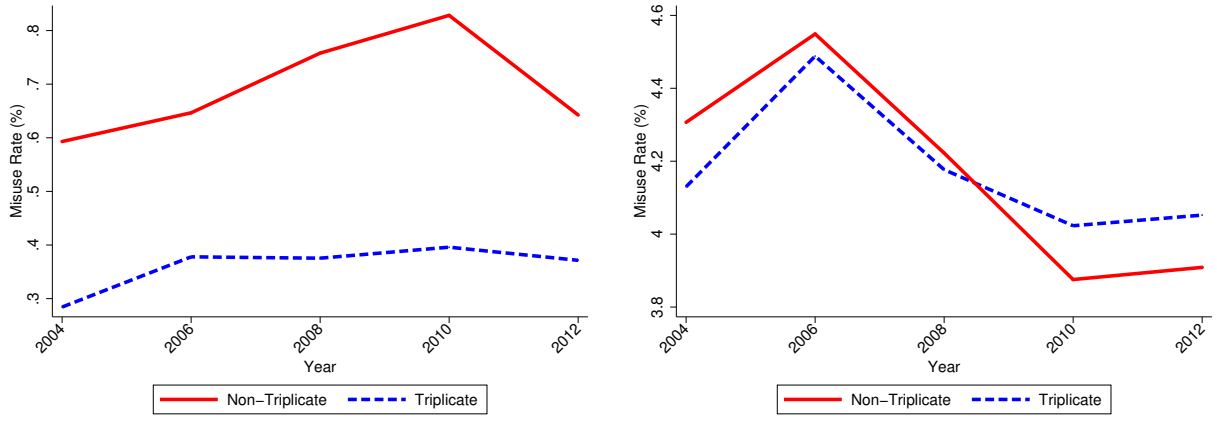
Notes: Panel A uses SDUD data; Panel B uses ARCOS data. Not all states report in all quarters in the SDUD. In such cases, we annualize their prescribing rates. Arizona and Tennessee are excluded from Panel A due to insufficient data in 1996.

Figure A5: Event Study: Medicaid Oxycodone (non-OxyContin) Prescriptions



Notes: The outcome is Medicaid oxycodone prescriptions (from the SDUD) per 1,000 beneficiaries, excluding OxyContin prescriptions. This figure shows estimates from an event study comparing non-triplicate states to triplicate states, conditioning on state and year fixed effects. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in 1995. Sample is limited to 1991-2005. We end the analysis at 2005 because of the implementation of Medicare Part D in 2006.

Figure A6: Non-Medical Use Rates by Triplicate State Status



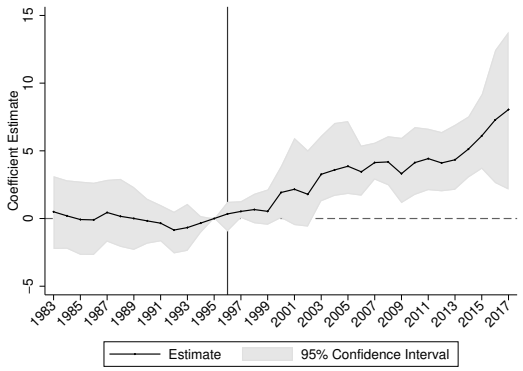
A: OxyContin

B: Pain Relievers excluding OxyContin

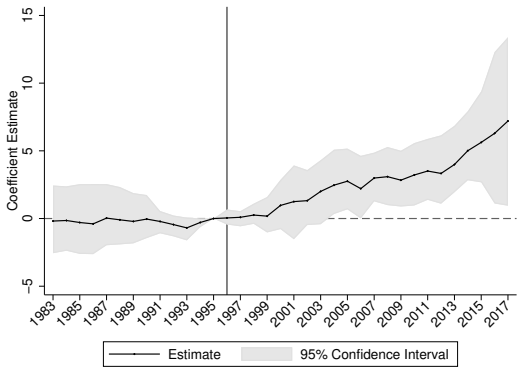
Notes: Misuse rates are calculated from the National Survey on Drug Use and Health. Each year refers to a two-year wave such that "2004" refers to 2004-2005, "2006" refers to 2006-2007, etc.

Figure A7: Event Study: Drug Overdose Deaths with and without Weights and Covariates

Unweighted, Without Covariates

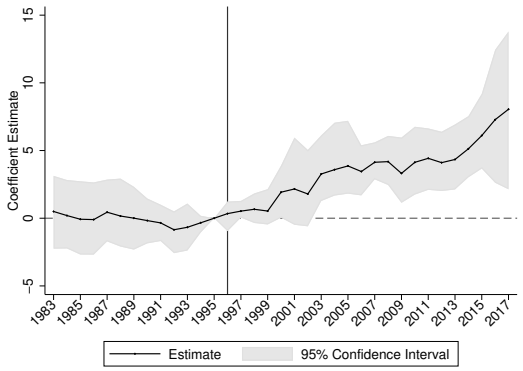


A: All Drug Overdoses per 100,000

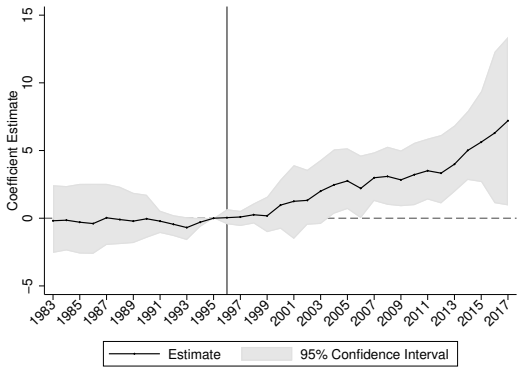


B: Opioid Overdoses per 100,000

Unweighted, With Covariates

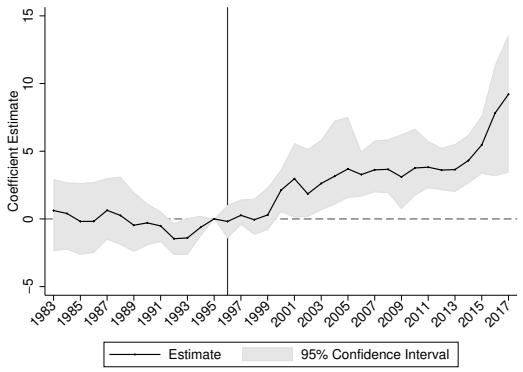


C: All Drug Overdoses per 100,000

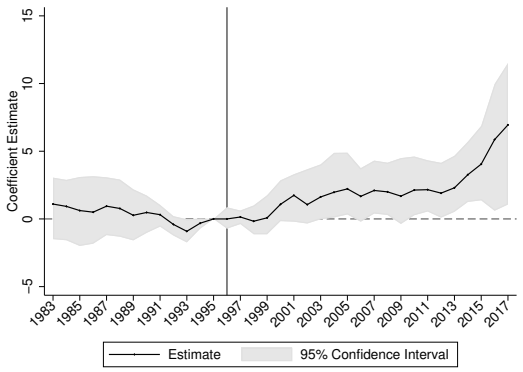


D: Opioid Overdoses per 100,000

Weighted, With Covariates



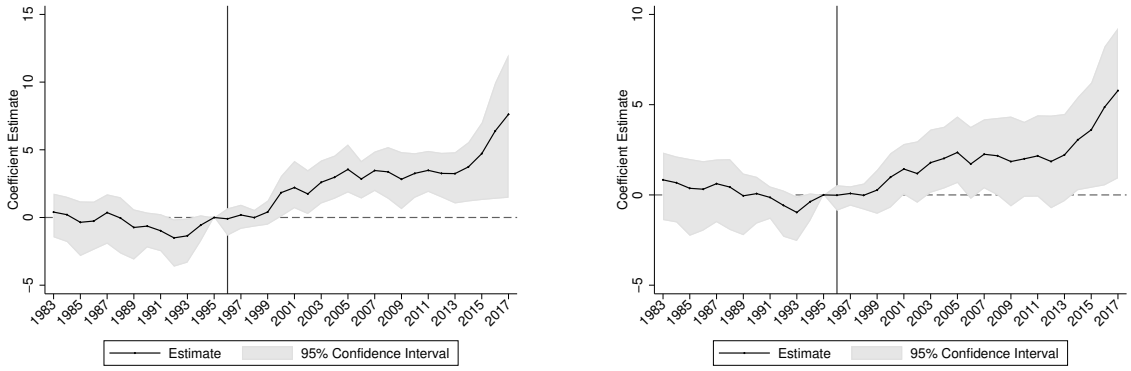
E: All Drug Overdoses per 100,000



F: Opioid Overdoses per 100,000

Notes: We use geocoded NVSS data to construct all drug overdose and opioid overdose deaths 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 1995. All models include state and year fixed effects. When covariates are specified, the models include the fraction non-Hispanic White, fraction non-Hispanic Black, fraction Hispanic, log of population, fraction with college degree, fraction ages 25-44, fraction ages 45-64, and fraction ages 65+. Panels E and F are population-weighted; the others are not.

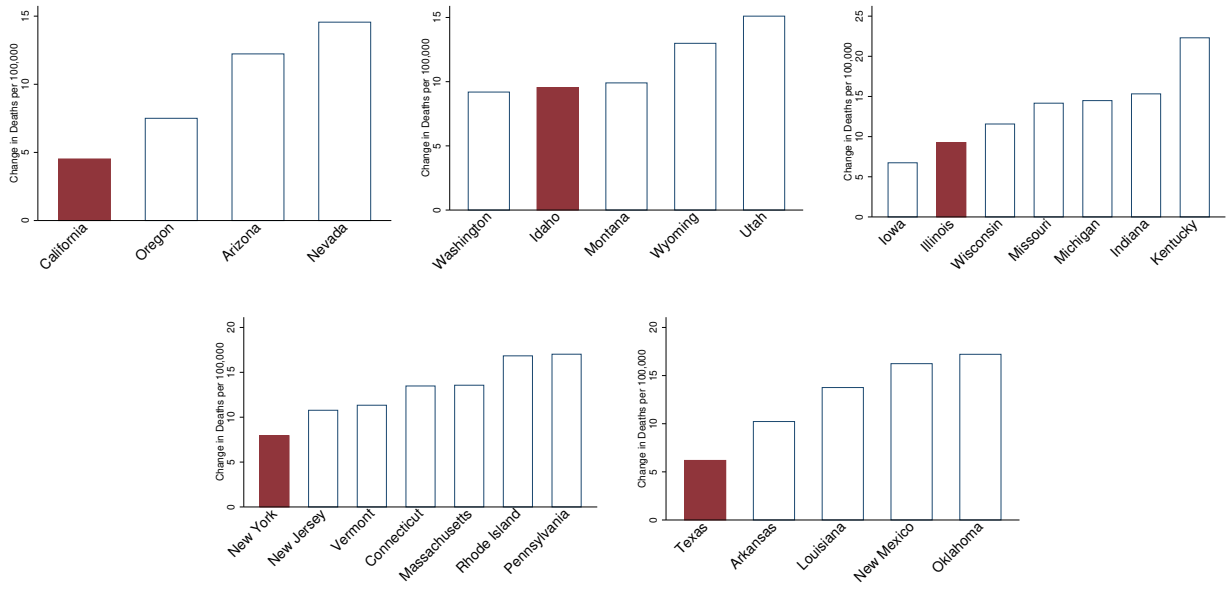
Figure A8: Event Study: Drug Overdose Death Rate with Census Region × Year Interactions



A: All Drug Overdoses per 100,000 B: Opioid Overdoses per 100,000

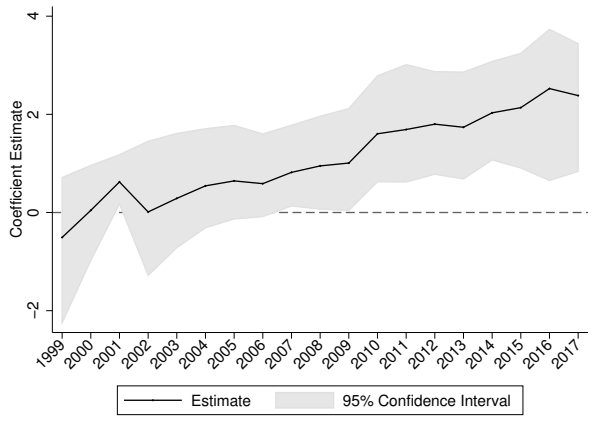
Notes: We use geocoded NVSS data to construct all drug overdose and opioid overdose deaths per 100,000. See text for exact ICD codes used in each period. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in 1995. All models include state and region-year fixed effects for Census regions. The models also include the fraction non-Hispanic White, fraction non-Hispanic Black, fraction Hispanic, log of population, fraction with college degree, fraction ages 25-44, fraction ages 45-64, and fraction ages 65+.

Figure A9: Drug Overdose Death Rate Changes: Triplicate States vs. Bordering States (2008-2017 Relative to 1986-1995)

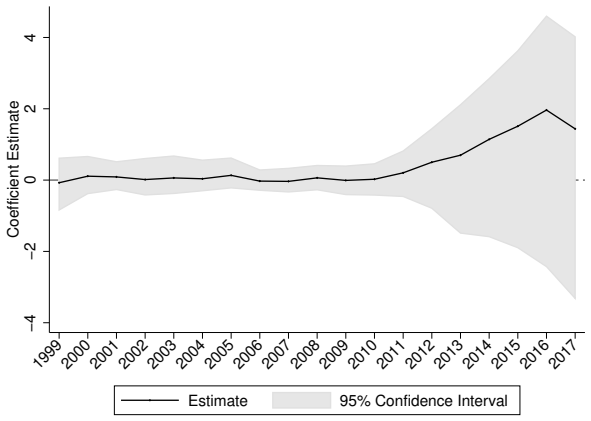


Notes: We construct the change in all drug overdose deaths per 100,000 for 2008-2017 relative to 1986-1995. We plot this change for each triplicate state relative to its bordering states.

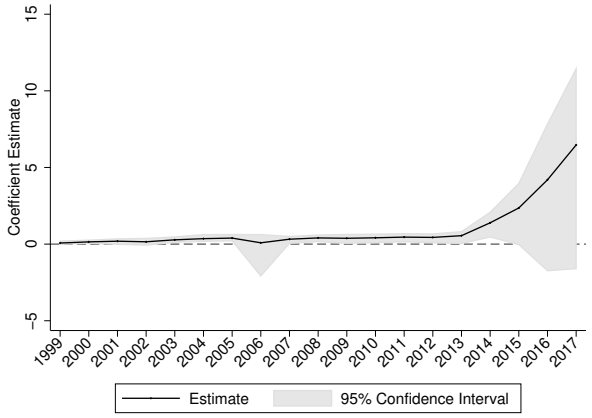
Figure A10: Overdose Death Rate Differences by Type of Opioid for 1999-2017



A: Natural/Semisynthetic Opioids (T40.2)



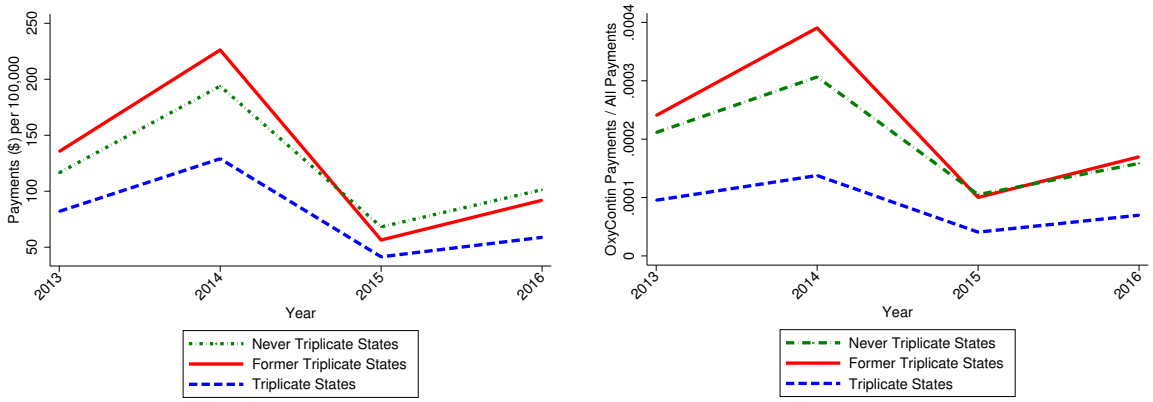
B: Heroin (T40.1)



C: Synthetic Opioids (T40.4)

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

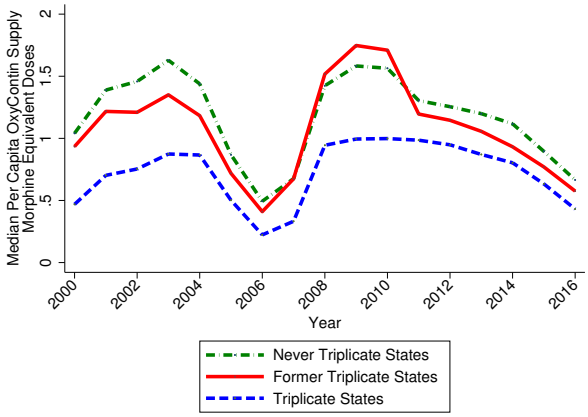
Figure A11: OxyContin Promotional Payments to Physicians – Former Triplicates



A. OxyContin Spending per 100,000 B. OxyContin Spending / Total Spending

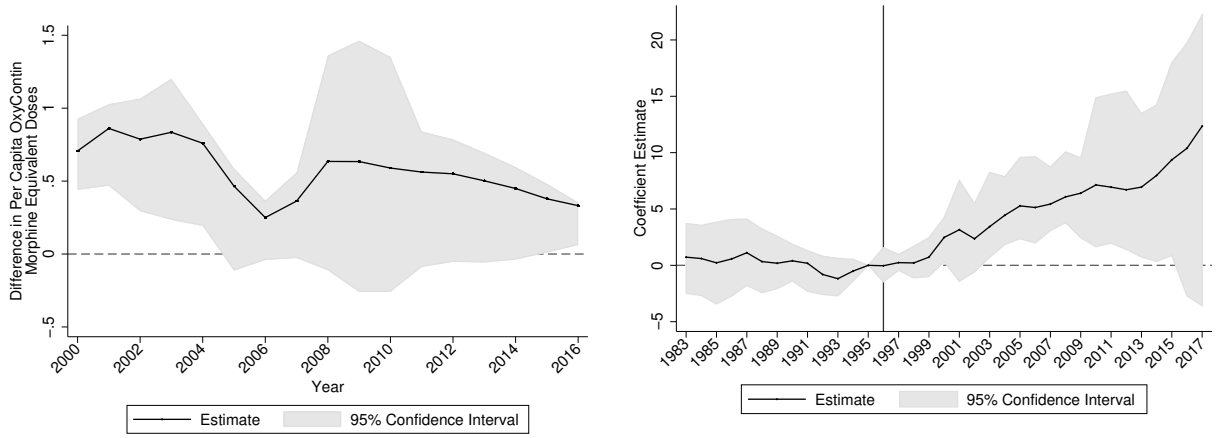
Notes: We used CMS Open Payments Data to calculate total payments and gifts made to physicians regarding OxyContin. We scaled this measure by population. The outcomes correspond to August 2013 – December 2016. Because the 2013 data only cover a partial year, we annualize the rate in that year. "Triplicate States" refers to the states with triplicate programs in 1996. "Former Triplicate States" refers to state with triplicate programs prior to 1996 (but not in 1996).

Figure A12: Median OxyContin Supply for Never-Triplicates, Former-Triplicates, and 1996 Triplicates



Notes: We calculate the median OxyContin distribution, measured in morphine equivalent doses, using the ARCOS data by former and 1996 triplicate status. "Triplicate States" refers to the states with triplicate programs in 1996. "Former Triplicate States" refers to state with triplicate programs prior to 1996 (but not in 1996).

Figure A13: Event Study: Comparing States with Low Initial Oxycodone Prescribing

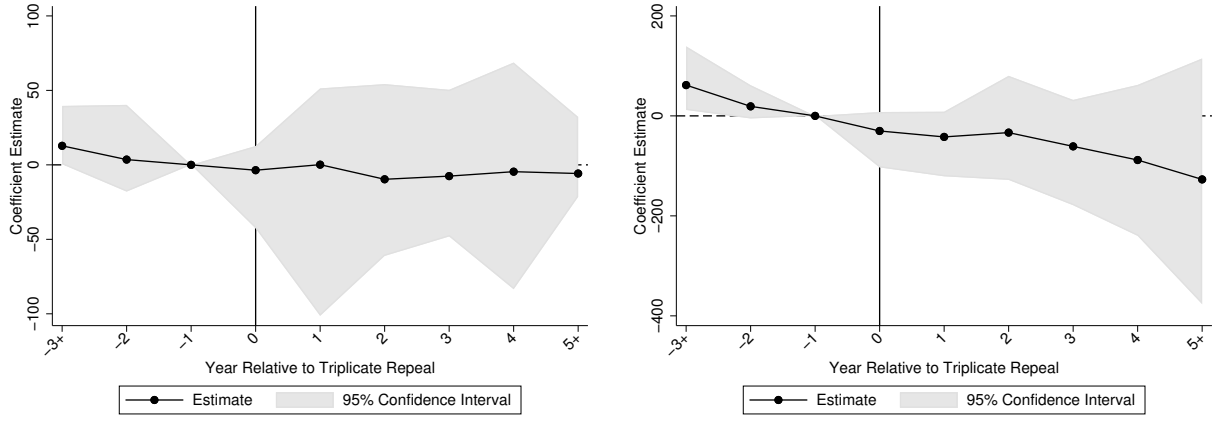


A: OxyContin Distribution

B: Overdose Deaths per 100,000 (Event Study)

Notes: Panel A estimates the differences in OxyContin morphine equivalent doses per capita between "low oxycodone" non-triplicate and triplicate states. "Low oxycodone" states are defined as having the lowest oxycodone Medicaid prescriptions per 1,000 beneficiaries in 1991-1995. Panel B estimates our main event study for all drug overdoses per 100,000 (as in Figure IV) using the triplicate states as the comparison group, allowing separate coefficients for never-triplicate states and former-triplicate states. State and year fixed effects are included in the event study model. Regressions are population-weighted. Confidence intervals are generated by a clustered (by state) wild bootstrap.

Figure A14: Event Study: Effects of Triplicate Repeal on Prescribing

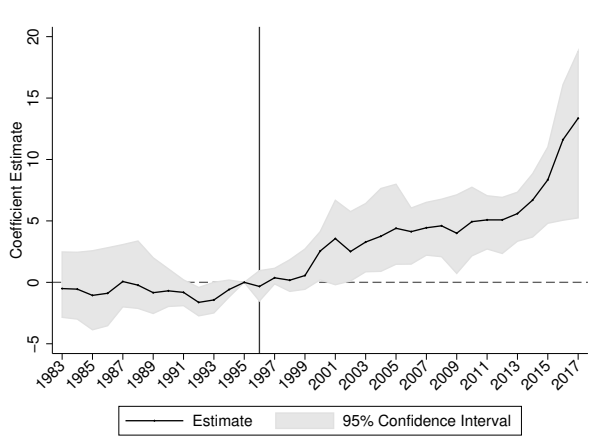


A: OxyContin Prescriptions

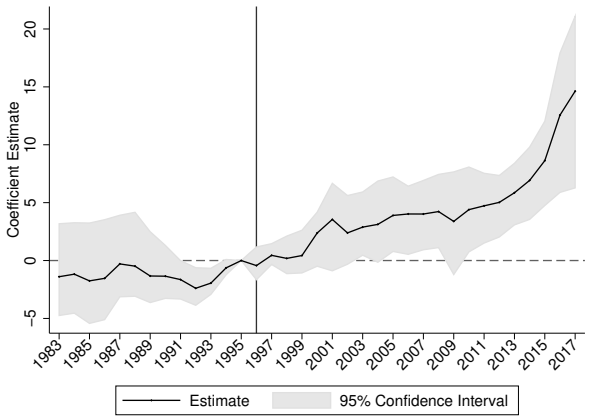
B: Oxycodone Prescriptions

Notes: We study Medicaid OxyContin and oxycodone prescriptions per 1,000 beneficiaries. We exclude the former triplicate states since they repealed their programs prior to OxyContin's introduction. The sample period for OxyContin prescriptions is 1996-2005; the sample for oxycodone prescriptions is 1991-2005. For states not reporting in each quarter, we annualize their outcomes. We include state and year fixed effects in addition to the time-relative-to-event indicators. Confidence intervals are generated by a wild bootstrap.

Figure A15: County-Level Overdose Death Rate Event Studies By Metropolitan Area Size



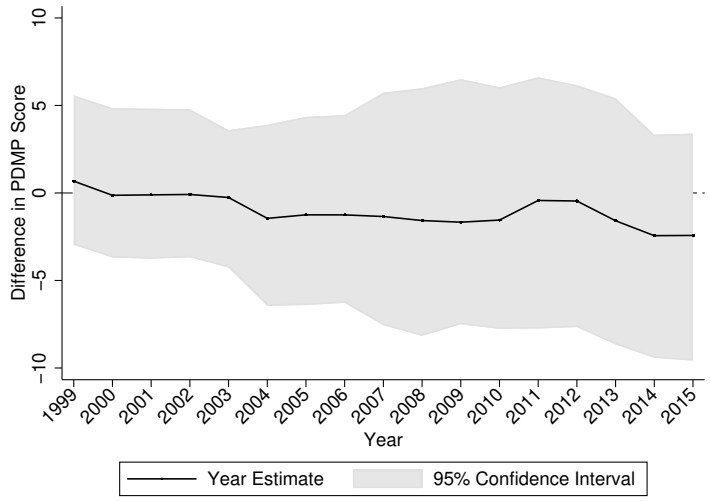
A: Counties of metro areas



B: Central counties of metro areas of 1 million population or more

Notes: The outcome is county-level overdose deaths per 100,000. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in 1995. Counties are categorized by the United States Department of Agriculture's Economic Research Service in 1993. We estimate the main event study specification at the county-level. County and year fixed effects included in all models. $N = 28{,}910$ (826 counties) for Panel A; $N = 6{,}125$ (175 counties) for Panel B.

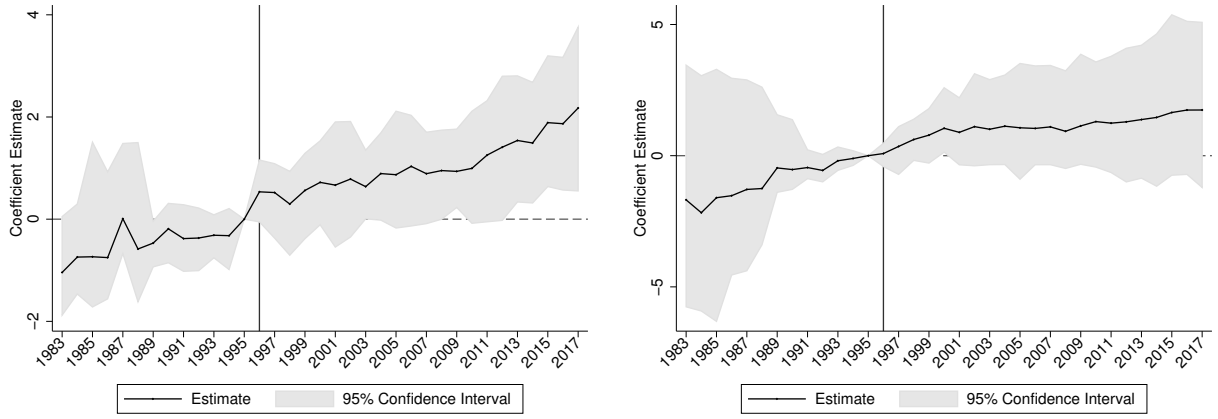
Figure A16: Comparing PDMP Strength by Triplicate State Status



Notes: Each estimate represents the cross-sectional difference in the outcome variable, comparing non-triplicate states relative to triplicate states, for the available years of the index (1999-2015). The outcome is the Pardo (2017) index of PDMP strength. 95% confidence intervals generated using wild bootstrap clustered by state. We select on states with any type of PDMP in 1996.

Figure A17: Event Study: Other Deaths of Despair

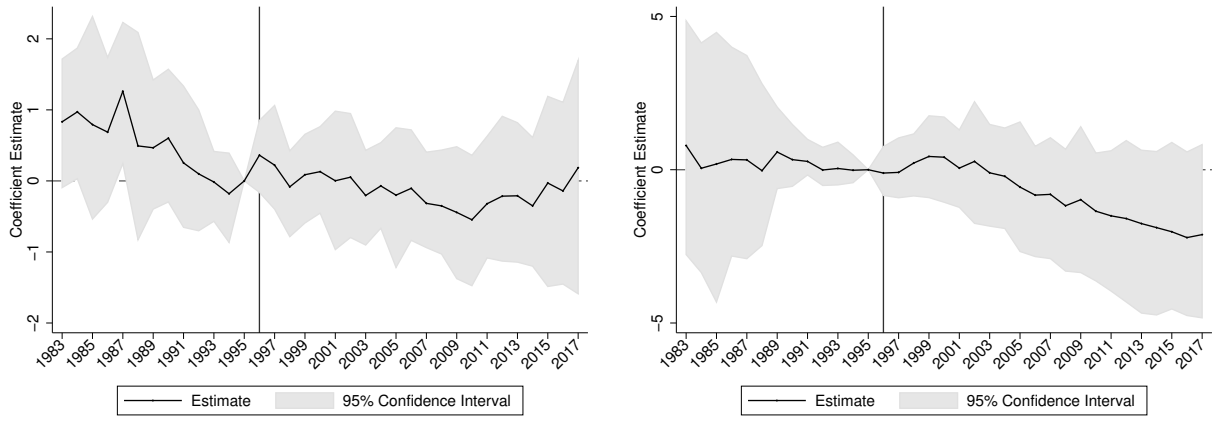
Main Estimates



A: Suicides

B: Alcohol-Related Liver Diseases

Detrended

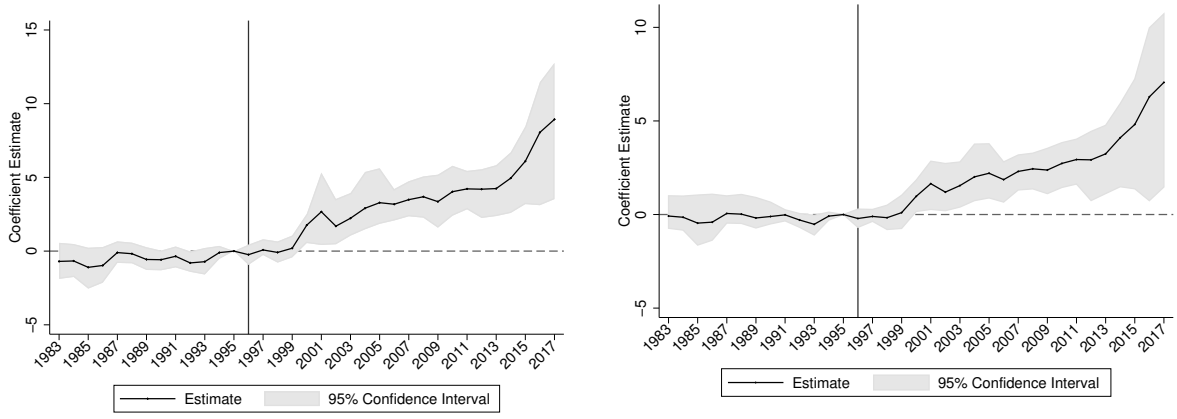


C: Suicides

D: Alcohol-Related Liver Diseases

Notes: We use geocoded NVSS data to construct suicides (excluding those involving overdoses) and alcohol-related liver disease deaths per 100,000. These figures report event study estimates from a population-weighted regression which includes state and year fixed effects. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in 1995. In Panel C and D, we show estimates after detrending. We detrend by first estimating a model with state fixed effects, year fixed effects, and a linear time trend interacted with non-triplicate status. This model is estimated using only pre-1996 data. We then use the residualized outcome to estimate the event study.

Figure A18: Event Study: Drug Overdose Deaths Excluding Cocaine

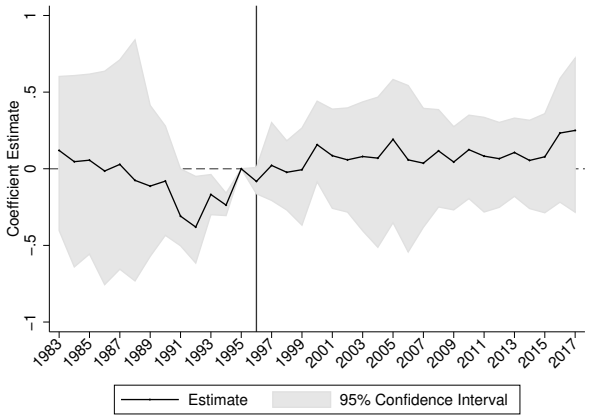


A: Overdose deaths excluding cocaine

B: Opioid overdose deaths excluding cocaine

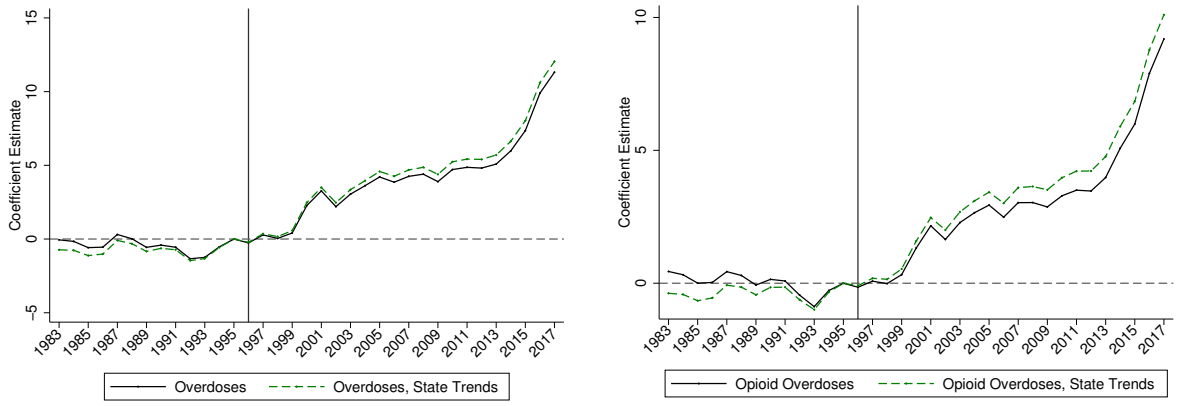
Notes: We use geocoded NVSS data to construct all drug overdose deaths per 100,000 and opioid overdose deaths per 100,000. We exclude overdoses also involving cocaine in both of these measures. Event study estimates include state and year fixed effects. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in 1995.

Figure A19: Event Study: Cocaine Overdose Death Rates, Excluding Opioids



Notes: We use geocoded NVSS data to construct cocaine overdose deaths (excluding opioids) per 100,000. We report event study estimates from a regression which includes state and year fixed effects. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in 1995.

Figure A20: Event Study – Accounting for State-Specific Trends

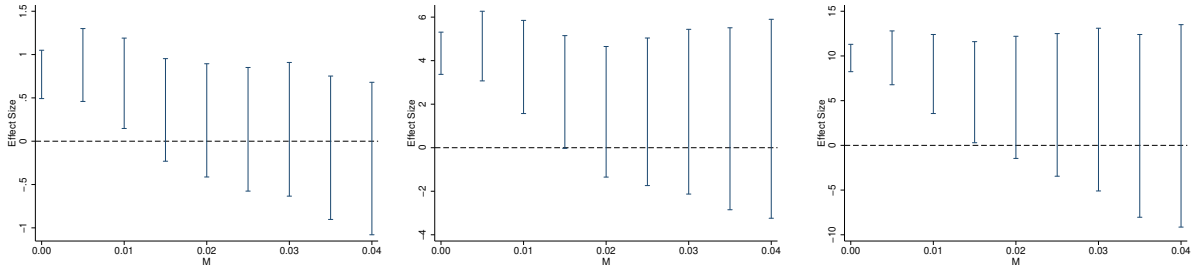


A. All Overdose Deaths B. Opioid Overdose Deaths

Notes: We use geocoded NVSS data to construct all drug overdose deaths and opioid overdose deaths per 100,000. We repeat the estimates in Figures IV.B and IV.D. We also de-trend the overdose rates and opioid overdose rates in each state using pre-1996 data to estimate the linear trend (and extrapolate to the end of the sample). We use this residualized variable as the outcome and estimate equation (1). 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in 1995.

Figure A21: Sensitivity to Non-Parallel Trends

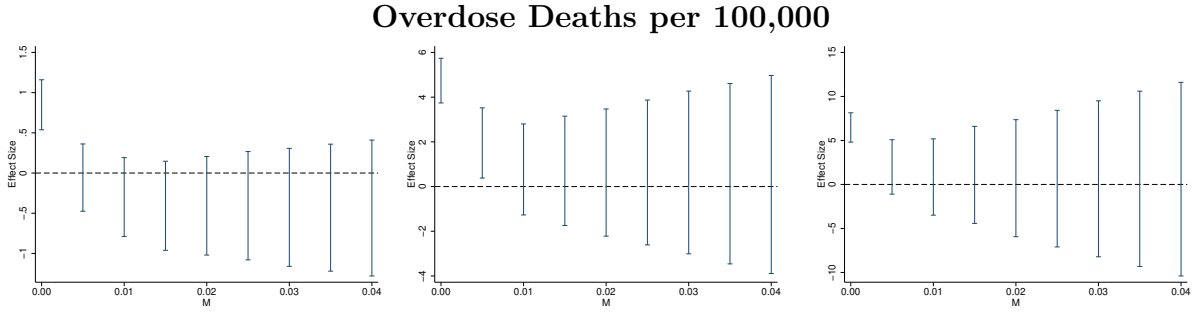
Overdose Deaths per 100,000



A: 1996-2000 B: 2001-2010 C: 2011-2017

Notes: The outcome is all drug overdoses per 100,000 people. We estimate fixed length confidence intervals (FLCIs) using the approach introduced in Rambachan and Roth (2020) for different values of deviations from the parallel trends assumption. The x-axis includes different values of M, which represents the maximum change in the slope between consecutive periods. See equation (3) of Rambachan and Roth (2020) and discussion in the text.

Figure A22: Placebo Sensitivity to Non-Parallel Trends: Five Placebo States



A: 1996-2000 B: 2001-2010 C: 2011-2017

Notes: The outcome is all drug overdoses per 100,000 people. We assign placbeo triplicate status to the five non-triplicate states with the *lowest* overdose rate growth. We estimate fixed length confidence intervals (FLCIs) using the approach introduced in Rambachan and Roth (2020) for different values of deviations from the parallel trends assumption. The x-axis includes different values of M, which represents the maximum change in the slope between consecutive periods. See equation (3) of Rambachan and Roth (2020) and discussion in the text.

Appendix Tables

Table A1: 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	1982		
Last Year	2004	1997	2000	2001	1999		
Annual Overdose Death Rates							
Overdoses per 100,000	7.02	3.10	4.62	5.95	3.85	5.66	3.89
Overdose Rate Rank	3	27	17	9	20	–	–
Overdoses (excluding cocaine) per 100,000	5.57	2.85	2.79	2.74	2.73	3.84	3.14
Overdose (excluding cocaine) Rate Rank	4	21	22	24	25	–	–
Opioid Overdoses per 100,000	2.92	0.52	2.23	3.63	0.80	2.47	1.03
Opioid Overdose Rate Rank	5	34	10	2	21	–	–
Demographics							
% White, Non-Hispanic	54.1%	91.6%	73.1%	67.3%	58.3%	61.3%	79.7%
% Black, Non-Hispanic	7.1%	0.4%	14.9%	14.8%	11.7%	10.9%	12.6%
% Hispanic	28.0%	6.0%	9.0%	13.2%	27.5%	21.4%	4.8%
% Ages 25-44	34.1%	32.3%	32.3%	32.4%	32.8%	33.1%	31.8%
% Ages 45-64	17.6%	19.2%	19.1%	20.0%	17.7%	18.4%	19.6%
% Ages 65+	10.6%	12.5%	12.5%	13.0%	10.2%	11.3%	13.2%
% College Degree	24.5%	23.5%	23.5%	24.5%	21.4%	23.6%	21.2%
Population (in thousands)	31,180	1,109	11,799	18,346	18,168	16,120	3,894

Notes: All summary statistics are population-weighted means, except the population variable which is unweighted.

Table A2: Difference-in-Differences Estimates: Aggregating Event Study Estimates

	A: All Drug Overdose Deaths per 100,000			
Non-Triplicate ×	(1)	(2)	(3)	(4)
1996-2000	1.173**	1.278***	1.132	1.131*
	[0.390, 2.374]	[0.419, 2.438]	[-0.284, 2.417]	[-0.077, 2.483]
2001-2010	3.667**	4.474***	3.530**	3.215**
	[1.521, 6.210]	[2.176, 6.384]	[0.841, 6.153]	[0.919, 5.573]
2011-2017	6.061**	7.772***	5.595***	4.996***
	[2.812, 9.371]	[4.032, 10.380]	[3.547, 7.841]	[2.038, 7.769]
Joint P-Value	0.016	0.000	0.001	0.017
Weighted	No	Yes	Yes	Yes
Covariates	No	No	Yes	Yes
Region-Time Dummies	No	No	No	Yes
Mean 1991-1995	3.890	4.436	4.436	4.436
N	1,377	1,377	1,377	1,377
	B: Opioid Overdose Deaths per 100,000			
Non-Triplicate ×	(5)	(6)	(7)	(8)
1996-2000	0.634**	0.612**	0.579	0.723
	[0.083, 1.573]	[0.114, 1.605]	[-0.604, 1.744]	[-0.254, 1.779]
2001-2010	2.614**	2.930***	1.979*	2.212**
	[1.115, 4.382]	[1.214, 4.242]	[-0.366, 4.576]	[0.077, 4.707]
2011-2017	5.002**	5.869***	3.531***	3.456**
	[1.480, 8.292]	[1.772, 8.842]	[1.486, 6.151]	[0.659, 6.582]
Joint P-Value	0.039	0.010	0.066	0.151
Weighted	No	Yes	Yes	Yes
Covariates	No	No	Yes	Yes
Region-Time Dummies	No	No	No	Yes
Mean 1991-1995	1.189	1.476	1.476	1.476
N	1,377	1,377	1,377	1,377

Notes: ***Significance 1%, **Significance 5%, *Significance 10%. Outcome is all drug overdose deaths or opioid overdose deaths per 100,000. The reported coefficients refer to average of the event study estimates (see Figures IV, A6, A7) for the given time period. Estimates are relative to pre-period 1991-1995. 95% confidence intervals reported in brackets are estimated by wild bootstrap. All models include state and year fixed effects. Covariates include the fraction non-Hispanic White, fraction non-Hispanic Black, fraction Hispanic, log of population, fraction with college degree, fraction ages 25-44, fraction ages 45-64, and fraction ages 65+. "Joint P-Value" refers to the p-value from a joint hypothesis test that all three non-triplicate post effects are equal to zero and is also estimated using a restricted wild bootstrap.

Table A3: Initial State Oxycodone Prescribing Prevalence, 1995

State	Medicaid Prescriptions per 1,000 Benes (1995)
Texas	1.44
Illinois	2.28
California	9.87
Michigan	9.95
Kentucky	12.64
New York	12.85
Idaho	17.53
South Dakota	17.94
Indiana	24.39
Arkansas	26.56
Mississippi	27.12
Oregon	29.43
Minnesota	30.09
Iowa	31.57
Oklahoma	34.67
North Dakota	34.85
Alabama	37.24
Florida	38.73
Georgia	39.09
Rhode Island	39.72
South Carolina	41.21
Wyoming	42.08
Missouri	42.20
District Of Columbia	43.55
Kansas	45.58
Louisiana	46.15
North Carolina	48.33
Nebraska	49.51
West Virginia	50.46
Ohio	50.68
Nevada	53.44
New Jersey	60.28
Washington	61.44
Virginia	63.08
New Mexico	63.88
Wisconsin	66.40
Hawaii	72.76
Pennsylvania	78.00
Montana	79.24
Utah	82.11
Delaware	88.18
Alaska	95.17
Maryland	114.23
Vermont	133.40
Connecticut	146.59
Maine	148.82
Massachusetts	156.80
New Hampshire	157.52
Colorado	No Data
Tennessee	No Data
Arizona	No Data

Notes: This table sorts states by Medicaid oxycodone prescriptions per 1,000 beneficiaries for 1995. Triplicate states as of 1996 are bolded; former triplicate states are italicized. In a few circumstances, states are missing data for one or more quarters in 1995. In these cases, we annualize the data within that year by multiplying the number of prescriptions by four divided by the number of quarters in the data. Three states do not report data for any quarters in 1995.

Table A4: Initial State Oxycodone Prescribing Prevalence, 1991-1995

State	Medicaid Prescriptions per 1,000 Benes (1991-1995)
Texas	1.68
Illinois	2.73
California	7.61
Kentucky	8.03
Michigan	10.25
New York	11.25
Idaho	19.18
Indiana	21.00
Washington	21.43
South Dakota	22.43
Rhode Island	23.02
Arkansas	25.87
Minnesota	26.95
Mississippi	27.56
Iowa	30.34
Oklahoma	30.40
North Dakota	30.90
Nebraska	34.75
Tennessee	36.06
Alabama	36.33
South Carolina	38.62
District Of Columbia	39.77
Kansas	40.52
Georgia	40.61
Missouri	41.20
West Virginia	42.26
Oregon	43.86
Florida	44.15
North Carolina	44.57
Louisiana	45.27
Ohio	45.36
Wyoming	52.09
Wisconsin	56.44
Virginia	61.33
Colorado	62.02
Nevada	62.78
New Jersey	65.51
New Mexico	68.59
Pennsylvania	69.93
Hawaii	72.25
Delaware	74.05
Montana	76.13
Utah	91.15
Alaska	93.21
Maryland	97.37
Maine	111.52
New Hampshire	125.88
Vermont	131.27
Massachusetts	132.75
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. In a few circumstances, states are missing data for one or more quarters within a year. In these cases, we annualize the data within that year by multiplying the number of prescriptions by four divided by the number of quarters in the data. If a state is missing data for an entire year, we simply take the average over the years with data.

Table A5: Robustness Tests: Opioid Overdose Deaths per 100,000

Non-Triplicate ×	Baseline Results	Select on Population Size	Select on PDMP States in 1996	Control for Policy Variables
	(1)	(2)	(3)	(4)
1996-2000	0.725	2.235*	1.131	0.630
	[-0.244, 1.621]	[-0.095, 3.781]	[-1.514, 3.618]	[-0.394, 1.625]
2001-2010	2.081**	3.837**	3.880	1.633*
	[0.151, 4.192]	[1.378, 6.445]	[-2.411, 9.117]	[-0.344, 3.418]
2011-2017	3.334***	3.314**	6.255**	3.317***
	[1.415, 5.613]	[0.566, 7.693]	[1.018, 11.543]	[1.524, 5.202]
Joint P-Value	0.034	0.097	0.033	0.015
Mean 1991-1995	1.476	1.852	2.016	1.476
N	1,377	216	405	1,377

Notes: ***Significance 1%, **Significance 5%, *Significance 10%. Outcome is opioid overdose deaths per 100,000. 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 year fixed effects and time-varying covariates (see Table I for details). Column (1) repeats the column 7 results from Table I. Column (2) selects on the four non-triplicate states with the largest populations 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 (any PDMP and electronic PDMP), "must access" PDMPs, pain clinic regulation, medical marijuana laws, and operational/legal medical marijuana dispensaries. "Joint P-Value" refers to the p-value from a joint hypothesis test that all three non-triplicate post effects are equal to zero and is also estimated using a restricted wild bootstrap.

B OxyContin's Launch and Promotional Activities

OxyContin is a long-acting formulation of oxycodone, a morphine-like drug, produced by Purdue Pharma. It is classified as a Schedule II controlled substance given its high potential for abuse. The Food and Drug Administration (FDA) approved OxyContin in 1995 and the drug was introduced to the market in January 1996. OxyContin entered the market as Purdue Pharma's patent for MS Contin-a long-acting form of morphine used for treating late-stage cancer pain-was set to expire. Purdue Pharma aimed both to replace MS Contin with OxyContin and to expand into additional markets: patients in the earlier stages of cancer (positioning OxyContin as "the opioid to start with and to stay with") and the much larger market for non-cancer pain. Prior to OxyContin's launch, patients with non-cancer pain would have been typically treated (if at all) with non-opioid painkillers (e.g., Tylenol) or short-acting combination products that combine much smaller doses of either oxycodone or hydrocodone with acetaminophen (e.g., Percocet, Tylox, Vicodin).[1]

OxyContin's initial marketing strategy centered on claims that the drug had low abuse potential and was safer than other opioid drugs, claims that would later prove to be false. 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." Additionally, marketing materials relied heavily on a 100-word letter to the editor in the *New England Journal of Medicine* (Porter and Jick, 1980) to support the claim that the risk of addiction among opioid users was "much less than one percent." Some marketing materials failed to include any information about its addiction potential (Van Zee, 2009). These misinformed or misleading claims were important in convincing doctors who had been cautious about prescribing opioids to switch from less potent painkillers to OxyContin for treating non-cancer pain. To achieve growth in that non-cancer chronic pain market – a previously untapped market for opioids – Purdue Pharma also heavily targeted marketing to 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 (General Accounting Office, 2003).

In 2001, the FDA product label for OxyContin was revised to remove the incorrect statements about its abuse liability and to 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 those who require "a continuous around-the-clock analgesic for an extended period of time." This may have further expanded the market for chronic pain. Internal documents show that Purdue Pharma believed that the new label "created enormous opportunities" and "in effect, the FDA has expanded the indication for

[1]The dosage 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 (General Accounting Office, 2003). This purity allows OxyContin to be used at much higher dosages to treat more severe levels of pain than the combination products.

OxyContin." They further noted that "this broad labeling is likely to never again be available for an opioid seeking FDA approval" (Purdue Pharma, 2002).

Purdue Pharma's advertising campaign was unusually aggressive for a prescription drug and unprecedented for an opioid. The promotional budget between 1996 and 2001 for OxyContin was six- to twelve-times more than Purdue Pharma had spent on advertising for MS Contin during its first six years on the market, and what Janssen Pharmaceutical Products spent in promoting Duragesic, one of OxyContin's competitors (General Accounting Office, 2003). Purdue Pharma employed an enormous sales force to promote the drug to doctors, a sales force that doubled in size between 1996 and 2002.[2] Additionally, Purdue Pharma promoted OxyContin heavily through a variety of other channels such as sponsoring pain-related educational programs and conferences,[3] distributing coupons and gifts,[4] and advertising in medical journals. These marketing efforts contributed to OxyContin's blockbuster success. Revenue from OxyContin sales skyrocketed from $48 million in 1996 to $1.1 billion in 2000 (Van Zee, 2009) and $3.1 billion in 2010 (IMS Institute for Healthcare Informatics, 2011).

Despite the marketing claims, concerns about widespread abuse of OxyContin grew as quickly as its sales. Users of the drug quickly 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. Some of the earliest reports of OxyContin abuse and diversion occurred in Appalachia and rural areas. However, by 2001, the DEA Administrator reported that abuse had also moved to urban areas, especially Boston and Philadelphia.[5] OxyContin became one of the leading prescription drugs of abuse in the U.S., surpassing all other forms of oxycodone and hydrocodone combined (Cicero et al., 2005). The aggressive marketing of OxyContin eventually concerned local and state governments, leading to a series of lawsuits.

[2]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 (General Accounting Office, 2003).

[3]Purdue Pharma funded more than 20,000 pain-related educational programs from 1996-2002 (General Accounting Office, 2003). They also provided significant amounts of funding to several medical societies such as the American Pain Society and JCAHO (`https://ag.ny.gov/sites/default/files/oag_opioid_lawsuit.pdf`), organizations that recommended more aggressive diagnosis and treatment of pain.

[4]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."

[5]See DEA Administrator Asa Hutchinson's Testimony on December 11, 2001: `https://www.govinfo.gov/content/pkg/CHRG-107hhrg77734/html/CHRG-107hhrg77734.htm`, last accessed November 4, 2019.

C Additional Robustness Tests

C.1. Economic Conditions

In this section, we study the role of economic conditions and labor demand shocks. These results are included in Appendix Table C1. First, we include the annual unemployment rate (from the Bureau of Labor Statistics) as a control in Column (1). While this covariate is potentially endogenous if opioid misuse affects labor supply, the estimates are generally larger in magnitude. Next, we control for economic shocks that provide an exogenous source of variation in economic conditions. Charles et al. (2019) use a shift-share (Bartik) instrument to predict changes in manufacturing employment share, finding that reductions in manufacturing jobs increase drug overdose rates. We construct a shift-share instrument using the Current Population Study, fixing industry composition by state at its 1995 levels, and interacting these 1995 compositions with national-level industry-specific employment levels (excluding each state's own employment). Column (2) of Table C1 presents the results for overdose deaths per 100,000, controlling for this variable. The results are not meaningfully affected by the including this extra control. In Column (3), we add a shift-share instrument related to all industries (similar to Betz and Jones (2018)). The inclusion of both shift-share measures permits manufacturing shifts to have differential effects relative to broader labor demand shocks. Again, the results are similar.

Finally, Pierce and Schott (2020) find that areas disproportionately harmed by international trade policy (specifically, the granting of Permanent Normal Trade Relations (PTNR) by the United States to China in 2000), experienced faster growth in fatal drug overdoses and other deaths of despair. We constructed state-level measures of this metric by evaluating equation (2) in Pierce and Schott (2020) at state-level (instead of county-level) employment measures.[6] We interact this metric of exposure to trade liberalization with year indicators. The results are generally unaffected when we control for these variables. Columns (5)-(8) provide the same sensitivity tests for opioid overdose deaths.

In addition, we estimate our event study in equation (1) controlling for the Pierce-Schott measure of exposure to trade policy interacted with year fixed effects. Figure C1 shows the estimates for the non-triplicate interaction terms (Panels A and C) and the trade policy interaction terms (Panels B and D) estimated jointly. The non-triplicate pattern is unaffected by the including the trade exposure variable, suggesting that our main estimates are not driven by differential exposure to PTNR.

C.2. Outliers

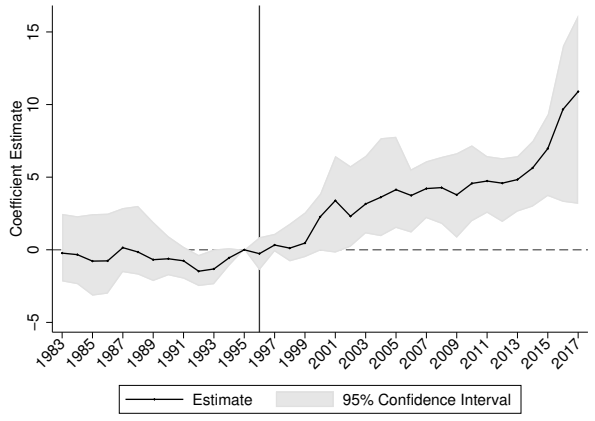
We implement a "leave one out" test to see whether any specific state (triplicate or non-triplicate) is driving the results. To facilitate summarizing the findings from this analysis,

[6]Data downloaded from `https://www.aeaweb.org/doi/10.1257/aeri.20180396.data`, last accessed September 7, 2020.

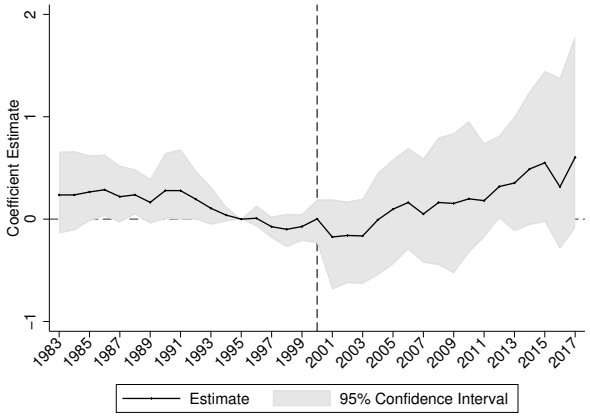
we focus on a specification with *one* post-treatment indicator, instead of the three used throughout the paper. This will make the comparisons across samples more straightforward. In each case, we regress the overdose death rate on state fixed effects, year fixed effects, and 1(Non-Triplicate) $\times$ 1(Year $\geq$ 1996). We present the estimate on this last interaction. In each case, we drop one state. The results are shown in Figure C3. All of the estimates are large and statistically significant from zero.

Figure C1: Event Study: Controlling for Pierce-Schott Trade Exposure Effect

All Drug Overdose Deaths per 100,000

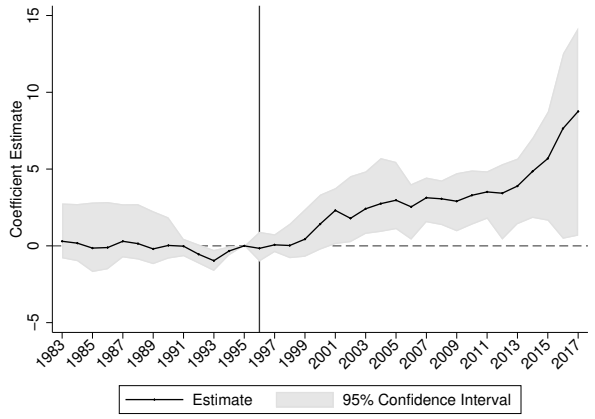


A: Non-Triplicate Effect

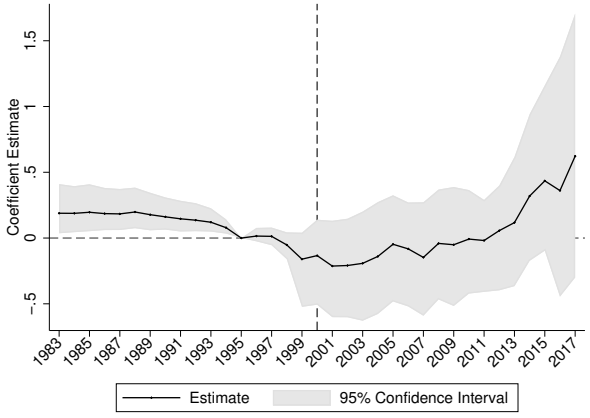


B: Trade Effect

Opioid Overdose Deaths per 100,000



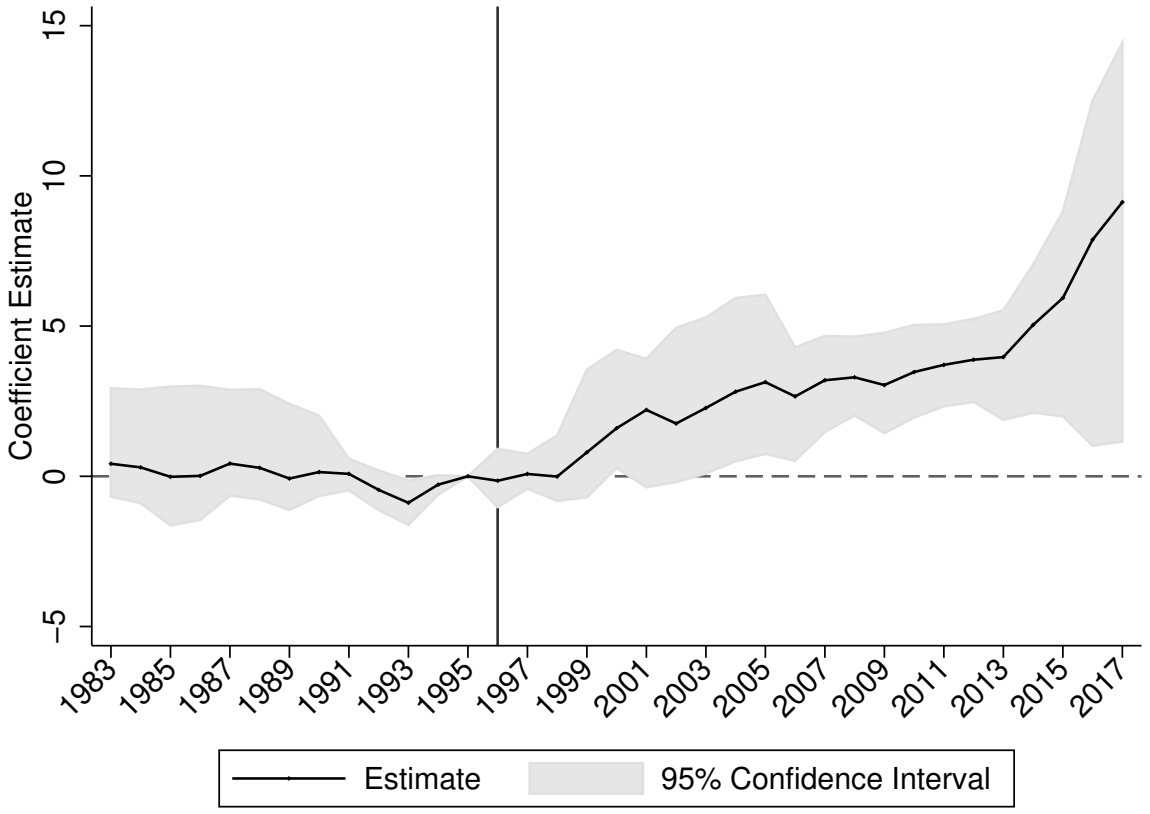
C: Non-Triplicate Effect



D: Trade Effect

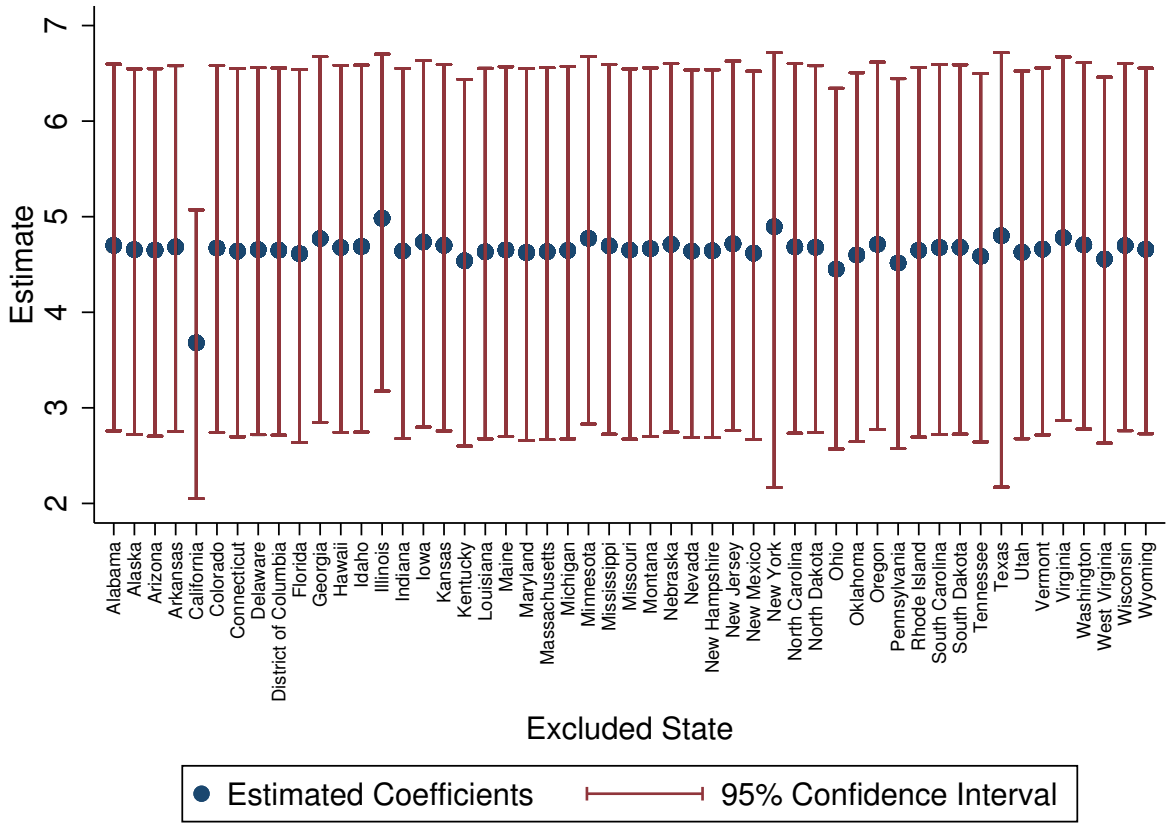
Notes: We use geocoded NVSS data to construct all drug overdose and opioid overdose deaths per 100,000. See text for exact ICD codes used in each period. Panels A and B are estimated jointly. Panel A shows the non-triplicate effect; Panel B shows the effect of exposure to trade liberalization. Panels C and D are also estimated jointly. Trade policy changed in 2000 (denoted by the vertical dashed line) and the exposure to the policy is defined in the same manner as Pierce and Schott (2020). All regressions include state and year fixed effects. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. All estimates are normalized to 0 in 1995.

Figure C2: Event Study: Opioid Overdose Death Rate Excluding Unspecified (T40.6) Overdoses



Notes: We use geocoded NVSS data to construct opioid overdose deaths per 100,000. We study opioid-specific overdose deaths excluding unspecified narcotics (coded T40.6 in ICD-10). Event study estimates include state and year fixed effects. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in 1995.

Figure C3: Leave-One-Out Test



Notes: We regress overdose deaths per 100,000 people on state fixed effects, year fixed effects, and the interaction of Non-Triplicate and Post-1996 for the 1991-2017 time period. We report the estimates on this interaction term above. Each state is dropped once and listed on the x-axis. Regressions are weighted by population. 95% confidence intervals are generated using a clustered (at state) wild bootstrap.

Table C1: Difference-in-Differences Estimates: Controlling for Unemployment and Economic Shocks

	All Drug Overdose Deaths per 100,000			
Non-Triplicate ×	(1)	(2)	(3)	(4)
1996-2000	1.447**	1.269**	1.349**	1.634**
	[0.003, 2.799]	[0.081, 2.255]	[0.207, 2.294]	[0.447, 2.679]
2001-2010	3.948**	3.600***	3.598**	4.151***
	[0.815, 6.838]	[1.358, 5.673]	[1.104, 5.793]	[1.500, 6.715]
2011-2017	6.681***	5.271***	5.264***	5.637***
	[4.358, 8.966]	[3.177, 7.140]	[3.144, 7.388]	[3.295, 7.937]
Joint P-Value	0.001	0.001	0.002	0.003
	Opioid Overdose Deaths per 100,000			
Non-Triplicate ×	(5)	(6)	(7)	(8)
1996-2000	1.005*	0.721*	0.849*	1.088**
	[-0.170, 2.177]	[-0.294, 1.652]	[-0.139, 1.742]	[0.106, 1.999]
2001-2010	2.647**	2.020*	2.017*	2.549**
	[0.166, 5.236]	[-0.038, 4.234]	[-0.260, 4.406]	[0.194, 5.162]
2011-2017	4.698***	3.285***	3.275***	3.592***
	[2.218, 7.272]	[1.385, 5.536]	[1.546, 5.427]	[1.823, 5.737]
Joint P-Value	0.032	0.038	0.029	0.016
Unemployment Rate	Yes	No	No	No
Bartik Manufacturing	No	Yes	Yes	Yes
Bartik All Industries	No	No	Yes	Yes
Trade Exposure	No	No	No	Yes

Notes: N = 1,377. ***Significance 1%, **Significance 5%, *Significance 10%. Outcomes are all drug overdose and opioid overdose deaths per 100,000. 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 year fixed effects as well as the fraction non-Hispanic White, fraction non-Hispanic Black, fraction Hispanic, log of population, fraction with college degree, fraction ages 25-44, fraction ages 45-64, and fraction ages 65+. In Columns (1) and (5), we add the unemployment rate. In the rest of the columns, we include labor demand shocks. First, we include a shift-share instrument related specifically to manufacturing. Next, we also add a more general shift-share instrument which uses all industries. Finally, we also include a measure of exposure to trade liberalization interacted with year dummies. "Joint P-Value" refers to the p-value from a joint hypothesis test that all three non-triplicate post effects are equal to zero and is also estimated using a restricted wild bootstrap.

D Synthetic Control Estimates

While we observe little evidence of pre-existing trends in our results, the triplicate states began with higher levels of overdoses. One way to address differences in pre-treatment levels and trends is to construct synthetic controls for each treated state using the synthetic control method (Abadie et al. (2010, 2015)).[7] Here, we estimate synthetic controls for each triplicate state using non-triplicate states as potential components of the synthetic controls. In our difference-in-differences analyses, we aggregate overdoses to the annual level because all our time-varying covariates vary annually and since difference-in-differences only uses the (adjusted) means. However, synthetic control estimation benefits from the additional information in more disaggregated data (even if serially-correlated) so we use quarterly overdoses rates for this analysis.[8]

The "treatment" is triplicate state status in 1996 (unlike the prior analyses where the treatment was non-triplicate state status in 1996), because 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 difference in the triplicate states relative to their synthetic controls. The negative sign makes the estimates comparable to those presented throughout the paper. We also present the time series overdose rates for the triplicate and synthetic triplicate states.

The results are shown in Figure D1. The synthetic control weights are provided in Table D2. We estimate similar overdose reductions as our main estimates.[9] We summarize the findings by aggregating the estimates for the three periods used throughout the paper. 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. To aggregate the five estimates, we present both unweighted averages (Column 1) and population-weighted averages (Column 2) in Table D1. The two sets of results are similar. The estimates for overdose deaths (the top half of the table) and opioid overdose deaths (the bottom half) are similar to the main difference-in-differences estimates in the paper. Compared to the placebo estimate distribution, these estimates are statistically rare.

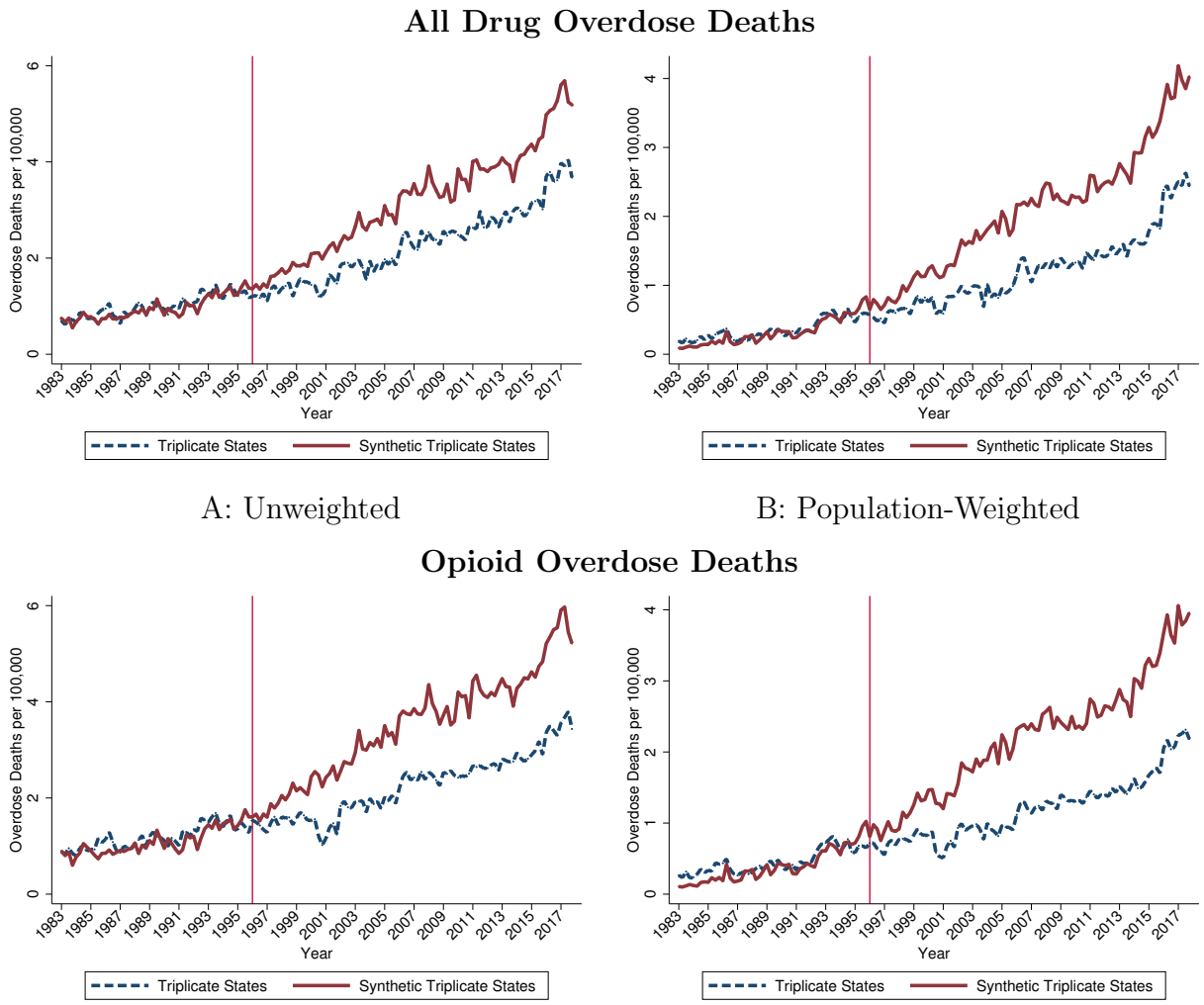
These results suggest that our main estimates are not driven by any initial outcome differences in overdose rates between the triplicate and non-triplicate states. We also compare each state to its synthetic control state, using the same framework as Figure V. These results are provided in Figure D2. Each state experienced smaller overdose death rate growth than its synthetic control.

[7] Concerns about synthetic control estimation and some possible modifications are discussed in Ben-Michael et al. (2018); Arkhangelsky et al. (2019); Abadie (forthcoming); Powell (2020); Ferman and Pinto (2019); Doudchenko and Imbens (2016) among others. We use the traditional approach here.

[8] 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.

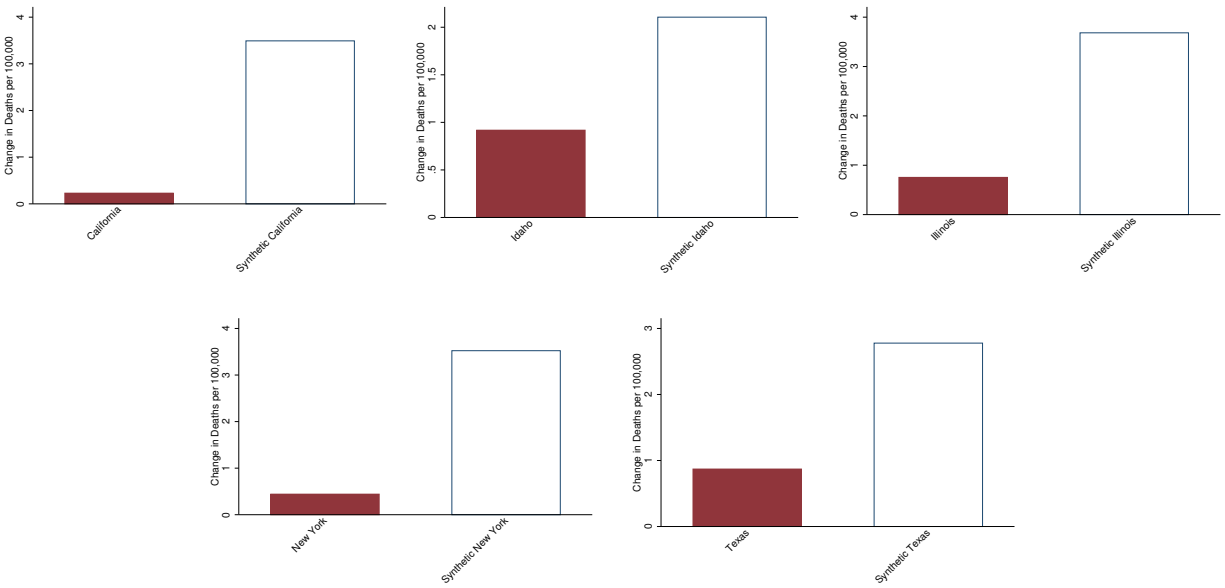
[9] The scales are different due to the use of quarterly overdose rates versus annual. The Table D1 adjust for this differences to produce more comparable estimates.

Figure D1: Synthetic Control Results: Quarterly Overdose Death Rates



Notes: The outcome is *quarterly* overdose deaths per 100,000 (results in the main paper refer to annual rates). We construct a synthetic control for each triplicate state. We then take the unweighted or population-weighted average of each triplicate state and its synthetic control. See Table D2 for the synthetic control weights.

Figure D2: Drug Overdose Death Rate Changes: Triplicates vs. Synthetic Triplicates (1996-2005 Relative to 1986-1995)



Notes: We construct the change in all drug overdose deaths per 100,000 for 1996-2005 relative to 1986-1995. We plot this change for each triplicate state relative to its synthetic control.

Table D1: Synthetic Control Results: Drug Overdose Death Rate

Non-Triplicate ×	All Drug Overdose Deaths per 100,000 (1)	(2)
1996-2000	1.586	2.114
	[1 / 1000]	[1 / 1000]
2001-2010	3.669	5.132
	[1 / 1000]	[1 / 1000]
2011-2017	5.014	6.847
	[1 / 1000]	[1 / 1000]
Unweighted/Weighted	Unweighted	Population-Weighted
Non-Triplicate ×	Opioid Overdose Deaths per 100,000 (3)	(4)
1996-2000	1.216	1.502
	[1 / 1000]	[1 / 1000]
2001-2010	3.473	4.104
	[1 / 1000]	[1 / 1000]
2011-2017	5.064	5.522
	[4 / 1000]	[1 / 1000]
Unweighted/Weighted	Unweighted	Population-Weighted

Notes: We estimated synthetic controls for each triplicate state and report the average of the synthetic control outcomes (which are non-triplicates) minus the triplicate state outcomes. 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, in brackets, we report the rank of that estimate relative to the 999 placebo estimates and the main estimate itself, produced by randomly-assigning non-triplicate states to "triplicate" status and repeating the entire strategy. We multiply the point estimates by four to make the quarterly estimates comparable to the annual estimates in the main text. The columns differ based on how the 5 estimates are weighted.

Table D2: Synthetic Control Weights

	Overdoses					Opioid Overdoses				
State	CALIFORNIA	IDAHO	ILLINOIS	NEW YORK	TEXAS	CALIFORNIA	IDAHO	ILLINOIS	NEW YORK	TEXAS
ALABAMA	0	0	0	0	0	0	0.166	0	0	0
ALASKA	0	0	0.03	0	0.052	0	0	0	0	0
ARIZONA	0.03	0	0	0	0.02	0	0	0.054	0	0
ARKANSAS	0	0	0	0	0.023	0	0.186	0	0	0
COLORADO	0	0	0	0	0.094	0	0	0	0	0.043
CONNECTICUT	0	0	0	0.352	0	0	0	0	0.34	0
DELAWARE	0	0	0	0	0	0	0	0.01	0	0
DISTRICT OF COLUMBIA	0.19	0	0.041	0	0	0	0.097	0.011	0.007	0
FLORIDA	0	0	0.078	0	0	0	0	0	0	0
GEORGIA	0	0	0	0	0	0	0	0	0	0
HAWAII	0	0	0	0	0	0	0	0	0	0.031
INDIANA	0	0	0	0	0	0	0	0	0	0
IOWA	0	0	0	0	0.151	0	0	0	0	0
KANSAS	0	0	0	0	0	0	0.118	0	0	0
KENTUCKY	0	0	0	0	0	0	0	0	0	0.308
LOUISIANA	0	0	0	0	0	0	0	0	0	0
MAINE	0	0	0	0	0	0	0.125	0	0	0
MARYLAND	0	0.122	0.058	0	0	0	0	0	0	0.173
MASSACHUSETTS	0	0	0	0	0	0	0	0	0.133	0
MICHIGAN	0	0	0	0	0	0	0	0	0	0
MINNESOTA	0	0	0	0	0	0	0	0	0	0
MISSISSIPPI	0	0	0	0	0.096	0	0	0	0	0.073
MISSOURI	0	0	0.052	0	0	0	0	0	0	0.035
MONTANA	0	0	0	0.016	0	0	0.152	0	0	0
NEBRASKA	0	0.46	0.133	0.083	0.07	0	0	0	0	0.052
NEVADA	0.478	0	0	0	0	0.049	0.048	0	0	0.059
NEW HAMPSHIRE	0	0	0	0	0.033	0	0	0	0	0.038
NEW JERSEY	0	0.12	0	0	0	0	0	0	0	0
NEW MEXICO	0.135	0	0.133	0.282	0.11	0	0	0	0.416	0
NORTH CAROLINA	0	0.187	0	0	0	0	0	0	0	0.015
NORTH DAKOTA	0	0.032	0	0	0	0	0	0	0	0.001
OHIO	0	0	0	0	0	0	0	0	0	0
OKLAHOMA	0	0	0	0.206	0	0	0	0	0	0
OREGON	0	0	0.202	0	0.03	0	0	0.103	0	0.067
PENNSYLVANIA	0	0	0	0	0	0	0	0	0	0
RHODE ISLAND	0	0	0.024	0	0.009	0	0	0	0.055	0
SOUTH CAROLINA	0	0	0	0	0.207	0	0	0	0	0.038
SOUTH DAKOTA	0	0	0	0.054	0	0	0	0	0	0
TENNESSEE	0	0	0	0	0	0	0	0	0	0
UTAH	0	0	0.067	0	0	0	0	0	0	0
VERMONT	0	0	0	0	0	0	0	0	0	0
VIRGINIA	0	0	0	0	0	0	0	0.119	0	0
WASHINGTON	0.168	0	0	0	0	0.951	0	0.579	0	0
WEST VIRGINIA	0	0	0.18	0	0	0	0.102	0	0.047	0.02
WISCONSIN	0	0	0	0	0	0	0	0	0	0
WYOMING	0	0.078	0	0.007	0.106	0	0.008	0.124	0	0.048

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.

E Alternative Inference Methods

In this section, we consider the sensitivity of our results to alternative statistical inference methods. First, we show our main results with cluster-robust standard errors, the most commonly used method for accounting for within-state dependence. This method produces confidence intervals that are too small when there are too few clusters (or treated/untreated units), so we avoid using them in the main analyses. These results are presented in Appendix Table E1. As expected, confidence intervals are much tighter when using this traditional approach, which is consistent with biases discussed often in the literature.

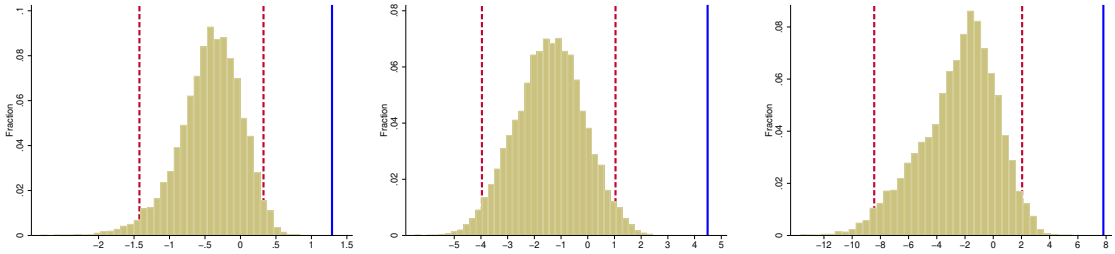
We also compute p-values using permutation-style tests. We randomly assign triplicate status to 5 non-triplicate states and re-estimate equation (2). We repeat this procedure 10,000 times. In each permutation, we estimate the coefficient and t-statistic for each of the three post-periods. Then, we compare these estimates to the main estimates and t-statistics when the 5 triplicate states are correctly assigned and determine the rank. In Appendix Figure E1, we show the distribution of the placebo estimates for each of the three time periods while marking the 2.5 and 97.5 percentiles with vertical dashed lines. The actual estimate is shown as a solid line. We also report the rank of this estimate (one-sided test) and the rank of the absolute value of the estimate (two-sided test). We find that it is statistically rare to observe our main overdose patterns for triplicate versus non-triplicate states using other combinations of states. For each time period, the estimate is larger than all the placebo estimates. In fact, it is impossible to find any combination of 5 non-triplicate states that would produce estimates as large as the actual estimates in any of the three time periods.

Next, we repeat the exercise but using t-statistics, as recommended in MacKinnon and Webb (2020). The results are presented in Appendix Figure E2. Again, we find that it is statistically rare to observe our main overdose patterns for triplicate versus non-triplicate states using other combinations of states. For the earliest time period (1996-2000), the actual t-statistic ranks 258 out of 10,000. For later time periods, it ranks first out of 10,000. When we jointly test the t-statistics for the three time periods, we find that it is extremely rare to observe three t-statistics at the magnitude observed for our main effects.

Figure E3 replicates the above approach but considers 1995 as the "post" period and 1991 as the "pre" period. This designation tests for differential pre-treatment trends or shocks. In this case, we find that the estimates and t-statistics when triplicate states are correctly assigned are generally closer to the middle of the placebo distribution. This result suggests that even if we selected on placebo combinations that produced estimates or t-statistics to the right of the blue vertical lines in Figure E3, our main post-treatment effect estimates (and t-statistics) would still be uniquely large (given the results in Figures E1 and E2).

Figure E1: Permutation Tests using Coefficient Estimates

All Drug Overdose Deaths per 100,000



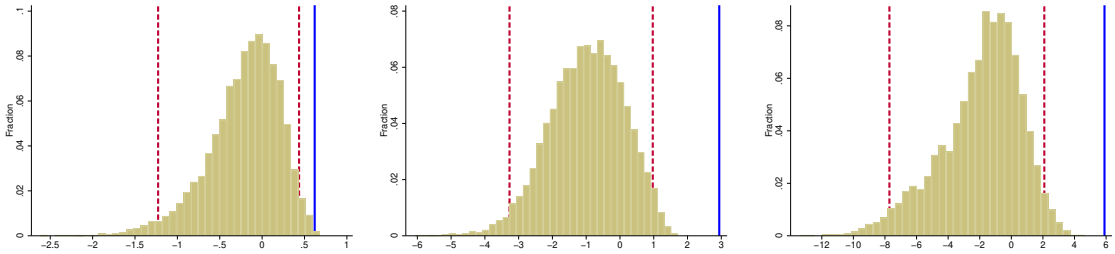
Rank of δ_1: 1/10,000
Rank of $|\delta_1|$: 397/10,000
A: 1996-2000

Rank of δ_2: 1/10,000
Rank of $|\delta_2|$: 71/10,000
B: 2001-2010

Rank of δ_3: 1/10,000
Rank of $|\delta_3|$: 424/10,000
C: 2011-2017

Joint Test (one-sided): $\hat{P}(\delta_1 < \delta_1^{(k)}, \delta_2 < \delta_2^{(k)}, \delta_3 < \delta_3^{(k)}) = 0.0000$
Joint Test (two-sided): $\hat{P}(|\delta_1| < |\delta_1^{(k)}|, |\delta_2| < |\delta_2^{(k)}|, |\delta_3| < |\delta_3^{(k)}|) = 0.0125$

Opioid Overdose Deaths per 100,000



Rank of δ_1: 14/10,000
Rank of $|\delta_1|$: 1584/10,000
D: 1996-2000

Rank of δ_2: 1/10,000
Rank of $|\delta_2|$: 493/10,000
E: 2001-2010

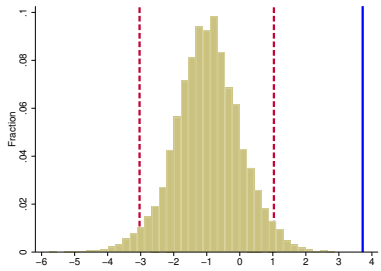
Rank of δ_3: 1/10,000
Rank of $|\delta_3|$: 881/10,000
F: 2011-2017

Joint Test (one-sided): $\hat{P}(\delta_1 < \delta_1^{(k)}, \delta_2 < \delta_2^{(k)}, \delta_3 < \delta_3^{(k)}) = 0.0000$
Joint Test (two-sided): $\hat{P}(|\delta_1| < |\delta_1^{(k)}|, |\delta_2| < |\delta_2^{(k)}|, |\delta_3| < |\delta_3^{(k)}|) = 0.0002$

Notes: The dashed vertical lines represent the 2.5 and 97.5 percentiles of the placebo estimates. The solid blue vertical line is the coefficient estimate when the five triplicate states are assigned correctly. The x-axis represents the value of the coefficient estimates; the y-axis represents the density. Estimating equation (2), regressions include state and time fixed effects and are population-weighted. In the joint tests, k indexes the placebo estimates.

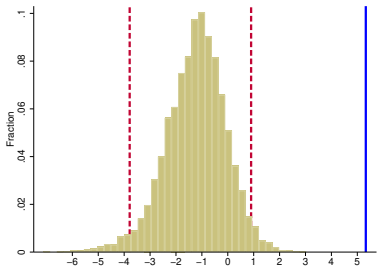
Figure E2: Permutation Tests using T-Statistics

All Drug Overdose Deaths per 100,000



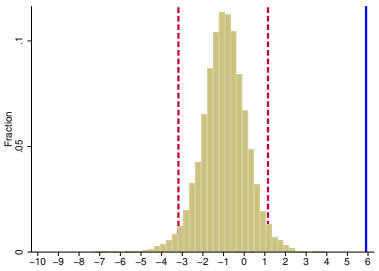
Rank of T_1: 258/10,000
Rank of $|T_1|$: 796/10,000

A: 1996-2000



Rank of T_2: 1/10,000
Rank of $|T_2|$: 56/10,000

B: 2001-2010



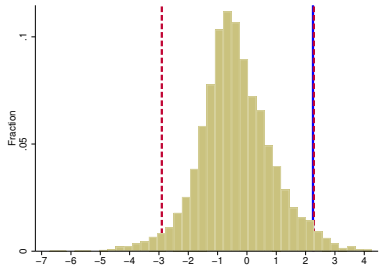
Rank of T_3: 1/10,000
Rank of $|T_3|$: 69/10,000

C: 2011-2017

Joint Test (one-sided): $\hat{P}(T_1 < T_1^{(k)}, T_2 < T_2^{(k)}, T_3 < T_3^{(k)}) = 0.0000$

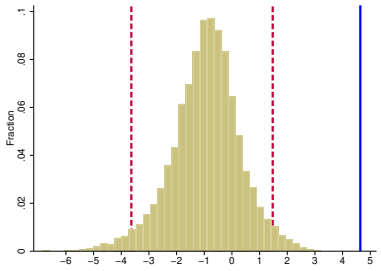
Joint Test (two-sided): $\hat{P}(|T_1| < |T_1^{(k)}|, |T_2| < |T_2^{(k)}|, |T_3| < |T_3^{(k)}|) = 0.0000$

Opioid Overdose Deaths per 100,000



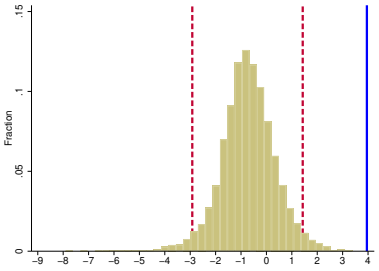
Rank of T_1: 271/10,000
Rank of $|T_1|$: 843/10,000

D: 1996-2000



Rank of T_2: 1/10,000
Rank of $|T_2|$: 54/10,000

E: 2001-2010



Rank of T_3: 1/10,000
Rank of $|T_3|$: 70/10,000

F: 2011-2017

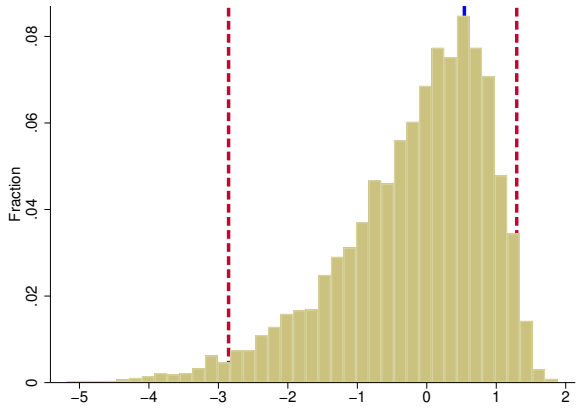
Joint Test (one-sided): $\hat{P}(T_1 < T_1^{(k)}, T_2 < T_2^{(k)}, T_3 < T_3^{(k)}) = 0.0000$

Joint Test (two-sided): $\hat{P}(|T_1| < |T_1^{(k)}|, |T_2| < |T_2^{(k)}|, |T_3| < |T_3^{(k)}|) = 0.0001$

Notes: The dashed vertical lines represent the 2.5 and 97.5 percentiles of the placebo t-statistics. The solid blue vertical line is the t-statistic when the five triplicate states are assigned correctly. The x-axis represents the value of the t-statistics; the y-axis represents the density. t-statistics are calculated using clustered (by state) standard errors as recommended by MacKinnon and Webb (2020) from the same analysis as presented in Figure E1. In the joint tests, k indexes the placebo t-statistics.

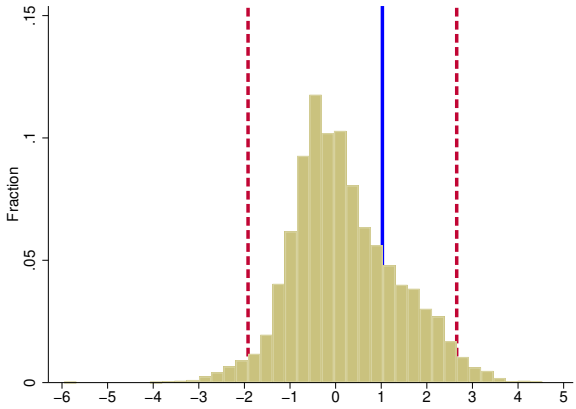
Figure E3: Permutation Tests – Comparing 1991 to 1995

All Drug Overdose Deaths per 100,000



Rank of δ_0: 2,843/10,000
Rank of $|\delta_0|$: 5,943/10,000

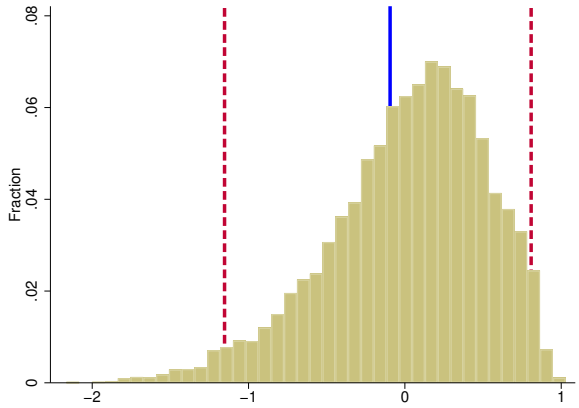
A: Coefficients



Rank of T_0: 2,277/10,000
Rank of $|T_0|$: 3,423/10,000

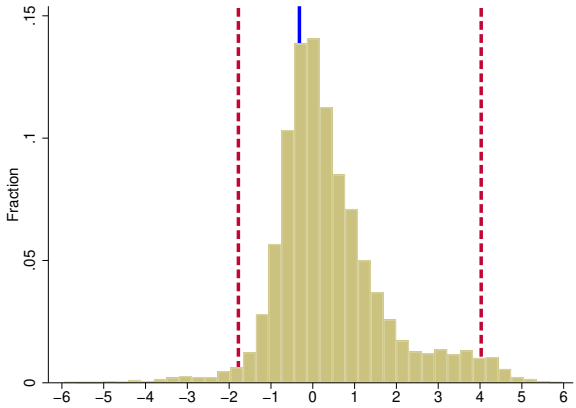
B: T-Statistics

Opioid Overdose Deaths per 100,000



Rank of δ_0: 6,371/10,000
Rank of $|\delta_0|$: 8,536/10,000

C: Coefficients



Rank of T_0: 7,192/10,000
Rank of $|T_0|$: 7,115/10,000

D: T-Statistics

Notes: The dashed vertical lines represent the 2.5 and 97.5 percentiles of the placebo t-statistics. The solid blue vertical line is the t-statistic when the five triplicate states are assigned correctly. The x-axis represents the value of the t-statistics; the y-axis represents the density. t-statistics are calculated using clustered (by state) standard errors as recommended by MacKinnon and Webb (2020). For this analysis, we regress the overdose rate on state fixed effects, time fixed effects, and Non-Triplicate $\times 1(t = 1995)$. The sample is limited to years 1991 and 1995. Regressions are population-weighted.

Table E1: Table I with Clustered (not bootstrapped) Confidence Intervals

	Overdose Deaths per 100,000			
Non-Triplicate ×	(1)	(2)	(3)	(4)
1996-2000	1.173***	1.290***	1.267**	1.229**
	[0.426, 1.921]	[0.594, 1.987]	[0.270, 2.263]	[0.217, 2.241]
2001-2010	3.667***	4.488***	3.561***	3.232***
	[1.819, 5.515]	[2.796, 6.179]	[1.574, 5.548]	[1.349, 5.115]
2011-2017	6.061***	7.806***	5.240***	4.714***
	[3.372, 8.751]	[5.150, 10.461]	[3.305, 7.176]	[2.387, 7.041]
Weighted	No	Yes	Yes	Yes
Covariates	No	No	Yes	Yes
Region-Time Dummies	No	No	No	Yes
N	1,377	1,377	1,377	1,377
	Opioid Overdose Deaths per 100,000			
Non-Triplicate ×	(5)	(6)	(7)	(8)
1996-2000	0.634**	0.620**	0.725	0.821*
	[0.078, 1.191]	[0.067, 1.173]	[-0.148, 1.598]	[-0.024, 1.666]
2001-2010	2.614***	2.940***	2.081**	2.271**
	[1.278, 3.949]	[1.667, 4.212]	[0.227, 3.935]	[0.501, 4.041]
2011-2017	5.002***	5.899***	3.334***	3.284**
	[2.212, 7.792]	[2.903, 8.895]	[1.403, 5.264]	[1.019, 5.550]
Weighted	No	Yes	Yes	Yes
Covariates	No	No	Yes	Yes
Region-Time Dummies	No	No	No	Yes
N	1,377	1,377	1,377	1,377

Notes: ***Significance 1%, **Significance 5%, *Significance 10%. This table replicates Table I 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 year fixed effects. Covariates include the fraction non-Hispanic White, fraction non-Hispanic Black, fraction Hispanic, log of population, fraction with college degree, fraction ages 25-44, fraction ages 45-64, and fraction ages 65+.

F Extrapolation Exercise

We consider a hypothetical experiment in which OxyContin was never launched and promoted to estimate how much of the national growth in drug overdose deaths can be attributed to OxyContin's introduction. This back-of-the-envelope extrapolation is a partial equilibrium exercise. To make this calculation, we need to scale the event-study mortality estimates (Figure IV, Panel B) by the difference in initial OxyContin exposure between non-triplicate and triplicate states. This will allow us to quantify the relationship between one unit of initial OxyContin exposure and overdose deaths in each year. We then apply these estimates to the national trend in overdose deaths, given national rates of initial OxyContin exposure, to extrapolate how many deaths are attributable to OxyContin's introduction in each year. Finally, we subtract off these deaths from the national trend in overdose deaths to produce a counterfactual trend showing how many deaths would have occurred in the absence of OxyContin's introduction.

In order to estimate differences in "exposure" to OxyContin's initial launch across triplicate and non-triplicate states, we use the 2000 ARCOS OxyContin supply, as measured in morphine equivalent doses (MEDs). We select 2000 since it is the first year available in the ARCOS data and also to allow OxyContin supply to reach a "steady state" during its initial launch period. Figure III (Panel A) shows that, in 2000, non-triplicate states had 1.14 OxyContin MEDs per capita compared to 0.43 MEDs per capita for triplicate states for a difference of 0.71 MEDs. Thus, we assume that the mortality differences presented in Figure IV (Panel B) are due to the initial difference of 0.71 MEDs per capita. For example, in 2017, we estimate that non-triplicate states experienced an additional 11.3 drug overdose deaths per 100,000 people relative to triplicate states. These additional deaths are due to the additional initial OxyContin exposure in these states (or 0.71 MEDs per capita). This implies that one additional OxyContin MED per capita led to an additional 15.9 (11.3/0.71) deaths per 100,000 in 2017. We can repeat this calculation to estimate the impact of one additional OxyContin MED per capita for each year in the post-period using the estimates from Figure IV (Panel B).

Next, we extrapolate these estimates to the national trend of drug overdose deaths (shown in Figure I). In 2000, the national rate of OxyContin MEDs per capita was 0.92. Thus, we need to scale our estimates of the impact of each MED by 0.92 to estimate the number of national deaths attributable to OxyContin. Returning to our example, in 2017, we estimate that OxyContin's launch and promotion led to an additional 14.6 ($\frac{11.3}{0.71} \times 0.92$) overdose deaths per 100,000 nationally.

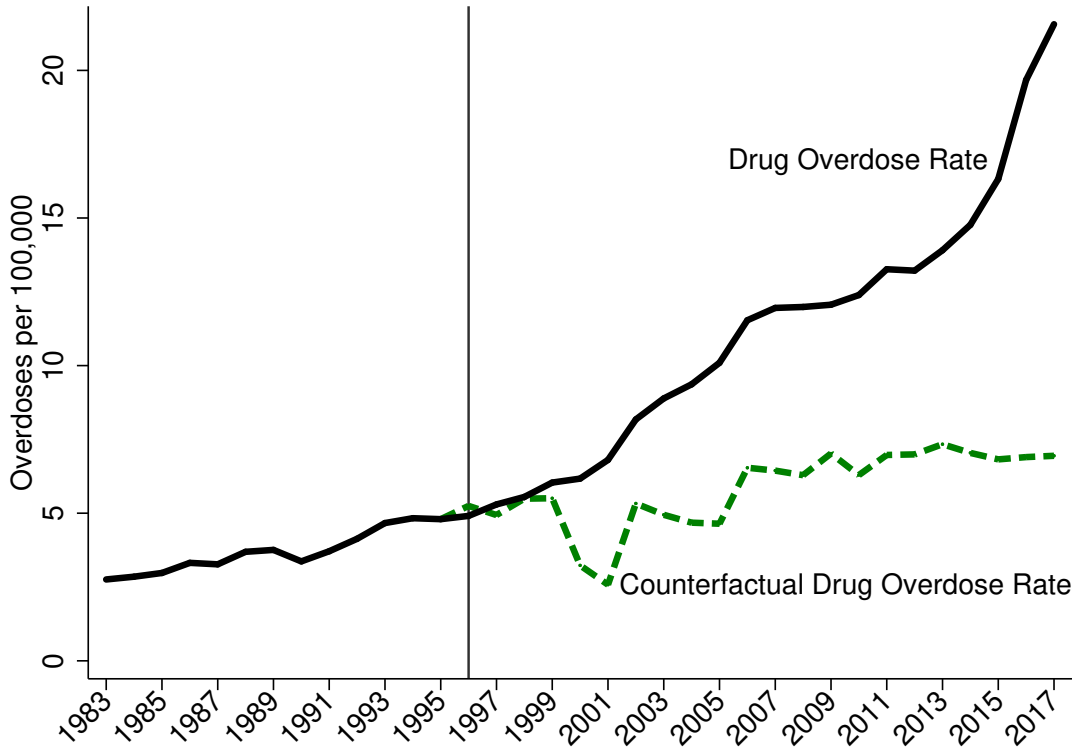
We rescale all of the Figure IV (Panel B) estimates in the post-period by 0.92/0.71 to calculate the number of deaths attributable to OxyContin's launch. Then we subtract off these estimates from the trend line in Figure I to plot the resulting counterfactual national overdose death rate trend (see Figure F1) in which we "eliminate" OxyContin's introduction (i.e., decreasing initial national OxyContin exposure from 0.92 MEDS to 0 MEDs). After subtracting off this estimate of the impact of OxyContin, we find that the overdose death

rate would have grown by 1.44 overdoses per 100,000, comparing the average overdose rate for the post-period (1996-2017) to the pre-period (1991-1995), in the absence of OxyContin. Instead, it increased by an average of 6.89 deaths per 100,000. This extrapolation suggests that the introduction of OxyContin explains 79% of the rise in the overdose death rate since 1996. Thus, in the absence of OxyContin, overdose death rate levels would be substantially lower and unlikely to rise to the level of an opioid "crisis." In fact, the counterfactual overdose rate does not rise above the 1995 overdose death rate until 2006.

This extrapolation exercise does *not* assume that the overdose death rate differences between triplicate and non-triplicate states are only due to differences in per capita OxyContin MEDs. Instead, we use the ARCOS data as a proxy for "exposure," which implicitly encapsulates all by-products (e.g., promotion of strong opioids) and spillovers (e.g., to other oxycodone products and illicit drugs in the later years of the opioid crisis) resulting from this initial differential exposure. The main assumption is that observed differences in initial OxyContin supply reflect differences in "exposure" to promotional activity, supply, etc. Moreover, this exercise assumes that the effect of OxyContin exposure is linear in MEDs. We are extrapolating out-of-sample (i.e., no part of the United States was unexposed to OxyContin), which could affect the accuracy of our estimates if there are important non-linearities in the relationship between exposure and long-term overdose death rates. However, it is difficult in our context to estimate any non-linear relationships.

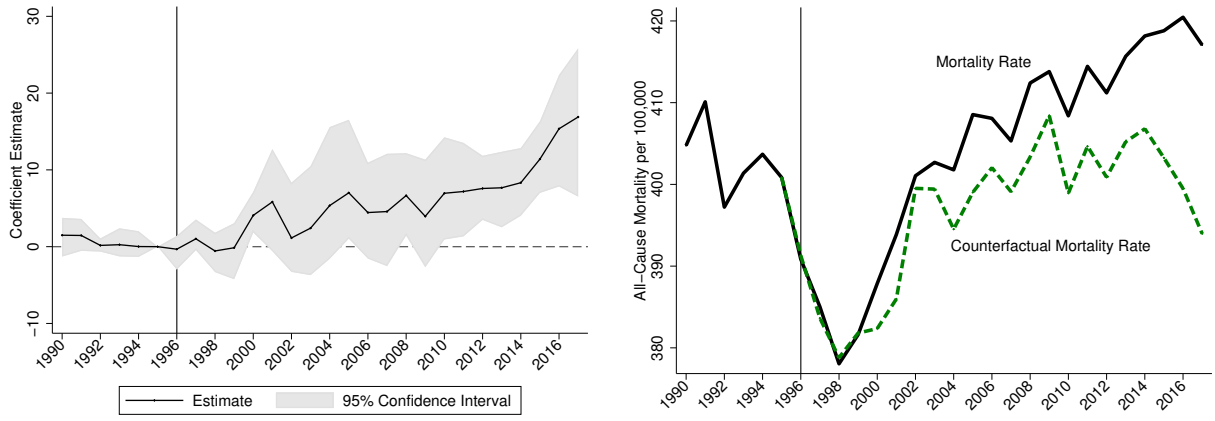
We conduct a similar extrapolation exercise for all-cause mortality focusing on non-Hispanic Whites ages 45-54, a population highlighted in Case and Deaton (2015) as experiencing the largest reversal in mortality trends after 1998. We first replicate our main event study in Panel A of Figure F2 for overdose death rates for this demographic group. The estimates tend to be larger (and noisier) relative to the overall estimates in Figure IV, Panel B. We then use these estimates to perform the same extrapolation exercise as performed above; we subtract off the estimated effect of OxyContin from the all-cause mortality rate. The all-cause mortality rate and this counterfactual rate are shown in Panel B of Figure F2. We find that the mortality reversal would have occurred even in the absence of OxyContin; however, OxyContin does explain a large share of the mortality rise. Relative to 1998, all-cause mortality for this demographic group increased by 29.4 deaths per 100,000 over the 1999-2017 time period. We estimate that OxyContin can explain 8.9 deaths per 100,000, or 30% of the total increase in all-cause mortality. Thus, for this population, we estimate that OxyContin's introduction can explain about one-third of the rise in all-cause mortality since 1998.

Figure F1: Estimated National Drug Overdose Death Rate in Absence of OxyContin



Notes: The "Drug Overdose Rate" is the national time series, previously shown in Figure I, for all drug overdose deaths per 100,000. The "Counterfactual" rate is the result from an extrapolation using the estimates presented in Figure IV, Panel B. Those estimates refer to the effect of differences in initial OxyContin exposure, which we define as the difference in OxyContin supply in 2000 between non-triplicate and triplicate states, equal to 0.71 morphine equivalent doses (MEDs) per capita. In 2000, the national OxyContin supply was 0.92 MEDs per person. So, we multiply each estimate by $\frac{0.92}{0.71}$. We subtract these estimates from the observed national overdose rate. These are our estimates of what would have happened if the United States had 0 MEDs of OxyContin. We graph the population-weighted average. We do not include pre-1996 counterfactual rates since (as should be clear from Figure IV) the counterfactual rate and observed rate are similar.

Figure F2: All-Cause Mortality for Non-Hispanic Whites Ages 45-54 (1990-2017)



A: Drug Overdose Deaths (Event Study)

B: All-Cause Mortality

Notes: The outcome in Panel A is all drug overdose deaths per 100,000 for non-Hispanic Whites ages 45-54. We estimate the event study as in Figure IV.B. The sample is limited to 1990-2017 due to the availability of ethnicity information in the NVSS. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in 1995. The regression is population-weighted. Panel B plots the all-cause mortality rate for non-Hispanic Whites ages 45-54. In addition, we plot the counterfactual rate which is the observed all-cause mortality rate minus the estimated impact of OxyContin's introduction. We estimate the impact of OxyContin's introduction using the same approach as in Figure F1. In 2000, non-triplicate states had 1.14 morphine equivalent doses (MEDs) per person, while triplicate states had only 0.43 MEDs per capita. In 2000, the national OxyContin supply was 0.92 MEDs per person. So, we multiply each estimate by $\frac{0.92}{0.71}$. We subtract these estimates from the observed national overdose rate. These are our estimates of what would have happened if the United States had 0 MEDs of OxyContin. We graph the population-weighted average. We do not include pre-1996 counterfactual rates since (as should be clear from Panel A) the counterfactual rate and observed rate are similar.

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