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

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August 2021

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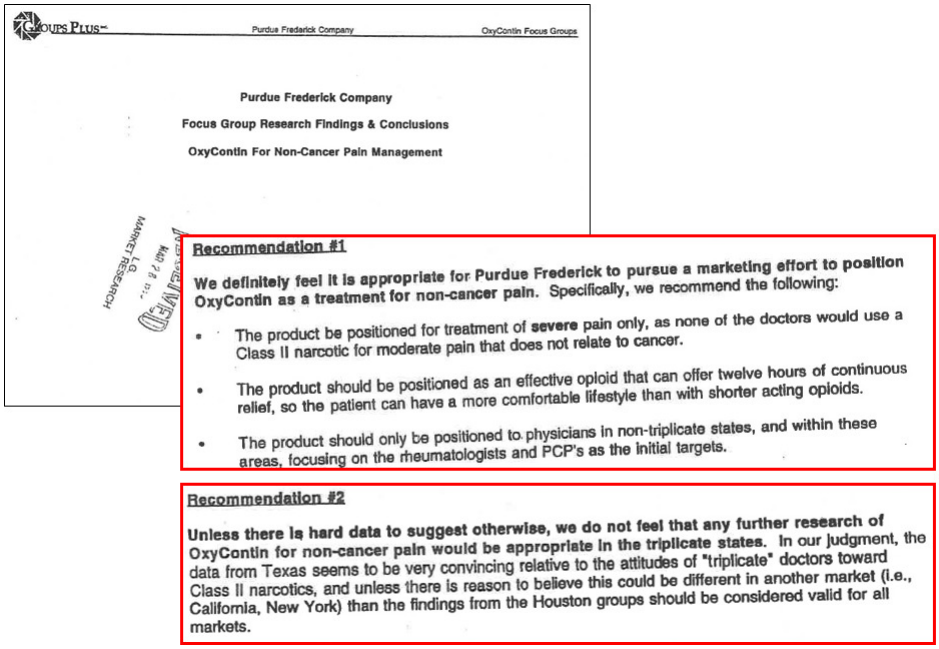


Purdue Fredarick Company — OxyContin Focus Groups

Purdue Frederick Company

Focus Group Research Findings & Conclusions

OxyContin For Non-Cancer Pain Management

Recommendation #1

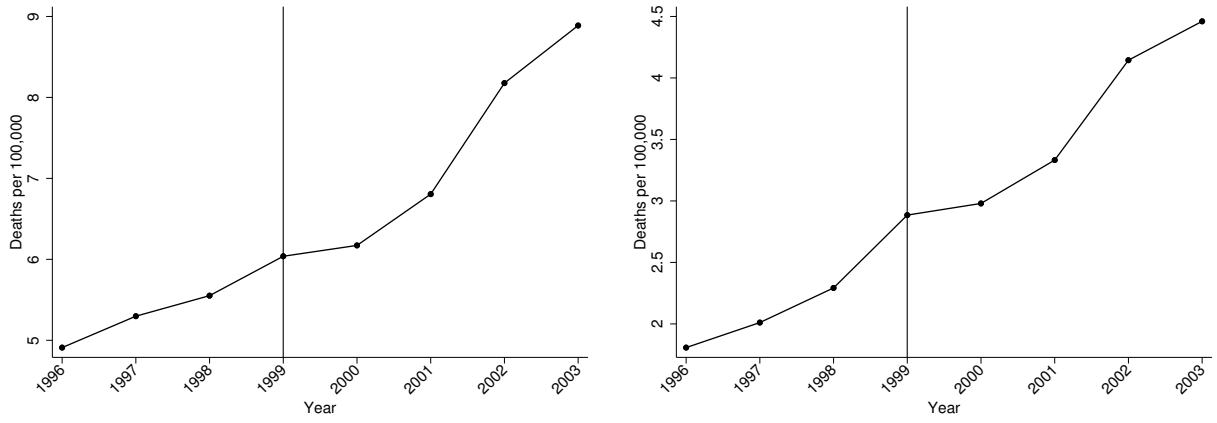
We definitely feel it is appropriate for Purdue Frederick to pursue a marketing effort to position OxyContin as a treatment for non-cancer pain. Specifically, we recommend the following:

- 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.

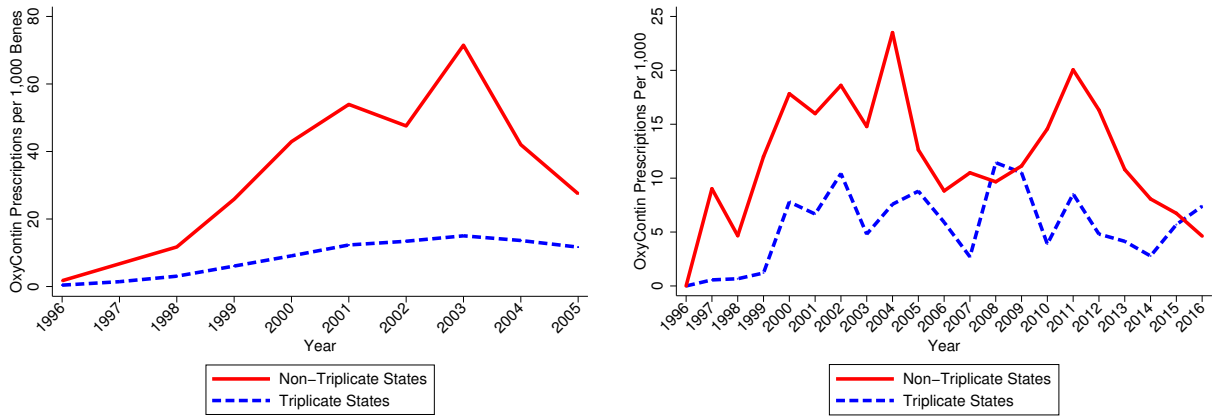
Figure A2: ICD Code Change in 1999



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

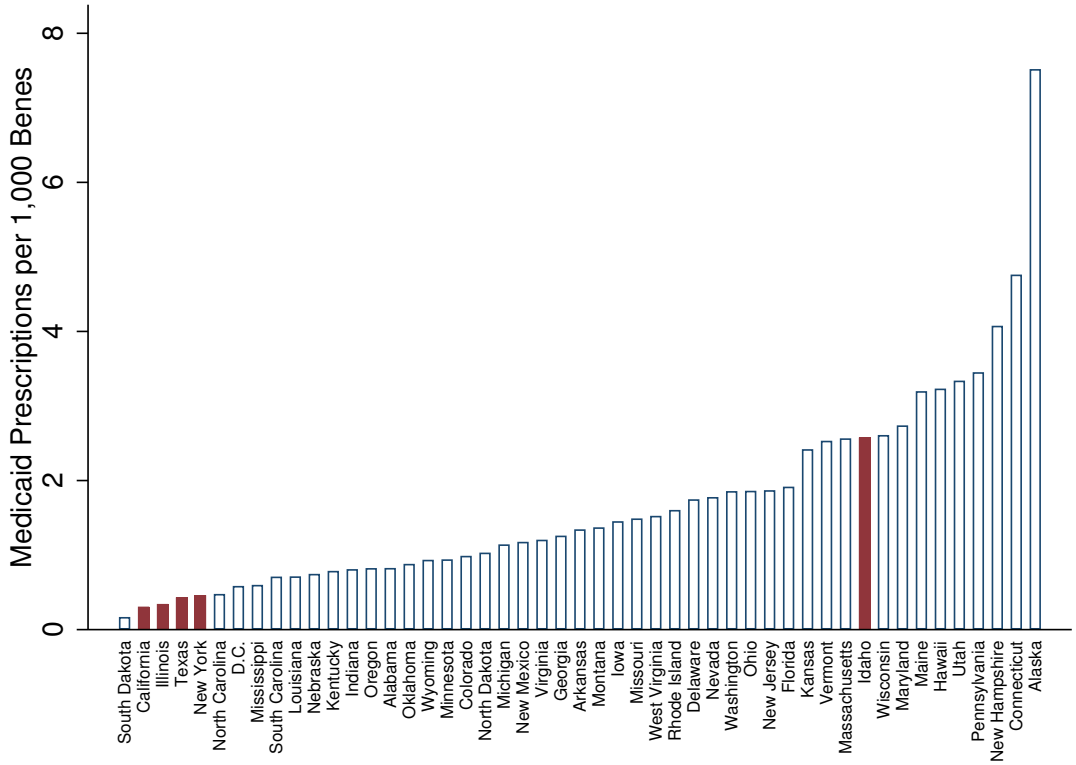


A: OxyContin Prescriptions (Medicaid) B: OxyContin Prescriptions (MEPS)

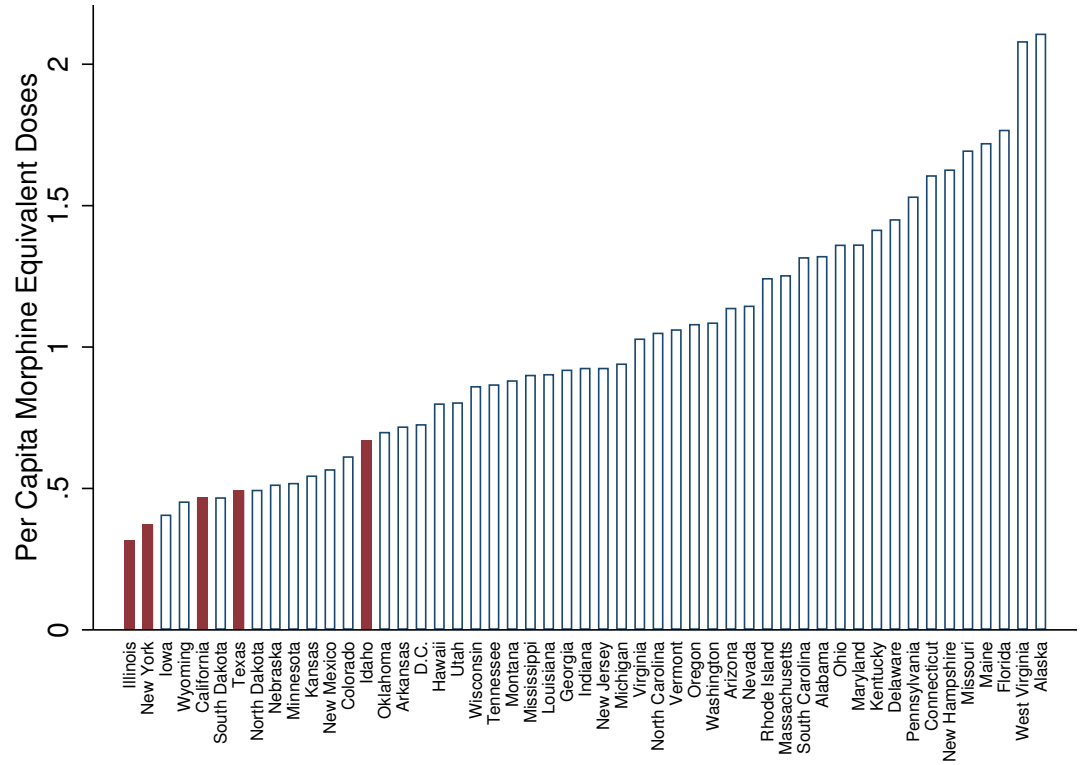
Notes: In Panel A, we report the number of prescriptions per 1,000 beneficiaries from the Medicaid SDUD. We end this time series in 2005 due to the introduction of Medicare Part D. Prescribing rates are annualized for states not reporting for all four quarters in a year. In Panel B, we report the number 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

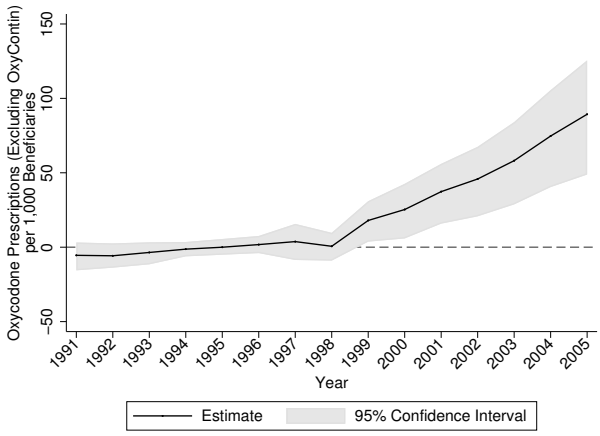


B. ARCOS Per Capita OxyContin Morphine Equivalent Doses in 2000



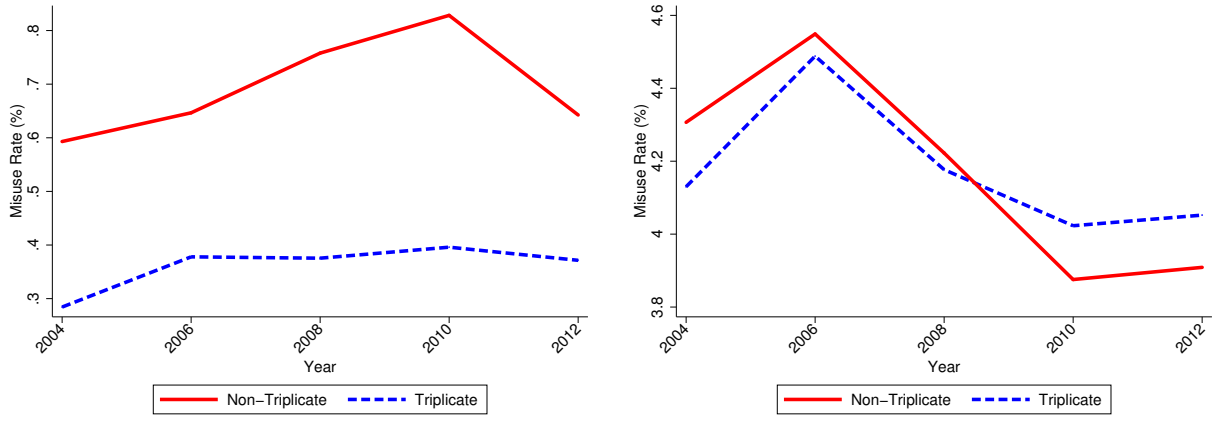
Notes: Panel A uses SDUD data; Panel B uses ARCOS data. Not all states report in all quarters in the SDUD. In such cases, we annualize their prescribing rates. Arizona and Tennessee are excluded from Panel A due to insufficient data in 1996.

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 and states without any missing years of data ($N = 615$). For states reporting less than 4 quarters in year, we annualize prescribing rates. 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



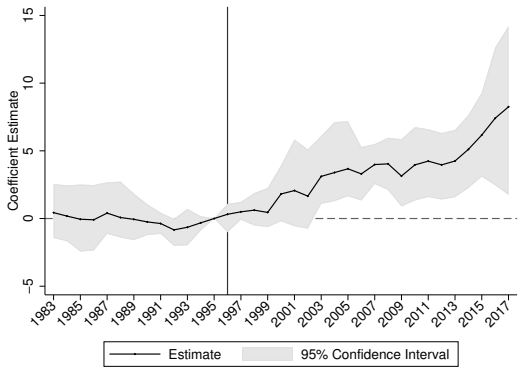
A: OxyContin

B: Pain Relievers excluding OxyContin

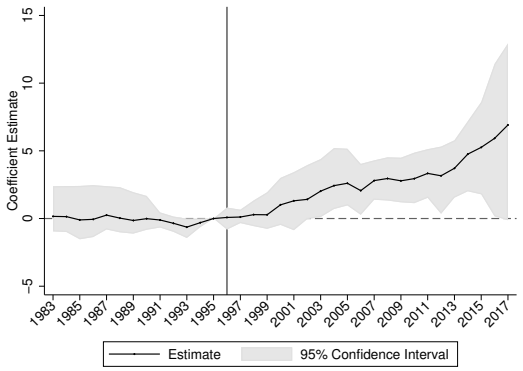
Notes: Misuse rates are calculated from the National Survey on Drug Use and Health. Each year refers to a two-year wave such that "2004" refers to 2004-2005, "2006" refers to 2006-2007, etc.

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

Unweighted, Without Covariates

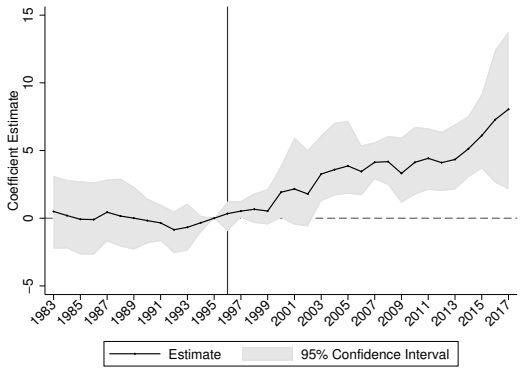


A: All Drug Overdoses per 100,000

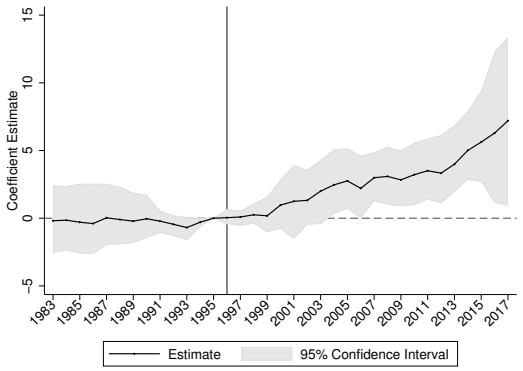


B: Opioid Overdoses per 100,000

Unweighted, With Covariates

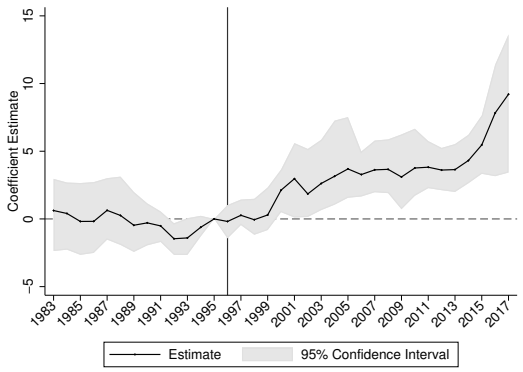


C: All Drug Overdoses per 100,000

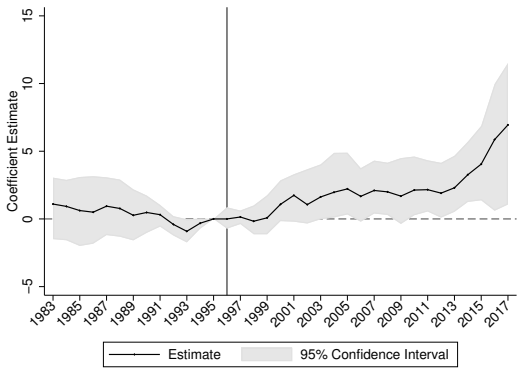


D: Opioid Overdoses per 100,000

Weighted, With Covariates



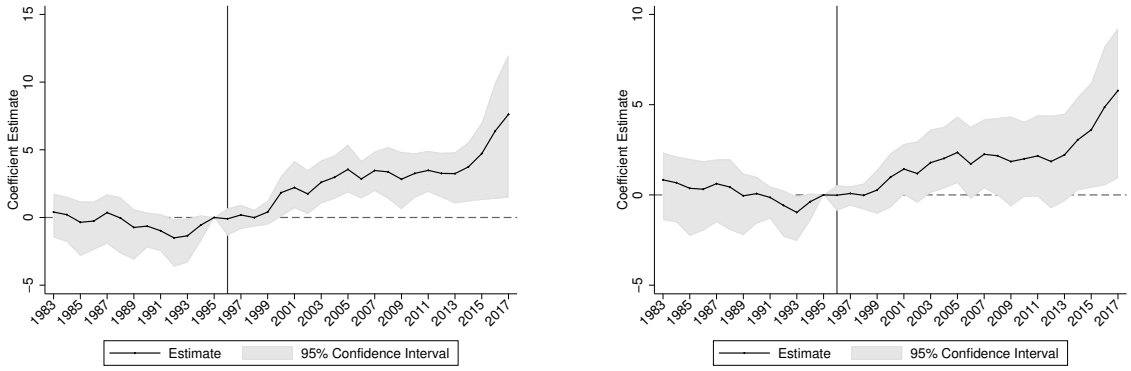
E: All Drug Overdoses per 100,000



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.

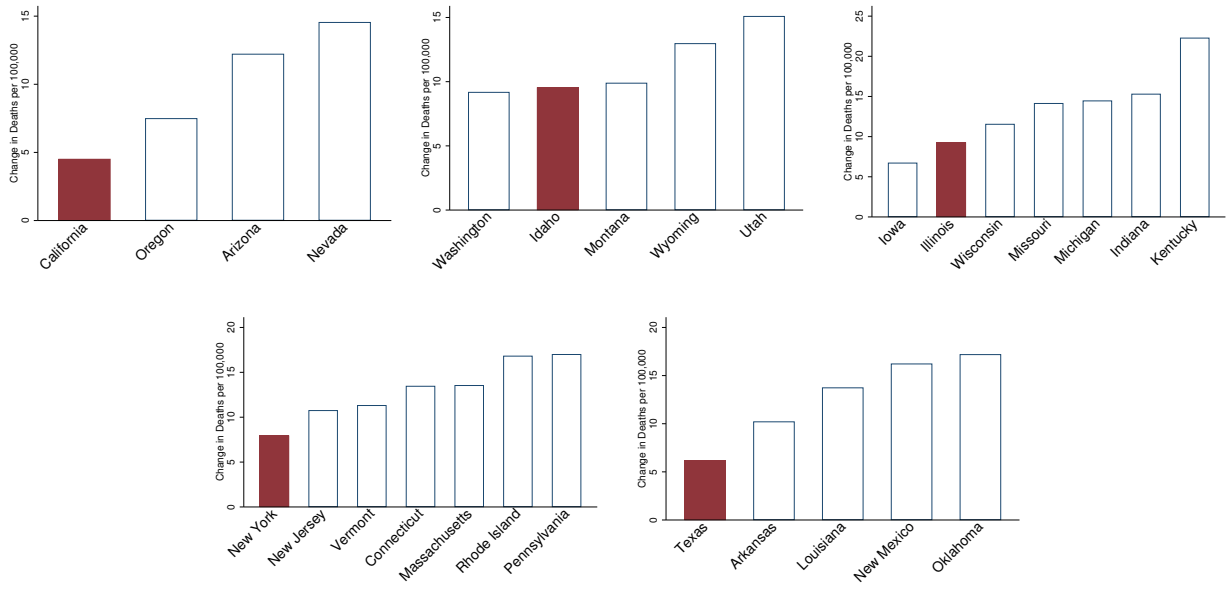
Figure A8: Event Study: Drug Overdose Death Rate with Census Region × Year Interactions



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

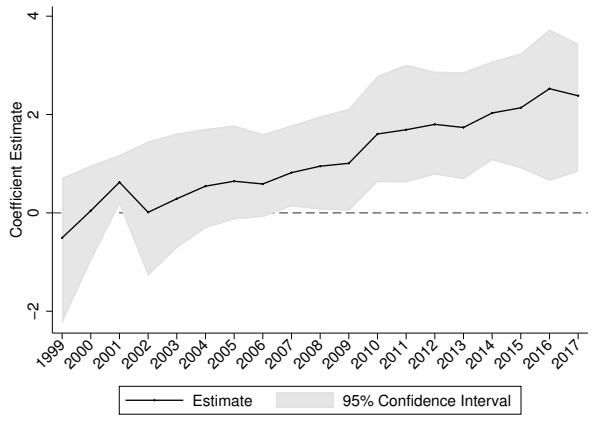
Notes: We use geocoded NVSS data to construct all drug overdose and opioid overdose deaths per 100,000. See text for exact ICD codes used in each period. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to 0 in 1995. All models include state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

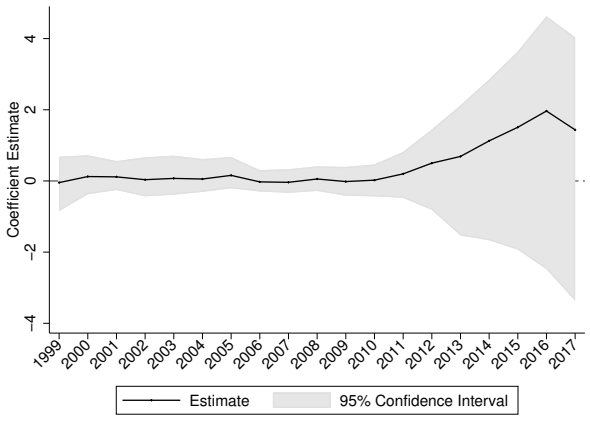


Notes: We construct the change in all drug overdose deaths per 100,000 for 2008-2017 relative to 1986-1995. We plot this change for each triplicate state relative to its bordering states.

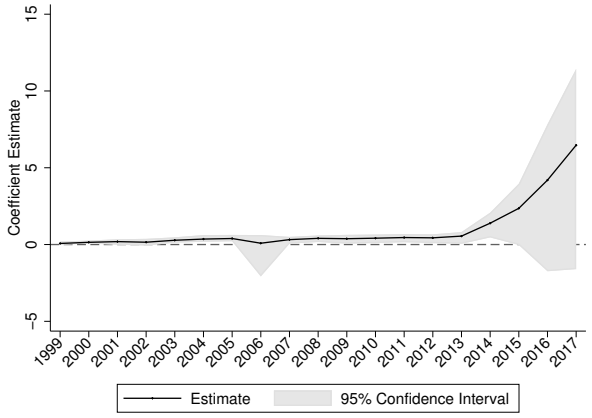
Figure A10: Overdose Death Rate Differences by Type of Opioid for 1999-2017



A: Natural/Semisynthetic Opioids (T40.2)



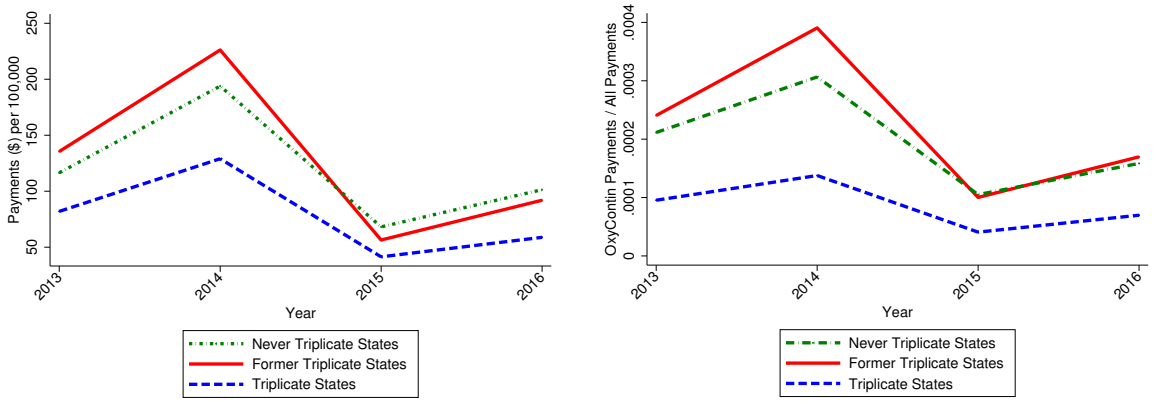
B: Heroin (T40.1)



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.

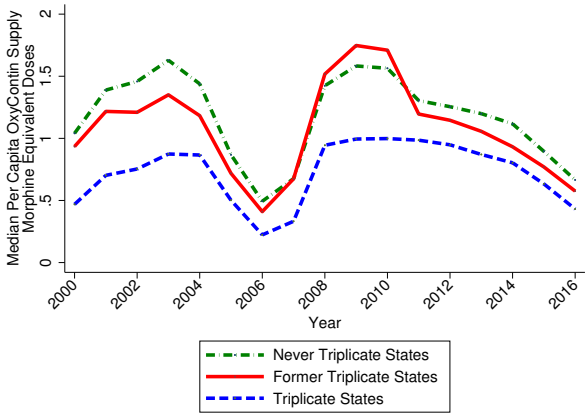
Figure A11: OxyContin Promotional Payments to Physicians – Former Triplicates



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

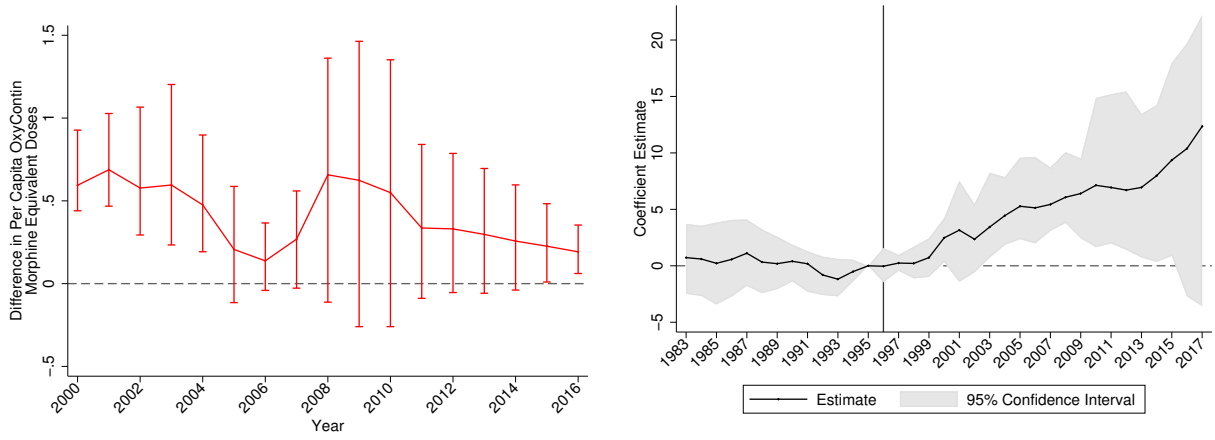
Notes: We used CMS Open Payments Data to calculate total payments and gifts made to physicians regarding OxyContin. We scaled this measure by population. The outcomes correspond to August 2013 – December 2016. Because the 2013 data only cover a partial year, we annualize the rate in that year. "Triplicate 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

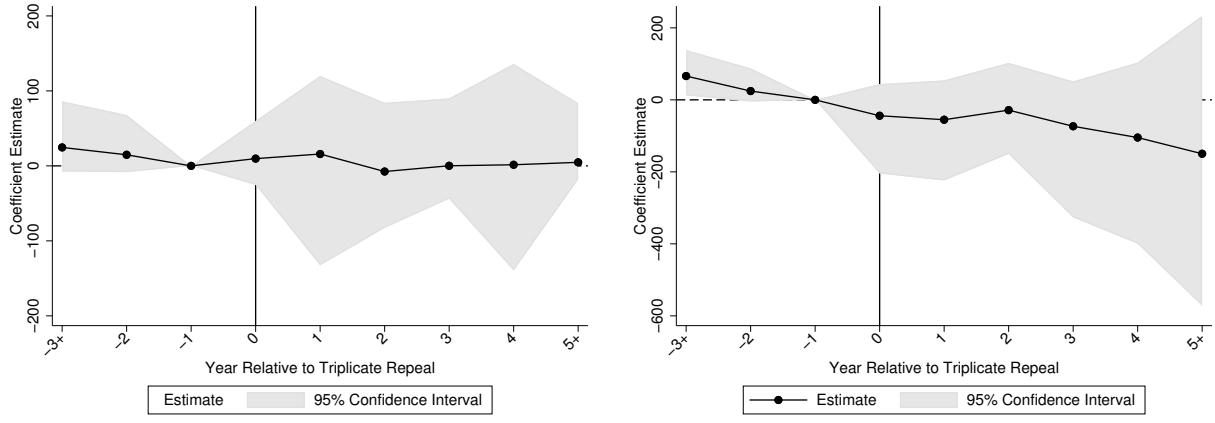


A: OxyContin Distribution

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

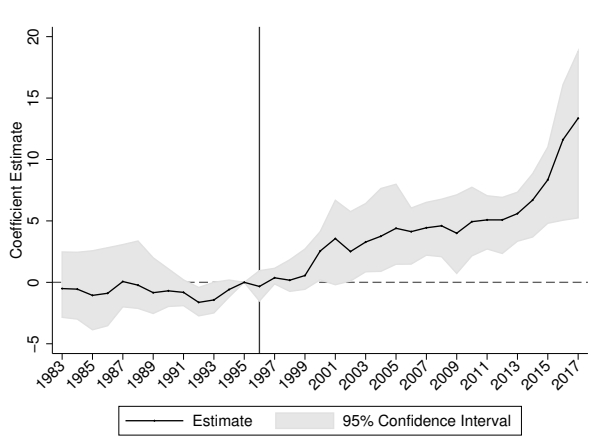


A: OxyContin Prescriptions

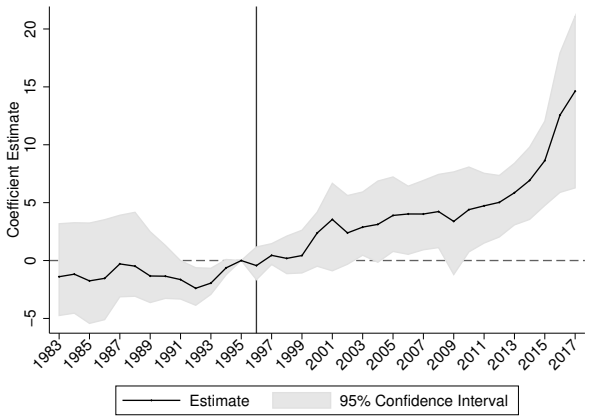
B: Oxycodone Prescriptions

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. We weight by the number of Medicaid beneficiaries. Confidence intervals are generated by a wild bootstrap.

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



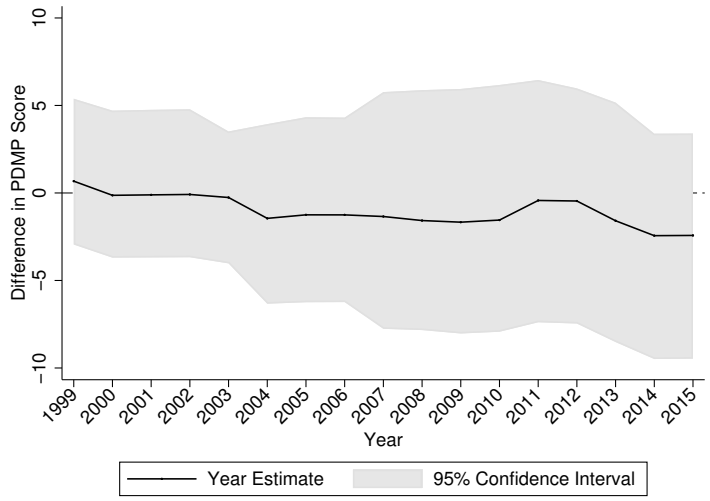
A: Counties of metro areas



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.

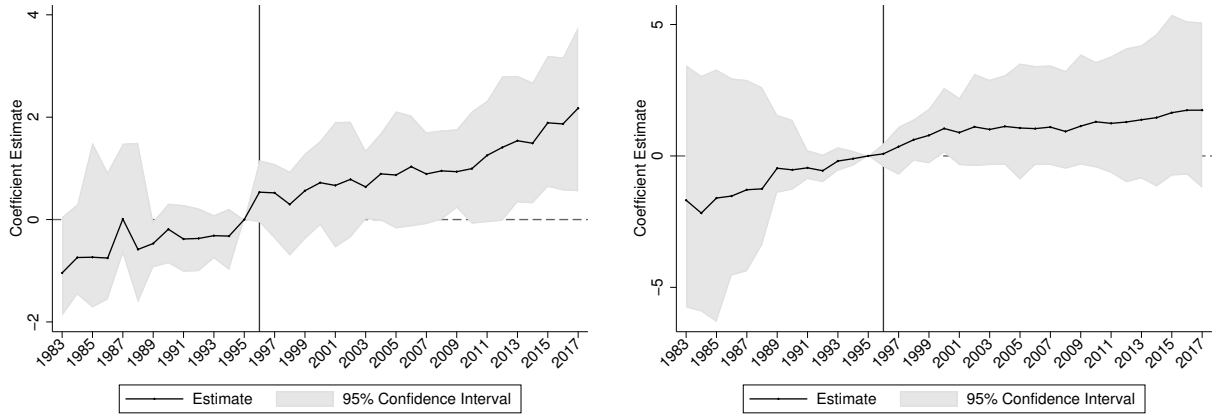
Figure A16: Comparing PDMP Strength by Triplicate State Status



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.

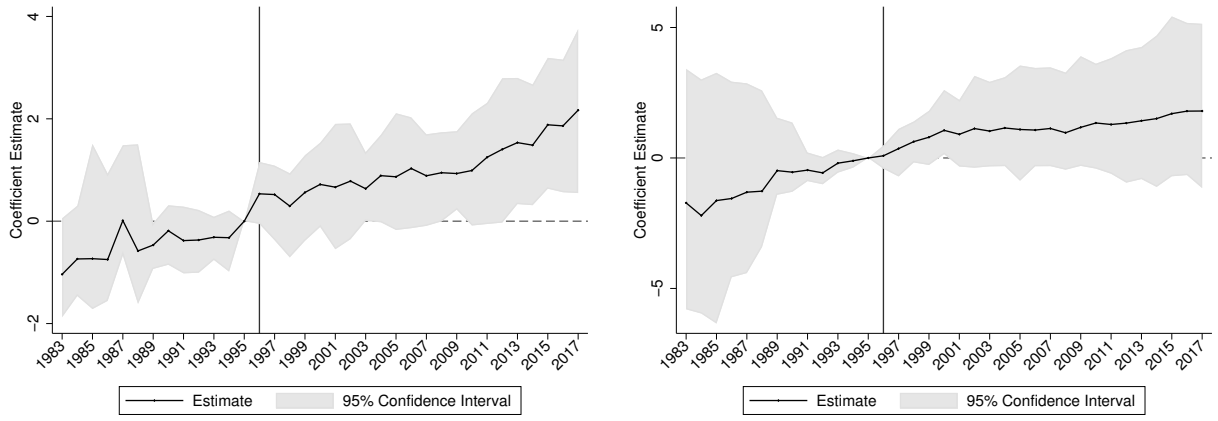
Figure A17: Event Study: Other Deaths of Despair

Main Estimates



A: Suicides B: Alcohol-Related Liver Diseases

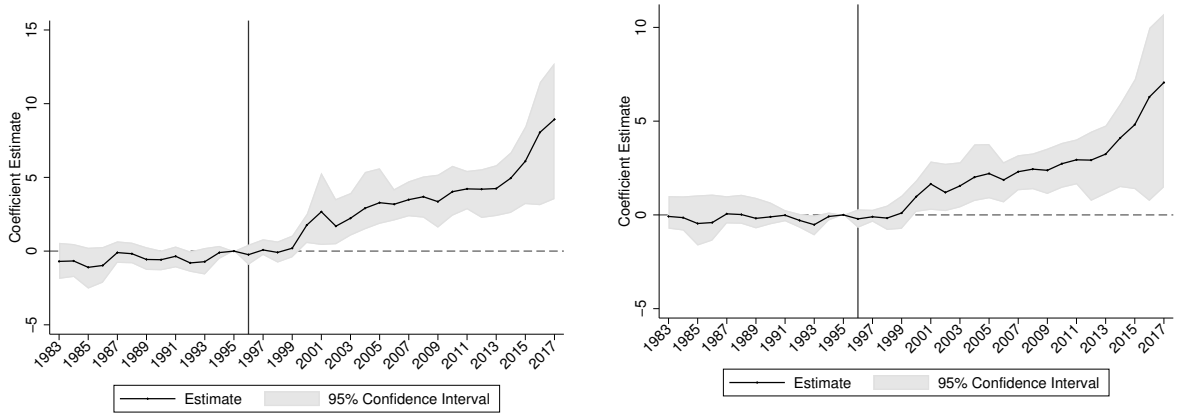
Detrended



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

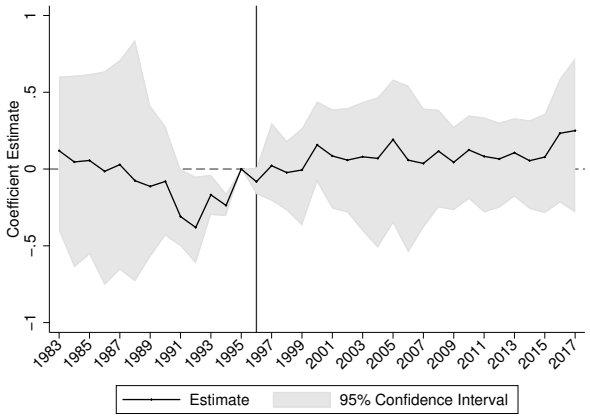


A: Overdose deaths excluding cocaine

B: Opioid overdose deaths excluding cocaine

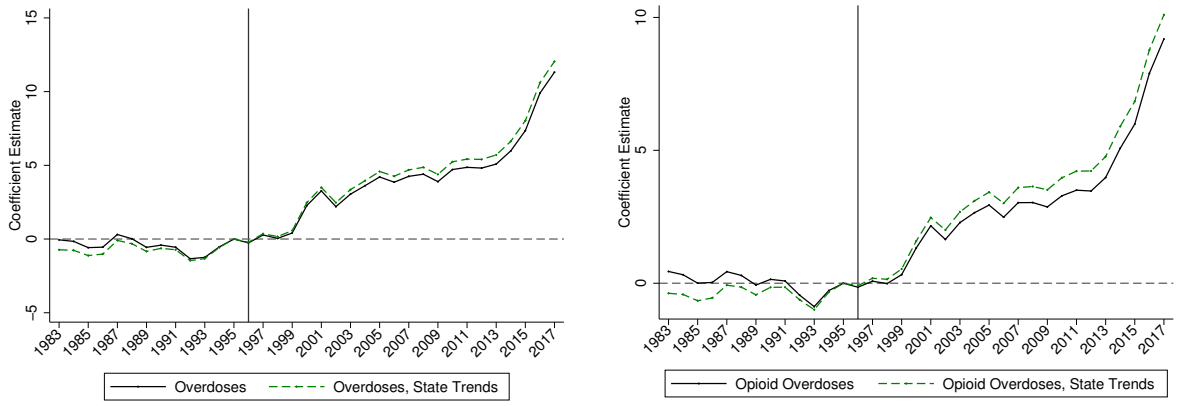
Notes: We use geocoded NVSS data to construct all drug overdose deaths per 100,000 and opioid overdose deaths per 100,000. We exclude overdoses also involving cocaine in both of these measures. Event study estimates include state and year fixed effects. 95% confidence intervals are generated using a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

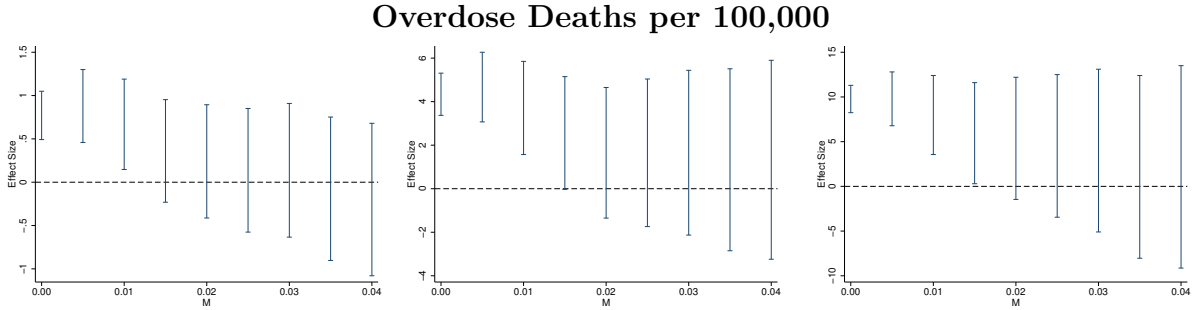
Figure A20: Event Study – Accounting for State-Specific Trends



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.

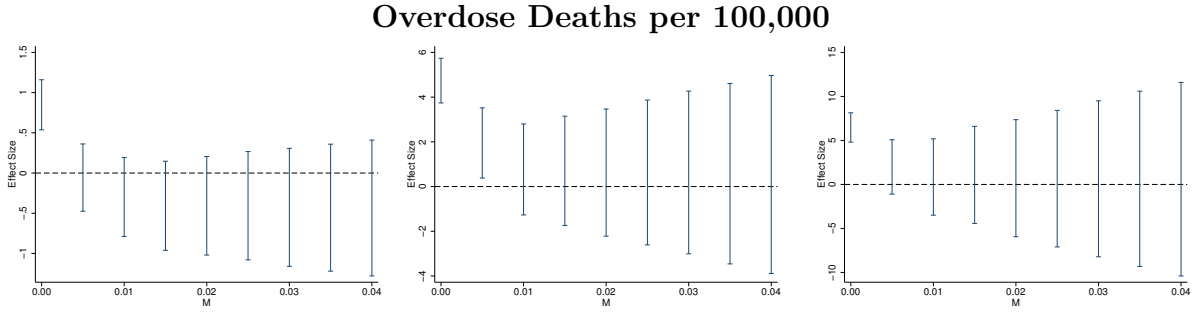
Figure A21: Sensitivity to Non-Parallel Trends



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 similar 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

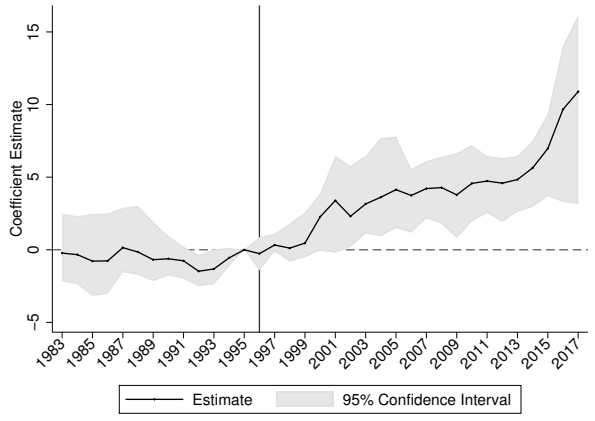
We implement a "leave one out" test to see whether any specific state (triplicate or non-triplicate) is driving the results. To facilitate summarizing the findings from this analysis,

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

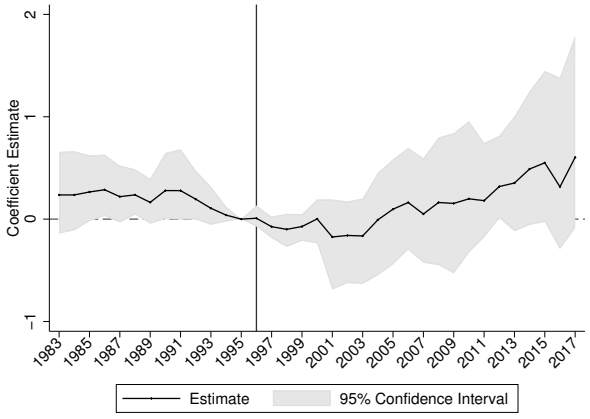
we focus on a specification with *one* post-treatment indicator, instead of the three used throughout the paper. This will make the comparisons across samples more straightforward. In each case, we regress the overdose death rate on state fixed effects, year fixed effects, and 1(Non-Triplicate) $\times$ 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

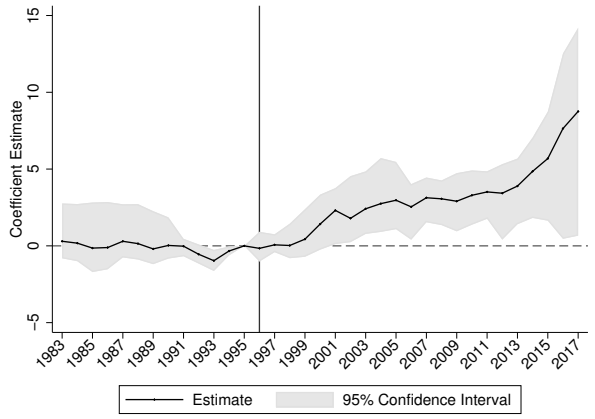


A: Non-Triplicate Effect

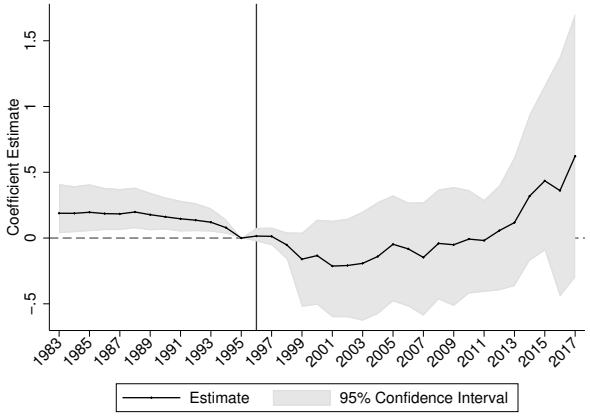


B: Trade Effect

Opioid Overdose Deaths per 100,000



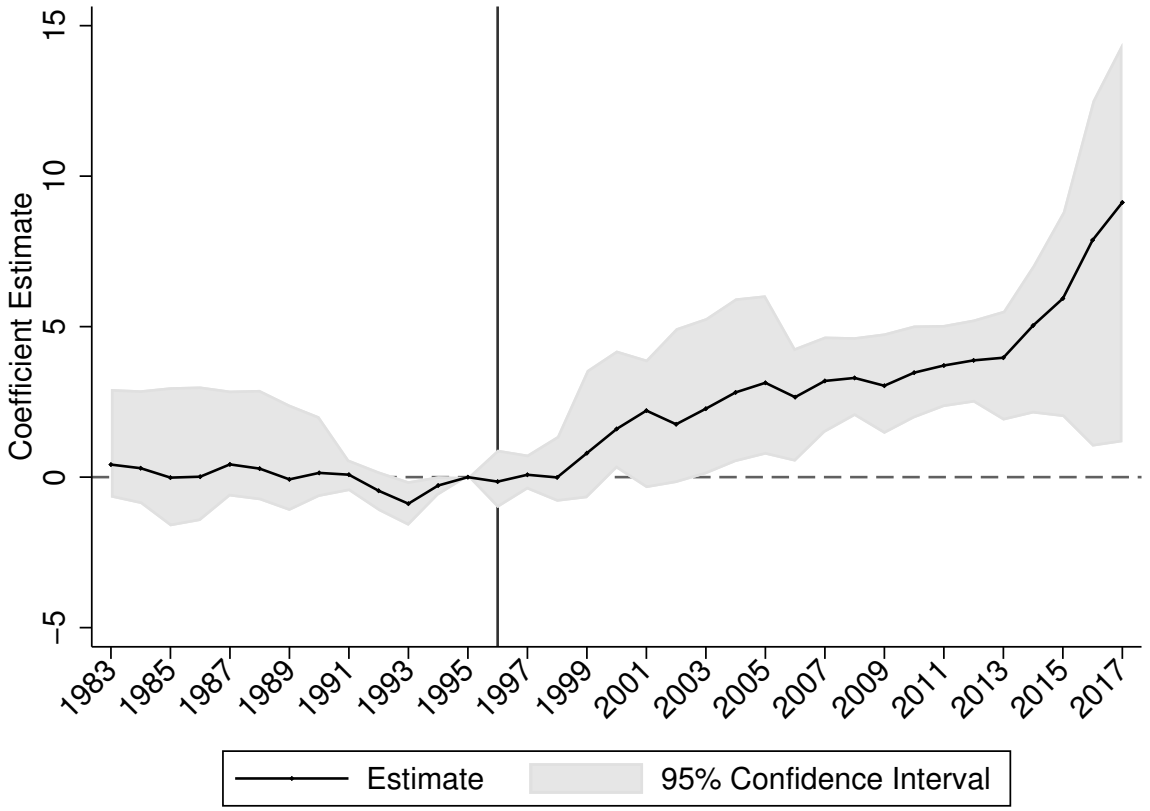
C: Non-Triplicate Effect



D: Trade Effect

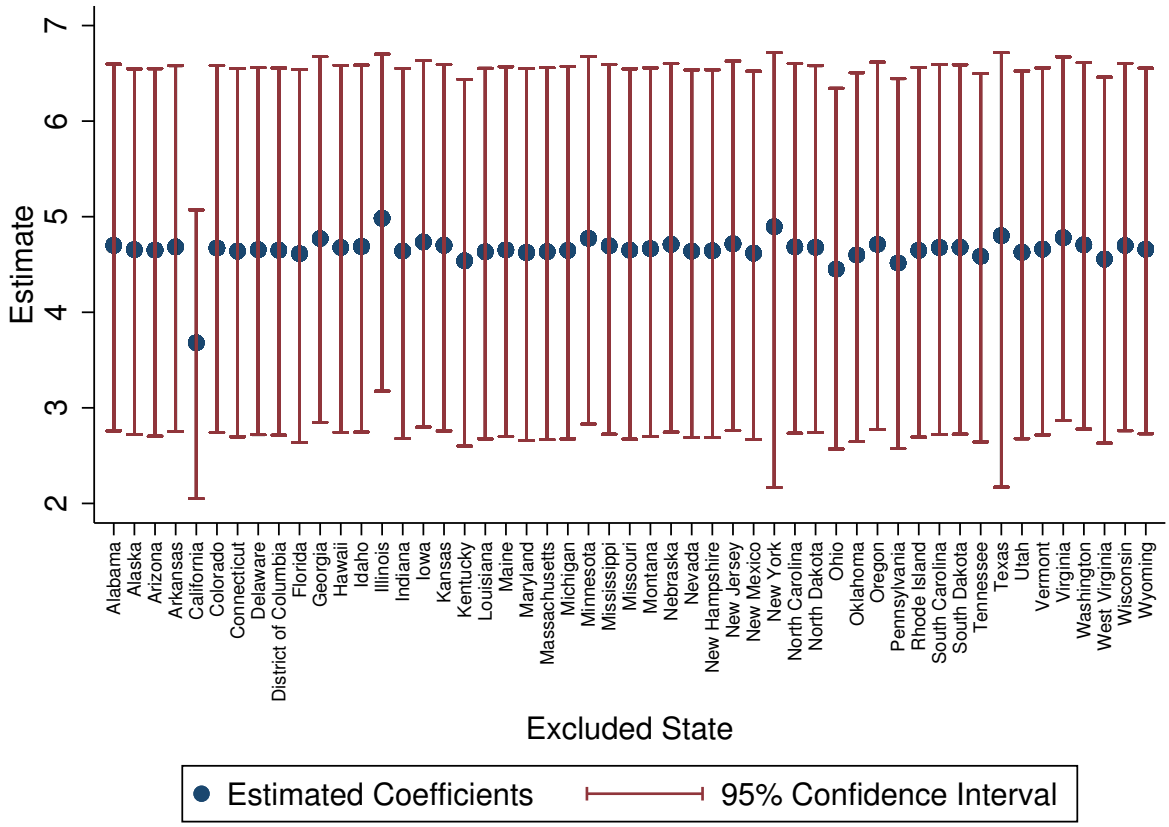
Notes: We use geocoded NVSS data to construct all drug overdose and opioid overdose deaths per 100,000. See text for exact ICD codes used in each period. Panels A and B are estimated jointly. Panel A shows the non-triplicate effect; Panel B shows the effect of exposure to trade liberalization. Panels 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	1.106*	1.269**	1.349**	1.634**
	[-0.155, 2.199]	[0.081, 2.255]	[0.207, 2.294]	[0.447, 2.679]
2001-2010	3.242**	3.600***	3.598**	4.151***
	[0.847, 5.530]	[1.358, 5.673]	[1.104, 5.793]	[1.500, 6.715]
2011-2017	5.046***	5.271***	5.264***	5.637***
	[3.120, 7.000]	[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	0.731	0.721*	0.849*	1.088**
	[-0.264, 1.624]	[-0.294, 1.652]	[-0.139, 1.742]	[0.106, 1.999]
2001-2010	2.094**	2.020*	2.017*	2.549**
	[0.182, 4.290]	[-0.038, 4.234]	[-0.260, 4.406]	[0.194, 5.162]
2011-2017	3.342***	3.285***	3.275***	3.592***
	[1.408, 5.643]	[1.385, 5.536]	[1.546, 5.427]	[1.823, 5.737]
Joint P-Value	0.037	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 report 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.

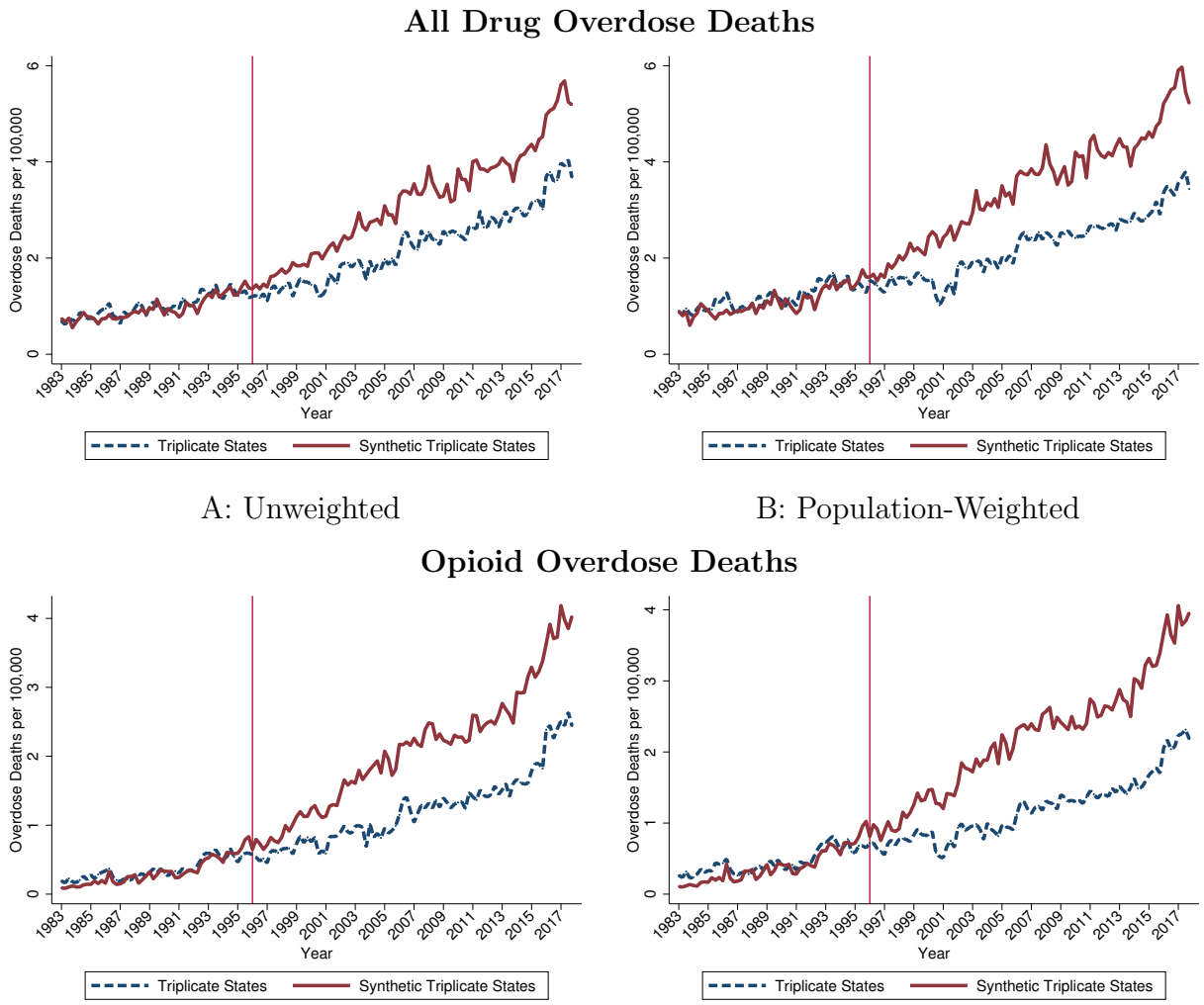
These results suggest that our main estimates are not driven by any initial outcome differences in overdose rates between the triplicate and non-triplicate states. We also compare each state to its synthetic control state, using the same framework as Figure V. These results are provided in Figure D2.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

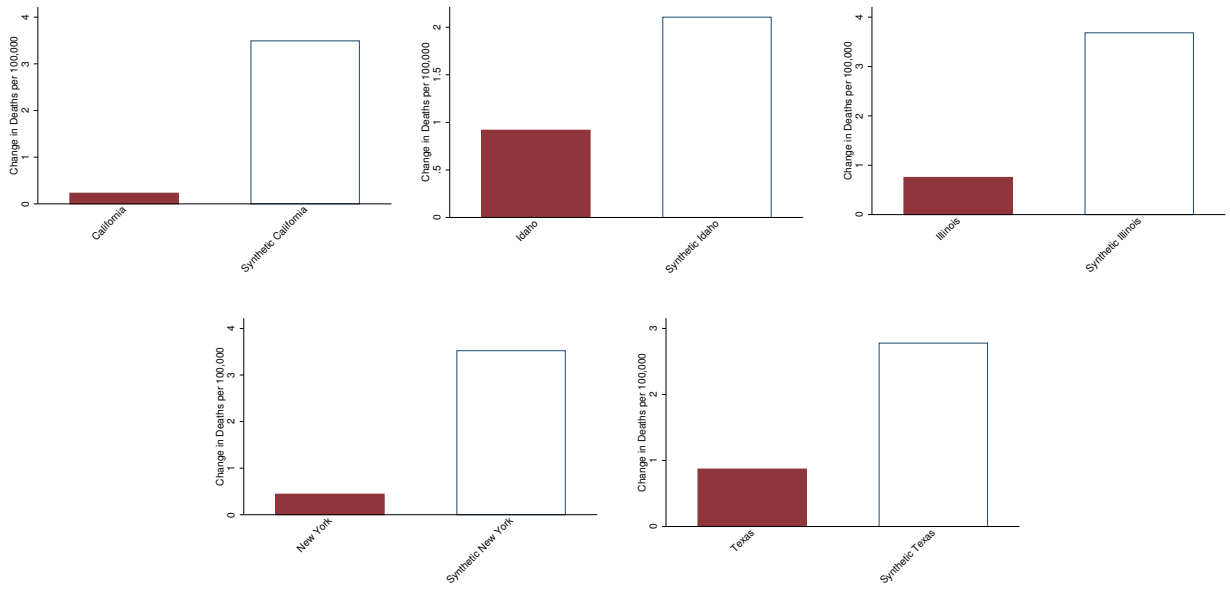
[9] The scales are different due to the use of quarterly overdose rates versus annual. The Table D1 results adjust for this differences to produce more comparable estimates.

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	2.132
	[1 / 1000]	[1 / 1000]
2001-2010	3.669	5.114
	[1 / 1000]	[1 / 1000]
2011-2017	5.014	6.851
	[1 / 1000]	[1 / 1000]
Unweighted/Weighted	Unweighted	Population-Weighted
Non-Triplicate ×	Opioid Overdose Deaths per 100,000 (3)	(4)
1996-2000	1.216	1.510
	[1 / 1000]	[1 / 1000]
2001-2010	3.473	4.111
	[1 / 1000]	[1 / 1000]
2011-2017	5.064	5.708
	[8 / 1000]	[2 / 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 analyses using triplicate variation should not rely on standard error estimates produced by this approach. We provide them here to show that the confidence intervals are substantially smaller. 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.

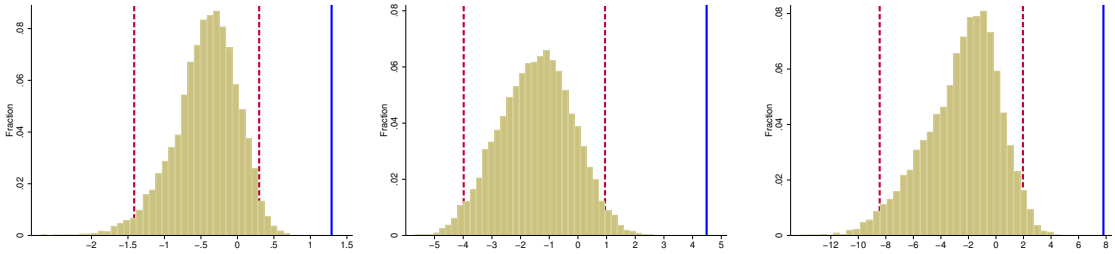
We also compute p-values using permutation-style tests. We randomly assign triplicate status to 5 non-triplicate states and re-estimate equation (2). We repeat this procedure 10,000 times. In each permutation, we estimate the coefficient and t-statistic for each of the three post-periods. Then, we compare 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, for all overdose deaths, 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. 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



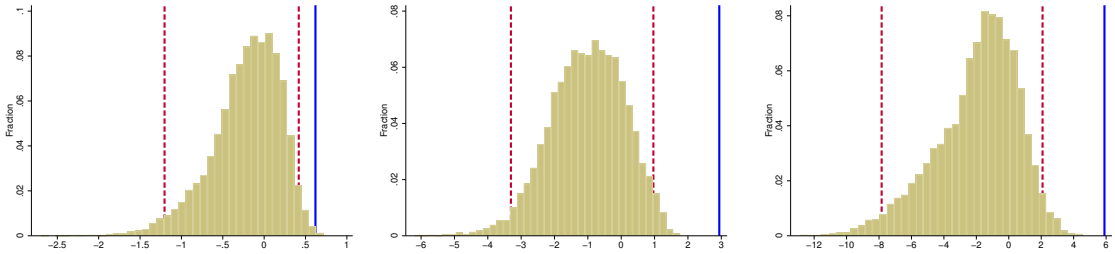
Rank of δ_1: 1/10,000
Rank of $|\delta_1|$: 385/10,000
A: 1996-2000

Rank of δ_2: 1/10,000
Rank of $|\delta_2|$: 66/10,000
B: 2001-2010

Rank of δ_3: 1/10,000
Rank of $|\delta_3|$: 399/10,000
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): $\hat{P}(|\delta_1| < |\delta_1^{(k)}|, |\delta_2| < |\delta_2^{(k)}|, |\delta_3| < |\delta_3^{(k)}|) = 0.0002$

Opioid Overdose Deaths per 100,000



Rank of δ_1: 14/10,000
Rank of $|\delta_1|$: 1599/10,000
D: 1996-2000

Rank of δ_2: 1/10,000
Rank of $|\delta_2|$: 478/10,000
E: 2001-2010

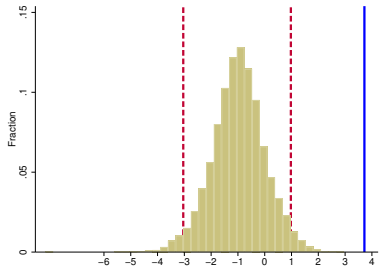
Rank of δ_3: 1/10,000
Rank of $|\delta_3|$: 834/10,000
F: 2011-2017

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): $\hat{P}(|\delta_1| < |\delta_1^{(k)}|, |\delta_2| < |\delta_2^{(k)}|, |\delta_3| < |\delta_3^{(k)}|) = 0.0114$

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.

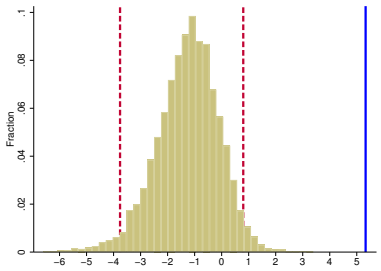
Figure E2: Permutation Tests using T-Statistics

All Drug Overdose Deaths per 100,000



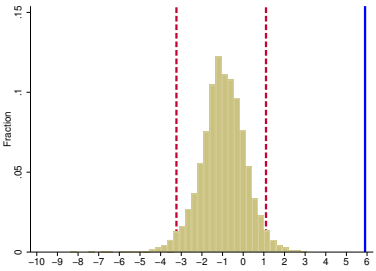
Rank of T_1: 1/10,000
Rank of $|T_1|$: 59/10,000

A: 1996-2000



Rank of T_2: 1/10,000
Rank of $|T_2|$: 35/10,000

B: 2001-2010



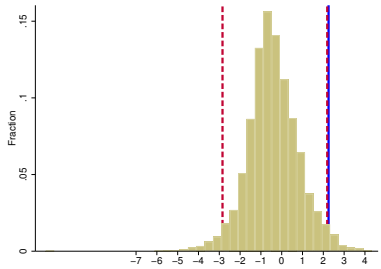
Rank of T_3: 1/10,000
Rank of $|T_3|$: 5/10,000

C: 2011-2017

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

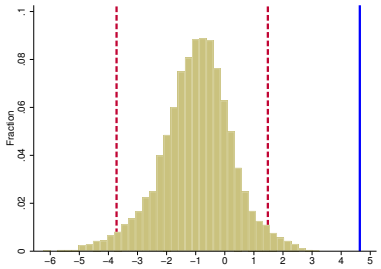
Joint Test (two-sided): $\hat{P}(|T_1| < |T_1^{(k)}|, |T_2| < |T_2^{(k)}|, |T_3| < |T_3^{(k)}|) = 0.0000$

Opioid Overdose Deaths per 100,000



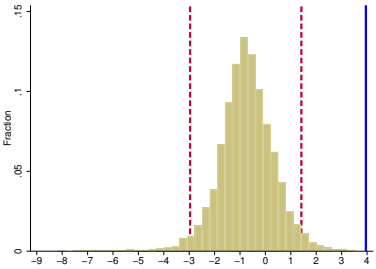
Rank of T_1: 221/10,000
Rank of $|T_1|$: 783/10,000

D: 1996-2000



Rank of T_2: 1/10,000
Rank of $|T_2|$: 60/10,000

E: 2001-2010



Rank of T_3: 1/10,000
Rank of $|T_3|$: 72/10,000

F: 2011-2017

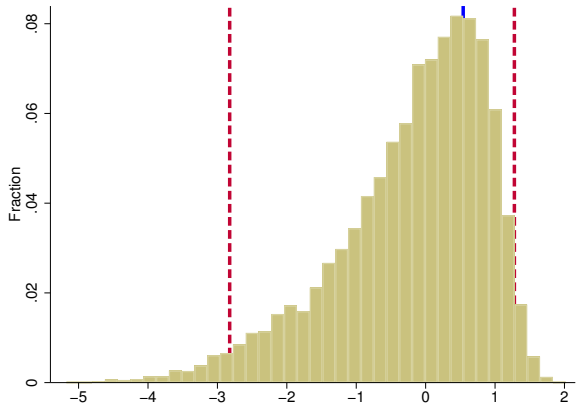
Joint Test (one-sided): $\hat{P}(T_1 < T_1^{(k)}, T_2 < T_2^{(k)}, T_3 < T_3^{(k)}) = 0.0000$

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

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.

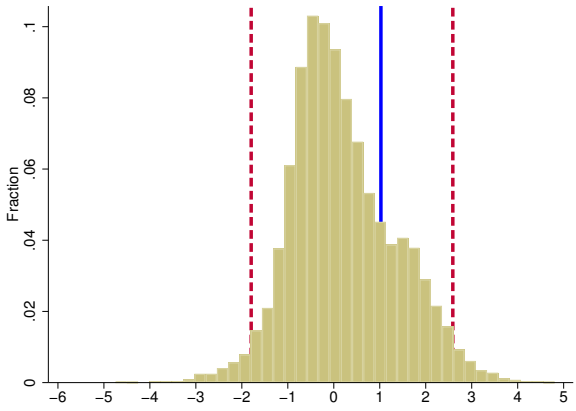
Figure E3: Permutation Tests – Comparing 1991 to 1995

All Drug Overdose Deaths per 100,000



Rank of δ_0: 2,810/10,000
Rank of $|\delta_0|$: 5,943/10,000

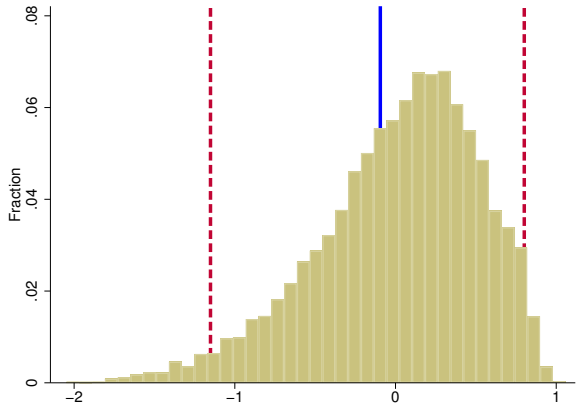
A: Coefficients



Rank of T_0: 2,277/10,000
Rank of $|T_0|$: 3,384/10,000

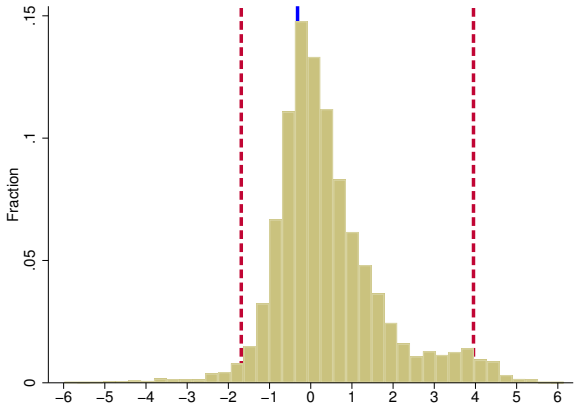
B: T-Statistics

Opioid Overdose Deaths per 100,000



Rank of δ_0: 6,320/10,000
Rank of $|\delta_0|$: 8,608/10,000

C: Coefficients



Rank of T_0: 7,170/10,000
Rank of $|T_0|$: 7,185/10,000

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.

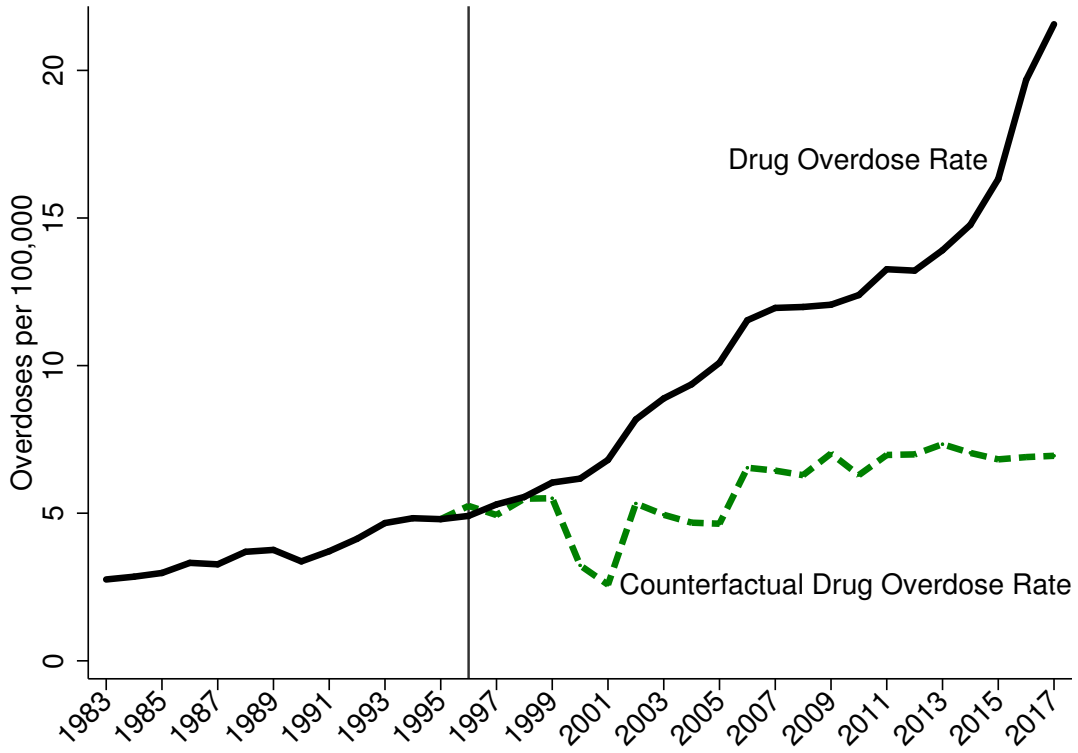
We rescale all of the Figure IV (Panel B) estimates in the post-period by 0.92/0.71 to calculate the number of deaths attributable to OxyContin's launch. Then we subtract off these estimates from the trend line in Figure I to plot the resulting counterfactual national overdose death rate trend (see Figure 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.

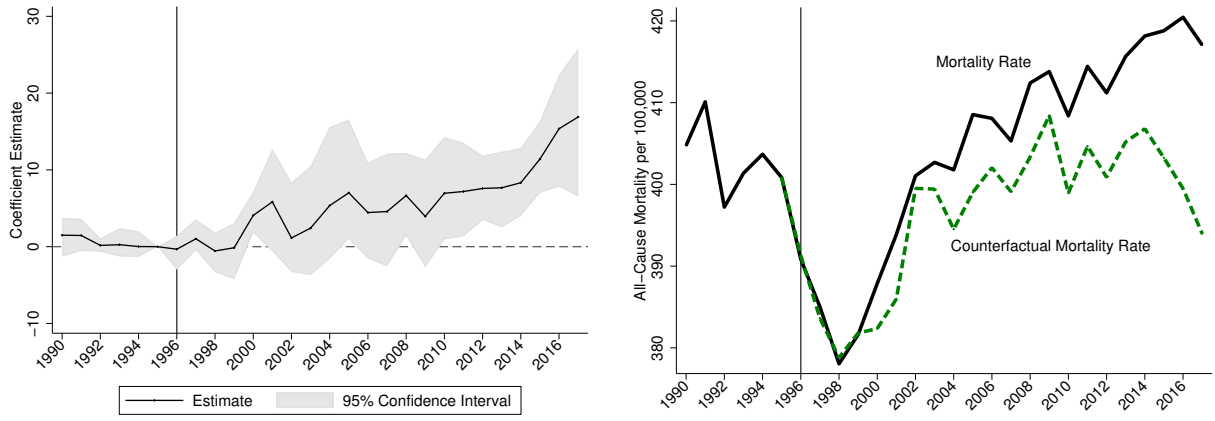
We conduct a similar extrapolation exercise for all-cause mortality focusing on non-Hispanic Whites ages 45-54, a population highlighted in Case and Deaton (2015) as experiencing the largest reversal in mortality trends after 1998. We first replicate our main event study in Panel A of Figure F2 for overdose 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.

Appendix References

Abadie, Alberto, "Using Synthetic Controls: Feasibility, Data Requirements, and Methodological Aspects," *Journal of Economic Literature*, forthcoming.

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

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

Arkhangelsky, Dmitry, Susan Athey, David A Hirshberg, Guido W Imbens, and Stefan Wager, "Synthetic difference in differences," Technical Report, National Bureau of Economic Research 2019.

Ben-Michael, Eli, Avi Feller, and Jesse Rothstein, "New perspectives on the synthetic control method," Technical Report, Technical report, UC Berkeley 2018.

Betz, Michael R and Lauren E Jones, "Wage and employment growth in America's drug epidemic: Is all growth created equal?," *American Journal of Agricultural Economics*, 2018, *100* (5), 1357–1374.

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

Charles, Kerwin Kofi, Erik Hurst, and Mariel Schwartz, "The transformation of manufacturing and the decline in US employment," *NBER Macroeconomics Annual*, 2019, *33* (1), 307–372.

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

Doudchenko, Nikolay and Guido W Imbens, "Balancing, regression, difference-in-differences and synthetic control methods: A synthesis," Technical Report, National Bureau of Economic Research 2016.

Ferman, Bruno and Cristine Pinto, "Synthetic controls with imperfect pre-treatment fit," *arXiv preprint arXiv:1911.08521*, 2019.

General Accounting Office, *Prescription drugs OxyContin abuse and diversion and efforts to address the problem: Report to Congressional requesters.*, DIANE Publishing, 2003.

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

MacKinnon, James G and Matthew D Webb, "Randomization inference for difference-in-differences with few treated clusters," *Journal of Econometrics*, 2020, *218* (2), 435–450.

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

Pierce, Justin R and Peter K Schott, "Trade liberalization and mortality: Evidence from US counties," *American Economic Review: Insights*, March 2020, *2*, 47–64.

Porter, Jane and Hershel Jick, "Addiction rare in patients treated with narcotics.," *The New England Journal of Medicine*, 1980, *302* (2), 123–123.

Powell, David, "Imperfect Synthetic Controls," Technical Report, RAND 2020.

Purdue Pharma, "2002 Budget Plan," Technical Report 2002.

Rambachan, Ashesh and Jonathan Roth, "An Honest Approach to Parallel Trends," 2020.

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