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Early OxyContin Marketing Linked To Long-Term Spread Of Infectious Diseases Associated With Injection Drug Use

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ABSTRACT **The initial marketing of the opioid analgesic OxyContin in 1996 increased fatal drug overdoses over the course of the opioid epidemic in the US. However, the long-term impacts of this marketing on complications of injection drug use, a key feature of the ongoing crisis, are undetermined. This study evaluated the effects of exposure to initial OxyContin marketing on the long-term trajectories of injection drug use–related outcomes in the US. We used a difference-in-differences analysis to compare outcomes in states with high versus low exposure to initial marketing before and after the 2010 reformulation of OxyContin, which facilitated the use of illicit drugs and the spread of infectious disease. Exposure to initial OxyContin marketing statistically significantly increased rates of fatal synthetic opioid–related overdoses; acute hepatitis A, B, and C viral infections; and infective endocarditis–related deaths. The greatest burden of adverse long-term outcomes has been in states that experienced the highest exposure to early OxyContin marketing. Our findings indicate that OxyContin marketing decisions from the mid-1990s increased viral and bacterial complications of injection drug use and illicit opioid–related overdose deaths twenty-five years later.**

The opioid crisis in the United States caused more than half a million deaths between 1999 and 2020.[1] This ongoing epidemic is frequently divided into a pharmaceutical period between the 1990s and 2010; a heroin period beginning in 2010; and a synthetic opioid period, mainly driven by the use of fentanyl, after 2013.[2] In recent years, public health experts have also referred to the opioid epidemic as a "converging public health crisis," as injection drug use has driven increased transmission of infectious diseases, including HIV and the viral hepatitides.[3]

The introduction of OxyContin, a prescription opioid analgesic, was a key contributor to the opioid epidemic.[2,4,5] OxyContin, a Schedule II extended-release preparation of oxycodone, was developed by Purdue Pharma in anticipation of generic competition for the company's MS Contin, a morphine-based drug used to treat pain in patients with cancer.[6] Purdue sought to expand the market for OxyContin beyond cancer-related pain by promoting it as a treatment for people with moderate and chronic pain—who made up a substantially larger patient pool than those seeking treatment for cancer pain alone—even though physicians were historically reluctant to prescribe opioids in this setting because of the elevated risk for addiction.[5–8] Employing aggressive sales tactics and exploiting data on physician prescribing patterns, Purdue targeted the marketing of OxyContin to leading opioid prescribers, normalized its use as a treatment for noncancer pain, and downplayed its potential for addiction.[5,8,9] These ef-

forts were effective. Purdue launched OxyContin in 1996. By 2002, sales for OxyContin reached $1.5 billion, representing more than seven million prescriptions.[10] Eager to capitalize on Purdue's success, other pharmaceutical companies followed suit, using similar tactics to introduce and market competing opioids.[7,11]

Previous analyses have found that OxyContin marketing decisions at the time of the drug's introduction led to long-term increases in opioid-related overdose deaths in the US.[7,12] Using internal information on Purdue's marketing strategies disclosed in court materials, these studies separately identified two novel sources of geographic variation in the introduction of OxyContin. First, Abby Alpert and colleagues reported that Purdue was unwilling to promote OxyContin in five states with triplicate prescribing programs for Schedule II drugs. These programs required prescriptions to be written on an official form, with the prescriber, pharmacy, and state each preserving a copy for documentation and governmental oversight. This placed a regulatory burden on physicians and effectively decreased the potential market for OxyContin, thus shielding these states from Purdue's promotional activities and preventing many overdose fatalities.[12] Second, Carolina Arteaga and Victoria Barone reported that Purdue originally promoted OxyContin to oncologists and primary care physicians treating patients with cancer and then strategically used primary care physicians as a conduit to reach noncancer patients. Areas with a greater cancer burden in the mid-1990s, and thus more exposure to OxyContin marketing, endured larger increases in overdose fatalities and adverse social and infant health outcomes compared with other areas.[7]

Despite this compelling evidence and the critical implications for contemporary public health, however, the effects of early OxyContin marketing on viral and bacterial complications of injection drug use have been unexplored to date. Injection drug use with nonsterile syringes has long been recognized as an important risk factor for the transmission of hepatitis C virus and HIV.[13,14] Since the start of the heroin phase of the opioid crisis in 2010, injection drug use–related infectious diseases have dramatically increased in the US.[15] During this transition, states introduced policies such as prescription drug monitoring programs to curb misuse, while the supply of heroin, which was inexpensive, potent, and strongly linked to injection drug use, dramatically expanded.[2,4,16–20] Notably, this transition has also been attributed to an August 2010 chemical reformulation of OxyContin, which made the drug "abuse deterrent."[21,22] Before the reformulation, the extended-release pills could be crushed and the entire dose could be ingested through snorting or injecting. Afterward, the pills were more difficult to crush and misuse, resulting in widespread substitution to heroin. A body of work has shown that this reformulation increased heroin- and fentanyl-related overdose deaths and the transmission of infectious diseases such as hepatitis B and C,[21–25] yet the impact of marketing decisions made more than a decade earlier by Purdue on infectious sequelae of injection drug use are as yet undetermined.

In this study we evaluated the causal effects of initial OxyContin marketing on the long-term trajectories of injection drug use–related outcomes in the US. We used data from the Centers for Disease Control and Prevention (CDC) on all fifty states and Washington, D.C. (referred to as "states"), spanning the mid-to-late 1990s through 2020. Our analysis leveraged two separate events that affected the supply of OxyContin: geographic variation in marketing from its 1996 introduction and the supply shock resulting from its 2010 reformulation. We used a quasi-experimental, difference-in-differences framework to evaluate the extent to which states with high exposure to initial OxyContin marketing (the treatment group) experienced worse health outcomes compared with states with low exposure (the control group). We examined this difference before and after the 2010 reformulation.

Study Data And Methods

EXPOSURE TO INITIAL OXYCONTIN MARKETING

We employed a proxy for initial OxyContin marketing. This proxy combined two features of geographic variation in the introduction of OxyContin that was identified in previous studies: the targeting of physicians who had patients with cancer and the avoidance of states with triplicate prescribing programs.[7,12] To construct this proxy, we first calculated each state's cancer burden during 1993–95, defined as cancer-related mortality rates per 100,000 averaged over those years (similar to previous work).[7] We used data from CDC Wide-ranging Online Data for Epidemiologic Research (WONDER) compressed mortality files and the Surveillance, Epidemiology, and End Results definition of all malignant cancers (International Classification of Diseases, Ninth Revision, codes 140–208 and 238.6).[26,27] We did not age-adjust cancer-related mortality rates because we were interested in the total state cancer burden regardless of a state's age distribution. We then categorized states into terciles of 1993–95 cancer burden.

Next, we assigned the states with triplicate

Our results underscore the need for urgent policy actions to address the lingering impacts of OxyContin marketing.

prescribing programs in 1996 to the lowest tercile of 1993–95 cancer burden. With this step, we assumed that states with either triplicate prescribing programs or the lowest cancer burdens were exposed to less OxyContin marketing than all other states. Of the triplicate prescribing states, Illinois and New York were originally in the middle tercile and California, Idaho, and Texas were already in the lowest tercile.[12]

Our proxy for initial OxyContin marketing thus categorized each state into a high-, middle-, or low-exposure group at the time of its 1996 introduction (online appendix figure S1).[28] We assessed our use of this proxy by examining the extent to which each exposure group experienced differential increases in shipments of oxycodone (which includes OxyContin), shipments of other opioids, and fatal prescription- and all opioid-related overdose rates during the next two decades. (See appendix A for additional details.)[28] Consistent with the findings of previous analyses, appendix figure S2 generally shows a dose-response divergence.[7,12,28]

OUTCOMES Our primary outcomes were rates of fatal heroin-related overdoses and synthetic opioid–related overdoses, which included fentanyl; incidences of acute hepatitis A, acute hepatitis B, and acute hepatitis C; incidence of new diagnoses of HIV attributed to injection drug use; and rates of infective endocarditis–related deaths among people ages 15–54. Injection drug use is an important risk factor for these outcomes.[29,30] As secondary outcomes, we also examined overdose deaths related to stimulant overdoses, including cocaine and methamphetamines.

For mortality outcomes, we collected publicly available CDC WONDER multiple cause of death data from the period 1999–2020.[31] We identified drug overdose deaths and infective endocarditis–related deaths, using International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), codes. We restricted infective endocarditis deaths to people ages 15–54 to avoid the inclusion of deaths not associated with injection drug use (for example, deaths attributable to cardiac device endocarditis).[32] We calculated mortality rates per 100,000 population, using the associated state populations provided by CDC WONDER (compressed mortality files before 1999 and multiple cause of death data beginning in 1999).[26,31] These population data were also used to weight our analyses. In addition, we used a data smoothing algorithm to estimate suppressed death counts and generated undercounting-adjusted overdose deaths for use in a robustness test. For specific ICD-10 codes and additional details, see appendix B.[28]

We obtained data on acute hepatitis A, acute hepatitis B, and acute hepatitis C incidence rates per 100,000 population, by state, from the period 1995–2020 from publicly available CDC Viral Hepatitis Surveillance reports.[33,34] Data were not available for all states in all years, and surveillance systems and data quality may vary across states. (For additional details, see appendix C.)[28] The CDC has advised that hepatitis testing was disrupted by the COVID-19 pandemic, which may have substantially lowered the number of reported cases in 2020.[34]

Rates of new diagnoses of HIV attributed to injection drug use per 100,000 population from 2008 to 2019 were collected from AIDSVu, which compiles data from the CDC National HIV Surveillance System.[35] We calculated these rates as the rate of new diagnoses of HIV per 100,000 multiplied by the share of new diagnoses of HIV attributed to injection drug use.

STATISTICAL ANALYSIS We used a difference-in-differences framework to estimate the effect of high versus low exposure to initial OxyContin marketing. We examined outcomes before and after the 2010 OxyContin reformulation, which facilitated the use of illicit drugs and spread of infectious disease.[21–25] First, we compared long-term trends in the mean values of our outcomes by exposure group. Next, we restricted the sample to states in the high- and low-exposure groups and employed an event study model to estimate differences between these groups for each year pre- and post-reformulation, relative to the year before the reformulation, using linear regression. We also used linear regression to estimate average effects for the full post-reformulation period and for three-year subperiods to document dynamic effects (2010–13, 2014–17, and 2018 and later). We accounted for state characteristics that do not change over time and national shocks to all states, using state and year fixed effects, respectively. All regressions were

weighted by state population, and standard errors were clustered by state. (See appendix D for specifications.)[28]

Our estimated coefficients represent the causal effects of exposure to initial OxyContin marketing under the identifying assumption that, in the absence of the 2010 OxyContin reformulation, outcome trends in the high-exposure group would have been parallel to trends in the low-exposure group. We examined this parallel trends assumption by assessing any statistically significant differences in trends between the two groups before 2010.

As a robustness test, we incorporated controls for multiple state-level policy changes that may have been associated with initial OxyContin marketing and outcomes. (See appendix E for additional information on these variables.)[28] We also conducted a series of falsification tests to assess the validity of our results. First, we replaced our proxy for initial OxyContin marketing with early shipments of oxycodone and other opioids (such as hydrocodone, morphine, and codeine), separately, in our differences-in-differences strategy to investigate which would have a larger impact on outcomes. In addition, we similarly examined the extent to which other explanatory factors could have driven our results, including high initial levels of poverty, high preexisting use and misuse of drugs, high initial levels of chronic pain, high initial prevalence of chronic health conditions, and higher levels of injection drug use in states whose labor markets were the most adversely affected by the Great Recession. (See appendix F for detailed information on our falsification tests.)[28]

LIMITATIONS Our study had several limitations. First, we relied on an aggregate proxy measure for OxyContin marketing, which categorized states into three exposure levels, and used state-level surveillance data. Although the analyses would have been strengthened by access to Purdue Pharma's actual marketing data, as well as by the use of more granular outcome data, this information is not publicly available. Second, because of differences in surveillance systems, data quality for our hepatitis outcomes may have varied across states, although we do not believe that this affected our findings. (This is discussed further in appendix C.)[28] Next, our study design did not address all state-level policy changes that occurred in the post-reformulation period. Even though we used event studies to assess differences in trends between high- and low-exposure states before 2010 and conducted robustness tests to account for multiple important policies, subsequent events that we did not account for may have differentially affected injection drug use–related morbidity and mortality. Finally, constraints on our study design and data did not permit a causal analysis of all relevant injection drug use–related outcomes. Although we included HIV attributed to injection drug use, these data are only available beginning in 2008, which limited our ability to assess parallel pre trends and make causal claims. Furthermore, because of data limitations, we were unable to examine additional outcomes of interest (for example, skin and soft tissue infections and nonfatal overdoses). In addition, we only included acute hepatitis C virus infections in this study, as chronic hepatitis C virus data likely reflect a substantial number of infections related to the transfusion of blood products before 1990.[14]

Study Results

BASELINE STATE CHARACTERISTICS Exhibit 1 presents mean state characteristics at baseline, before the 2010 OxyContin reformulation, by exposure group, using data from the IPUMS USA American Community Survey 2005–09 five-year sample.[36] Consistent with having a greater 1993–95 cancer burden, the populations of states in the high-exposure group were somewhat older than those in the low-exposure group and were disproportionately non-Hispanic White and not foreign born. The high- and low-exposure groups were similar in terms of share of the population that was non-Hispanic Black, educational attainment, share of the population with income at or below the federal poverty level, and outcomes. Appendix table S1 presents means and variable information for all outcomes and years by exposure group.[28]

TRENDS BY EXPOSURE GROUP Before the 2010 reformulation of OxyContin, outcomes generally exhibited similar levels and trends by exposure group (appendix figures S3–S5).[28] After 2010, mean trends in the high-exposure group diverged from those in the low-exposure group for all outcomes, including fatal overdose rates (appendix figure S3), acute hepatitides rates (appendix figure S4), rates of new diagnoses of HIV attributed to injection drug use (appendix figure S5), and infective endocarditis–related mortality rates (appendix figure S5).[28] This divergence occurred immediately post-reformulation for fatal heroin-related overdoses, acute hepatitis B, acute hepatitis C, and infective endocarditis–related mortality but was delayed for fatal synthetic opioid–related overdoses (2014, corresponding to reports of increases of fentanyl in the illicit drug supply),[37] HIV (2017), and acute hepatitis A (2018). Consistent with a dose-response effect of initial OxyContin marketing, the middle-exposure group similarly diverged from the low-exposure group, but with a

EXHIBIT 1

Characteristics of US states by exposure to initial OxyContin marketing before the 2010 reformulation

	Exposure groups		
	Low[a]	Middle[b]	High[c]
No. of states	19	15	17
State population, averaged 2005–09 (unweighted)	7,786,712	3,975,627	5,506,866
Cancer-related mortality in 1993–95 (rate per 100,000)	178.6	206.0	236.2
Demographic characteristics in 2005–09 (%)			
Female	50.4	50.9	51.2
Ages 0–17	25.6	24.4	23.3
Ages 18–44	38.5	36.8	36.1
Ages 45 and older	35.9	38.8	40.6
Black (non-Hispanic)	10.9	14.9	12.2
Hispanic (any race)	22.9	5.9	8.6
White (non-Hispanic)	56.8	74.4	74.6
Foreign born	17.7	7.0	9.8
High school or less educational attainment	63.0	64.0	65.2
Some college or more educational attainment	37.0	36.0	34.8
Income at or below federal poverty level	15.8	15.9	15.9
Outcomes, averaged 2005–09 (rate per 100,000)			
Fatal heroin-related overdoses	0.8	1.1	0.8
Fatal synthetic opioid–related overdoses	0.7	0.9	0.9
Acute hepatitis A incidence[d]	1.2	0.8	0.9
Acute hepatitis B incidence[d]	1.4	1.3	1.7
Acute hepatitis C incidence[d]	0.2	0.4	0.3
New diagnoses of HIV attributed to injection drug use[e]	1.6	1.5	1.7
Infective endocarditis–related deaths[f]	0.8	1.0	1.1

SOURCE Authors' analysis of data on mortality and population counts from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER); demographic characteristics from the IPUMS USA American Community Survey 2005–09 5-year sample; acute hepatitides, including hepatitis A, hepatitis B, and hepatitis C, from CDC Viral Hepatitis Surveillance reports; and new diagnoses of HIV attributed to injection drug use from AIDSVu. **NOTES** Exposure groups were formed as terciles of cancer burden in 1993–95 and also accounted for states' use of triplicate prescribing, as described in the text. Cancer-related mortality and demographic characteristic means were weighted using the average of the 2005–09 state populations. Outcome means were weighted using state populations. [a]These states constitute the control group: Alaska, Arizona, California, Colorado, Georgia, Hawaii, Idaho, Illinois, Minnesota, Nevada, New Mexico, New York, South Carolina, Texas, Utah, Vermont, Virginia, Washington, and Wyoming. [b]Connecticut, Indiana, Kansas, Louisiana, Maryland, Michigan, Mississippi, Montana, Nebraska, New Hampshire, North Carolina, North Dakota, Oregon, South Dakota, and Wisconsin. [c]These states constitute the treatment group: Alabama; Arkansas; Delaware; Florida; Iowa; Kentucky; Maine; Massachusetts; Missouri; New Jersey; Ohio; Oklahoma; Pennsylvania; Rhode Island; Tennessee; Washington, D.C.; and West Virginia. [d]Outcome is missing data for some state-years. [e]Only 2008–09 available. [f]For people ages 15–54.

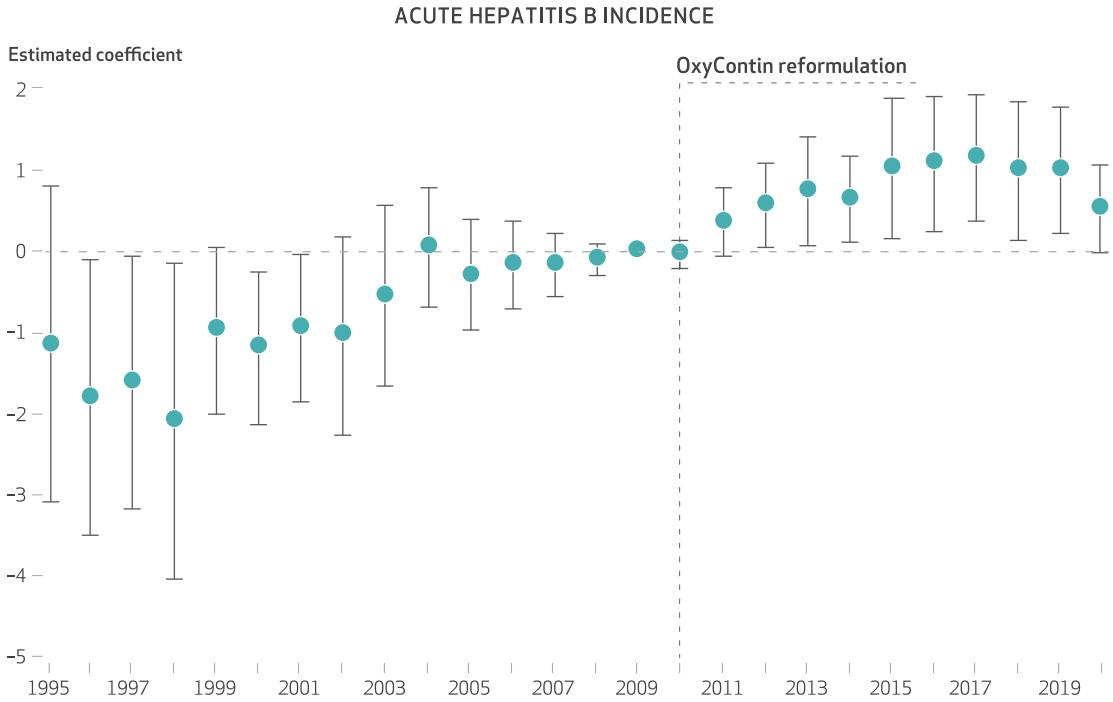
smaller magnitude, for all outcomes except HIV.

EVENT STUDIES The event studies mirror these results. Before the 2010 OxyContin reformulation, outcome trends in the high-exposure group were generally parallel to trends in the low-exposure group for fatal overdose rates, acute hepatitides rates, and infective endocarditis–related mortality rates (exhibits 2–4 and appendix figure S6).[28] For the acute hepatitides and infective endocarditis, trends were parallel in the immediate years leading up to 2010, but there were some statistically significant differences in earlier years. These differences in the hepatitides appear to be driven by elevated reports of hepatitis in a handful of states (for example, acute hepatitis A in Arizona in 1997 and acute hepatitis C in Missouri and New Jersey in 2001). Because of this early volatility, our preferred estimates of average effects during the post-reformulation period used a sample that began in 2004, once trends had stabilized. This better quantified estimates relative to the immediate period before the reformulation (results for the full sample period are in appendix table S2b).[28]

After the reformulation, we saw statistically significant differences between the high-exposure group and the low-exposure group for most outcomes. Notably, fatal synthetic opioid–related overdoses (beginning in 2014, appendix figure S6), rates of acute hepatitis B (exhibit 2), rates of acute hepatitis C (exhibit 3), and infective endocarditis–related mortality (exhibit 4) showed substantial, sustained divergences, whereas differences in fatal heroin-related overdoses and acute hepatitis A were less extreme

EXHIBIT 2

Differences in incidence of acute hepatitis B between US states with high versus low exposure to initial OxyContin marketing, 1995–2020



SOURCE Authors' analysis of the proxy for initial OxyContin marketing from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) and rates of acute hepatitis B per 100,000 from CDC Viral Hepatitis Surveillance reports. **NOTES** The estimated coefficient represents the estimated difference between the high-exposure and low-exposure groups of states (95% confidence intervals are also shown as whiskers). The states in each group are in the exhibit 1 notes. Differences are relative to 2009, the year before the OxyContin reformulation. Event study models were estimated using linear regression, which included state and year fixed effects. All regressions were weighted by state population, and standard errors were clustered by state.

(appendix figure S6).[28] We were unable to investigate parallel pre trends for HIV (appendix figure S6)[28] because of limited data availability before 2010, and we did not see a statistically significant difference between the high- and low-exposure groups after 2010.

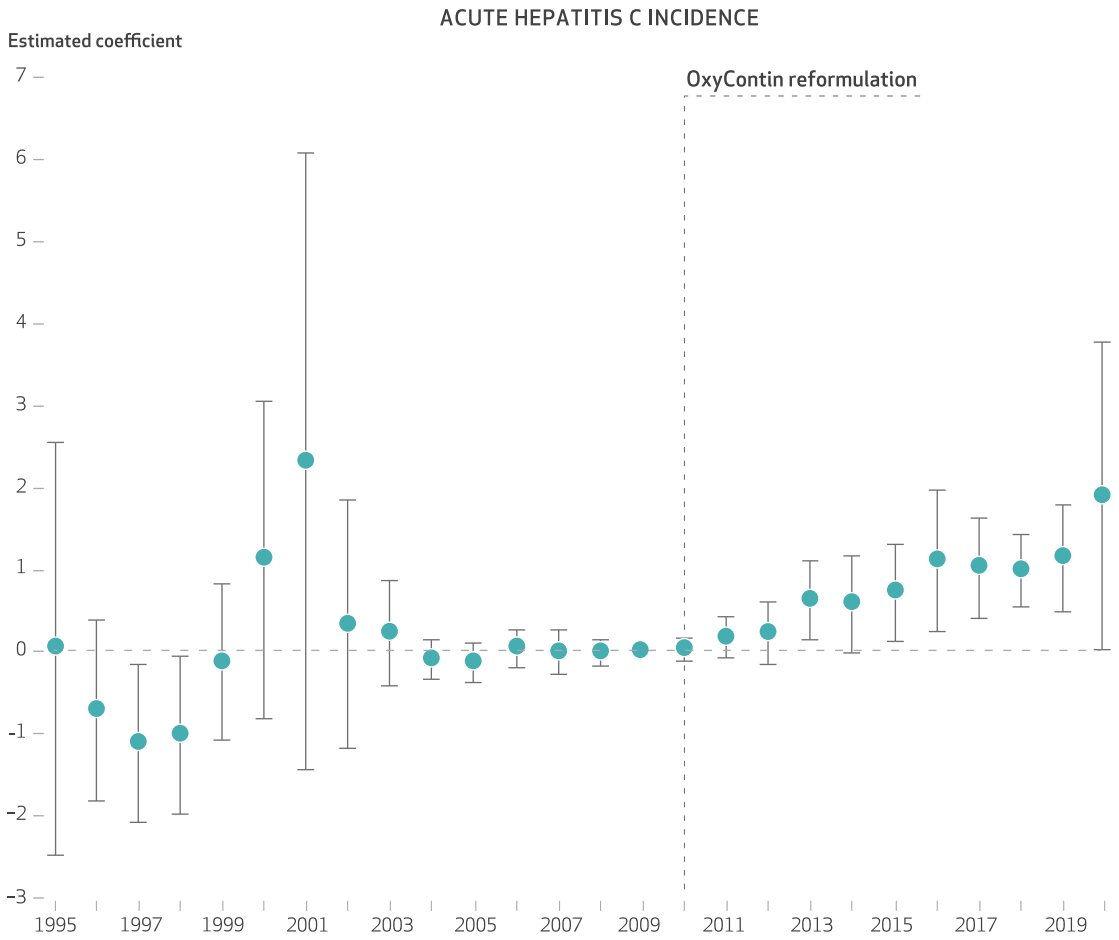
DIFFERENCE-IN-DIFFERENCES Our difference-in-differences estimates averaged over the full post-reformulation period, presented in appendix tables S2a and S2b,[28] showed that exposure to early OxyContin marketing statistically significantly increased fatal synthetic opioid–related overdoses by 5.3 deaths per 100,000 ($p < 0.001$), infective endocarditis–related mortality by 0.62 deaths per 100,000 ($p < 0.001$), acute hepatitis A incidence rates by 2.1 cases per 100,000 ($p = 0.004$), acute hepatitis B incidence rates by 0.85 cases per 100,000 ($p = 0.03$), and acute hepatitis C incidence rates by 0.83 cases per 100,000 ($p < 0.001$).

Appendix tables S2a and S2b also present estimates averaged over three-year subperiods to represent dynamic effects.[28] Although the estimated impact on acute hepatitis A was statistically significant for the full post-reformulation period, our event study and dynamic effect findings suggest a delayed effect that emerged after 2018, likely driven by outbreaks in Kentucky, Tennessee, and West Virginia. This timing corresponds to initial reports of an outbreak of hepatitis A in 2017–18, representing a change in the recent epidemiology of hepatitis A virus transmission in the US.[30] Before this outbreak, transmission generally occurred through food contamination; afterward, it occurred through person-to-person community spread via direct contact in populations who used drugs or were experiencing homelessness. As a result, we attribute this impact to exposure to initial OxyContin marketing. Impacts on fatal heroin-related overdoses and new diagnoses of HIV attributed to injection drug use were not statistically significant, with effects of 1.2 deaths per 100,000 ($p = 0.16$) and −0.03 cases per 100,000 ($p = 0.92$), respectively.

SECONDARY OVERDOSE MORTALITY OUTCOMES In secondary outcomes, we found that fatal cocaine-related overdoses mirrored our findings

EXHIBIT 3

Differences in incidence of acute hepatitis C between US states with high versus low exposure to initial OxyContin marketing, 1995–2020



SOURCE Authors' analysis of the proxy for initial OxyContin marketing from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) and rates of acute hepatitis C per 100,000 from CDC Viral Hepatitis Surveillance reports. **NOTES** The estimated coefficient represents the estimated difference between the high-exposure and low-exposure groups of states (95% confidence intervals are also shown as whiskers). The states in each group are in the exhibit 1 notes. Differences are relative to 2009, the year before the OxyContin reformulation. Event study models were estimated using linear regression, which included state and year fixed effects. All regressions were weighted by state population, and standard errors were clustered by state.

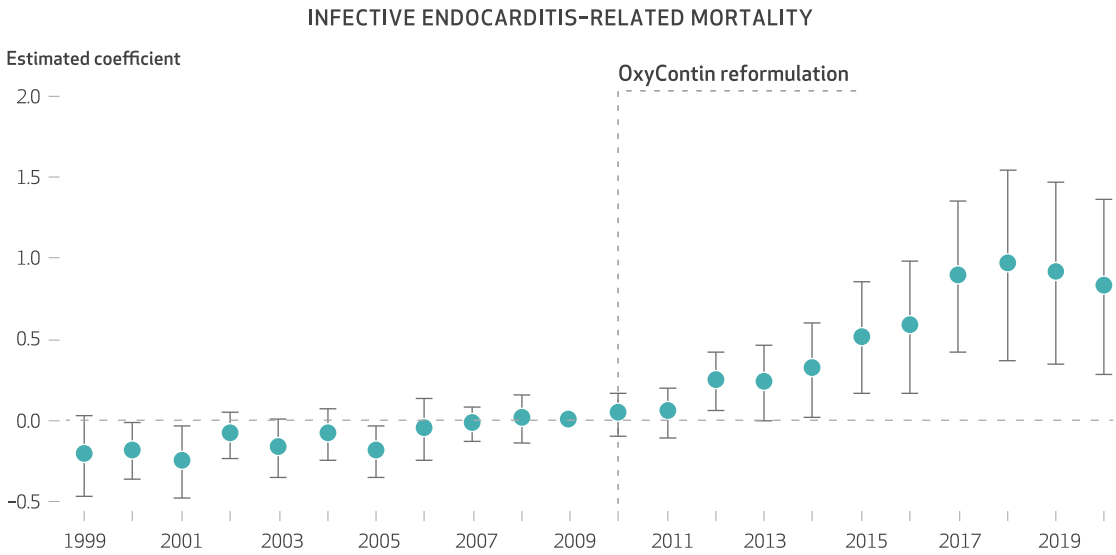
for other outcomes, exhibiting mostly parallel pre trends (except in 2008) between the high- and low-exposure groups and a dose-response divergence after 2010 (appendix figure S7).[28] Exposure to early OxyContin marketing yielded an average statistically significant increase of 1.9 deaths per 100,000 ($p = 0.001$) over the course of the full post-reformulation period. Although fatal psychostimulant-related overdoses (excluding cocaine), which included overdoses from methamphetamines, also exhibited parallel pre trends, they did not exhibit a statistically significant divergence after 2010 ($p = 0.86$) (appendix figure S7).[28]

ROBUSTNESS AND FALSIFICATION TESTS Results from our robustness tests that included state-level policy indicators were similar to our main findings (appendix figures S8a and S8b and appendix table S3).[28] Furthermore, the results of robustness tests that analyzed underreporting-adjusted fatal heroin- and synthetic opioid–related overdoses were also similar to our main findings, but they suggest that we may have understated the effects for these outcomes (appendix figure S9 and appendix table S3).[28]

Finally, our falsification tests demonstrated that the best explanation for these results is indeed exposure to initial OxyContin marketing. Replicating our analyses using early oxycodone shipments versus other opioids shipments showed that oxycodone shipments most closely matched our findings (appendix figures S10a

EXHIBIT 4

Differences in infective endocarditis–related mortality rates between US states with high versus low exposure to initial OxyContin marketing, 1999–2020



SOURCE Authors' analysis of the proxy for initial OxyContin marketing and infective endocarditis–related mortality rates per 100,000 for people ages 15–54 from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER). **NOTES** The estimated coefficient represents the estimated difference between the high-exposure and low-exposure groups of states (95% confidence intervals are also shown as whiskers). The states in each group are in the exhibit 1 notes. Differences are relative to 2009, the year before the OxyContin reformulation. Event study models were estimated using linear regression, which included state and year fixed effects. All regressions were weighted by state population, and standard errors were clustered by state.

and S10b and appendix table S4).[28] Moreover, when examining the effects of alternative hypotheses, we found that the proxy for initial OxyContin marketing had the largest, and most statistically significant, positive impact (appendix figures S11a–S11e and appendix table S4).[28]

Discussion

This study provides evidence linking OxyContin marketing from 1996 to a host of complications of injection drug use decades later. We show that exposure to initial OxyContin marketing statistically significantly increased fatal synthetic opioid–related overdose rates; incidence of acute hepatitis A, hepatitis B, and hepatitis C; and infective endocarditis–related mortality rates after the 2010 OxyContin reformulation. Our estimated effects for heroin-related overdose deaths and incidence of HIV attributed to injection drug use were not statistically significant, and we could not causally interpret the HIV results. Nonetheless, the observed divergence in trends by exposure group for these outcomes provides suggestive evidence of impacts. The results for illicit opioid–related overdose deaths are consistent with evidence from previous work,[7,12] although our findings on the infectious complications of injection drug use are entirely novel.

Our findings were robust to the inclusion of multiple state policy variables. In addition, our falsification tests indicated that, first, early shipments of oxycodone, rather than early shipments of other opioids, best explain our results and, second, alternative hypotheses do a comparatively poor job of explaining these findings. Nonetheless, our analysis relied on a proxy measure for OxyContin marketing, used state-level surveillance data, was unable to account for all post-2010 policy changes, and did not analyze all relevant outcomes. Future research should consider and address these constraints.

Despite these limitations, our results underscore the need for urgent policy actions to address the lingering impacts of OxyContin marketing, which have been magnified over time by the nature of addiction and its association with infectious diseases. Policy makers should provide aid to communities that continue to endure the consequences of OxyContin marketing through expanded access to treatment for opioid use disorder and increased availability of harm reduction services to prevent overdoses and the transmission of infectious diseases. Furthermore, policy makers should take action to proactively prevent future public health crises. This could be accomplished by implementing specific recommendations of the Stanford-*Lancet* Com-

mission on the North American Opioid Crisis to limit the influence of the pharmaceutical industry on both opioid prescribers and regulators.[38]

A large literature has documented the effects of various policy and environmental exposures on long-term outcomes.[39,40] Our analysis contributes to an emerging literature that examines the long-term health, social, and economic consequences of another critical exposure: the targeted marketing of OxyContin to physicians treating patients with cancer and states with fewer regulatory barriers.[7,12]

Our findings are also consistent with the notion that the opioid epidemic is creating a "converging public health crisis," as it is "fueling a surge in infectious diseases," particularly the viral hepatitides, infective endocarditis, and HIV.[3] Previous work has shown that these infections, often along with skin and soft tissue infections and overdose, are associated with each other, offering further support to the observations about a converging health crisis among people who inject drugs.[32] In fact, this study provides additional, new evidence that these infections and health events (for example, overdose) are clustering together across the US, with the greatest burden seen in states with the highest exposure to initial OxyContin marketing by Purdue.

Finally, many of the lawsuits against opioid manufacturers, including Purdue Pharma, have been concluded with settlements made or in process, although our findings could influence the enumeration of damages for any future or currently unresolved cases. At the very least, our study may inform the allocation of funds awarded in settled cases. For example, funds could be used to address the infectious complications of injection drug use (such as supporting syringe service programs).

Conclusion

We found that exposure to Purdue Pharma's OxyContin marketing in 1996 increased multiple complications of injection drug use after the 2010 OxyContin reformulation, including rates of fatal synthetic opioid–related overdoses, acute hepatitis A, acute hepatitis B, acute hepatitis C, and infective endocarditis–related mortality. Our results suggest that the mortality and morbidity consequences of OxyContin marketing continue to be salient more than twenty-five years later. This study highlights a critical need for actions to address the spread of viral and bacterial infections and overdose associated with injection drug use, both in the states that were subject to Purdue's promotional campaign and across the US more broadly. ■

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NOTES

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