CAN PHARMACEUTICAL PROMOTION TO PHYSICIANS LEAD TO ADVERSE HEALTH OUTCOMES? EVIDENCE FROM THE OPIOID EPIDEMIC IN THE US

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Can Pharmaceutical Promotion to Physicians lead to Adverse Health Outcomes? Evidence from the Opioid Epidemic in the US*

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Abstract

The sales of opioid painkillers nearly quadrupled in the US since 1999. Opioid-related adverse health outcomes such as addiction, overdose, death and the number of babies born with severe withdrawal syndrome after in-utero exposure to opioids increased by similar magnitudes. This paper estimates the effect of pharmaceutical promotion of opioid drugs to physicians on adverse health outcomes in the US at the county-level. Our results indicate that counties where sales representatives of opioid drugs reach more doctors have higher opioid overdose mortality rates. In addition, we find that infants born in counties with higher opioid promotion during pregnancy are more likely to present symptoms in line with the neonatal abstinence syndrome. We identify the effects by using the presence of state-level bans on pharmaceutical promotion to physicians and the distance between counties and pharmaceutical companies' headquarters to instrument opioid promotion. To study the link between worsened health outcomes and opioid promotion, we use Medicare prescription data and show that doctors receiving promotion for opioid drugs prescribe more opioid painkillers.

JEL Codes: I12, I18, K42, L65, M37

Keywords: Prescription drugs; pharmaceutical promotion; detailing; opioid overdose death; neonatal withdrawal syndrome

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1 Introduction

Every ten minutes one US-American dies from drug overdose (CDC, 2016). Since 1999, the rate of drug overdose deaths has nearly quadrupled, with opioid prescription overdoses accounting for 40% of the overdose deaths in 2014 (CDC, 2015). Incidents of drug overdoses have increased so drastically that all-cause mortality rates for white non-Hispanics in the ages between 45 and 54 years rose in the last decade, reversing the long-run trend of decreasing mortality rates in previous decades (Case and Deaton, 2015). The amount of opioid pain relievers prescribed in the United States skyrocketed in the same period, with no simultaneous increase in pain reported by patients (Chang et al., 2014). The public costs of the epidemic are not limited to higher mortality rates. The misuse of opioids contributed to the increase in hospitalization rates[1] and the number of babies born with neonatal abstinence syndrome. Babies born to women taking opioid drugs during pregnancy are more likely to suffer from respiratory and feeding problems, to be born prematurely and to be admitted to the neonatal intensive care unit (Tolia et al., 2015).

Why did health care professionals increase their opioid prescription rates so extensively in the last two decades? In the 1990s health experts in the US increasingly became concerned with the optimal management of pain. For example, pain was classified as the fifth vital sign, next to body temperature, pulse rate, respiration rate and blood pressure. At the same time, state medical boards started to relax restrictions on prescribing opioid drugs for the treatment of non-malignant chronic pain. Pharmaceutical companies initiated aggressive marketing campaigns to promote opioid medication as an effective treatment option for non-terminally ill pain patients to health care professionals. Some of the manufacturers downplayed the risk of addiction and other adverse health outcomes, partly relying on limited or faulty empirical evidence (Van Zee, 2009).

This study examines the impact of pharmaceutical promotion of opioid analgesics targeted to health care professionals on opioid-related adverse health outcomes in the US in 2014 and 2015. We identify the effects by using the presence of state bans on pharmaceutical promotion to physicians and the distance of the counties to the pharmaceutical companies' headquarters as instruments for receiving pharmaceutical promotion.[2] We find that higher promotional activities for opioid analgesics were associated with higher mortality rates from opioid overdoses in 2014 and 2015. The most conservative estimate of our instrumental variable (IV) regressions indicates that increasing the number of doctors reached by sales representatives by 1% increases overdose deaths by 0.16% (the 95% confidence interval ranges from 0.03% to 0.3%). This means that reducing promotion in the average county to zero would decrease death rates by 1.9 per 100,000 inhabitants (0.2 standard deviations). Besides mortality, the use of opioid painkillers has been linked to higher rates of neonatal abstinence syndrome. We therefore explore whether promotional intensity of

[1] According to the CDC, more than 1,000 US-Americans are admitted to the emergency room every day because of abuse of opioid drugs (Crane, 2013). They also estimate that one out of four patients who receive prescription opioids are struggling with addiction (SAMHSA, 2014).

[2] Engelberg et al. (2014) follow a similar empirical strategy by instrumenting promotion to physicians using the distance to the closest headquarters of pharmaceutical manufacturers. They analyze prescription behavior of Medicare Physicians in the US in 2013 and consider the promotion of all types of drugs.

opioid painkillers in a county is also related to adverse neonatal health outcomes. Our IV estimates indicate that ten additional doctors receiving opioid promotion in a county in the nine months prior to birth lead to an increased likelihood for a baby i) to be born with a low birth weight by 0.5 percentage points, ii) to be born prematurely by 1.2 percentage points and iii) to need assisted ventilation by 0.3 percentage points. These numbers are not negligible, because the probability of an infant to be born with symptoms in line with withdrawal is generally low. On average 15 physicians receive opioid promotion in the nine months prior in the county of birth. An increase of 15 physicians leads to an increase of babies needing assisted ventilation for more than six hours by 0.1 percentage points which is 10% of the mean of the outcome variable. To shed light on the mechanism of increased overdose death rates and worsened neonatal health outcomes, we show that doctors receiving promotion for opioid drugs have higher opioid prescription rates. The IV regression implies that promotion has a positive and statistically significant effect on the number of opioid prescriptions with an elasticity of 0.1. The estimates are within the range of elasticity coefficients found in other work analyzing the impact of pharmaceutical promotion on prescription behavior. Kremer et al. (2008) conduct a meta-analysis on the impact of pharmaceutical promotion and find elasticity estimates between 0.05 and 0.15.

Why do physicians prescribe opioid painkillers so extensively despite potential negative health consequences for their patients? One important reason is that medical research on the effectiveness and side effects of opioid analgesics in combating chronic non-cancer pain was scarce, until recently. In recent years, medical research has concluded that there is no evidence for the effectiveness of long-term opioid therapy for improving non-malignant chronic pain, while there is a risk of dependency (Chou et al., 2015). Manchikanti et al. (2012) argue that inappropriate prescription patterns lie at the heart of the epidemic, resulting from knowledge deficits and (wrongly) perceived safety of opioid drugs. They state that 60% of all deaths occur while patients are following the physicians' prescriptions (CDC, 2012). Patients who are prescribed opioids can also acquire opioid painkillers illicitly or switch to illegal opioid drugs, such as heroin. According to the National Survey on Drug Use and Health (NSDUH), between 2002 and 2011 80% of recent heroin initiates report prior use of opioid pain relievers (Muhuri et al., 2013).

The incidence of neonatal abstinence syndrome increased in similar magnitudes as opioid overdose deaths in the last decade (Tolia et al., 2015). Recent medical research shows negative neonatal health outcomes after in-utero exposure to opioids (Patrick et al., 2015). There is no clear empirical evidence yet on the long-run consequences of suffering from neonatal abstinence syndrome. There is, however, evidence for a steep rise in health care expenditures due to increasing hospitalization rates and associated charges (Patrick et al., 2012). Additionally, studies show a significant negative relationship between low birth weight and long-run outcomes, such as educational attainment and earnings (Behrman and Rosenzweig, 2004; Black et al., 2007; Royer, 2009).

We combine county-level data on death rates (CDC Wonder, December 2016) with recently released and rich data on pharmaceutical promotion payments to physicians aggregated at the county-level (CMS, 2016). We first establish that opioid promotion and overdose death rates are

positively correlated using OLS estimations. We then use a difference-in-difference estimation to show that the positive correlation between promotion and death rates is not driven by unobservable time-invariant county characteristics. The level of promotion, however, is unlikely to be exogenously distributed across counties with respect to opioid overdose death rates. The promotion of opioid painkillers could, for example, be higher in counties where demand for those products is higher. Promotion could also be higher in places with low demand for opioid drugs if pharmaceutical companies are trying to open new markets. We therefore adopt an instrumental variable approach to establish causality, in which opioid promotion is instrumented with the presence of state bans on pharmaceutical promotion to physicians and the distance of the counties to the pharmaceutical companies' headquarters. The estimation of the causal effects of pharmaceutical promotion on death rates is robust to several specification checks. First, to rule out the concern of endogenous sorting of headquarters, we only include companies that had opened their headquarters before 1995, the onset of large-scale promotional activities of opioid analgesics. Many of these remaining headquarters opened in the 19th century, rendering the concern of endogenous sorting less likely. Second, we control for county characteristics that could potentially correlate with the counties' locations and opioid overdose rates. Economic conditions, such as unemployment rates, are shown to be important determinants of prescription pain reliever use (Carpenter et al., 2017). The robustness of our results to the inclusion of these county characteristics limits the concern that we are solely picking up a county-specific, time variant relationship of higher demand for opioid pain relievers and ultimately more overdose deaths. Third, we take advantage of the fact that the states of Minnesota, Vermont and Massachusetts introduced some form of ban on pharmaceutical promotion to physicians at different points in time to limit promotional activities towards physicians.[3] Fortunately for our empirical analysis, pharmaceutical promotion to physicians in these states is banned or limited for every type of drug, not opioid painkillers in particular. We show that, prior to the introduction of these bans, the trends in opioid overdose rates of the introducing states were statistically indistinguishable from the rest of the US. This result suggests that the three states did not introduce the state bans as a response to increasing overdose death rates.

We also use the CDC 2014 Natality Detail Data Set to analyze the impact of opioid promotional activities on neonatal health outcomes. We aggregate promotion in the nine months prior to the birth in the county of birth. Medical research points out that in-utero exposure to opioids in the third trimester of the pregnancy is particularly detrimental for neonatal health outcomes (Desai et al., 2015). In line with this finding, we document that promotion in the third trimester of the pregnancy displays the highest correlation with negative health outcomes. This helps us to rule out the concern that counties with high opioid promotion rates are just counties with higher morbidity rates in general and thus adverse neonatal health outcomes. Promotion in the first and the second

[3]Minnesota introduced the law in 1997, while Vermont and Massachusetts introduced it in 2009. Vermont bans most gifts from pharmaceutical manufacturers to health care professionals, while Minnesota allows gifts with a value of less than $50 per year. Massachusetts initially strictly prohibited pharmaceutical and medical device sales representatives to provide any meals of any value, but amended the law in 2012. Now meals can be provided to health care professionals if they are of "modest value".

trimester should show similar correlations with adverse health outcomes if counties with a generally unhealthy population receive high levels of promotion.

To study the link between worsened health outcomes and opioid promotion, we use physician level Medicare Part D prescription data for 2013 and 2014 and follow the same empirical strategy as in the county level analysis. We instrument the receipt of a physician's opioid promotion with the proximity of the physician's practice to an opioid producing company's headquarters and the presence of a state ban on pharmaceutical promotion to physicians. Physicians write more opioid prescriptions if they received opioid promotion in the corresponding year. Their opioid prescription behavior, however, is not influenced by pharmaceutical promotion of other drugs. This substantiates the interpretation that it is not pharmaceutical promotion per se, but specific promotion of opioid medications, that is driving increases in opioid prescriptions.

We find similar results if, as an alternative, we instrument the number of physicians who receive opioid promotion with the number of physicians in the respective county who receive promotion for drugs unrelated to pain and opioids (such as blood thinner and diabetes medication). The idea behind this alternative instrument is that physicians receive opioid promotion simply because the sales representatives are also promoting unrelated drugs. Finding coefficient estimates of comparable magnitudes increases our confidence of a causal relationship between promotion and overdose deaths.

Since the data on promotional activities is only available from August 2013 onwards, we cannot use our data to explain the overall increase in drug poisoning mortality over time. Our approach, however, is useful to understand why some places have much higher rates of drug overdose mortality than others. McDonald et al. (2012) document large geographic variations in opioid prescription rates in the US in 2008 and argue that these variations cannot be explained by differences in morbidity in the population.

This paper contributes to a growing literature on policies addressing the opioid epidemic in the US. Researchers find that improving access to opioid antagonists such as naloxone can decrease opioid abuse and related health outcomes (Mueller et al., 2015; Rees et al., 2017). Declines of overdose death rates have been found for the introduction of "Good Samaritan Laws" which provide immunity from prosecution for drug possession to anyone who is experiencing an opiate-related overdose or is observing one and is seeking medical attention (Rees et al., 2017). Others analyze the impacts of the introduction of state-level prescription drug monitoring programs (Kilby, 2015; Dave et al., 2017). Bachhuber et al. (2014) establish that opioid-overdose related death rates decreased in states that legalized the use of medical marijuana. The idea is that the use of opioid painkillers is reduced due to the availability of an alternative non-opioid painkiller to combat chronic or severe pain.

As pointed out, physician knowledge deficits appear to be one of the core causes of the opioid epidemic. Researchers have thus tried to understand which factors determine such deficit. Schnell and Currie (2017) find that physicians who graduated from higher ranking medical schools prescribe significantly fewer opioids. Previous work establishes that pharmaceutical promotion to physicians

influences their prescription behavior (Datta and Dave, 2017; Engelberg et al., 2014; Kremer et al., 2008). To the best of our knowledge, this is the first study to examine whether opioid painkiller promotion to physicians plays a significant role in explaining the opioid epidemic.[4]

Our paper also contributes to the literature on the political economy of special interest groups. Special interest groups (SIGs) aim to influence welfare relevant institutions to further their cause. Well-known examples are lobbying groups that intend to influence politicians, bureaucrats and the media (Grossman and Helpman, 2001; Mian et al., 2010; Reuter and Zitzewitz, 2006). Similarly, pharmaceutical companies affect the prescription behavior of health care professionals through pharmaceutical promotion. The interaction between SIG and institutions may, in principle, benefit welfare as the SIG can share valuable and specific information. However, the SIG's optimal choice of information disclosure does not necessarily maximize public welfare. The opioid epidemic exemplifies the large welfare costs that can arise from such information asymmetry.

The paper is structured as follows. Section 2 provides background information on the practice of pharmaceutical promotion to physicians in the US. Section 3 describes the data sources and provides basic descriptive statistics. Section 4 discusses the empirical strategy, followed by the estimation results (Section 5). Section 5.3 explores the channel of increasing prescription rates. Section 5.4 reports robustness checks and Section 6 concludes.

2 Background Information: Pharmaceutical Promotion to Physicians

Pharmaceutical promotion to physicians is a common practice in many countries. Pharmaceutical companies in the US spend billion dollars every year on advertisement of their drugs and medical devices. The largest share of their advertisement budget is generally devoted to direct advertisement to physicians and other health care professionals (Cegedim, 2013). In 2012 pharmaceutical companies spent 27 billion USD on promotion – more than 24 billion USD directed towards physicians. A nationally representative study showed that more than 80% of all physicians in the US received some form of gift by a pharmaceutical representative in 2004 (Campbell et al., 2007).

In the economic literature, previous studies show that interactions of physicians with pharmaceutical sales representatives influence the prescribing practices of the former. Engelberg et al. (2014) find that physicians receiving promotion of branded drugs reduce prescription rates for generic drugs and increase prescriptions in favor of the paying firm's drugs (similarly Datta and Dave (2017)). Other work suggests that promotional activities lower the price sensitivity of general practitioners (Windmeijer et al., 2006).

It is important to understand why promotional efforts change prescription behavior: do pharmaceutical companies provide new information or are physicians' incentives distorted due to financial motives? Physicians may act in the best interest of their patients by prescribing the promoted drug,

[4]David et al. (2010) find a positive relationship between different kinds of pharmaceutical promotion of drugs for certain conditions and adverse drug events, such as overdoses and allergic reactions, in the US.

if the pharmaceutical company uses the sales representatives visits to inform about new drugs, their effectiveness and side effects. However, patient health may be adversely affected if the provided information is incorrect or the physician's decision making is distorted by rent-seeking behavior. It is difficult to empirically differentiate between the two mechanisms of information acquisition and rent-seeking behavior. Engelberg et al. (2014) find that payments cause shifts in prescriptions towards branded drugs over generic equivalents, arguing that additional information cannot play a large role in explaining the effectiveness of promotion. Without data on the information provided to the physician it is impossible to rule out the explanation of new information acquisition as sales representatives can, for example, emphasize that their drug causes fewer side effects even when they are talking about pharmaceutical equivalents. In promoting directly to physicians pharmaceutical sales representatives have room for misinformation. Studies show that the information provided by sales representatives is not always accurate. Villanueva et al. (2003) assess the accuracy of promotional material circulated by pharmaceutical companies in Spain and come to the conclusion that in 44% of the claims made in advertisements, the references provided did not support the statements. Similar results have been found for promotional material distributed in the US. In the study by Wilkes et al. (1992) they ask medical professionals to assess the accuracy of statements made in pharmaceutical advertisement. For 44% of the claims the reviewers feel that it would lead to improper prescription behavior, if a physician had no other information about the drug.

Purdue Pharmaceuticals was among the first companies promoting the opioid analgesic OxyContin, for the treatment of chronic (non-cancer related) pain in 1996. In its promotional campaign, Purdue asserted that the risk of addiction from OxyContin was extremely small and sales representatives claimed that the risk of addiction was less than 1%, a statement that cannot be backed up with empirical evidence from medical studies (Van Zee, 2009). Purdue's sales grew from $48 million in 1996 to $1 billion in 2000. Simultaneously, its number of sales representatives doubled from 1996 to 2001 (GAO, 2003). During the late 1990s, other pharmaceutical manufacturers followed the promotional efforts of Purdue and extended the marketing of their opioid pain relievers. The key message of these campaigns was that opioids can be used to treat long-term pain of non-terminally ill patients. Promotion was not only directed at pain specialists, oncologists or palliative care specialists but also at primary care physicians (Van Zee, 2009). As stated in the previous section there is no evidence for the superiority of opioid drugs over other medications and forms of therapy in improving non-malignant chronic pain. There is, however, evidence for the risk of dependency, overdose death and negative health consequences for unborn babies who are exposed to opioids in-utero.

A growing number of legal actions against opioid manufacturers suggests that this commercial success has not been harmless. For instance, in 2007 Purdue Pharmaceuticals pleaded guilty to the charges of the misbranding of OxyContin and paid a fine of $634 million. In the past two years, different counties have pressed charges against some of the pharmaceutical companies promoting opioid medications for misbranding and underrepresentation of the risk of addiction.[5] Pfizer Phar-

[5]The City of Chicago, Orange County and Santa Clara Counties filed lawsuits against Purdue Pharma LP, Teva

maceuticals and the City of Chicago reached a settlement in 2016 in which Pfizer committed to disclose in their promotional material the risk of opioid medication and stop the promotion for "off-label" uses, such as long-term back pain. Additionally, they admitted that there is no convincing empirical evidence for the long-term use of opioid medication (for more than 12 weeks), in non-terminally ill patients. Compared to the other opioid producing pharmaceutical companies, Pfizer's sales of opioid medications is small.

The Centers for Medicare and Medicaid Services (CMS) publishes data on a yearly basis on the promotional payments made by manufacturers to physicians and teaching hospitals, who are covered under one of the three federal programs. These data on promotional activities are available from August 2013 until December 2015. In Figure 2 we split counties into high and low promotional activity counties and show the evolution of overdose death rates over time. Counties are defined as high promotion areas if promotional activities for opioid medication are above the median level of activity in the years 2013-2015. The median number of physicians receiving opioid-related promotion between 2013 and 2015 is 27 in a given county. Overdose rates between high and low promotion are statistically indistinguishable between 1982 and 1998. Overdose rates for high promotion areas start to increase at a higher rate than in low promotion areas, providing qualitative evidence for our hypothesis.[6]

3 Data and Descriptive Statistics

We combine multiple sources of data to conduct our analysis. An overview of all datasets used and the corresponding time periods can be found in Table A1.

Following the introduction of the Physician Payments Sunshine Act in 2010, all manufacturers of drugs and other medical supplies that have at least one of their products covered by one of the three federal health care programs (Medicare, Medicaid, and State Children's Health Insurance Program), must disclose their financial relationships with physicians and teaching hospitals. Manufacturers are required to submit data on payments made to covered recipients, with information on the amount, the date, the nature of the payment and to which drug it relates to the Centers for Medicare & Medicaid Services (CMS). The CMS provides open access to the payment data (CMS, 2016). The payment data used in this study covers the period from January 2014 to December 2015. The data is available from August 2013 to December 2016. Our main outcome of interest, opioid-related overdose death rates, are only available for the years until 2015. We therefore restrict our analysis to 2014 and 2015, the two years for which we have information on both payment data and overdose death rates.

Pharmaceutical Industries Ltd, Johnson & Johnson, Endo Health Solutions Inc and Allergan PLC in 2014.

[6]For the years before 1999, we observe overdose mortality rates for opioid-relate drugs only in counties with more than 100,000 inhabitants. Calculations in Figure 2 are based on 403 counties for which we have data over the entire time span. In the Appendix we show that before the expansion of pharmaceutical promotion of opioid drugs for non-terminally ill patients in 1996, the mortality rates are following a parallel trend (see Figure A1a). For the years from 1999 on we have mortality data for all counties. In Figure A1b we can see that mortality rates are statistically significantly higher in counties that receive high levels of promotion from 2005 on.

We are primarily interested in payments made to physicians and teaching hospitals regarding opioid medication. These payments can be made for research activities, gifts, in form of speaking fees, meals, or travel. The dollar amount in the dataset can thus refer to the amount directly paid to the physician for speaking fees or represent the dollar value of the lunch or other gifts.

The payment data provides the National Drug Code (NDC) of the drug the payment was made for. With the NDC Drug Code Directory published by the FDA we obtain details on the drug, such as the substance names that allows us to classify the drug group. We classify a drug an opioid analgesic following the Anatomical Therapeutic Chemical (ATC) Classification System of the WHO (ATC code N02A). We exclude opiates that are given to patients to reverse opioid overdose, such as naloxone.[7] If a payment occurred for more than one drug we split the amount paid by the number of drugs promoted.

Table 1 presents summary statistics for the payments made in 2014 and 2015. On average, 11 doctors in a county received promotion for opioid medication in 2014. Not all payment entries are complete: we can see that in both years around 30% of the payments made do not have a drug identifier. Some measurement error in our independent variable is likely, as there is reason to believe that also some transactions regarding opioid medication are not classified as such. We expect a downward bias in the reporting of the payments. Pharmaceutical companies may have an incentive to under-report payments because it is difficult to detect such underreporting and because the information on the payments made are freely accessible for all patients, all physicians and their competitors. Patients who observe the financial relations of their physician with pharmaceutical companies may question the physician's prescription recommendation.

On average, pharmaceutical companies spent 1,200 USD per county for opioid promotion in 2014. Average spending on opioid promotion increased from 2014 to 2015 to 2,500 USD. Many counties (in 2015 more than 50%) do not receive any pharmaceutical promotion for opioid medications according to the Open Payment Data. The data indicates that physicians and teaching hospitals receive on average visits by one opioid manufacturer a year. This suggests that the different manufacturers seem not to be competing in convincing physicians to prescribe their opioid over a different opioid (intensive margin). It is possible that manufacturers are targeting physicians to prescribe opioid painkillers over alternative treatment options. Manufacturers spent, on average, 2,400 USD in 2014 to promote painkillers, other than opioid analgesics. In 2015, pharmaceutical companies spent less money on promoting non-opioid painkillers to physicians, compared to 2014.

Our outcome of interest is the count of opioid overdose deaths at the county level. We use the Multiple Cause of Death Data from 1999 to 2015, provided by the Center for Disease Control (CDC Wonder, December 2016). The Multiple Cause of Death Dataset is constructed from summarizing death certificates provided by state agencies. Even though every death certificate includes a single underlying cause of death, up to twenty additional causes can be indicated in the certificate. The death counts reported in this dataset summarize the number of times that a particular cause of death has been mentioned. This means that a deceased person can be counted as having died from

[7] See Table A2 in the Appendix for a list of keywords used.

opioid-related overdose and as having died from cancer. The WHO and the CDC (guideline for opioid prescription in March 2016) recommend the prescription of opioid medication for terminally-ill or cancer patients. We do not want to make welfare statements about terminally-ill patients who instead of dying from their fatal disease, die from an overdose of opioid medication. We therefore subtract from the count of the fatalities caused not only by overdose but also by neoplasms (ICD-10 Code: C00-D48) the count of deaths by neoplasms only, to obtain the count of fatalities due to opioid overdose only. Table 1 summarizes the mortality rates for opioid overdoses for the years 2014 and 2015 (ICD-10 Code: T40.0-T40.4).

To calculate the distance of the counties' centroids to the headquarters of the opioid promotion pharmaceutical companies, we retrieved the location of the headquarters and their opening date from the webpages of the companies. Table A3 in the Appendix displays the list of companies that have been promoting opioid medication to physicians in 2014 and 2015, according to the CMS Open Payment Data. Headquarters are excluded from our final analysis if they have been opened after 1995 and for pharmaceutical companies that generate most of their revenues from opioid medication (Purdue, INSYS).[8] We consulted state legislations for the presence of some form of state bans on pharmaceutical promotion to physicians. In Minnesota gifts to physicians with a value of more than 50$ are prohibited since 1997[9], while Vermont[10] and Massachusetts[11] introduced limits on gifts to physicians in 2009. The state of Massachusetts amended the law in 2012, allowing pharmaceutical and medical device representatives to provide meals to health care professionals outside their office of "modest value". This value is not further specified. In none of the states are financial relations between physicians/hospitals and pharmaceutical companies completely banned.

We use the CDC 2014 Natality Detail Data Set to analyze the impact of promotional activities on neonatal health outcomes. The data set contains information on all available births registered in the US in 2014. It provides information on the county and month of birth, mother's characteristics such as demographics and health status, information on delivery and prenatal care and neonatal health outcomes. Summary statistics are depicted in Table 2. We calculate promotion exposure by summing the number of physicians that received opioid promotion in the nine months prior to the birth of the child in the county of birth, normalizing by county population. On average 15 physicians received opioid promotion in the county of birth in the nine months prior to the birth. Neonatal health outcomes in line with the neonatal abstinence syndrome are rare: 8% of all babies are admitted to the neonatal intensive care unit (NICU), 1% of the neonates need assisted ventilation for more than six hours after birth. Around 11% of babies are born prematurely (before gestational week 37) and 8% have low birth weight (less than 2500g).

Another data source used is the Medicare Provider Utilization Data 2013 and 2014 collected by

[8] Results are not sensitive to the exclusion of these two companies. Results available upon request.

[9] Minnesota Statues 151.461: `https://www.revisor.mn.gov/statutes/?id=151.461` (accessed on July 31, 2017).

[10] Vermont Statues 18 V.S.A. § 4632: `http://legislature.vermont.gov/statutes/section/18/091/04632` (accessed on July 31, 2017).

[11] Commonwealth of Massachusetts Statues 105 CMR 970.000: `http://www.massmed.org/Advocacy/Regulatory-Issues/Overview-of-Massachusetts-Physician-Gift-Ban-Law/#.WWY6fumxWbg` (accessed on July 31, 2017).

the CMS. These files contain information on Medicare Physicians, such as their names, specialties and addresses and the number of opioid prescriptions they wrote in 2013 and 2014. These are the two most recent files available. For 2014 we have data on the entirety of payments made, while for 2013 the payments are only available from August to December. We use the prescription data of 2013 to control for the lagged prescription behavior of the physician. We cannot run a difference in difference regression due to the lack of data of payments made before August 2013.

Table 3 summarizes average number of opioid claims made by Medicare Physicians in 2014 and the payments they received from pharmaceutical sales representatives in 2014. The average Medicare Physician prescribes 106 opioid prescriptions per year. 2.6% of all physicians in this dataset receive promotion for opioid medications and 5.5% of the opioid-prescribing physicians. If a physician receives promotion from pharmaceutical companies for opioid, he/she receives a payment of 100 USD in one year, on average. There is large variation across physicians in the amount of opioid prescriptions made (up to 26,500 claims) and the average number of all drug services performed by the physician. The mean distance to the closest headquarters of a physician is about 800km and around 5% of Medicare Physicians work in a state that has some form of ban on pharmaceutical promotion to physicians in 2014. To receive more information on the characteristics of the physician, we merge the prescription data from 2014 with the most recent Medicare Physician Compare data provided by the CMS. This data set includes information on the gender of the physician, his/her graduation year and hospital affiliations, if available. Average characteristics can be found in Table 3. 60% of doctors for whom this information is available are male and on average they graduated from medical school in 1994. Another characteristics we would like to analyze is whether a physician is affiliated to a hospital with strict conflict of interest policies. Unfortunately, we only have information available on these policies for teaching hospitals in the US, and not the universe of hospitals. The AMSA scorecard assigns grades to all medical schools based on policy domains regulating the interaction of the student with the pharmaceutical industries.[12] We can see that this information is only available for 67,000 physicians in the Medicare Part D prescription data set and that of 90% are affiliated to a hospital that bans sales representatives from entering the hospital.

Lastly, we collect socio-economic county characteristics that could correlate with opioid overdose mortality rates from different data sources. Medicare Part D enrollment data for 2013-2015 is provided by the CMS. The Bureau of Labor Statistics produces unemployment rates and industry employment shares at the county level for the years 2013-2015. We classify counties into two categories of urbanization (urban/rural) according to the NCHS Urban-Rural Classification Scheme for Counties 2013 (Ingram and Franco, 2012). The U.S. Census Bureau provide in their "Small Area Income and Poverty Estimates (SAIPE) Program" estimates on county poverty rates and median household income levels for the years 2013-2015. Table A4 summarizes county characteristics for 2014 and 2015.

[12]These domains are: i) whether it is forbidden to accept meals and gifts from pharmaceutical sales representatives, ii) whether sales representatives have access to school facilities, iii) whether the school has a formal curriculum on conflict of interests iv) how well the policies are enforced and sanctioned and v) other domains.

4 Empirical Analysis

4.1 Pharmaceutical Promotion and Opioid Overdose Deaths

The goal of the empirical analysis is to test whether pharmaceutical promotion of opioid drugs is related to drug overdose deaths. Our conceptual framework includes three agents: pharmaceutical companies, physicians, and patients. Pharmaceutical companies invest in promotion of their drugs. Physicians decide whether to prescribe opioid drugs or not. Patients receive their treatment and health outcomes (e.g. drug overdoses) are determined. We expect that higher levels of pharmaceutical promotion of opioid drugs are related to higher numbers of fatal drug overdoses through an increase in the prescription of these drugs.

As a starting point, we use cross-sectional variation in pharmaceutical promotion to explain drug overdose deaths by running the following OLS regression:

$$OD_c = \alpha_s + \beta^{OLS} Prom_c + X_c^{'}\Gamma + \varepsilon_c \tag{1}$$

where OD_c denotes the opioid overdose death rate in county c, normalized by the county population (100,000 inhabitants). State fixed-effects are captured by α_s. The vector X is included to control for socio-economic conditions at the county-level such as Medicare enrollment rates, poverty rates and labor market conditions. Our measure of pharmaceutical promotion at the county level is $Prom_c$. Finally, ε_c denotes the error term.

We observe promotion and overdose deaths for two consecutive years (2014, 2015). This allows us to run a fixed effect regression which controls for time-invariant county characteristics and addresses potential targeting bias at the county level. The next equation we estimate is:

$$OD_{c,t} = \theta_1 CountyFE_c + \theta_2 TimeFE_t + \beta^{FE} Prom_{c,t} + X_{c,t}^{'}\Gamma + \varepsilon_{c,t} \tag{2}$$

It is likely that the OLS estimates are biased because of omitted variables and/or measurement error. One possibility is that pharmaceutical companies may be targeting physicians and counties who have a high demand for opioid drugs instead of causing high demand. They could also target counties with initially low demand for opioid painkillers to open new markets by convincing physicians of the advantages of opioid painkillers over alternative treatment options. The fact that physicians are on average visited by one manufacturer only hints to the interpretation that sales representatives try to convince physicians of the superiority of opioid painkillers over alternative treatment options. If pharmaceutical companies were trying to convince physicians, who already write many opioid prescriptions to prescribe their drug, we would observe that multiple manufacturers promote to physicians. Next to the omitted variable bias, OLS regression results may suffer from measurement error. Pharmaceutical companies have, as argued earlier, an incentive to under-report payments made to physicians, especially regarding controlled drugs such as opioids in a period of heightened public attention. 30% of all payments made by manufacturer do not have a drug identifier and it is reasonable to assume that also payments regarding opioid painkillers were

not reported.

To overcome these issues, we propose the following IV strategy. We use two instruments for promotion: the distance between the county centroid and the closest headquarters of opioid manufacturers, and the presence of state laws banning pharmaceutical promotion to physicians. The idea behind the first instrument is that we expect that counties closer to firms' (i.e. opioid producers) headquarters are more likely to receive promotion of opioid drugs. This relationship could arise, for instance, because managers located in the headquarters can monitor sales representatives more easily or sales representatives can reach these counties easier. Additionally, sales representatives are reimbursed for their travel expenses by the manufacturers. The further they travel, the higher the costs for the pharmaceutical company (MedReps, 2017). As described in Section 3 three states (Minnesota, Vermont, Massachusetts) have introduced some forms of state bans on pharmaceutical promotion. The three states have introduced state bans for all kinds of pharmaceutical promotion, not opioid medication in particular. We will show in the robustness checks (Section 5.4) that the introduction was not related to differential trends in overdose death rates in these states. The presence of these state bans thus provides additional exogenous variation in the likelihood of physicians receiving promotional material related to opioid analgesics directly from the manufacturers.

This setup leads us to estimate the first-stage equation:

$$Prom_c = \phi + \rho_1 Dist_c + \rho_2 Ban_c + X_c^{'}\Psi + \mu_c \tag{3}$$

where we predict the promotion of opioid drugs, $Prom_c$, with the distance to the closest headquarters of opioid manufacturers, $Dist_c$ and the presence of state bans, Ban_c. We presume ρ_1 to be negative because promotion is expected to be lower in counties further away from headquarters. Similarly, ρ_2 should be negative because counties with bans are less likely to receive promotion. The vector X denotes the above described county controls. These county characteristics should account for the fact that the location of the counties may be correlated with socio-economic characteristics, that also determine opioid overdose rates.

The second-stage equation is:

$$OD_c = \alpha + \beta^{IV}\widehat{Prom_c} + X_c^{'}\Gamma + \varepsilon_c \tag{4}$$

where $\widehat{Prom_c}$ is the prediction from the first-stage (Equation 3). The parameter of interest is β^{IV}, which captures the effect of pharmaceutical promotion of opioids on overdose deaths. If this coefficient is positive, it would imply that promotion increases deaths related to opioid overdoses. The identifying assumption for the IV estimation is that distance to the closest headquarters and state bans only affect drug overdose deaths through the promotion of opioid drugs. We deal with some concerns related to this assumption in Section 5.4.

4.2 Pharmaceutical Promotion and Neonatal Health Outcomes

The use of opioid painkillers and illicit opioid in pregnant women increased in the last decade (Desai et al., 2014; Bateman et al., 2014), despite evidence for detrimental health outcomes for unborn babies. With this empirical analysis we investigate whether the negative health impact we observe in opioid overdose deaths rates can also be found in neonatal health measures. We analyze whether the intensity of opioid promotion in the county of birth of a newborn in the nine months prior to delivery is negatively related with health outcome measures. For this we regress the number of doctors that received opioid promotion on neonatal health outcomes following the same empirical approach as depicted in Section 4.1. We instrument the number of physicians receiving promotion with the distance of the county centroid to the closest headquarters and the presence of a state ban on promotion. We will display OLS regression results and the first and second stage of the 2SLS estimations. In all regressions we include mother characteristics at birth, such as demographics and health measures, delivery information (prenatal care, form of delivery, physician attended delivery) and neonate characteristics (gender, birth order and number of babies born). We control for month of birth fixed effects and state fixed effects. Medical research has found an increase of respiratory and feeding problems in neonates after in-utero exposure to opioids. The babies are more likely to need assisted ventilation, to be admitted to the neo-natal intensive care unit, to have low birth weight and to be born prematurely. We will regress the number of opioid receiving physicians in the county of birth on the before mentioned health outcomes. We also analyze the impact on the APGAR 5 score, as it includes a score on how well the infant is breathing after delivery. The literature has found that these effects are particularly pronounced after exposure in the third trimester and long-term exposure. We will therefore investigate whether late exposure has larger negative impacts on health outcomes. The variation in promotion is at the county level such that we cluster standard errors at the county level.

4.3 Channel: Promotion and Prescriptions of Opioid Drugs

Physicians' prescription behavior is the main channel through which pharmaceutical promotion to physicians affects patient health. To document the relationship between opioid drugs prescription and pharmaceutical promotion of such drugs, we follow the same approach as in Section 4.1 using physician-level information. We estimate the following first and second stage equations:

$$Prom_{i,t} = \pi + \gamma_1 Dist_i + \gamma_2 Ban_{is} + \theta Spec_i + \zeta Pres_{i,t-1} + \nu_{iz} \tag{5}$$

$$Pres_{i,t} = \lambda + \delta^{IV} \widehat{Prom_{i,t}} + \kappa Spec_i + \eta Pres_{i,t-1} + \epsilon_{iz} \tag{6}$$

We instrument opioid promotion to Medicare physicians using the distance of the office to the closest opioid promoting headquarters ($Dist_i$) and the presence of a state ban on promotion (Ban_{is}). We control for the specialty of the physician, denoted by $Spec_i$, and the number of opioid prescriptions issued in the previous year ($Pres_{i,t-1}$) in the first and second stage.

$Pres_{i,t}$ is equal to the number of prescription claims of opioid drugs written by physician i in

year t. We use different measures of $Prom_{i,t}$. First, we create a dummy variable equal to one if physician i received payments related to opioid drugs from pharmaceutical companies in the corresponding year, and zero otherwise. Second, we use the (log) dollar amount of the payments made from opioid manufacturers to physician i. We sum up all payments a physician has received in a corresponding year. The error term is denoted by ϵ_{iz}, as we cluster standard errors at the zip-code level. According to our hypothesis, we expect δ^{IV} to be positive, suggesting that higher promotion of opioid drugs is associated with more prescriptions of such drugs.

5 Results

5.1 Promotion and Mortality of Opioid Overdoses

We begin by presenting the OLS estimates of the association between promotion of opioid drugs and opioid overdose mortality. In Table 4, we report the estimated coefficients of Equation 1. The point estimates in columns 1 and 2 are both positive and statistically significant, indicating that higher promotion is correlated with higher death rates. These figures imply that increasing the number of doctors reached by sales representatives by 1% increases the number of opioid overdose deaths by 0.1%. Column 3 in Table 4 suggests that contemporaneous promotion of opioid medication is related to opioid overdoses while pre-year levels of promotion have no significant relationship with overdoses. The different measures of promotion imply different elasticities: increasing the dollar amount spent on opioid promotion in a county by 1% increases the death rate by 0.05%.

The county fixed effect regressions display smaller coefficients than the OLS results and are less precisely estimated, mainly because we have less variation within counties over time than across counties. In Table 5 we can see that increasing the number of physicians receiving promotion by 1%, increases the number of opioid deaths by 0.04%. Again, the coefficients on the dollar amount spent are smaller than on the number of physicians reached, but it is not statistically significant at conventional levels. Although these figures are suggestive, it is problematic to provide a causal interpretation to these estimates due to omitted variables concerns.

Thus, we turn to discuss the IV results, reported in Table 6. We pool the regression results for all our estimates from here on for the two years 2014 and 2015.[13] The OLS estimates display coefficient estimates of the same magnitude for the two years, such that we can pool our data to increase efficiency. In column 1, we use the distance to the closest headquarters as one of the instruments for promotion. One potential concern with this instrument is that firms choose the headquarters location based on factors related to marketing activities. These factors can be correlated with opioid overdose deaths. To deal with issue, in columns 2 and 3 we restrict the headquarters to those opened before 1995, the year before the beginning of promotional activities of opioid drugs.[14] We present both sets of results to demonstrate that endogenous sorting of

[13] IV regression results for 2014 and 2015 are very similar and available upon request.

[14] Table A3 lists the manufacturers promoting opioid analgesics in 2014 and 2015, the date of their headquarters opening and a dummy indicating whether they are included in the reduced set of headquarters.

pharmaceutical headquarters is not a threat to our identification strategy.

The first stage results in Panel A display that the closer a county is to a headquarters, the more doctors receive promotion for opioid medication. This is true for both sets of considered headquarters. Dropping the before described companies decreases the coefficient estimates in the first and second stage. The first stage also reveals that the state bans on pharmaceutical promotion appear to be effective: states with a ban have significantly fewer doctors receiving promotion. The partial F-Value of the two used instruments can be found in the last row of Table 6. Our instruments are strong and work in the expected direction.

The second-stage results show that promotion of opioid drugs and overdose deaths are positively linked. The regression results indicate that increasing promotion by 1% in the respective year increases deaths rates by 0.33%. Compared to the OLS estimates, these coefficients are much larger, suggesting that the latter were potentially downward biased. Engelberg et al. (2014) follow the same identification strategy and also find higher coefficient estimates in the IV regression compared to the OLS results. They argue that the IV coefficients may be larger as closeness to headquarters does not only increase the likelihood of receiving promotion that is ultimately displayed in the Open Payment Data, but also other forms of promotions, such as marketing events or conferences.

In the third column we additionally control for county characteristics. The county characteristics we control for are shown to be important determinants of opioid overdose rates (Carpenter et al., 2017). For example, unemployment rates are positively correlated with overdose death rates and explain around 2% variation in deaths in our study period. The characteristics we include are unemployment rates, population, the share of the population that is enrolled in the Medicare Prescription Drug Plan, industry shares, income levels, poverty rates and an urbanization dummy. The coefficient on promotion remains unchanged when we control for these variables. The robustness to the inclusion of the county characteristics limits the concern that we are only picking up a relationship of higher morbidity and therefore higher demand for opioid pain relievers and ultimately more overdose deaths. Additionally, other work suggests that state variation in opioid prescription patterns cannot be explained by underlying health status differences of the population (Paulozzi et al., 2014).

We measure the intensity of opioid promotion with the number of doctors receiving promotion for the following reason. We are not differentiating between the informative and persuasive nature of promotion. If additional information is driving changes in prescription rates, there is no reason to believe that every additional dollar given to one physician would change her/his prescription patterns in a linear way. In Section 5.4 we perform multiple robustness checks. We can show that our results carry through if instead of proxying promotional levels with the number of doctors we proxy it with the logarithm of the USD amount given to physicians. Again as in the OLS and fixed effect regressions, the coefficient are around half the size compared to the coefficients on the number of physicians. All these findings indicate that the effect on the extensive margin of promotion is larger than on the extensive margin: reaching many physicians with sales representatives has higher elasticities than spending more money on the same physicians.

5.2 Promotion and Neonatal Health Outcomes

The positive relationship we have documented between opioid promotion and death rates can also be found in terms of negative neonatal health outcomes. Table 7 displays the OLS regression results described in 4.2. It shows the relationship between the number of physicians receiving opioid related promotion in the nine months prior to delivery on the following health outcomes: the infant was admitted to the neonatal intensive care unit (NICU), the infant needed assisted ventilation i) right after birth and ii) for more than six hours, the infant's APGAR score in minute 5, its birth weight and whether she/he was born prematurely. A baby is considered to have low birth weight if its weight is below 2500g. Prematurity is defined by neonates born at less than 37 weeks' gestation. Panel A of Table 7 shows that opioid promotion is correlated with more babies being admitted to the NICU, needing assisted ventilation for more than six hours, being born prematurely, with low birth weight and low APGAR 5 score. There is no statistically significant relationship between promotion and the need of assisted ventilation immediately after birth. Promotion is normalized by ten, meaning that an additional ten physicians receiving promotion is associated with a lower birth weight of a baby born in the corresponding county of 4.7 gram. On average 15 physicians in a county receive opioid promotion. The probability of neonates being born with symptoms in line with NAS is generally low. The relationship between promotion and negative health outcomes is therefore sizable: an increase of 15 physicians leads to an increase of babies needing assisted ventilation for more than six hours by 0.1 percentage points which is 10% of the mean of the outcome variable.

Panel B of Table 7 splits the promotion into in which trimester of the pregnancy the promotion occurred. In line with previous findings of the medical literature, promotion levels in the third trimester of the pregnancy are associated with the largest impact on negative health outcomes. Low birth weight is positively associated with promotion in all trimesters with similar magnitudes. We are regressing promotion on many health measures and therefore need to account for multiple hypothesis testing. We display the Bonferroni adjusted p-values in Panel A and Panel B. All coefficient estimates in the regressions on promotion during the entire pregnancy are still statistically significant at conventional levels. The coefficient estimate on promotion in the third trimester on low APGAR 5 score loses statistical significance.

Table 8 depicts the results of the first and second stage regressions of the 2SLS equation described in Section 4.2 and 4.1. We instrument the number of physicians that received opioid promotion in the nine months prior to delivery with the distance of the counties centroid to the closest headquarters promoting opioid medication and the presence of a state ban on pharmaceutical promotion to physicians. Panel A shows that again the coefficients following the IV estimation are larger than in the OLS estimation but we lose precision in the estimates. We find a statistically and economically significant relationship between promotion levels and the probability of neonates being born prematurely, with low birth weight and needing assisted ventilation for more than six hours after birth. Ten additional physicians receiving promotion leads to an increase in the likelihood of a neonate needing assisted ventilation for more than six hours of 0.3 percentage points,

which is one third of the mean of the outcome variable (0.03 of a standard deviation). For the remaining outcome variables, the coefficient estimates have the same sign as in the OLS regressions, larger magnitudes but lack statistical significance at conventional levels. The coefficient estimates and the partial F-Values of the first stage are displayed in Panel B of Table 8. Being born in a county far away from opioid producing headquarters reduces the number of physicians receiving promotion and so does living in a state with a ban on pharmaceutical promotion to physicians. The regression shows a strong first stage with F-Statistics around 40.3.[15]

To be able to derive policy implications, it is important to understand for which mothers opioid promotion seems to be having a detrimental effect on the baby's health outcomes. Our data allows us to analyze hetereogenous effects of promotion on health outcomes by the age of the mother, whether the mother is a smoker and by insurance status. Previous research establishes that physicians are more likely to prescribe opioids to Medicare or Medicaid patients (Olsen et al., 2006). Medical research also shows that opioid use is particularly detrimental for the unborn if accompanied with additional risk factors, such as smoking during pregnancy, or alcohol abuse (Desai et al., 2015). The negative effects of promotion on neonatal health outcomes are not driven by mother's who smoke, nor by mother's below the age of 30. The effects are indeed slightly larger for smoking mothers, but also non-smokers are affected. The effect is entirely driven by women who are Medicaid recipients (44% of mother's in our sample are Medicaid recipients). For mothers with a private insurance there is no effect of promotion on neonatal health outcomes. It is possible that receiving Medicaid is a proxy for mother's with worse health status. It is also possible that physicians prescribe opioid painkillers to patients more often if they are covered by Medicaid than to patients who are covered by a private fee-for-service insurance.[16]

5.3 Promotion and Prescription Behavior

After establishing a positive link between promotion and opioid overdose deaths and neonatal health outcomes, we turn our attention to the mechanism. The key channel between promotion and negative health outcomes is physician prescription behavior. Table 9 reports the OLS estimates from regressing prescription claims on pharmaceutical promotion. Our results show that physicians receiving promotion - measured as the dollar amount of payments or as an indicator of receiving payments - write more prescription of opioid drugs. We control for county fixed effects, the specialty of the physician and opioid prescription rates in the previous year. Column (1) suggests that physicians who receive any promotion write on average 45 opioid prescriptions more than physicians who receive no promotion.[17] The results in column (2) suggest that increasing the dollar amount given to a physician in form of opioid-medication promotion by 100% leads to an increase of 15 additional opioid prescriptions. Table 9 also displays the regression results of the first and second

[15] When we instrument promotion in the third trimester only, our coefficient estimates double in size, in line with the findings of the OLS regressions. Statistical significance does not change from the specification in which we measure promotion during the entire pregnancy. Results are available upon request.

[16] Results for heterogeneous effects are available upon request.

[17] To see results for other empirical specifications, see Table A5 in the Appendix.

stage of Equations (5) and (6). As in the regression of overdose mortality rates at the county level, we find that distance decreases the likelihood of receiving pharmaceutical promotion and so does the presence of a state ban. Partial F-statistics of the first stage result can be found in the last row of Table 9, showing that our instruments are highly relevant in explaining differences in promotion to physicians. The set of considered headquarters is the reduced set explained in Section 3. Our estimates here are very comparable to the coefficients we have found in the OLS estimations. They imply that increasing the USD given to a physician for opioid promotion by 100% increases opioid prescriptions by 14. The elasticity in the OLS and IV regressions are identical and of magnitude 0.1 (see Table A5). These estimates are in line with elasticity coefficients found in other work. Kremer et al. (2008) conduct a meta-analysis on the impact of pharmaceutical promotion and find elasticity estimates between 0.05 and 0.15.

In Table 10 we run a placebo regression to show that it is not promotion per se, but particularly promotion regarding opioid medications, that is driving increases in opioid prescriptions. The regression shows the relationship of the promotion received by the physician for different drugs and the number of opioid claims by the physician. Payments made for non-opioid non-painkiller drugs have no impact on the number of opioid prescriptions. The positive coefficient we find on painkillers, other than opioids, can be explained by the fact that these two sets of drugs are sometimes prescribed jointly for the pain management of patients. The coefficient on opioid promotion is very comparable to the one we find in Table 9, where we do not control for promotion other drugs.

To rule out that opioid promotion is driving up prescriptions for all kinds of drugs, we regress the share of prescriptions for opioid drugs over all prescriptions on opioid promotion. Table A6 displays regression results for OLS estimates with the share of opioid claims over all claims as a dependent variable. The table indicates that opioid promotion is not driving up total drug claim rates but in particular the share of opioid claims overall drug claims. Again, receiving promotion for non-opioid painkiller drugs or non-painkiller drugs (column 2) does not increase the share of opioid claims.

Next, we investigate which characteristics determine whether a physician receives opioid promotion and how much he or she reacts. Some hospitals have conflict of interest policies in place that are similar to the state bans on pharmaceutical promotion to physicians discussed earlier. Some hospitals ban pharmaceutical or medical device sales representatives from entering the hospital or offer classes on how to deal with conflicts of interest. The American Medical School Association (AMSA) collects data on these policies for all medical schools in the US since 2008. We expect physicians affiliated to a hospital with conflict of interest policies in place to first be less likely to receive opioid-related promotion and second to adjust their opioid prescription behavior less after engaging with sales representatives. Unfortunately, this data is not available for the universe of hospitals but only for teaching hospitals. We can therefore just analyze the behavior of Medicare Part D physicians who are affiliated to a teaching hospital in 2014. Table 11 displays the heterogeneous effects of receiving opioid promotion on opioid prescription rates. Column (1) shows

that physicians affiliated to a hospital where sales representatives are are not allowed access to any faculty or trainees react less to opioid promotion than physicians who are affiliated to a teaching hospital without such policies. In column (2) we add additional physician characteristics that could potentially influence the sensitivity towards promotion. Previous literature established that male physicians are more sensitive towards pharmaceutical promotion (Engelberg et al., 2014). We also find that male physicians react more strongly to opioid promotion than female physicians (column (2) in Table 11). We do not find that physicians that graduated before 1995 react differentially towards opioid promotion. The idea here is that physicians that graduated before the outbreak of the opioid epidemic may be less trained in pain management using opioid painkillers and thus react more to information provided by sales representatives. Physicians affiliated to a hospital with a ban on sales representatives do prescribe more opioid prescriptions if they receive any kind of promotion regarding opioid drugs. The opioid prescriptions increase is 50% smaller compared to the physicians who are affiliated to a teaching hospital without such a ban. This finding should not be interpreted in a causal manner: physicians with stricter opinions about how health care professionals should interact with the pharmaceutical industry could choose to work for hospitals reflecting his/her opinion. In the last column (3) we analyze which characteristics predict whether a physician receives opioid promotion. Male physicians are more likely to receive promotion and so are physicians who graduated before 1995. Physicians affiliated to a hospital that does not allow sales representatives to engage with its staff are naturally less likely to be visited by a sales representative promoting opioids.

Physicians receiving promotion of opioid medication prescribe more of these drugs because either they receive potentially biased information or because they value the payments made by companies. Although we cannot distinguish the relative importance of these alternative explanations, these estimates clearly indicate that promotion is positively related with prescriptions which lead to adverse health outcomes, such as death and neonates suffering from withdrawal.

5.4 Robustness Checks

Our main empirical analysis relies on the assumption of the exogeneity of our instruments. We use the presence of state bans on pharmaceutical promotion and the distance to the closest headquarters to instrument the likelihood of a county receiving pharmaceutical promotion related to opioid analgesics. We show that the introduction of the state bans was orthogonal to the evolution of opioid-related overdose deaths in the respective year. Readers may be concerned that state legislatures banned pharmaceutical promotion as a reaction to increased opioid misuse. Figure 3a plots the differences in overdose rates for Minnesota and the rest of the US from 1987-2007. Minnesota was the first state to introduce a state ban on pharmaceutical promotion in 1997. The graph shows that overdose rates of counties in Minnesota are statistically indistinguishable from other counties in the years leading to the introduction of the state ban. Overdose rates started to decrease in Minnesota compared to the rest of the US one year after the introduction and five years later the gap becomes statistically significant at the 5% level. Figure 3a shows the differences

in opioid overdose rates of Vermont and Massachusetts compared to the rest of the US, excluding Minnesota from 1999 to 2015. Before the introduction of the state ban in 2009, their overdose death rates are statistically indistinguishable from the rest of the US. After the introduction, death rates do not decline in these two states. It is important to note that Massachusetts and Vermont are small states with 14 counties. Additionally, death rates of opioid overdoses vary substantially from county to county in the late 2000s. Furthermore, Massachusetts amended the law in 2012. Initially, sales representatives were not allowed to provide any meals of any value to health care professionals outside their office. In 2012 this law was updated such that they are not able to provide meals of "modest value". It is therefore no surprise to not see any significant decline in the years following the ban for counties belonging to these two states.[18] It is important to note that the ban holds for all types of drugs, not only opioid medication and there is no anecdotal evidence that these bans were introduced as reactions to the opioid epidemic but rather to curtail financial conflicts of interest in general.

Our identification relies on the assumption that the distance to headquarters operating in 2014 and 2015 and promoting opioid drugs to physicians and teaching hospitals is exogenous to our outcome variable, opioid overdose rates in the respective years. For this we limit our set of pharmaceutical companies to the ones whose headquarters location in 2014/2015 was already determined before 1995.[19] All companies that started operations after 1995 or moved their headquarters after 1995 are dropped from our sample in the main analysis. We also show that opioid overdose rates before 1996 are independent from the distance to headquarters in 2015 in Figure 4. The location of the headquarters of the pharmaceutical companies, most of which also produce drugs besides opioid medications, is not significantly related to overdose rates before the large-scale onset of pharmaceutical promotion of opioid medication. Many of the headquarters are located on the East Coast. The reader may be concerned that our results are driven by outliers in terms of opioid death rates, that happen to be located close to the East Coast. West Virginia, Ohio and Kentucky have been hit particularly hard by the opioid epidemic and are located close to headquarters. Our results are not reliant on the inclusion of these three states. Excluding these states one by one, decreases our coefficient estimate from 0.31 to 0.25, but we do still find a positive and statistically significant relationship, confirming that our results are robust to outliers. Our estimates are mainly driven by counties located in the South and Midwest. We cannot capture the relationship of promotion and death for the West Coast, as distance to headquarters in kilometers is not relevant for these counties.[20]

To show that our results are not driven by small areas where opioid overdose rates are very

[18] In our empirical analysis we include a dummy for states that have any kind of ban in place in 2014 and 2015. We do not have a measure to which degree the laws prohibit promotion to physicians. As Massachusetts diluted the law in 2012, we perform a robustness check in which only Minnesota and Vermont are coded as states with bans. The partial F-Value of the first stage increases and our second stage coefficients of promotion on overdose death rates are larger. Results are available upon request.

[19] Before 1995, there is no evidence of pharmaceutical companies promotion opioid to physicians as treatment options for long-term non-malignant pain patients at large scales.

[20] Results are available upon request.

sensitive to small changes, we repeat our main analysis splitting our sample into two subsamples of counties with more and less than 100,000 inhabitants. Table 12 shows that coefficient estimates are identical for small and large counties. This also shows that the relationship we uncover for opioid promotion and overdoses is not exclusive to urban areas.

Although we have shown that overdose death rates of 1995 are unrelated to the location of pharmaceutical company headquarters one may still be concerned that promotion is particularly high in counties that have high demand for opioid drugs and that the location of the headquarters is related to previous levels of overdose rates. We therefore repeat our analysis of Equation (3) and (4) but additionally control for overdose death rates in the previous years. As seen in Table A8 overdose mortality rates are autocorrelated. We still find a positive and statistically significant relationship between opioid promotion and overdose death rates in the corresponding year. Our coefficient estimates are smaller once we control for previous death rates. Increasing promotion by 1% led to an increase in opioid death rates by 0.16%, The partial F-Value depicted in the last row of Table A8 implies that our instruments predict contemporaneous levels of promotion well, even when we control for previous overdose death rates. Additionally we show that it is not pharmaceutical promotion per se that is driving opioid overdose rates, but specifically promotion regarding opioid drugs. This helps us to rule out the concern that the counties with high levels of opioid promotion are just counties with high morbidity and high demand for all kinds of drugs. In the last column of Table A8 we control for pharmaceutical promotion spending of all drugs that are not opioid painkillers. Our coefficient estimates on opioid promotion do not change substantially. As we can see from the reduced partial F-Value in the last row, controlling for promotion of other drugs reduces the predictive power of our two instruments. This can be explained by the fact that the pharmaceutical companies that promote opioid drugs also promote other medication and devices. These estimates nevertheless speak against the interpretation that promotional efforts for all drugs are high due to higher morbidity and thus higher mortality.

To be able to derive policy implications, it is important to understand whether the promotion of opioid drugs leads to an increase in illicit drug overdoses or prescription opioids. We cannot distinguish whether the death in the mortality database occurred because the deceased followed the prescription of the physician or because he or she obtained the opioid drug through drug diversion or doctor shopping. However, we can distinguish whether an overdose occurred due to the consumption of an illicit (heroin) or legal opioid drug. Overdose death due to heroin intake is classified as T40.1 in the CDC multiple cause of death mortality data base. Table 13 displays the regression results of our two main regression, comparing the effect on all opioid overdose deaths with the effect on heroin overdoses. The coefficient from the 2SLS regression suggests that opioid promotion has a comparable effect on heroin overdoses as on prescription opioid overdoses. It is claimed that many patients who were prescribed opioid medications and became addicted, substituted to the use of illicit opioid drugs such as heroin. According to the National Survey on Drug Use and Health (NSDUH), between 2002 and 2011 80% of recent heroin initiates report prior use of opioid pain relievers (Muhuri et al., 2013).

We would expect pharmaceutical promotion to have a smaller impact on death rates if physicians are less sensitive towards promotion in their opioid prescription decisions. We investigate the heterogeneity of our effect on opioid death rates of two state policies that could lower the physicians' sensitivity towards opioid promotion. Many states introduced prescription monitoring programs (PMP) in the last years. Data about the prescription and dispensation of controlled substances (such as opioids) is collected and accessible by physicians, pharmacies and sometimes law enforcement officials. We expect pharmaceutical promotion to have a smaller impact on physicians behavior because their prescription behavior can be monitored by colleagues and potentially law enforcement officials and because the physicians can find out whether the patients have been receiving prescriptions for opioid drugs from other doctors. The second policy of interest is the legalization of medical marijuana. Again, we would expect that the physician's sensitivity towards promotion is lowered due to the availability of alternative non-opioid treatments for chronic or severe pain. In Table 14 we repeat our main estimation but splitting the sample into states with and without medical marijuana legalization and into states with and without prescription monitoring programs in place. In line with the hypothesis that these state laws decrease the physicians sensitivity towards opioid promotion we find that our coefficient estimates are smaller in counties where these laws are present (see column (1) and (3)).

Readers may still be concerned that counties with higher morbidity are the ones receiving more pharmaceutical promotion in general. To convince the readers that we are not only picking up the relationship of higher morbidity in general, we perform a placebo test. We show that death rates regarding diseases, that should be unrelated with opioid use and pain in general, is unrelated to opioid promotion. We run the same IV regression as depicted in Equation 3 and 4 but our dependent variable is now the rate of people that died from diabetes mellitus or from a stroke in the corresponding county (ICD Codes: E10-E14 and I60-I69). We pick death related to diabetes mellitus or strokes as our placebo outcomes, as they are among the ten leading causes of death in the US and deaths for which we expect no systematic relation with opioid misuse and overdose deaths.[21] Table A7 shows that the number of people dying from diabetes or strokes is not related with opioid promotion. This speaks against the interpretation that opioid death rates and promotion are high in counties with high levels of morbidity in general.

Throughout the empirical analysis at the county level we measure promotion with the number of physicians receiving promotion related to opioid drugs. In the Appendix we show that if we use the total dollar amount spent on opioid drug promotion instead, we still find a positive and statistically significant relationship with opioid-related overdose rates (Table A9). As in the OLS regressions,

[21]The other leading causes of death are heart diseases, cancer, chronic lower respiratory diseases, accidents (unintentional injuries), Alzheimers disease, influenza and pneumonia, nephritis, nephrotic syndrome, and nephrosis and intentional self-harm. None of these deaths would serve as good placebo tests. Research shows that opioid use could have adverse effects on the gastrointestinal, respiratory, cardiovascular, central nervous, musculoskeletal and endocrine system (Baldini et al., 2012). Additionally, the rates of suicides or accidents involving other drugs could be directly affected by the amount of opioids prescribed in the county. First, suicide attempts can include opioid drugs or heroin. Second, drug overdoses of other drugs could involve opioids without classification of opioid drugs in the death certificate (Ruhm, 2017). Third, opioid use could lead to addiction and substitution to other drugs.

our estimates are half the size compared to the regressions in which promotion is measured with the number of doctors receiving any kind of promotion.

In the last robustness check we investigate whether our results of a positive causal relationship between opioid promotion and overdose deaths hold if we use an alternative instrument. We instrument the number of physicians who receive opioid promotion with the number of physicians in the same county who receive pharmaceutical promotion for drugs, that are unrelated to pain or opioid medication (such as blood thinner or diabetes medication). The idea is that physicians get opioid promotion solely because sales representatives are also promoting unrelated drugs. This should affect opioid overdose deaths only through opioid promotion. We restrict our set of drugs to the 20 most promoted drugs in the corresponding years that are unrelated to opioids. An overview of the drugs, their purpose and the manufacturer can be found in Table A10 in the Appendix. Table A11 displays the results of the first and second stage regressions, based on Equations (3) and (4). Panel A indicates that the more physicians in a county receive promotion for unrelated drugs, the more physicians receive it for opioid medication as well. Both regressions control for county characteristics and the partial F-Value indicates that our instruments predicts our independent variable well. The second stage results show a positive relationship between opioid promotion and opioid overdoses. Again the IV estimates are larger than the OLS estimates in Table 4. The coefficient estimates of this alternative instrumental variable approach are close to the estimates of the baseline instrumental variable approach (see Table 6). Lastly, to affirm our results of opioid promotion leading to higher prescription rates by Medicare physicians and worsened neonatal health outcomes, we repeat the instrumental variable regressions using this alternative instrument. Results for neonatal health outcomes are depicted in Table A12. Coefficient estimates are similar for most of the symptoms analyzed. We also confirm the positive and statistically and economically significant relationship between promotion and prescription rates with the alternative instrument. Panel B in Table A13 shows that Medicare Physicians who receive promotion for medication unrelated to pain and opioids are more likely to receive opioid promotion. More opioid promotion ultimately leads to higher opioid prescription rates, as depicted in Panel A. The coefficient estimates are twice as large as in the OLS specification, mirroring the results of the analysis on opioid-related overdose death rates.

6 Conclusion

The opioid epidemic continues to be one of the most pressing public health concerns in the US. The public costs of the epidemic are staggering: in 2015, 33.000 people died of opioid overdoses. Hospitalization rates for opioid abuse increase steadily (1000 per day in the US in 2015). More and more babies are born with neonatal withdrawal symptoms, following the mothers' usage of opioid during pregnancy.

It is important to understand the causes of the epidemic to create optimal policies fighting the current epidemic and preventing future outbreaks. We show that pharmaceutical promotion

is positively related with opioid prescription rates of doctors and ultimately causes the number of overdose deaths to increase. The most conservative estimate from the fixed effect regression suggests that increasing pharmaceutical promotion by 1% from 2014 to 2015 increases death rates by 0.04%. This implies that 3% of the variation in death rates can be explained by promotion of opioid drugs. As an interesting case study, we also show that opioid overdose rates are significantly lower in Minnesota, after the introduction of the state ban on pharmaceutical promotion in 1997. Opioid overdose rates before 1995 are unrelated to the closeness of the counties to the headquarters of the pharmaceutical company and states that introduced a ban on promotional activities do not show differential overdose rates before the introduction, supporting the exogeneity assumption of our instruments.

In addition, we find that babies that are born in counties with high levels of pharmaceutical promotion of opioid-related drugs are more likely to be born with health outcomes in line with the neonatal abstinence syndrome: the neonates have lower birth weights, are more likely to be born prematurely and to need assisted ventilation. This negative effect seems to be particularly pronounced for promotion in the third trimester of the pregnancy, consistent with medical research showing that especially late in-utero exposure to opioids has detrimental health impacts for the babies.

We show that prescription rates are higher for Medicare physicians who receive pharmaceutical promotion for opioid analgesics, and our placebo test indicates that specifically receiving information and financial incentives for opioid analgesics is driving the increase in claim rates, not receiving any kind of promotion per se.

Physician opioid painkiller prescription behavior varies substantially, especially among general practitioners. The more opioid drugs are prescribed, the more people die of opioid-related overdoses (Schnell and Currie, 2017). Schnell and Currie (2017) find that parts of these variations can be explained by the quality of education physicians received in medical school. They argue that they cannot pin down precise differences in the curricula that ultimately lead to diverging prescription rates. One difference between the top and last ranking schools listed in their analysis is the score obtained by the American Medical Student Association on the conflict of interest policies at the medical schools (AMSA, 2016). Top ranking schools have good grades in the AMSA scorecard while low ranking schools show lower grades. Clearly, the presence of conflict of interest policies may correlate with other differences in the curricula of the schools. An interesting question for future research would be to investigate which medical school policies and curricula are the most effective in determining prescription behavior of the physicians. We find that physicians affiliated to hospitals with strict limits on interactions between sales representatives and health care professionals are less sensitive towards opioid promotion than physicians affiliated to teaching hospitals without such bans. In our analysis, unfortunately, we cannot rule out endogenous sorting of physicians nor patients into hospitals with stricter laws on the interaction between health care professionals and the pharmaceutical industry.

One of the causes of the epidemic is the room for misinformation of the pharmaceutical com-

panies in promoting directly to physicians and teaching hospitals. One solution to prevent further misbranding is to increase the FDA's ability to review and verify promotional material before its distribution.[22] In overseeing the promotional material of prescription drugs, there is no distinction for the FDA between controlled substance and other prescription drugs (GAO, 2003). All controlled substances have per definition potential for abuse and are dangerous when used incorrectly. Pharmaceutical companies are not allowed to run reminder advertisements in television or other forms of broadcast for controlled substance drugs (FDA Code of Federal Regulations 21CFR202.1). Extra caution should also be applied in verifying and controlling information that is distributed to physicians, in particular if it is mostly targeted at primary care physicians who may not have been adequately trained in pain management.

It is beyond the scope of this paper to make welfare statements about the benefits and harms of pharmaceutical promotion of controlled drugs to physicians in the US. Some physicians argue that they perceive promotion as beneficial, as it facilitates the learning about new medications. It is not clear how much physicians incorporate in their decision the fact that this information does not necessarily need to be accurate. To curtail the further spread of the opioid epidemic and to prevent future prescription mistakes we propose that promotional material must be verified by the FDA before manufacturers are allowed to distribute it and that failures to do so must be prosecuted.[23]

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[22] According to the Code of Federal Regulations Title 21 (Food and Administration (2015) and implementing regulations) manufacturers should submit their advertisement material to the FDA before distributing it. The FDA then reviews the material and verifies its accuracy. The FDA has a very limited number of staff responsible for the review of all the promotional material. Some opioid-promoting manufacturers distributed promotional material before it was verified by the FDA (Van Zee, 2009).

[23] A similar, albeit less demanding, recommendation has been put forth by the Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse, Board on Health Sciences Policy Health and Medicine Division: "Recommendation 6-5. Strengthen the post-approval oversight of opioids. The U.S. Food and Drug Administration should take steps to improve post-approval monitoring of opioids and ensure the drugs favorable benefit-risk ratio on an ongoing basis. Steps to this end should include [...] aggressive regulation of advertising and promotion to curtail their harmful public health effects." (Sciences et al., 2017).

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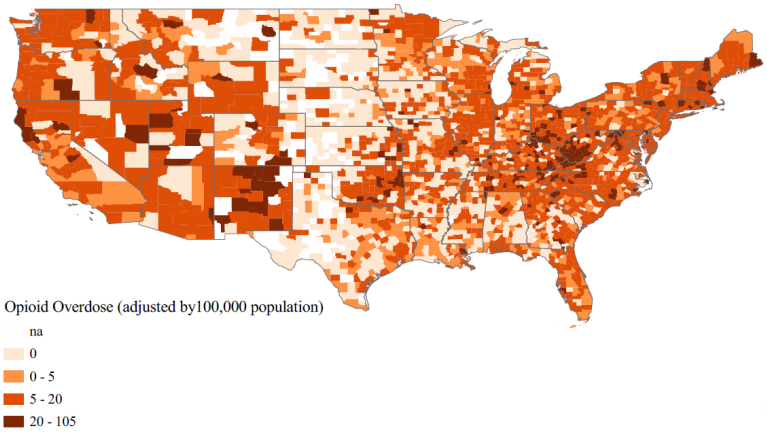
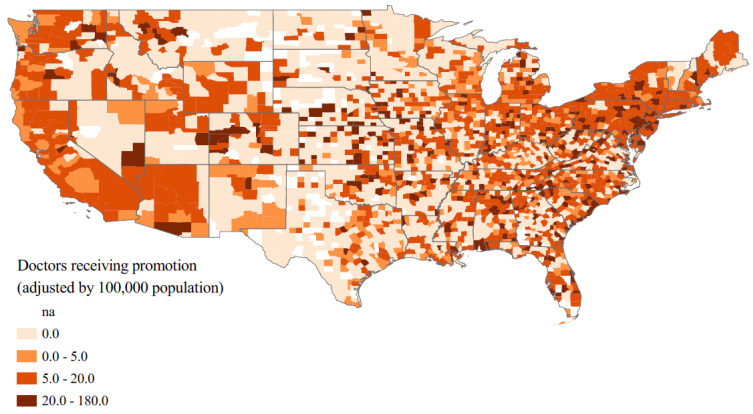
7 Figures and Tables

Figure 1: Number of opioid-related overdose death rates & Opioid Promotion in 2014

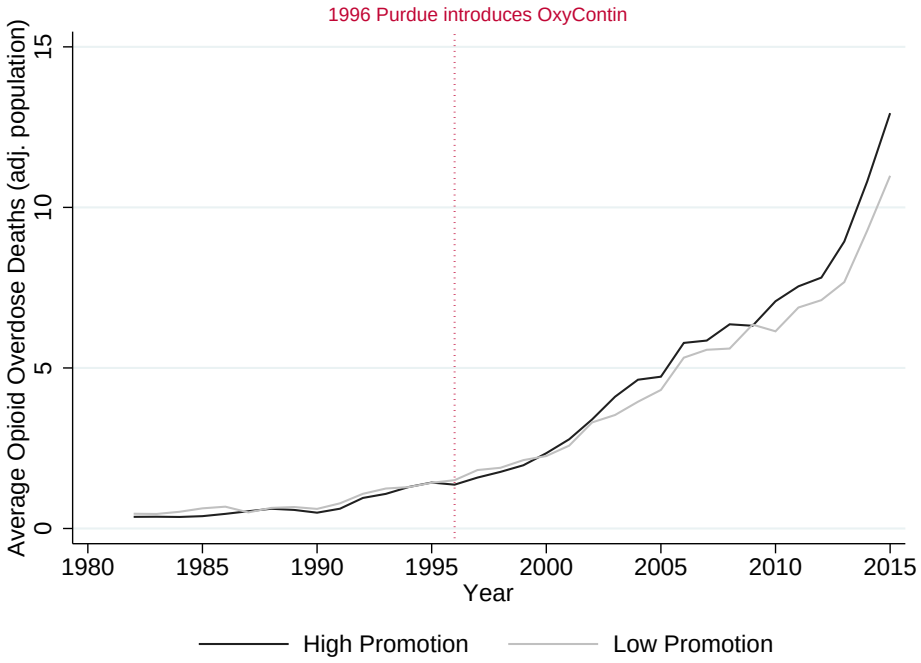


(a) Opioid-related overdoses in 2014. Source: CDC Wonder Mortality MCD Data



(b) Doctors receiving opioid promotion in 2014. Source: CMS Open Payments Data 2014

Figure 2: Diverging overdose rates



Average death rates (adj. 100.000 population) for high and low (below median) opioid promotion counties. Data available for 403 counties before 1999, counties with more than 100,000 inhabitants. Source: CMS Open Payments Data and CDC Wonder Mortality MCD Data

Table 1: Summary statistics US counties pharmaceutical promotion & opioid-related death rates 2014-2015

	Observations	Mean	Median	Std. Dev	Min	Max
2014						
County Aggregates						
Doctor receiving Opioid Promotion	3142	11.25	1.00	33.96	0	639
Doctor receiving Other Painkiller Promotion	3142	18.84	1.00	61.99	0	1539
Share of Payments with no Drug ID	2958	0.30	0.28	0.19	0.00	1.00
Total Payments for Opioids in $	3142	1161	7.15	19673	0	1067246
Total Payments for Opioids in $ (> 0)	1708	2137	79.62	26648	1.50	1067246
Total Payments for Painkillers in $	3142	2390	16.78	29996	0	1523839
Total Payments for Painkillers in $ (> 0)	1815	4137	156.11	39380	1.18	1523839
Visits to Physicians						
Av. visits by Opioid Sales Rep	1577	2.19	1.67	1.79	1.00	29.34
Av. visits by any Sales Rep	2958	6.56	5.35	4.76	1.00	28.02
Av. number of Manufacturers visiting for opioids	1483	1.00	1.00	0.00	1.00	1.00
Av. number of Manufacturers visiting for any drug	2957	1.25	1.24	0.19	1.00	4.00
Opioid-Related Overdose Death Rates (ICD-10 Code: T40.0-T40.4)						
Total Deaths	2929	9.55	2.00	26.87	0	449
Adjusted by Population (by 100,000)	2929	7.87	5.93	9.19	0	101
2015						
County Aggregates						
Doctor receiving Opioid Promotion	3142	9.88	0.00	33.10	0	729
Doctor receiving Other Painkiller Promotion	3142	21.79	2.00	70.63	0	1681
Share of Payments with no Drug ID	2905	0.29	0.26	0.20	0.00	1.00
Total Payments for Opioids in $	3142	2517	0.00	18510	0.00	439332
Total Payments for Opioids in $ (> 0)	1510	5238	80.41	26436	0.17	439332
Total Payments for Painkillers in $	3142	1952	20.68	12549	0.00	364560
Total Payments for Painkillers in $ (> 0)	1837	3339	160.83	16272	0.16	364560
Visits to Physicians						
Av. visits by Opioid Sales Rep	1511	1.00	1.00	0.10	1.00	5.00
Av. visits by any Sales Rep	2905	7.11	5.65	5.38	1.00	30.43
Av. number of Manufacturers visiting for opioids	1185	1.00	1.00	0.02	1.00	1.50
Av. number of Manufacturers visiting for any drug	2905	1.24	1.23	0.18	1.00	3.00
Opioid-Related Overdose Death Rates (ICD-10 Code: T40.0-T40.4)						
Total Deaths	2915	11.13	2.00	31.96	0	517
Adjusted by Population (by 100,000)	2915	9.00	6.39	10.4	0	131

Source: CMS Open Payment Data 2014 and 2015, CDC Wonder Multiple Cause of Death Data.

Table 2: Summary statistics neonatal health

	Observations	Mean	Median	Std. Dev	Min	Max
Health Outcomes						
Admission NICU	3845148	0.08	0	0.27	0	1
Assis. Ventilation Immedi.	3845148	0.04	0	0.18	0	1
Assis. Ventilation > 6 hrs	3845148	0.01	0	0.11	0	1
APGAR 5	3981330	8.78	9	0.84	0	10
Birth Weight	3994708	3272.89	3317	591.69	228	8165
Low Birth Weight (<2500g)	3994708	0.08	0	0.27	0	1
Born Prematurely (< 37 weeks)	3994872	0.11	0	0.32	0	1
Mother's Demographics						
Age	3998175	28.35	28	5.89	12	50
Born US (D=1)	3988351	0.78	1	0.41	0	1
White (D=1)	3866633	0.75	1	0.43	0	1
Educ. Attainment	3855275	4.29	4	1.80	1	9
Married	3998175	0.60	1	0.49	0	1
Smoker	3779767	0.08	0	0.28	0	1
Birth Order	3939398	2.48	2	1.57	1	8
Number of Babies born	3998175	1.04	1	0.19	1	5
Gest. Diabetes	3848302	0.05	0	0.23	0	1
Gest. Hypertension	3848302	0.05	0	0.22	0	1
Medicaid Recipient	3819768	0.44	0	0.50	0	1
Mother's BMI	3709225	26.54	25	6.55	13	68.90
Birth Characteristics						
Baby (Boy=1)	3998175	0.51	1	0.50	0	1
Vaginal Delivery	3852663	0.68	1	0.47	0	1
Prenatal Care Start 1st Trim.	3707352	0.77	1	0.42	0	1
Physician attended Delivery	3996146	0.90	1	0.30	0	1
Opioid Promotion: Number of Physicians						
During Pregnancy	3943598	15.89	11.89	14.33	0	235.45
1st Trimester	3952324	3.74	2.65	4.35	0	99.40
2nd Trimester	3943598	5.69	4.18	5.51	0	111.03
3rd Trimester	3943598	6.46	4.82	6.06	0	111.03
Min. Distance HQ in 1000 km	3943598	0.95	0.61	0.90	0	6.46
Presence State Ban (D=1)	3998175	0.04	0	0.19	0	1
Promotion Other Drugs[a]: Number of Physicians						
During Pregnancy	3943598	390.66	326.78	296.67	0	5011.16
1st Trimester	3952324	93.47	73.70	94.04	0	1736.54
2nd Trimester	3943598	136.42	112.79	104.34	0	1885.39
3rd Trimester	3943598	160.56	139.05	113.73	0	1885.39

[a]see Table A10 for list of drugs

Source: CMS Open Payments Data 2013 and 2014, CDC 2014 Natality Detail Data Set.

Table 3: Summary statistics Medicare prescribers 2014

	N	Mean	Std. Dev	Min	Max
Drug Claims 2013 & 2014					
Opioid Claims 2014	753975	106	310	0	26449
Opioid Claims 2014 (if > 0)	503757	159	368	11	26449
Opioid Claims 2013	970367	73	262	0	21519
Opioid Claims 2013 (if > 0)	414174	173	379	11	21519
Total Drug Claims 2014	1072851	1318	3171	11	226081
Total Drug Claims 2013	970367	1405	3255	11	191530
Share Opioid overall Drug Claims 2014	1072851	0.09	0.16	0.00	1.00
Payments Received					
Payments received for Opioids 2014	1072851	2.57	210.25	0.00	70488
Payments received for Opioids 2014 (if > 0)	27729	99	1304	0.21	70488
Payments received for Non-Painkiller 2014	1072851	1130	51439	0.00	43859980
Payments received for Non-Painkiller 2014 (if > 0)	430134	2819	81209	0.01	43859980
Payments received for Other Painkillers 2014	1072851	3.62	189	0.00	70249
Payments received for Other Painkillers 2014 (if > 0)	33867	115	1059	0.21	70249
Payments received for Drugs Unrelated to Pain 2014[a]	1072851	76.13	1867	0.00	304084
Payments received for Drugs Unrelated to Pain 2014[a] (if > 0)	153437	532.29	4914	0.16	304084
Closest HQ Distance & State Ban					
Min. Distance HQ in 1000 km	1072851	0.86	0.88	0	12.5
Presence State Ban (D=1)	1072851	0.05	0.21	0	1
Physician Specialty					
Internal Medicine	1072851	0.12	0.33	0	1
Nurse	1072851	0.10	0.30	0	1
Dentist	1072851	0.12	0.33	0	1
Emergency Medicine	1072851	0.04	0.20	0	1
Pain Management	1072851	0.00	0.06	0	1
Family Medicine	1072851	0.10	0.30	0	1
Others	1072851	0.51	0.50	0	1
Physician Characteristics					
Affiliated to Hospital with Ban on Sales Reps	67675	0.91	0.29	0	1
Physician Male	711125	0.60	0.49	0	1
Graduation Year	673922	1994	12.57	1943	2017

[a]see Table A10 for list of drugs

Source: CMS Medicare Opioid Prescriber Summary File for Number of Opioid Claims and other Claims 2013 and 2014. Additional physician characteristics from Medicare Compare and AMSA Scorecard.

Table 4: OLS: Opioid overdose deaths and opioid promotion

Dependent Variable: log Opioid Overdose Deaths	(1) 2014	(2) 2015	(3) 2015	(4) 2014	(5) 2015	(6) 2015
log Receiving Doctors 2014	0.0921***		0.00151			
	(0.0188)		(0.0221)			
log Receiving Doctors 2015		0.111***	0.110***			
		(0.0185)	(0.0225)			
log USD 2014				0.0554***		0.00892
				(0.00917)		(0.0108)
log USD 2015					0.0575***	0.0529***
					(0.00858)	(0.0104)
Mean Dep. Var.	1.615	1.714	1.714	1.615	1.714	1.714
SD Dep. Var.	1.175	1.204	1.204	1.175	1.204	1.204
Observations	2918	2905	2905	2918	2905	2905
R2	0.322	0.347	0.347	0.326	0.348	0.348
State F.E.	Y	Y	Y	Y	Y	Y
County Characteristics	Y	Y	Y	Y	Y	Y

Estimation result of Equation (1). Opioid overdoses and opioid promotion (number of doctors that receive promotion and dollar amount) normalized by county population. State fixed effects included in all regressions. County characteristics included in the regression: unemployment rate, log median income, poverty rate, population, industry shares, share of population enrolled in Medicare Prescription Drug Plan, dummy urban/rural. Standard errors in parentheses adjusted for heteroscedasticity, * (p<0.10), ** (p<0.05), *** (p<0.01). Source: CDC Wonder Mortality Data and CMS Open Payments Data 2014, 2015.

Table 5: Fixed effect regression: opioid overdose deaths and opioid promotion

Dependent Variable: log Opioid Overdose Deaths	(1)	(2)
log Receiving Doctors	0.0346*	
	(0.0205)	
log USD		0.0168
		(0.0106)
Mean Dep. Var.	1.689	1.689
SD Dep. Var.	1.181	1.181
Observations	5658	5658
R2	0.0227	0.0227
Year F.E.	Y	Y
County F.E.	Y	Y
Time Varying County Characteristics	Y	Y

Estimation result of Equation (2). Opioid overdoses and opioid promotion (number of doctors and dollar amount) normalized by county population. For list of time-varying county characteristics see footnote of Table 4. Standard errors in parentheses clustered at state level, * (p<0.10), ** (p<0.05), *** (p<0.01). Source: CDC Wonder Mortality Data and CMS Open Payments Data 2014, 2015.

Table 6: 2SLS: Opioid overdoses and opioid promotion

	Panel A: First Stage		
Dep. Var.: log Receiving Doctors	(1)	(2)	(3)
Dist. calculated to:	All Headquarters	Opened before 1995	
State Ban (D=1)	-0.913***	-0.803***	-0.963***
	(0.0634)	(0.0628)	(0.0608)
Distance closest HQ in km	-0.596***	-0.226***	-0.172***
	(0.0431)	(0.0243)	(0.0232)
Mean Dep. Var.	1.193	1.193	1.197
SD Dep. Var.	1.278	1.278	1.278
Observations	6284	6284	6266
R2	0.0517	0.0292	0.284
Partial F-Value	131.4	93.80	123.0
County Controls	N	N	Y
Year F. E.	Y	Y	Y

	Panel B: Second Stage		
Dep. Var.: log Opioid Overdose Deaths	(1)	(2)	(3)
Instruments: State ban and Distance to	All Headquarters	Opened before 1995	
log Receiving Doctors	0.687***	0.337***	0.317***
	(0.0652)	(0.0825)	(0.0782)
Mean Dep. Var.	1.664	1.664	1.664
SD Dep. Var.	1.191	1.191	1.190
Observations	5844	5844	5840
County Controls	N	N	Y
Year F. E.	Y	Y	Y

Estimation results of Equations (3) and (4). Partial F-value of first stage Equation (3) displayed in last row in Panel A. Opioid overdoses and the number of doctors receiving opioid promotion both normalized by county population. Control county characteristics: unemployment rate, log median income, poverty rate, population, industry shares, share of the population that is enrolled in the Medicare Prescription Drug Plan, dummy urban/rural. Standard errors in parentheses adjusted for heteroscedasticity, * (p<0.10), ** (p<0.05), *** (p<0.01).

Table 7: OLS: Neonatal health and opioid promotion

	(1) Admission NICU	(2) Ventilation Immediately	(3) Ventilation > 6hr	(4) APGAR 5	(5) Birth Weight	(6) Low BW < 2500g	(7) Premature Born
			Panel A: Promotion During Pregnancy				
Promotion 9 Months	0.00516***	0.000689	0.000855***	-0.0112***	-4.711***	0.00277***	0.00236***
before Delivery	(0.000905)	(0.000604)	(0.000281)	(0.00399)	(1.133)	(0.000463)	(0.000562)
R2	0.0710	0.0249	0.0189	0.0291	0.163	0.143	0.102
MHT adj. P-Value	0.00	1.00	0.02	0.04	0.00	0.00	0.00
			Panel B: Promotion By Trimester				
1st Trimester	0.00402**	-0.0000152	0.000210	-0.00793	-5.019***	0.00304***	0.00143
	(0.00161)	(0.00103)	(0.000516)	(0.00762)	(1.946)	(0.000848)	(0.00113)
2nd Trimester	0.00455***	-0.000911	0.000109	-0.00946*	-3.410**	0.00221***	0.00220**
	(0.00118)	(0.000854)	(0.000457)	(0.00546)	(1.629)	(0.000731)	(0.000990)
3rd Trimester	0.00641***	0.00258**	0.00193***	-0.0147**	-5.698***	0.00311***	0.00309***
	(0.00158)	(0.00105)	(0.000450)	(0.00678)	(1.929)	(0.000882)	(0.000898)
Mean Dep. Var.	0.0808	0.0351	0.0112	8.785	3280.2	0.0777	0.110
SD Dep. Var.	0.273	0.184	0.105	0.825	584.9	0.268	0.313
Observations	3436124	3436124	3436124	3429416	3439713	3439713	3440894
R2	0.0710	0.0249	0.0190	0.0291	0.163	0.143	0.102
MHT adj. P-Value	0.00	0.09	0.00	0.21	0.02	0.00	0.00
Mother's Demographics	Y	Y	Y	Y	Y	Y	Y
Birth Characteristics	Y	Y	Y	Y	Y	Y	Y
Month of Birth F.E.	Y	Y	Y	Y	Y	Y	Y
State F.E.	Y	Y	Y	Y	Y	Y	Y

Estimation result of Equation (1). Opioid promotion measured as number of doctors receiving opioid promotion in the county of birth during pregnancy (normalized by county population). Mother's characteristics controlled for in all regressions are age, race, educational attainment, marital status, insurance status, mother's health (BMI, hypertension, diabetes), whether mother was born in the US and whether the mother is a smoker. Characteristics of births included in all regressions: vaginal delivery, sex of the baby, birth order, number of babies, early prenatal visits, attendant at birth is physician. State fixed effects included in all regressions. Standard errors in parentheses clustered at county level, * (p<0.10), ** (p<0.05), *** (p<0.01). P-Values adjusted for multiple hypothesis testing (Bonferroni adjustment) displayed for promotion during the entire pregnancy in Panel A and for promotion in the third trimester in Panel B. Source: CDC 2014 Natality Detail Data Set and CMS Open Payments Data 2014, 2015.

Table 8: 2SLS: Neonatal health and opioid promotion

	(1) Admission NICU	(2) Ventilation Immediately	(3) Ventilation > 6hr	(4) APGAR 5	(5) Birth Weight	(6) Low BW < 2500g	(7) Premature Born
Panel A: Second Stage Results							
Promotion 9 Months before Delivery	0.00233	0.00183	0.00340***	-0.0103	-10.79*	0.00497***	0.0124***
	(0.00447)	(0.00363)	(0.00129)	(0.0205)	(5.849)	(0.00179)	(0.00291)
Mean Dep. Var.	0.0808	0.0351	0.0112	8.785	3280.2	0.0777	0.110
SD Dep. Var.	0.273	0.184	0.105	0.825	584.9	0.268	0.313
Observations	3436124	3436124	3436124	3429416	3439713	3439713	3440894
Mother's Demographics	Y	Y	Y	Y	Y	Y	Y
Birth Characteristics	Y	Y	Y	Y	Y	Y	Y
Month of Birth F.E.	Y	Y	Y	Y	Y	Y	Y
Panel B: First Stage Results							
β Dist. HQ 2014	-0.385***	-0.385***	-0.385***	-0.385***	-0.385***	-0.385***	-0.385***
	(0.0560)	(0.0560)	(0.0560)	(0.0560)	(0.0560)	(0.0560)	(0.0560)
β State Ban	-1.360***	-1.360***	-1.360***	-1.360***	-1.360***	-1.360***	-1.360***
	(0.152)	(0.152)	(0.152)	(0.152)	(0.152)	(0.152)	(0.152)
Partial F-Value	46.64	46.64	46.64	46.67	46.69	46.69	46.68

Estimation result of Equations (3) and (4). Opioid promotion measured as number of doctors receiving opioid promotion in the county of birth during pregnancy (normalized by county population). Partial F-value of first stage Equation (3) displayed in last row. Coefficient estimates and standard errors of first stage regression displayed in Panel B. Distance to closest HQ in 2014 measured in 1000km. HQ considered here are reduced set of HQ described in Section 1. Mother's characteristics controlled for in all regressions are age, race, educational attainment, marital status, mother medicaid recipient, mother's health (BMI, hypertension, diabetes), whether mother was born in the US and whether the mother is a smoker. Characteristics of births included in all regressions: vaginal delivery, sex of the baby, birth order, early prenatal visits, attendant at birth is physician. Standard errors in parentheses clustered at county level, * (p<0.10), ** (p<0.05), *** (p<0.01). Source: CDC 2014 Natality Detail Data Set and CMS Open Payments Data 2014, 2015.

Table 9: Opioid prescriptions and opioid promotion: OLS & 2SLS

Method:	OLS		2SLS	
Dependent Variable:	(1)	(2)	(3)	(4)
Opioid Prescriptions	# Pres. 2014	# Pres. 2014	# Pres. 2014	# Pres. 2014
Opioid Promotion (Dummy)	45.54***		42.07**	
	(2.602)		(20.50)	
Opioid Promotion (log USD)		15.55***		13.69**
		(0.895)		(6.644)
# Opioid Pres. 2013	0.976***	0.974***	0.978***	0.976***
	(0.00703)	(0.00707)	(0.00765)	(0.00818)
Mean Dep. Var.	114.9	114.9 .	114.9	114.9
SD Dep. Var.	322.3	322.3	322.9	322.9
Observations	633306	633306	686275	686275
R2	0.888	0.889	0.888	0.888
County F.E.	Y	Y	N	N
Physician Specialty	Y	Y	Y	Y
First Stage Results				
β Dist. HQ 2014			-0.00318***	-0.00970***
			(0.000288)	(0.000981)
β State Ban			-0.0155***	-0.0477***
			(0.000878)	(0.00310)
Partial F-Value			187.6	145.6

Number of opioid claims of Medicare Physicians and opioid-related promotion OLS and 2SLS estimates. 2SLS estimation results of Equations (5) and (6). First stage results depicted at the end of the Table. Promotion is instrumented with the distance of the physicians office to the closest headquarters (reduced set of headquarters) and the presence of a state ban on promotion. Promotional level measured as dummy for any promotion in column (1) and (3) and as log dollar amount in column (2) and (4), respectively. All regressions control for the specialty of the physician and opioid prescription in the previous year. OLS estimates additionally include county fixed effects. Standard errors in parentheses clustered at zip-code, * (p<0.10), ** (p<0.05), *** (p<0.01). Source: Medicare Opioid Prescriber Summary File and CMS Open Payments Data 2014.

Table 10: Placebo: Opioid prescriptions and non-opioid promotion

Method:	OLS
Dep. Var.:	(1)
Opioid Prescriptions	# Pres. 2014
Non-Opioid Non-Painkiller Promotion	0.0206
	(0.0671)
Non-Opioid Painkiller Promotion	4.349***
	(0.497)
Opioid Promotion	14.09***
	(0.824)
# Opioid Pres. 2013	0.972***
	(0.00722)
County FE	Y
Physician Specialty	Y
Mean Dep. Var.	114.9
SD Dep. Var.	322.3
Observations	633306
R2	0.889

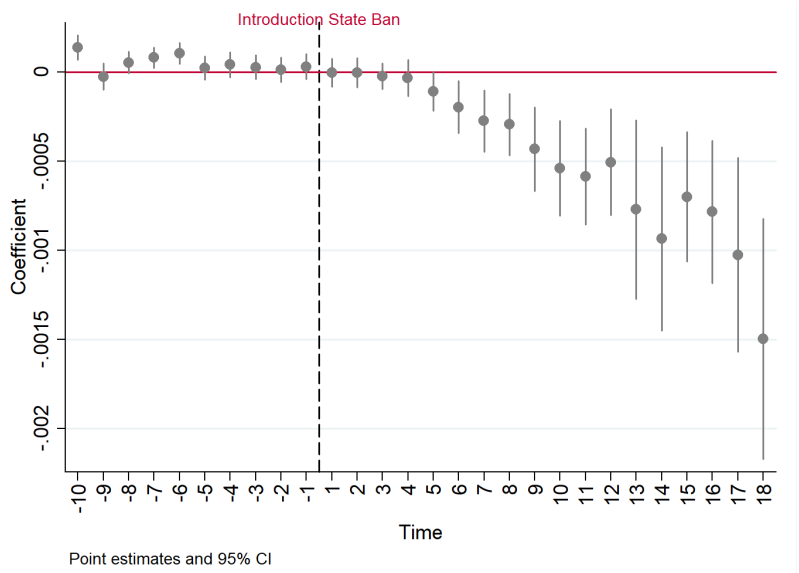
Number of opioid claims of Medicare Physicians and non-opioid and non-painkiller promotion. Promotion measured as log dollar amount received in corresponding year. Estimation result of Equation (5). All regressions control for specialty of physician, county fixed effects and opioid prescription in the previous year. Standard errors in parentheses clustered at zipcode level, * (p<0.10), ** (p<0.05), *** (p<0.01). Source: Medicare Opioid Prescriber Summary File and CMS Open Payments Data 2014.

Table 11: Opioid prescriptions and opioid promotion: Heterogeneity by physician characteristics

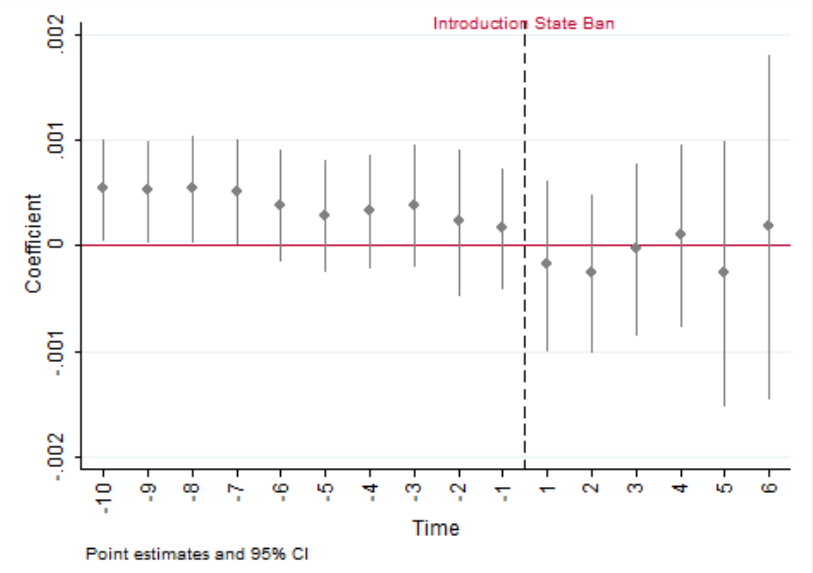
	(1) # Opioid Prescriptions	(2) # Opioid Prescriptions	(3) Received Opioid Promotion (D=1)
Received Opioid Promotion (D=1)	436.3***	278.7***	
	(68.75)	(71.27)	
Sales Rep. Ban	-11.15	-9.233	-0.00811**
	(7.780)	(7.578)	(0.00347)
Sales Rep. Ban * D	-127.8*	-144.5**	
	(72.52)	(72.69)	
Male		24.67***	0.0154***
		(2.245)	(0.00141)
Male * D		178.9***	
		(32.92)	
Graduated before 1995		51.08***	0.0203***
		(2.685)	(0.00166)
Graduated before 1995 * D		29.65	
		(41.31)	
County FE	Y	Y	Y
Physician Specialty	Y	Y	Y
Mean Dep. Var.	118.2	118.0	0.0272
SD Dep. Var.	288.2	288.2	0.163
Observations	43511	43196	67174
R2	0.267	0.280	0.0350

OLS estimates of the relationship between the number of opioid claims of Medicare Physicians and opioid promotion in columns (1) and (2), controlling for physician characteristics and the interactions with the receipt of promotion. The characteristics included are whether the physician is affiliated to a hospital with a ban on sales representatives entering the hospital in place, the gender of the physician and whether she or he graduated before 1995. Last column (3) shows the relationship between these characteristics and the probability to receive promotion for opioid drugs. All regressions control for specialty of physician and county fixed effects. Standard errors in parentheses clustered at zipcode level, * (p<0.10), ** (p<0.05), *** (p<0.01). Source: Medicare Opioid Prescriber Summary File, 2014 AMSA Scorecard and CMS Open Payments Data 2014.

Figure 3: Introduction state bans on promotion orthogonal towards opioid death rates

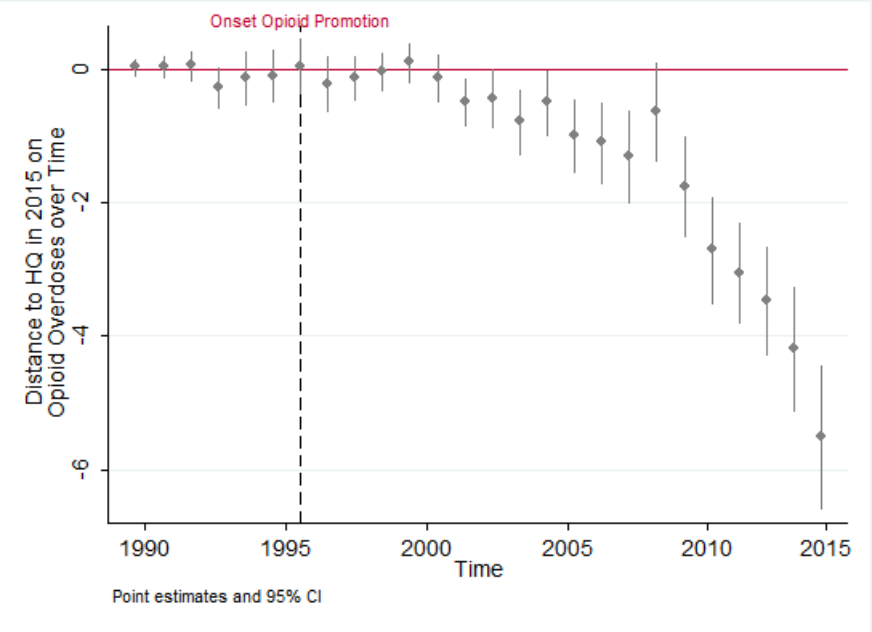


(a) Difference in opioid overdose death rates between Minnesota and the rest of the US, 1987-2015. Source: CDC Wonder Mortality MCD Data



(b) Difference in overdose rates between Massachusetts/Vermont and the rest of the US, 1999-2015 (excl. Minnesota). Source: CDC Wonder Mortality MCD Data

Figure 4: Reduced form estimates: Distance to headquarters and overdose death rates over time.



Coefficent estimates and 95% confidence intervals of distance of county centroids to opioid promoting HQs (in 1000km) in 2015 on opioid overdose death rates, 1990-2015. Source: CMS Open Payment 2015, CDC Wonder Mortality MCD Data, company homepages for HQ location.

Table 12: 2SLS overdoses and promotion: Small vs. large counties

Dependent Variable:	(1)	(2)
log Overdose Death in Counties with:	$<$ 100,000 inh.	$\geq$ 100,000 inh.
log Receiving Doctors	0.394***	0.399***
	(0.108)	(0.108)
Mean Dep. Var.	1.525	2.209
SD Dep. Var.	1.252	0.674
Observations	4662	1182
Partial F-Value	78.56	31.35
Year F. E.	Y	Y

2SLS regression results (see Eq. (3) and (4)), splitting set into counties with less and more than 100,000 inhabitants. Instrument: minimum distance to headquarters, that opened before 1995 and dummy for state ban on promotion. Standard errors in parentheses adjusted for heteroscedasticity, * (p<0.10), ** (p<0.05), *** (p<0.01).

Table 13: Illicit vs all opioid overdose deaths

	(1)	(2)	(3)	(4)
Method	OLS		IV	
log Overdose Deaths	All	Heroin	All	Heroin
log Receiving Doctors	0.102***	0.0644***	0.317***	0.336***
	(0.0138)	(0.00997)	(0.0782)	(0.0829)
Mean Dep. Var.	1.664	0.667	1.664	0.668
SD Dep. Var.	1.190	0.906	1.190	0.906
Observations	5823	5823	5840	5840
Partial F-Value	.	.	123.0	81.93
County Controls	Y	Y	Y	Y
Year F.E.	Y	Y	Y	Y

OLS and IV estimates for overdoses only including Heroin (T40.1) compared to all opioid overdoses. OLS estimate from Equation (1) and IV following Equation (3) and (4). Doctors receiving promotion instrumented by the distance to the closest headquarters (opened before 1995) and presence of state ban. First and second stage controls for county characteristics (see Table 6). Standard errors in parentheses adjusted for heteroscedasticity, * (p<0.10), ** (p<0.05), *** (p<0.01).

Table 14: 2SLS overdoses and promotion: Hetereogeneity by state legalization of medical marijuana and presence of PMP

Dep. Variable: log Overdose Death	(1)	(2)	(3)	(4)
State Law:	Med. Marijuana Legal	Med. Marijuana Not Legal	PMP	No PMP
log Receiving Doctors	0.297***	1.124***	0.382***	1.228***
	(0.103)	(0.149)	(0.108)	(0.217)
Mean Dep. Var.	1.799	1.600	1.694	1.361
SD Dep. Var.	1.132	1.212	1.182	1.237
Observations	1876	3949	5309	516
Partial F-Value	59.16	61.90	51.90	29.85
Year F.E.	Y	Y	Y	Y

IV estimates following Equation (3) and (4) for opioid-related overdose deaths and promotion in 2015. The sample is first split into counties with and without state laws legalizing the use of medical marijuana (column (1) and (2)). In column (3) and (4) the sample is split into counties with and without prescription monitoring programs. The number of doctors that receive promotion is instrumented by the distance to the closest headquarters (opened before 1995) and presence of state ban. Standard errors in parentheses adjusted for heteroscedasticity, * (p<0.10), ** (p<0.05), *** (p<0.01).

8 Appendix

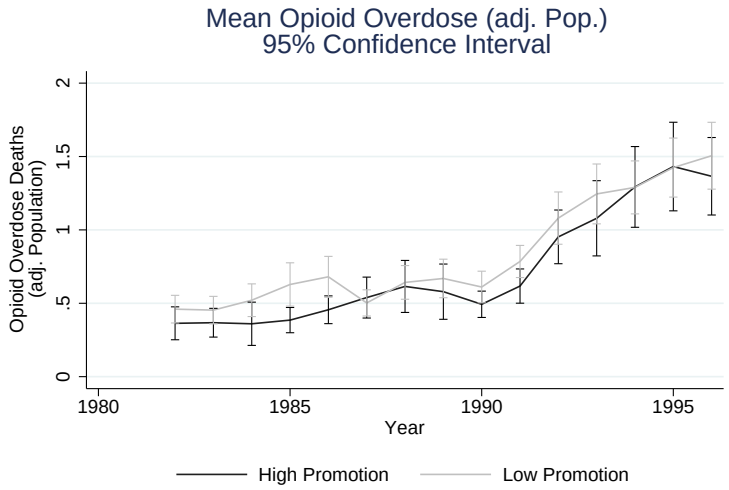
8.1 Data source overview

Table A1: Data availability

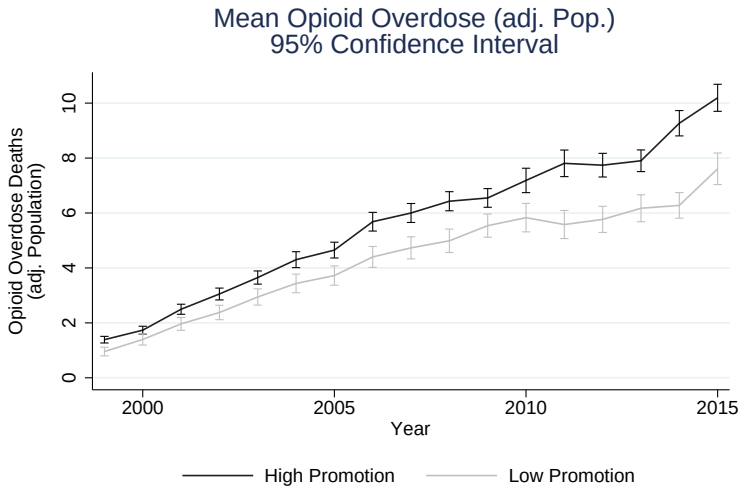
Data	Available Time Period	Unit	Source
Pharmaceutical Payment Data	08/2013 - 12/2015	Physician	CMS Open Payments Data
Opioid-related Overdose Death Rates (all counties)	1999-2015	County	CDC Wonder Mortality MCD Data
Opioid-related Overdose Death Rates (counties >100,000 inh.)	1982-2015	County	CDC Wonder Mortality MCD Data
Medicare Physician Prescription Data	2013-2014	Physician	Medicare Part D Provider Data
Medicare Physician Compare	2014-2016	Physician	CMS Physician Compare
AMSA Scorecard Medical Colleges Conflict-of-Interest Policies	2008-2016	Hospital	2014 AMSA Scorecard
Neonatal Health 2014	2014	Birth	CDC 2014 Natality Detail Data Set

8.2 Opioid overdose death rate evolution

Figure A1: Overdose Evolution



(a) Average death rates (adj. 100.000 population) for high and low (below median) opioid promotion counties, before introduction of OxyContin. Data available for 403 counties before 1999, counties with more than 100,000 inhabitants. Source: CDC Wonder Mortality MCD Data & CMS Open Payments Data 2013-2015



(b) Average death rates (adj. 100.000 population) for high and low (below median) opioid promotion counties 1999-2015, 95% confidence interval. All counties included. Source: CDC Wonder Mortality MCD Data & CMS Open Payments Data 2013-2015.

8.3 Substance names opioid analgesic & list of manufacturers promoting opioids

Table A2: Substance names used to identify opioid analgesic in payment data

Morphine	Opium	Hydromorphone
Nicomorphine	Oxycodone	Papaveretum
Ketobemidone	Pethidine	Fentanyl
Dextromoramide	Piritramide	Dextropropoxyphene
Bezitramide	Methadone	Pentazocine
Phenazocine	Butorphanol	Nalbuphine
Tilidine	Tramadol	Dezocine
Meptazinol	Tapentadol	

Source: Anatomical Therapeutic Chemical (ATC) Classification System WHOCC, ATC Code N02A

Table A3: List of Opioid promoting manufacturers

Manufacturer Operating in 2014	**Headquarters Opening**	**Reduced Set**	**Manufacturer Operating in 2015**	**Headquarters Opening**	**Reduced Set**
Galena Biopharma, Inc.	2015	No	Egalet US Inc	1995	Yes
Janssen Pharmaceuticals, Inc	1993	Yes	Galena Biopharma, Inc.	2015	No
Johnson & Johnson Health Care Systems Inc.	1886	Yes	INSYS Therapeutics Inc	1990	No
Mallinckrodt LLC	1867	Yes	Janssen Pharmaceuticals, Inc	1993	Yes
Marathon Pharmaceuticals, LLC	2010	No	Mallinckrodt LLC	1867	Yes
Mylan Pharmaceuticals Inc.	1976	Yes	Mylan Pharmaceuticals Inc.	1976	Yes
Pfizer Inc.	1961	Yes	Pfizer Inc.	1961	Yes
Purdue Pharma	2000	No	Purdue Pharma L.P.	2000	No
Upsher-Smith Laboratories Inc.	1919	Yes	The Medicines Company	1996	No
			Upsher-Smith Laboratories Inc.	1919	Yes

List of manufacturers promoting opioid medication in 2014 and 2015, respectively. Company dropped from list of headquarters to calculate closest distance if opened after 1995. INSYS Therapeutics Inc dropped for 2015 because most of the revenue generated from opioid medications. Results not sensitive to inclusion of this manufacturer.
Source: CMS Open Payments Data 2014, 2015 and company homepages for headquarters opening dates.

8.8 Reduced form: Presence of state ban and overdose death rates 1990-2015

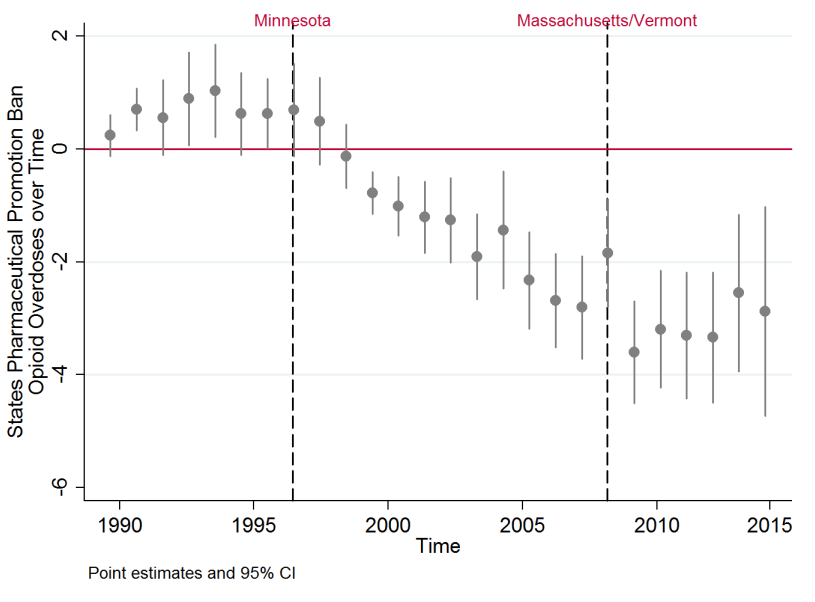


Figure A2: Coefficent estimates and 95% confidence intervals of state ban dummy (Minnesota, Vermont, Massachusetts) on opioid overdose death rates, 1990-2015. Source: State legislations, CDC Wonder Mortality MCD Data.

Table A4: Summary statistics US county characteristics 2014 and 2015

	Mean	Std. Dev	Min	Max
2014				
Promotion (adjusted by population)				
Doctors receiving Opioid Promotion	7.20	11.47	0.00	173.65
Doctors receiving other Painkiller Promotion	11.90	16.42	0.00	165.78
Share of Expenditures spent on opioids	0.004	0.02	0.00	0.66
Minimum Distance to Headquarters (km)	0.60	0.43	0.00	4.24
Socio-economic characteristics				
Rural Dummy	0.42	0.49	0	1
Unemployment Rates	0.06	0.02	0.01	0.24
Population ('000)	101.48	326.17	0.09	10171
Log Median Income	10.73	0.24	9.98	11.74
Poverty Share	16.84	6.46	3.20	52.20
Medicare Part D enrollment	0.11	0.04	0.01	0.27
Share Whites	0.72	0.29	0.00	0.99
Industry Shares				
Natural resources & mining	0.07	0.11	0.00	1.00
Construction	0.06	0.05	0.00	0.71
Manufacturing	0.15	0.12	0.00	0.78
Trade, transportation, & utilities	0.26	0.09	0.00	1.00
Information	0.01	0.01	0.00	0.15
Financial activities	0.05	0.03	0.00	0.37
Professional & business services	0.08	0.06	0.00	0.93
Education & health services	0.17	0.08	0.00	0.82
Leisure & hospitality	0.13	0.08	0.00	0.94
Other services	0.03	0.02	0.00	0.56
Unclassified	0.00	0.00	0.00	0.07
2015				
Promotion (adjusted by population)				
Doctors receiving Opioid Promotion	5.55	9.25	0.00	135.41
Doctors receiving other Painkiller Promotion	13.66	19.45	0.00	224.13
Share of Expenditures spent on opioids	0.004	0.03	0.00	1.00
Minimum Distance to Headquarters (km)	0.57	0.39	0.00	4.24
Socio-economic characteristics				
Rural Dummy	0.42	0.49	0	1
Unemployment Rates	0.06	0.02	0.02	0.24
Population ('000)	102.30	329.21	0.09	10171
Log Median Income	10.76	0.24	10.04	11.74
Poverty Share	16.26	6.44	3.40	47.40
Medicare Part D enrollment	0.11	0.04	0.01	0.27
Share Whites	0.71	0.29	0.00	0.99
Industry Shares				
Natural resources & mining	0.06	0.10	0.00	1.00
Construction	0.06	0.04	0.00	0.75
Manufacturing	0.14	0.12	0.00	0.78
Trade, transportation, & utilities	0.26	0.09	0.00	1.00
Information	0.01	0.01	0.00	0.13
Financial activities	0.05	0.03	0.00	1.00
Professional & business services	0.08	0.06	0.00	0.94
Education & health services	0.17	0.08	0.00	0.79
Leisure & hospitality	0.13	0.08	0.00	0.93
Other services	0.03	0.02	0.00	0.28
Unclassified	0.00	0.00	0.00	0.08

8.4 Physician level: opioid prescriptions and promotions

Table A5: OLS estimates promotion & prescriptions: different functional specifications

Functional Form	Linear	Log	Elasticity	Deciles
Dep. Var.:	(1)	(2)	(3)	(4)
Opioid Prescriptions	# Pres. 2014	# Pres. 2014	# Pres. 2014 (log)	# Pres. 2014
Opioid Promotion (USD)	0.00526**			
	(0.00238)			
Opioid Promotion (log USD)		15.55***	0.114***	
		(0.895)	(0.00168)	
D=1 Decile 10 (< 11 USD)				25.54***
				(4.576)
D=1 Decile 20 (13 USD)				26.31***
				(4.537)
D=1 Decile 30 (15 USD)				23.49***
				(3.674)
D=1 Decile 40 (18 USD)				22.92***
				(4.904)
D=1 Decile 50 (23 USD)				21.40***
				(4.494)
D=1 Decile 60 (29 USD)				28.96***
				(4.136)
D=1 Decile 70 (38 USD)				38.59***
				(5.560)
D=1 Decile 80 (54 USD)				58.39***
				(6.487)
D=1 Decile 90 (98 USD)				75.21***
				(8.686)
D=1 Decile 100 (> 98 USD)				151.5***
				(12.87)
Mean Dep. Var.	114.9	114.9	2.958	114.9
SD Dep. Var.	322.3	322.3	2.176	322.3
Observations	633306	633306	633306	633306
R2	0.888	0.889	0.752	0.889
County F.E.	Y	Y	Y	Y
Specialty F.E.	Y	Y	Y	Y
Previous Prescription Rates	Y	Y	Y	Y

Number of opioid claims of Medicare Physicians and opioid-related promotion. Estimation result of Equation (5). All regressions control for specialty of physician, prescription rates in the previous year and county fixed effects. Standard errors in parentheses clustered at zip-code level, * (p<0.10), ** (p<0.05), *** (p<0.01). Source: Medicare Opioid Prescriber Summary File and CMS Open Payments Data 2014.

Table A6: Promotion and share of opioid claims over all claims

	(1) % Opioid Claims	(2) % Opioid Claims
Opioid Promotion	0.00239***	0.00400***
	(0.000200)	(0.000215)
Non-Opioid Non-Painkiller Promotion		-0.00156***
		(0.0000692)
Non-Opioid Painkiller Promotion		-0.000390**
		(0.000156)
% Opioid Claims 2013	0.943***	0.943***
	(0.00153)	(0.00153)
County FE	Y	Y
Mean Dep. Var.	0.125	0.125
SD Dep. Var.	0.177	0.177
Observations	633306	633306
R2	0.688	0.689

Outcome variable: share of opioid claims over all claims by Medicare Physicians and pharmaceutical promotion. Estimation result of Equation (5), for opioid promotion, painkiller promotion and non-opioid/non-painkiller promotion. Promotion measured as log dollar amount received in corresponding year. All regressions control for specialty of physician, prescription shares in the previous year and county fixed effects. Standard errors in parentheses clustered at zipcode level, * (p<0.10), ** (p<0.05), *** (p<0.01). Source: Medicare Opioid Prescriber Summary File and CMS Open Payments Data 2014.

8.5 Opioid promotion and placebo deaths

Table A7: Diabetes mellitus/strokes & promotion: 2SLS

Dep. Var.: log Deaths	(1) Diabetes	(2) Stroke
log Receiving Doctors	0.0426	0.0257
	(0.0339)	(0.0252)
Mean Dep. Var.	3.456	3.822
SD Dep. Var.	0.483	0.450
Observations	2861	3624
R2	0.487	0.557
Partial F-Value	44.04	73.52
County Characteristics	Y	Y
Year F. E.	Y	Y

Death rates caused by diabetes or strokes (ICD-Codes: E10-E14 and I60-I69) and opioid-related promotion. Regression results of Equations (3) and (4). Promotion instrumented with the distance of a county to the closest headquarters and the presence of a state ban. Partial F-Value of first stage displayed in last row. All regressions control for county characteristics (see Table 6 for details). Standard errors in parentheses adjusted for heteroscedasticity, * (p<0.10), ** (p<0.05), *** (p<0.01). Source: CDC Wonder Mortality MCD Data and CMS Open Payments Data 2014 and 2015.

8.6 Opioid promotion and overdose death robustness: Non-opioid promotion and pre-year overdose deaths

Table A8: IV 2SLS Overdoses and promotion: Pre-Year level of overdose deaths and non-opioid promotion

Dep. Var.: log Opioid Overdose Deaths	(1)	(2)	(3)
log Opioid Promotion Receiving Doctors	0.317***	0.166**	0.359*
	(0.0782)	(0.0718)	(0.198)
log Opioid Overdose Deaths in t-1		0.418***	
		(0.0180)	
log Non-Opioid Promotion Receiving Doctors			-0.0388
			(0.0829)
Mean Dep. Var.	1.664	1.682	1.664
SD Dep. Var.	1.190	1.182	1.190
Observations	5840	5748	5840
Partial F-Value	123.0	130.2	22.61
County Characteristics	Y	Y	Y
Year F.E.	Y	Y	Y

2SLS regression results (see Eq. (3) and (4)). First column shows main specification. Second column controls for pre-year level of overdoses. Column (3) controls for non-opioid promotion in the corresponding year. Instrument: minimum distance to headquarters, that opened before 1995 and dummy for state ban on promotion. Standard errors in parentheses adjusted for heteroscedasticity, * (p<0.10), ** (p<0.05), *** (p<0.01).

8.7 Opioid promotion dollar value and opioid overdose

Table A9: Overdose & promotion: 2SLS and OLS promotion in USD

Empirical Strategy	OLS	IV	IV
Dependent Variable:	(1)	(2)	(3)
log Opioid Overdose Deaths			
log Opioid Promotion USD	0.0571***	0.154***	0.132**
	(0.00655)	(0.0449)	(0.0577)
log Non-Opioid Promotion USD			0.0125
			(0.0260)
Mean Dep. Var.	1.664	1.664	1.664
SD Dep. Var.	1.190	1.190	1.190
Observations	5823	5840	5840
R2	0.331	0.147	0.159
Partial F-Value	.	75.00	48.39
County Characteristics	Y	Y	Y
Year F.E.	Y	Y	Y

Number of opioid overdose deaths in a county and opioid-related promotion. Promotion measured as logarithm of sum of USD amount spent on opioid promotion in a given county. Measures adjusted by population (100,000 inhabitants). Regression results of Equations (3) and (4). Promotion instrumented with the distance of a county to the closest headquarters and the presence of a state ban. In column (3) we additionally control in the first and second stage for all pharmaceutical promotion spending in the county, that is not related to opioid drugs. Partial F-Value of first stage displayed in last row. All regressions control for county characteristics (see Table 6 for details). Standard errors in parentheses adjusted for heteroscedasticity, * (p<0.10), ** (p<0.05), *** (p<0.01). Source: CDC Wonder Mortality MCD Data and CMS Open Payments Data 2014 and 2015.

8.9 Opioid promotion: IV promotion unrelated drugs

In this section we check for robustness of our results by following a different 2SLS IV strategy. We now instrument the number of doctors who receive promotion for opioid drugs in a county with the number of doctors that receive promotion for unrelated drugs. We pick the 20 most promoted drugs in a given year, that are independent of opioid medication, such as drugs for diabetes or hypertension. We follow the same empirical strategy as described in Equations (3) and (4) and control for county characteristics in the first and second stage. See footnote of Table 6 for details on county characteristics.

Table A10: List of unrelated promoted drugs

Top 20 Promoted Drug in 2014	Purpose	Manufacturer	Top 20 Promoted Drug in 2015	Purpose	Manufacturer
Eliquis	Blood Thinner	Bristol-Myers Squibb & Pfizer	Xarelto	Blood Thinner	Janssen
Myrbetriq	Overactive Bladder	Astellas	Eliquis	Blood Thinner	Bristol-Myers Squibb & Pfizer
Azor	Hypertension	Daiichi Sankyo	Levemir	Diabetes Type 2	Novo Nordisk
Eylea	Retina Diseases	Bayer	Nexplanon	Contraceptive	Merck
Aczone	Acne	Allergan	Victoza	Diabetes Type 2	Novo Nordisk
Prepopik	Clean colon before colonoscopy	Ferring	Cleviprex	Hypertension	Chiesi
Celebrex	Athritis	Pfizer	Pradaxa	Blood Thinner	Boehringer Ingelheim
Bydureon	Diabetes Type 2	AstraZeneca	Quillivant	ADHD	Pfizer
Januvia	Diabetes Type 2	Merck	Namenda	Alzheimer's Disease	Merz
Aptiom	Anti-seizure	Sunovion	Brilinta	Lower risk heart attack	AstraZeneca
Toviaz	Overactive Bladder	Pfizer	Toujeo	Diabetes Type 2	Sanofi-Aventis
Tanzeum	Diabetes Type 2	GSK	Invokana	Diabetes Type 2	Janssen
Novolog	Diabetes Type 2	Novo Nordisk	Vytorin	Reduce Cholesterol	Merck
Quillivant	ADHD	Pfizer	Arestin	Microbial Plaque	Valeant
Victoza	Diabetes Type 2	Novo Nordisk	Bydureon	Diabetes Type 2	AstraZeneca
Apidra	Diabetes Type 1/2	Sanofi-Aventis	Uloric	Gout	Takeda
Brisdelle	Relief Hot Flashes	Sebela	Neox	Ascariasis/Enterobiasis	Bristol-Myers Squibb
Welchol	Diabetes Type 2	Daiichi Sankyo	Duavee	Relief Hot Flashes	Pfizer
Premarin	Relief Hot Flashes	Pfizer	Edarbyclor	Hypertension	Arbor & Takeda
Colcrys	Treat gout attacks	Takeda	Entresto	Heart Failure	Novartis

List of top 20 drugs unrelated to pain or opioid medication, promoted in 2014 and 2015, respectively. Source: CMS Open Payments Data 2014, 2015 and manufacturer homepages for purpose and manufacturer names.

Table A11: Overdose & promotion: 2SLS IV unrelated drugs

	Panel A: First Stage	
Dependent Variable: log Opioid Promotion	(1)	(2)
log Unrelated Promotion	0.332***	0.349***
	(0.00753)	(0.00829)
log Opioid Overdose Death in t-1		0.0828***
		(0.0126)
Mean Dep. Var.	1.299	1.095
SD Dep. Var.	1.307	1.241
Observations	3133	3133
R2	0.447	0.408
Partial F-Value	1927.8	1805.3

	Panel B: Second Stage	
Dep. Var.: log Opioid Overdose Deaths	(1)	(2)
log Opioid Promotion	0.275***	0.182***
	(0.0289)	(0.0283)
log Opioid Overdose Death in t-1		0.411***
		(0.0146)
Mean Dep. Var.	1.664	1.682
SD Dep. Var.	1.190	1.182
Observations	5840	5748
R2	0.152	0.302
County Characteristics	Y	Y
Year F.E.	Y	Y

Number of opioid overdose deaths in a county and opioid-related promotion (number of doctors receiving promotion). Panel A displays first stage results. Opioid promotion is instrumented with the number of doctors that receive pharmaceutical promotion for unrelated drugs to opioids (see above for description). In the second column we additionally control for opioid overdose death rates in the previous year. All regressions control for county characteristics in Panel A and Panel B. Standard errors in parentheses adjusted for heteroscedasticity, * (p<0.10), ** (p<0.05), *** (p<0.01). Source: CDC Wonder Mortality MCD Data and CMS Open Payments Data 2014 and 2015.

Table A12: 2SLS IV unrelated drugs: Neonatal health and opioid promotion

	(1) Admission NICU	(2) Ventilation Immediately	(3) Ventilation > 6hr	(4) APGAR 5	(5) Birth Weight	(6) Low BW < 2500g	(7) Premature Born
Panel A: Second Stage Results							
Promotion 9 Months before Delivery	0.00949***	0.00163	0.00154***	-0.0187***	-11.03***	0.00522***	0.00503***
	(0.00162)	(0.00104)	(0.000473)	(0.00602)	(1.824)	(0.000773)	(0.000916)
Mean Dep. Var.	0.0808	0.0351	0.0112	8.785	3280.2	0.0777	0.110
SD Dep. Var.	0.273	0.184	0.105	0.825	584.9	0.268	0.313
Observations	3436124	3436124	3436124	3429416	3439713	3439713	3440894
Mother's Demographics	Y	Y	Y	Y	Y	Y	Y
Birth Characteristics	Y	Y	Y	Y	Y	Y	Y
Month of Birth F.E.	Y	Y	Y	Y	Y	Y	Y
State F.E.	Y	Y	Y	Y	Y	Y	Y
Panel B: First Stage Results							
β Promotion Unrelated Drugs	0.0331***	0.0331***	0.0331***	0.0331***	0.0331***	0.0331***	0.0331***
	(0.00175)	(0.00175)	(0.00175)	(0.00175)	(0.00175)	(0.00175)	(0.00175)
Partial F-Value	359.7	359.7	359.7	359.6	360.0	360.0	360.0

Estimation result of Equations (3) and (4). Opioid promotion measured as number of doctors receiving opioid promotion in the county of birth during pregnancy (normalized by county population). Partial F-value of first stage Equation (3) displayed in last row. Coefficient estimates and standard errors of first stage regression displayed in Panel B. Number of physicians receiving opioid promotion instrumented with number of physicians receiving promotion for unrelated drugs (see Table A10 column 2014 for list of drugs). Mother's characteristics controlled for in all regressions are age, race, educational attainment, marital status, mother medicaid recipient, mother's health (BMI, hypertension, diabetes), whether mother was born in the US and whether the mother is a smoker. Characteristics of births included in all regressions: vaginal delivery, sex of the baby, birth order, early prenatal visits, attendant at birth is physician. State fixed effects included in all regressions. Standard errors in parentheses clustered at county level, * (p<0.10), ** (p<0.05), *** (p<0.01). Source: CDC 2014 Natality Detail Data Set and CMS Open Payments Data 2014, 2015.

Table A13: 2SLS IV unrelated drugs: Physician prescriptions and opioid promotion

	Panel A: Second Stage Results	
Dependent Variable:	(1)	(2)
Opioid Prescriptions	# Pres. 2014	# Pres. 2014
Opioid Promotion (Dummy)	102.3***	
	(9.617)	
Opioid Promotion (log USD)		27.77***
		(2.727)
# Opioid Pres. 2013	0.968***	0.967***
	(0.00797)	(0.00814)
Mean Dep. Var.	114.9	114.9
SD Dep. Var.	322.3	322.3
Observations	633306	633306
County F.E.	Y	Y
Physician Specialty	Y	Y
	Panel B: First Stage Results	
β Promotion Unrelated	0.0826***	0.0660***
Drugs	(0.00114)	(0.000949)
Partial F-Value	5640.5	5187.1

Number of opioid claims of Medicare Physicians and opioid-related promotion. Estimation results of Equations (5) and (6). Promotional level measured as dummy for any promotion in column (1) and as log dollar amount in column (2). Opioid promotion instrumented with the receipt of promotion for unrelated drugs (see Table A10 column 2014 for list of drugs). Coefficient estimate and partial F-statistics from first stage displayed in Panel B. All regressions control for specialty of physician, previous prescription rates and county fixed effects. Standard errors in parentheses clustered at zip-code, * (p<0.10), ** (p<0.05), *** (p<0.01). Source: Medicare Opioid Prescriber Summary File and CMS Open Payments Data 2014.

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