Pharmaceutical Opioid Marketing and Physician Prescribing Behavior

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Abstract

Physicians' relationships with the pharmaceutical industry have recently come under public scrutiny, particularly in the context of opioid drug prescribing. This study examines the effect of doctor-industry marketing interactions on subsequent prescribing patterns of opioids using linked Medicare Part D and Open Payments data for the years 2014-2017. Results indicate that both the number and the dollar-value of marketing visits increase physicians' patented opioid claims. Furthermore, direct-to-physician marketing of safer abuse-deterrent formulations of opioids is the primary driver of positive and persistent spillovers on the prescribing of less safe generic opioids - a result that we show appears to be driven by insurance coverage policies. These findings suggest that pharmaceutical marketing efforts may have unintended public health implications.

Keywords: Healthcare; Direct-to-physician marketing; Medicare Part D; Opioid prescriptions; Opioid misuse; Physician payments; Open payments; Abuse-deterrent formulations; Spillover Effects; Heterogenous Treatment Effects.

JEL Classification: I11; I12; I18

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1 Introduction

The abuse of prescription opioids and the resulting overdose deaths have reached unparalleled levels in the United States over the last few years. In 2016, 63,632 individuals died from drug overdoses, with 66.4% of the cases involving opioids. Among opioid-related deaths, 40.4% involved prescription opioids (Centers for Disease Control and Prevention, 2018). Furthermore, two million people in the United States suffer from opioid addiction due to prescription opioid drugs (Schuchat et al., 2017). Policymakers are attempting to combat the opioid epidemic through various approaches, especially focusing on limiting opioid prescriptions. For example, the Centers for Medicare and Medicaid Services (CMS) recently finalized a number of new policies to help Medicare plan sponsors combat prescription opioid overuse and misuse by imposing limits on initial opioid prescriptions fills and identifying high-risk opioid users. Additionally, some physicians and pharmaceutical industry representatives have encouraged the use of abuse-deterrent formulations (ADFs) – patented opioids with properties that make misuse more difficult – arguing that they provide a safer option for treatment of ongoing pain compared to the traditional formulations (Webster et al., 2017).

These changes are occurring at the same time as pharmaceuticals are being intensively marketed to doctors. In 2015, about 48% of physicians received industry-related payments (Tringale et al., 2017). Pharmaceutical companies spend more than $20,000 annually per physician on direct-to-physician advertising that may include gifts, samples, travel, consulting fees, and pharmaceutical detailing visits where company sales representatives educate a physician, usually over a meal, about their drugs in order to sway the physician to prescribe them (Weiss, 2010). In an effort to reduce pharmaceutical industry influence on prescribing, a large number of US hospitals and academic medical centers have imposed limits on interactions between physicians and pharmaceutical sales representatives. The question of how pharmaceutical marketing efforts aimed at physicians affect the consequent prescribing behavior has received considerable attention in the marketing literature and, to a smaller extent, in the economics literature (Datta and Dave, 2017).

Studies looking at the link between direct-to-physician marketing and physician prescribing have uncovered mixed results in terms of the effectiveness of industry payments on increasing prescribing (Kremer et al., 2008; Dave, 2013, 2014). Some inconsistency in the results may be explained by the fact that the effects of the direct-to-physician promotion may be different depending on which pharmaceutical drugs are being examined and other data related differences.[1] However, the primary empirical concern is variation in how well the studies account for the targeting bias, where high-prescribing physicians are more likely to be targeted for marketing interactions by drug producers.

This study contributes to the literature of pharmaceutical promotion by quantifying the effect of doctor-industry interactions on subsequent prescribing patterns of opioids. Using longitudinal physician data from Medicare Part D and the Open Payments program for years 2014-2017, we examine how direct-to-physician marketing of patented opioid drugs affects physicians' patented and generic opioid claims. Because opioid-promoting companies target doctors who already prescribe large quantities of opioids (whether due to patient population characteristics or some unobserved doctor preferences), it is important to account for the high-prescriber selection into marketing relationships with opioid firms. We use physician fixed effects to control for the observed and unobserved doctor characteristics and prescribing preferences which may lead to such selection. Additionally, we include the interacted zip-code-by-year fixed effects in order to account for the unobserved geographical demand shocks that vary over time, which may affect both opioid promotion and prescribing behavior.

Results suggest that physician interactions with opioid companies indeed increase prescribing of patented opioid drugs. Specifically, detailing interactions with pharmaceutical sales representatives over meals drive the positive effect on patented prescribing, with higher-cost meals reinforcing the impact of promotional interactions on claims. Our findings indicate that the average number of yearly promotional visits by pharmaceutical sales

[1]See, for example, Berndt et al. (1995); Dave and Saffer (2012); Iizuka and Jin (2007); Rizzo (1999). For a comprehensive review of the pharmaceutical promotion literature, see Kremer et al. (2008) and Dave (2013, 2014).

representatives causes physicians to increase their patented opioid prescribing by 13.3%. Interestingly, we document considerable heterogeneity in these effects across provider specialities, gender and geographic location. We also show that there exist unintended consequences of opioid promotion in the form of spillover effects on generic opioid prescribing. Instead of substituting away from relatively unsafe, misuse prone generic drugs, the average number of promotional interactions related to patented opioids induces physicians to increase generic prescribing by about 3.6%. Furthermore, the spillover effects on generic claims are persistent over the years and arise primarily from the marketing of abuse-deterrent opioids - the very drugs designed to prevent misuse. These spillover results are consistent with the pervasive insurance company policies that encourage generic prescribing and restrict patient access to costlier, but safer abuse-deterrent drugs. Using formulary data from 2017, we are able to further support this hypothesis by showing that doctors in insurance networks with greater ADF coverage experience smaller spillover effects of patented promotion on their generic opioid prescribing.

In addition to the main empirical strategy, we employ an instrumental variable (IV) approach as a robustness check to show that our results hold under an alternative specification. We use the number of opioid marketing interactions and the value total industry payments for other doctors in the zip code as instruments for opioid-related interactions of a given doctor. This approach relies on the fact that a physician is more likely to have an opioid marketing interaction if other local doctors are being frequented by opioid sales representatives.

Accounting for physician selection into marketing relationships with pharmaceutical firms is essential in order to accurately estimate the effect of direct-to-physician advertising on prescribing behavior. A number of studies utilize instrumental variable approaches, finding relatively smaller effects of marketing compared to studies that do not control for endogeneity (Azoulay, 2002; Kalyanaram, 2009; Rosenthal et al., 2003). Very few studies utilize the panel data framework, where physician fixed effects can be used to control for observed and unobserved physician heterogeneity in prescribing preferences that may also

be correlated with targeted marketing activity. The exceptions are Datta and Dave (2017) and Mizik and Jacobson (2004) who use longitudinal data to look at the role of physician marketing on prescribing of various drugs.[2] Both studies find that the effect of direct-to-physician marketing is quite modest relative to studies not utilizing physician fixed effects, suggesting that selection bias plays a role in the observed relationship between promotion and drug sales.

One reason that some studies find little-to-no effect of advertising on sales is brand switching. One firm's promotional efforts reduce the rivals' sales, thereby causing the competing firms to increase their marketing activity (Bagwell, 2007). For example, in analyzing how pharmaceutical detailing affects prescribing of branded and generic drugs for treatment of Herpes infection, Datta and Dave (2017) find that while detailing does not crowd out cheaper generic prescriptions, class-level demand for branded drugs is only minimally affected. They find that physicians tend to substitute from prescribing one drug to prescribing a more expensive drug as the result of promotion.[3]

Recently, a large number of lawsuits have been brought against the opioid manufacturers in connection to the role that pharmaceutical promotion to physicians has played in the opioid epidemic. Importantly, while policy measures are being taken to reduce opioid prescribing, opioid manufacturers continue to pay doctors large sums of money to promote their products in an attempt to induce physicians to prescribe more opioid drugs. However, surprisingly little is known about the relationship between direct-to-physician promotional activities and opioid prescribing. To our knowledge, only four studies have looked at the relationship between opioid-related payments and prescribing. These studies are Hadland et al. (2017), Hadland et al. (2018), Nguyen et al. (2019b), and Fernandez and Zejcirovic (2018).

Using Open Payments database, where payments made by drug companies to physi-

[2]Additionally, Dong et al. (2009, 2011) use full-information Bayesian methods in the framework of a physician-level panel data.

[3]Substitution between branded and generic drugs has not been well addressed in the literature. Only Janakiraman et al. (2008) include both on-patent and off-patent drugs, out of all physician-level longitudinal studies reviewed by Kremer et al. (2008).

cians are recorded, Hadland et al. (2017) calculate that 375,266 non-research, opioid-related payments were made to 68,177 US physicians totaling $46,158,388 between 2013 and 2015. They also find that one in twelve physicians received an industry payment involving an opioid, with most common types of payments belonging to the food and beverage category, comprising 93.9% of all payments. In a follow-up study, they link the Open Payments data to Medicare Part D opioid prescribers to show that the receipt of any non-research payment related to an opioid product in 2014 was associated with 9.3% more opioid claims in 2015 (Hadland et al., 2018). Nguyen et al. (2019b) also uncover positive association between opioid-related promotions and opioid prescribing, finding that prescribers who receive promotional opioid payments prescribe 8,784 more opioid daily doses per year relative to physicians who did not receive any marketing payments. However, these studies do not account for the endogeneity of opioid-related industry payments to physicians. Since pharmaceutical sales representatives target doctors who are most likely to prescribe their products, such as physicians who are already high-prescribers of opioids and/or physicians who have patient populations with high demand for opioid drugs, not accounting for this selection will lead to estimates that overstate the effect of opioid marketing to physicians.[4] While Fernandez and Zejcirovic (2018) attempt to control for this endogeneity, they focus on estimating the effects of opioid promotion on opioid overdose mortality at a more-aggregated, county level.

As various policy initiatives designed to reduce overall opioid prescribing and increase substitution from generic to ADF opioids have been put forth, the question of how direct-to-physician marketing affects physician's opioid prescriptions and which type of opioids are affected (generic, patented, or abuse-deterrent) grows in relevancy. The answer to this question may inform about the effectiveness of policies that restrict physician access to the pharmaceutical company representatives and access to potentially valuable drug

[4]Datta and Dave (2017) look at a very specific class of drugs designed to treat herpes viral infections. Mizik and Jacobson (2004) examine three unknown drugs produced by one, undisclosed, firm. Thus, while these studies control for high-prescribing physician selection, the estimated effects in these two studies may not be applicable to direct-to-physician opioid promotion.

information that such interactions may provide.[5] Importantly, examining how direct-to-physician marketing may affect susceptible-to-abuse generic prescribing, may provide important insights about possible channels through which pharmaceutical interactions may affect the risks of addiction and mortality from overdoses.

Our findings suggest that opioid promotion to physicians may hinder the current state and national efforts to reduce opioid prescribing. Furthermore, while policymakers promote abuse-deterrent opioids as a way to reduce the risk of opioid misuse and addiction, the marketing of these safer medications may have the opposite effect. Since detailing visits drive the spillovers on misuse-prone generic prescribing, restricting or limiting opioid detailing may be an appropriate policy response in the battle with the opioid epidemic in the United States. Alternatively, the practice of "academic detailing", where trained clinical educators visit physicians to discuss safest and most effective medications for patients based on current research, may be a way to get important opioid information to physicians and counteract the effect of marketing by opioid producers (Larson et al., 2018; Liebschutz et al., 2017).

This paper proceeds as follows. In Section 2, we discuss the abuse-deterrent formulations (ADFs) and the specifics surrounding Medicare Part D population. Data sources and sample construction are discussed in Section 3. In Section 4, we present the main empirical strategies. The results are shown and discussed in Section 5. In Section 6, we introduce various robustness checks and conclude in Section 7 by discussing some implications of our results.

[5]There exist two prevailing views on the influences of detailing visits. One view asserts that pharmaceutical interactions with physicians influence their prescribing in a way that is detrimental to patients' welfare, since they tend to promote excessive prescribing of costly brand-name drugs. On the other hand, interactions with pharmaceutical companies provide physicians with valuable information, such as information on new drugs with new indications, as well as how they may interact with existing drugs and dosage details, which positively affects consumers.

2 Background

2.1 Abuse-Deterrent Formulations and Policy

Policymakers consider the development of abuse-deterrent formulations (ADFs) of prescription opioids as an important strategy to combat the opioid epidemic. The main goal of ADFs is to deter an individual from chewing, inhaling, or intravenously injecting the drugs, which give the individual a greater degree of "rewarding" effect but also rapidly elevate the blood pressure and increase the risk of respiratory depression and a fatal overdose. In addition, non-oral routes of administration are associated with an increased risk of addiction and abuse, as well as a variety of other health consequences, including damage to nasal/oral structures and blood-borne infections (Dunn et al., 2010; Raffa and Pergolizzi, 2010; Katz et al., 2011). Because opioid medications continue to play a vital role in pain management, ADFs may be a valuable component of providers' opioid risk management plans (along with patient education, prescription drug monitoring programs, and other guidelines/policies). In order to encourage a shift from the traditional opioid formulations to ADFs, the U.S. Food and Drug Administration (FDA) released 43 new or revised product-specific guidance documents to push generic ADF development (U.S. Food and Drug Administration, 2018).

However, ADFs are not yet commonly prescribed, largely because these new formulations are available only as patented products, which are more expensive than a large number of non-abuse-deterrent opioids that are available in generic formulations. Furthermore, many insurance companies will not cover ADFs and/or limit their reimbursement, which deters doctors from prescribing them. For example, the Institute for Clinical and Economic Review (ICER) reviewed 2017 coverage policies and formularies for six New England state Medicaid programs, CMS, and 12 major "Silver-level" plans on individual marketplaces across New England, and identified coverage policies for four of the nine (available in 2017) ADF opioids.[6] They found that all plans maintained quantity limits

[6]OxyContin, Xtampza, Hysingla ER, and Embeda are the four ADFs identified.

for these opioids and the majority required prior authorization.[7] Several studies have examined the unwillingness of the insurance companies to cover tamper-resistant and ADF opioids, with access limitations that include requirements by the insurance carriers for patients to provide diagnosis of addiction, documentation of high-risk for abuse, and/or exclusions from formularies (Brushwood et al., 2010; Argoff et al., 2011; Schatman and Webster, 2015). In addition to prior authorization and other requirements, it is common for the commercial insurance plans to mandate that patients try generic equivalents or preferred brand name opioids first (Institute for Clinical and Economic Review, 2018). By encouraging utilization of relatively cheaper but abuse susceptible generic formulations, such "fail-first" policies may be undermining the national efforts to curb unsafe opioid prescribing.

Some parts of the multipronged, national strategy to combat the opioid epidemic include educating physicians to decrease prescribing of opioids, shortening the duration of opioid therapy, carefully monitoring prescribing, as well as mandatory substitution of generic opioid prescriptions with ADFs. State governments also tackle the epidemic in various ways, including the creation of executive-led task forces, physician education, prescription drug monitoring programs (PDMPs), and the allocation of more funding for abuse treatment options. Importantly, to increase patients' accessibility to ADFs, several states have introduced legislation mandating that ADFs be available on formularies and requiring that they be covered by the insurance companies. However, data on the impact of such policies is limited and inconsistent (Institute for Clinical and Economic Review, 2018). In 2015, the FDA issued a non-binding recommendation encouraging manufacturers to produce abuse-deterrent opioids, stating that "FDA considers the development of ADFs a high public health priority." (FDA, 2015)

[7]Prior authorization requirement means that the doctor must obtain approval from the insurance plan in order to prescribe the drug.

2.2 Medicare Part D

Because our study utilizes data on Medicare Part D claims, it is important to understand prescription opioid use and abuse in Medicare Part D beneficiary population. As people age, they become more likely to develop a painful chronic condition, involving degeneration in bones, joints, and muscles (Molton and Terrill, 2014). While about 30% of the general population reports pain, among older adults it is higher, with about 40% of the elderly reporting pain (Le Roux et al., 2016). According to the Office of Inspector General, about one in three beneficiaries received at least one opioid prescription through Medicare Part D in 2017. That year, Medicare Part D paid for 76 million opioid prescriptions, which amounts to about 5.4 opioid prescriptions per beneficiary. For comparison, 3.4 opioid prescriptions per person are written in the general U.S. population. About 1 in 10 Part D beneficiaries receive opioids on a regular basis (meaning, they are taken for 3 or more months), which substantially increases the risk of opioid dependence (HHS OIG Data Brief, 2018). In 2017, a total of 458,935 Part D beneficiaries received high amounts of opioids (average morphine equivalent dose of greater than 120mg a day for at least 3 months), who did not have cancer and were not in hospice care.[8] In addition, some states had higher proportions of Part D beneficiaries receiving prescription opioids compared to the national averages. While many of these prescriptions may have been necessary, such high numbers suggest that prescribing and utilization of these opioids may have been inappropriate.

While not the largest age group misusing opioids, older adults (aged 65+) are exhibiting sharp increases in mortality and hospitalization rates due to prescription opioid misuse (Benson and Aldrich, 2017). The Medicare population has among the highest and fastest-growing opioid use disorder rates,[9] with more than 6 of every 1,000 beneficiaries being diagnosed with opioid addiction (Lembke and Chen, 2016). Additionally, older adults with an opioid use disorder may be at a higher risk of death compared to the younger

[8]In 2017, Medicare covered 45 million beneficiaries.
[9]Opioid use disorder is sometimes referred to as "opioid addiction".

adults (Larney et al., 2015). Therefore, information regarding how patented opioid marketing influences the types of opioids being prescribed to the elderly may be important for policymakers' understanding about patient access to safer ADF medications.

3 Data

The majority of our data come from two databases maintained by the US Centers for Medicare and Medicaid Services (CMS). One contains all prescription claims reimbursed under the Medicare Part D program, which includes the number and type of prescriptions written by individual physicians nationally. The other, the Open Payments database, contains millions of records of payments and gifts made by pharmaceutical and medical device companies to doctors and teaching hospitals in the US.

The Open Payments program was established under the Physician Payments Sunshine Act as part of the Affordable Care Act in order to give the public more information about the financial relationships between physicians and drug and medical device manufacturers. Specifically, the program is designed to promote transparency about financial ties between medical care providers and the industry, to inform on the nature and extent of such relationships, and to help prevent inappropriate influence on research, education, and clinical decision making (CMS.gov, 2016). Starting in mid-2013, all payments made by the applicable manufacturers and group purchasing organizations to physicians and teaching hospitals must be reported to the Centers for Medicare & Medicaid (CMS), and are published in the Open Payments database.[10] The physicians are able to review and dispute the payments about them before it is published on the website. The Open Payments database contains information on the type of payment made by the manufacturer to a physician, physician's name and address, the monetary value of the transfers, the name of the firm making the payment, as well as the drug that is associated with the payment. In the 2014-2017, there were 936,891 US physicians with at least one pharmaceutical (or

[10]Payments/transfers of value that are less than $10 do not need to be reported, unless the total annual value of payments provided to a physician or teaching hospital by a single applicable manufacturer or GPO is more than $100 (CMS.gov, 2016).

medical device) payment.

In order to identify promotional interactions related to patented opioids, we utilize the list of opioid drugs that comes from the CMS's Prescriber Drug Category List for years 2014-2017.[11] Because prescriptions written for patented drugs cannot be substituted for generics by the pharmacist, only patented opioid promotional payments were used to study the effect on physicians' prescribing patterns.[12] We determined which opioid drugs on the CMS list were under patent for the time-frame of the study by using the U.S. Food and Drug Administration's Orange Book and DrugPatentWatch.com. If an individual payment in the Open Payments database contained an opioid drug name that matched a patented opioid drug name on the CMS list, then the marketing interaction was related to the promotion of patented opioids.[13]

The most common way to promote drugs to physicians is through pharmaceutical detailing, or sales pitches where drug details about safety, efficacy, and side effects are presented to the physician by a pharmaceutical sales representative, usually over a meal. Detailing is considered pharmaceutical firms' "highest-impact promotional weapon" (Campbell, 2008) and is captured by the category "Food & Beverage" in the dataset. Other types of interactions include payments for serving as faculty, speaking and consulting fees, payments related to services for continuing education programs, education-related payments, gifts, honorary payments, and travel and lodging payments.[14] During this 4-year period physicians received 565,892 patented opioid-related payments that were worth $41.9 million.[15] This study is limited to payments that may target physician prescribing and do not include research and non-equity payments, similar to other studies on direct-to-physician

[11]The list is based upon drugs included in the Medicare Part D Overutilization Monitoring System (CMS.gov, 2019).

[12]A minuscule amount of opioid payments involved the promotion of off-patent, generic opioids, usually as part of patented advertising. We also created separate generic-interactions variables and account for it in several specifications.

[13]Table A1 of the appendix contains the list of patented opioid drugs used to define patented opioid-related interactions.

[14]The full list of payment categories in the Open Payments data and their definitions are available at https://www.cms.gov/OpenPayments/About/Natures-of-Payment.html.

[15]Table A2 of the appendix contains detailed information on the type of opioid-related payments included in our data for the period 2014-2017.

promotion. Figure 1 shows the yearly changes in the total number of promotional interactions for patented opioid drugs (quadrant A), the dollar value of various types of payments (quadrant B), as well as the physician average number of interactions by interaction type (quadrant C) for our main sample of physicians.

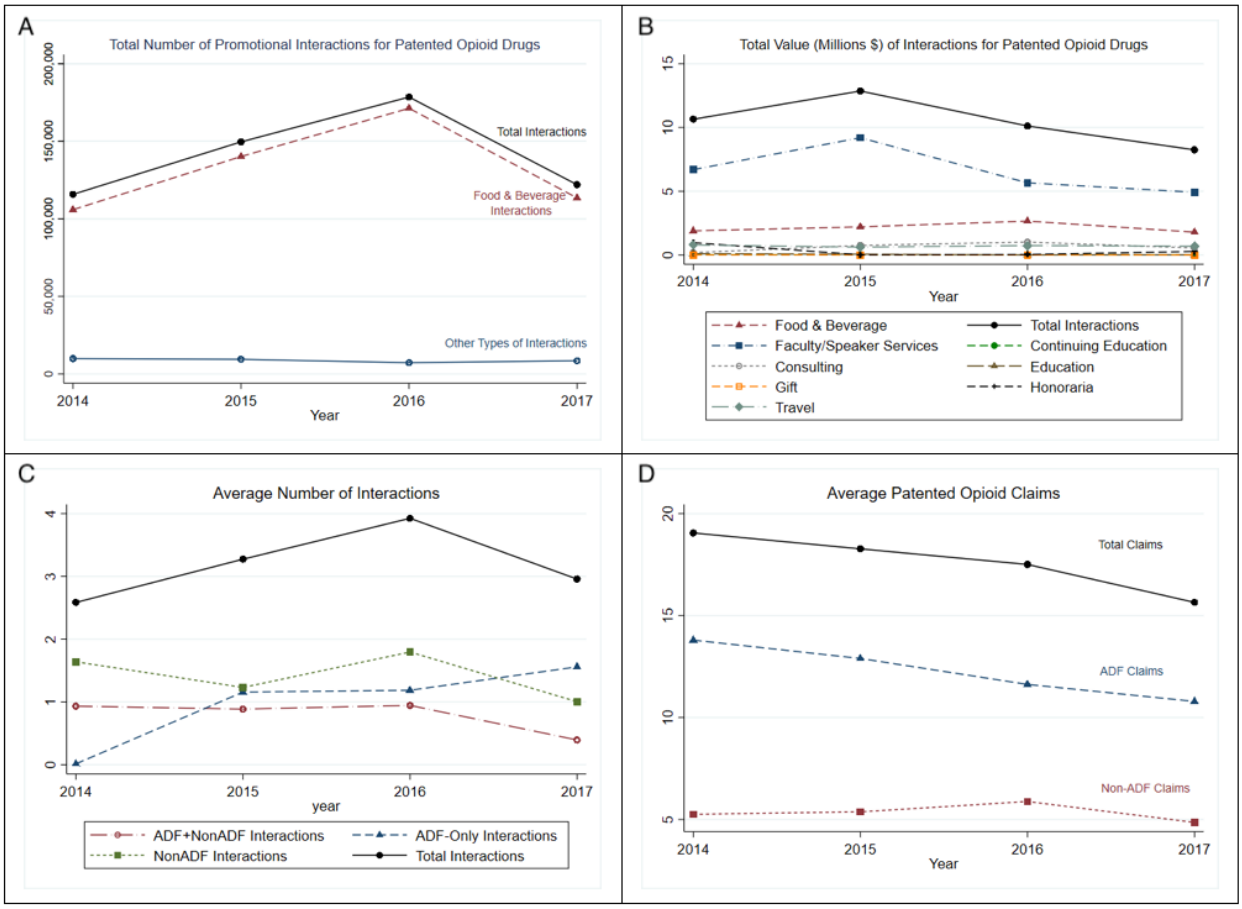

Figure 1: Descriptive Statistics

We use Medicare Part D Provider Utilization and Payment Data to capture physician's prescribing patterns, available on the CMS website (CMS.gov, 2019). This physician-level, publicly available dataset contains information on all Part D final-action prescription drug claims for Medicare beneficiaries.[16] In addition to information on counts and costs for individual physicians' prescription claims, this Part D database contains provider

[16]Submitted by both Medicare Advantage Prescription Drug plans and by stand-alone Prescription Drug Plans. While the dataset does not include prescriptions covered by payers other than Medicare Part D, it is the only publicly available data with information on both the prescribers and drug claims (Nguyen et al., 2019a).

names, business locations, specialty, national provider identifiers (NPIs) and patient-population information for 1,325,181 Part D prescribers.[17] Because the Part D claims database utilizes NPIs to identify prescribers and the Open Payments database uses its own identifiers for physicians, we linked the physicians listed in the Open Payments to Part D prescriber data using physician names and zip codes of practice location. We were able to match 726,288 Open Payment prescribers using this matching technique.[18]

For additional information on providers we used publicly available Physician Compare data. This dataset contains various performance scores for doctors, along with other characteristics designed to help Medicare patients and caregivers make informed decisions about providers by giving them the ability to search for and compare clinicians who participate in Medicare (Data.Medicare.gov, 2019).

Physicians who moved from one zip code to another during the period of the study could potentially have unusual prescribing patterns and, thus, were excluded from the sample. After removing physicians who moved during the time-frame of the study, providers that are in the dataset for only one year and doctors with missing control variables, we ended up with 663,922 US providers. However, since the central analysis relies on the within-physician variation, the main sample of analysis is restricted to physicians who had at least one industry interaction involving a patented opioid for years 2014-2017 or 48,276 US providers (about 7.3% of Medicare physicians). This estimate is very similar to calculation of Hadland et al. (2018) who find that about 7% of physicians who prescribed opioids under Medicare Part D had at least one non-research opioid related payment in 2014.

Quadrant D of Figure 1 shows the yearly changes in the various types of physician average patented opioid claims in our sample.[19] The summary statistics for the full and

[17] A small proportion of these prescribers may be organizational providers, such as nursing homes, group practices, and physician centers.

[18] Out of 210,603 unmatched Open Payment prescribers, only 5,693 physicians had any opioid payment for the time-frame of the study, averaging 2 interactions per year with $171 average spent on each doctor per year in opioid-related payments.

[19] The physician average generic opioid claims remained relatively unchanged for the study time period at about 464 yearly claims.

the main samples are presented in Table 1 (the "All" and "Ever Interacted" columns, respectively).

	All	Ever Interacted
Covariates:		
Patented Interactions	0.30 (3.30)	3.19 (10.57)
ADF-only interactions	0.09 (1.34)	0.97 (4.41)
ADF+nonADF interactions	0.07 (0.71)	0.80 (2.23)
Non-ADF interactions	0.14 (2.06)	1.43 (6.66)
Patented-only interactions	0.30 (3.28)	3.18 (10.50)
Patented+Generic interactions	0.001 (0.08)	0.01 (0.26)
Generic interactions	0.003 (0.15)	0.03 (0.45)
Non-opioid claims	2,096.88 (3870.14)	5,519.93 (6908.13)
Number of physicians in group	406.94 (950.72)	140.29 (362.04)
Beneficiaries	203.54 (218.92)	369.96 (277.54)
Beneficiaries over age 65	196.84 (205.94)	294.83 (238.31)
Low-income subsidy claims	954.17 (2538.95)	2,701.92 (5021.23)
Female beneficiaries	118.14 (131.38)	223.32 (170.07)
Black beneficiaries	14.52 (47.00)	29.36 (71.97)
Dual beneficiaries	53.95 (83.27)	103.46 (121.07)
Other variables:		
Patented opioid claims	2.66 (21.71)	17.66 (61.94)
ADF opioid claims	2.00 (15.15)	12.31 (41.85)
Non-ADF opioid claims	0.66 (9.04)	5.35 (27.09)
Generic opioid claims	100.20 (323.47)	463.92 (815.42)
Opioid payments total ($)	22.34 (1108.15)	236.24 (3637.84)
Observations	2,067,806	177,227
Number of physicians	663,922	48,276

Sample means are reported for years 2014-2017, with standard deviations in parentheses. For some variations, number of observations may be lower due to missing information.

Table 1: Summary Statistics (2014-2017)

4 Methodology

The following equation is used to estimate the effect of physician-directed marketing interactions on the prescriptions of opioid drugs:

$$Claims_{i,z,t} = \beta Interactions_{i,z,t} + \delta X_{i,z,t} + \lambda_{zt} + \theta_i + u_{i,z,t} \quad (1)$$

Equation 1 denotes that the number of opioid claims (*Claims*) by physician i in zip code z in year t depends on the number of opioid-related interactions with the pharmaceutical companies (*Interactions*). The parameter of interest is β, which captures the impact of physician-industry interactions related to patented opioids on opioid prescribing habits of the physician. In additional specifications, we add the quadratic term (*InteractionsSQ*) to examine potential non-linearities. The two dependent variables of interest are the number of patented opioid claims and generic opioid claims.[20]

It is crucial to address the selection of physicians into interactions with pharmaceutical firms. High prescribers of opioids, whether generic or brand-name, or those with higher probability of prescribing opioid medications (for example, physicians in certain specialties or in market areas with higher demand for opioids), are more likely to be targeted by the pharmaceutical company representatives. As Table 1 indicates, there are differences across the observed characteristics of physicians who have encounters with firms marketing opioid drugs ("Ever Interacted" column) and the average physicians ("All" column). The interacting physicians have higher level of both generic and patented opioid claims, write more non-opioid prescriptions, have more patients and work with fewer other doctors than physicians who did not have any industry relationships in 2014-2017. Since the observed characteristics of physicians with industry interactions differ from physicians with no interactions, this suggests that unobserved doctor differences are important to consider. Unobserved preferences such as brand loyalty, risk tolerance, tradeoffs among counter-indications, efficacy, and long-term use, potentially play an important role in both

[20] Generic opioid claims may include branded drugs, but these branded opioids were not patented at the time of the study. Any branded medications that are not patented can be substituted for the generic by the pharmacist, and in many states, the law requires the pharmacies to do so.

the physicians' prescribing decisions and the level of interactions with the pharmaceutical firms (Datta and Dave, 2017). Thus, our estimation strategy relies on within-doctor variation, where physician fixed effects (θ_i) account for these potentially confounding observed and unobserved time-invariant factors. Additionally, the inclusion of interacted zip code by year dummy variables (λ_{zt}) controls for zip code specific, time-varying demand shocks that may affect both prescribing and pharmaceutical marketing activity. For example, local shocks can be related to factors such as zip code level changes in prescribing, disease prevalence, area demographics, economic conditions, marketing levels, unobserved seasonal and national trends (such as shifts in Medicare Part D drug coverage that affect all beneficiaries), policies related to opioid prescribing, and pharmaceutical promotion trends aimed at consumers. Thus, the source of our model's identifying variation comes from within-doctor changes over time that differ across physicians within the same zip code. Because utilizing within-physician, within-zip code variation allows to control for regional, zip code-specific opioid demand shocks that may vary from year to year, the main threat to this identification strategy comes from physician-specific (non-regional) demand shocks not otherwise accounted for by the control variables.

Opioid prescribing also depends on the patient population of the physician. Not only are doctors with more elderly, chronic-pain-prone patients expected to write more opioid prescriptions, but they are also more likely to be targets for opioid marketing. Physicians working in certain settings (for example, hospitals or academic medical centers) may face restrictions on interactions with pharmaceutical companies and prescribe opioids in systematically different ways. Thus, to account for these time-varying factors, X contains a vector of variables such as physician i's number of claims, total number of doctors that work with i in the same group or practice, number of Part D beneficiaries (as well as Part D beneficiaries over age 65), number of low-income subsidy claims, number of beneficiaries who qualify to receive both Medicare and Medicaid benefits (dual beneficiaries), number of black beneficiaries, and number of female beneficiaries.

Advertising literature suggests that the effect of promotion may last beyond the time

of the promotional interaction (Datta and Dave, 2017). The effects may persist over time due to various factors, such as learning, reminders, and inertia (persistence in prescribing habits). Various studies utilizing distributed-lag models as well as other specifications find that the effect of non-pharmaceutical promotion on sales lasts between under a year to fifteen months (Bagwell, 2007). Research on direct to consumer marketing of pharmaceutical drugs suggests that the effects of promotion depreciate within six months to a year (Ling et al., 2002; Iizuka and Jin, 2005). To measure the persistence of opioid-related interactions, we estimate the following equation:

$$\begin{aligned} Claims_{i,z,t} = \beta_1 Interactions_{i,z,t} + \beta_2 Interactions_{i,z,t-1} + \beta_3 Interactions_{i,z,t-2} \\ + \gamma C_{i,z,t} + \lambda_{zt} + \theta_i + v_{i,z,t} \end{aligned} \tag{2}$$

Here the coefficients capture the effect on i's current opioid claims of promotional interactions in the current year (β_1), one year after the interaction (β_2), and two years after the interaction (β_3). In addition to control variables from equation 1, C is a vector containing variables that control for the number of generic-only opioid promotional interactions and the number of joint generic-patented opioid interactions. *Interactions* captures the effect of patented-only promotional payments.

We expect the promotion of ADFs to have a different effect on opioid claims compared to non-ADF interactions. For example, ADF promotion is likely to inform physicians about the relative safety of ADF opioids compared to misuse-prone generics and non-abuse-deterrent formulations. If physicians substitute away from non-ADF opioids as a result of ADF marketing, we would expect the spillover effect on generic and non-ADF claims to be negative. On the other hand, costlier abuse-deterrent drugs may face insurance coverage access limitations and "fail-first" requirements. Because "fail-first" policies promote the usage of generic opioids before more expensive ADFs are covered, any ADF-specific promotional spillovers on generic prescribing may be positive and larger than interactions related to non-ADF opioids. To examine how interactions related to the various types of promotion affect claims, we estimate the following equation:

$$
\begin{aligned}
Claims_{i,z,t} = {} & \alpha_1 ADF_{i,z,t} + \alpha_2 ADF_{i,z,t-1} + \alpha_3 ADF_{i,z,t-2} \\
& + \alpha_4 NonADF_{i,z,t} + \alpha_5 NonADF_{i,z,t-1} + \alpha_6 NonADF_{i,z,t-2} \\
& + \alpha_7 Both_{i,z,t} + \alpha_8 Both_{i,z,t-1} + \alpha_9 Both_{i,z,t-2} \\
& + \gamma C_{i,z,t} + \lambda_{zt} + \theta_i + e_{i,z,t}
\end{aligned} \tag{3}
$$

In this specification the *Interactions* variable is disaggregated into the number pharmaceutical interactions that involve the discussion of ADF opioids only (ADF), the number of promotional interactions involving non-ADF patented opioid drugs only ($NonADF$), and the number of payments that listed both ADF and non-ADF patented opioids being promoted ($Both$). All other variables are the same as in equation 2. This specification allows us to examine how different types of interactions affect ADF, non-ADF, and generic opioid claims, captured by $Claims_{i,z,t}$. In addition to examining the differential effects on generic prescribing, this specification allows to examine the effectiveness and spillover effects of ADF vs. non-ADF promotion on ADF and non-ADF claims.

While the specifications given by Equations (2) and (3) have allowed us to examine both the persistence, as well as the role of different types of detailing interactions, two concerns remain. The first relates to the fact that our model specification in Equation (1), which relies on linearity, might be misspecified if the true relationship between detailing and prescribing is nonlinear. Related to this, the effect of detailing may furthermore plausibly vary considerably with the characteristics of the providers. While such heterogeneity could be explored by the inclusion of a large number of interaction terms, this strategy would come at the expense of diminished statistical power and increased computational complexity. In order to circumvent these issues, we instead pursue a causal forest estimation approach (a la Athey (2019)) that allows us to utilize a highly flexible non-linear model in order to obtain heterogenous treatment effect estimates.

In adopting this approach, we follow the potential outcomes framework of Neyman (1923) and Rubin (1974), and have Y_{ist} denote the continuous patented claims measure for provider i, in state s, time period t, and have X_{ist} capture the features previously

described, and let W_{it} denote or continuous treatment variable represented by the number of patented interactions. Following the causal forest methodology (Athey et al. (2019)), for a given tree, this approach recursively splits the feature space (X_{ist}) into a set of leaves L, each containing a number of observations.[21] Next, within each resulting leaf of the tree, we estimate the partial treatment effect as:

$$\hat{\tau}_b(x) = \frac{Cov(Y_{ist}, W_{ist} \mid X_{ist} = x)}{Var(W_{ist} \mid X_{ist} = x)}. \tag{4}$$

Based on this approach, we construct an ensemble of B trees, each with an estimated $\hat{\tau}_b(x)$ (from equation (4)). Using these B estimates we construct our forest prediction of patented interactions on the number of patented opioid claims by taking the average over all the individual trees, that is:

$$\hat{\tau}(x) = \frac{1}{B} \sum_{b=1}^{B} \hat{\tau}_b(x). \tag{5}$$

Upon obtaining our provider specific average treatment effects we perform descriptive analysis of the estimated effects in order to explore potential sources of the observed treatment heterogeneities. In particular, we will seek to explore heterogeneities across provider specialties, provider gender and geographic location features, in order to better understand how treatment effects resulting from medical detailing influences different types of providers in different ways.

5 Results

Table 2 displays the coefficient estimates for the effect of interactions on physician's patented opioid claims. The coefficients across all specifications of the model imply that interactions with the opioid industry have a positive effect on the quantity of physician's

[21] Note, a key difference in terms of the causal forest vs. random forest approach lays with the specification of the splitting criterion function. While a random forest approach would split on the basis of minimizing the mean squared prediction error, the causal forest method splits on the basis of minimizing the mean squared predicted treatment effect error instead.

patented opioid claims. Column 1, the specification without the control variables, indicates that each interaction involving a patented opioid increases physician's patented opioid claims by about 3 per year. On average, physicians have 17.66 patented claims per year, so the estimate corresponds to about a 17% increase in the average patented opioid claims. The coefficient estimate is highly significant and adding controls and interacted zip code by year fixed effects in columns 2 and 3, respectively, reduces the estimates slightly to 2.1. Specification 4, the main specification, fully exploits the panel data and accounts for physician fixed effects, which capture a physician's observed and unobserved characteristics and preferences. When physician fixed effects are added, the average effect from an interaction falls substantially, with each interaction inducing the physician to generate 0.7 more patented opioid claims (or 4% of the average). The drastic reduction in the coefficient value as doctor fixed effects are added implies that physicians are likely targeted by firms based on physician heterogeneity in observed and unobserved characteristics and preferences, rather than merely zip code-level geographic heterogeneity. In column 5 the quadratic term is not statistically significant, implying that the average effect of each interaction on patented opioid prescriptions is relatively linear.

The results in Table 2 indicate that industry interactions associated with marketing of patented opioids have a statistically significant effect on patented opioid prescribing, with each interaction increasing physician's prescribing by 0.7 patented opioid claims. Since the average doctor in the main sample has 3.19 interactions with opioid producers per year, this estimate implies that, on average, these interactions will increase a physician's patented opioid claims by 12.8% per year. This provides evidence that firm interactions with physicians indeed push them toward prescribing more patented (and possibly costlier) opioid drugs. These estimates are substantially lower than in specifications that do not account for endogeneity, suggesting that a good amount of the observed association between direct-to-physician promotion and opioid sales reflects unobserved selection of physicians into industry relationships.

Table 3 presents the regression estimates for the average effect of interactions with the

	(1)	(2)	(3)	(4)	(5)
Interactions	2.975***	2.146***	2.082***	0.710***	0.728***
	(0.140)	(0.108)	(0.112)	(0.0628)	(0.0638)
InteractionsSQ					-0.000143
					(0.000351)
Mean Dep Var = 17.66					
Percent Change	16.8%	12.2%	11.8%	4.0%	4.1%
Controls	No	Yes	Yes	Yes	Yes
Zip Code x Year FEs	No	No	Yes	Yes	Yes
Physician FEs	No	No	No	Yes	Yes
N	177,227	177,227	177,227	177,227	177,227
R^2	0.258	0.420	0.518	0.935	0.935

Robust standard errors in parentheses. Clustered at zip code level. Mean Interactions=3.19. Control are physician-level variables that include the number of: non-opioid claims, other physicians in group, Part D beneficiaries, Part D beneficiaries under the age of 65, low-income subsidy claims, female beneficiaries, female beneficiaries, black beneficiaries, beneficiaries on Medicare and Medicaid (dual). * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table 2: Effect of Opioid Marketing Interactions on Patented Opioid Claims (2014-2017)

	(1)	(2)	(3)	(4)	(5)
Interactions	28.17***	12.80***	12.21***	5.260***	
	(1.600)	(0.879)	(0.899)	(0.501)	
Patented-only					5.132***
					(0.501)
Mean Dep Var = 463.92					
Percent Change	6.1%	2.8%	2.6%	1.1%	1.1%
Controls	No	Yes	Yes	Yes	Yes
Zip Code x Year FEs	No	No	Yes	Yes	Yes
Physician FEs	No	No	No	Yes	Yes
N	177,227	177,227	177,227	177,227	177,227
R^2	0.133	0.605	0.676	0.969	0.969

Robust standard errors in parentheses. Clustered at zip code level. Mean Interactions=3.19. Control are physician-level variables that include the number of: non-opioid claims, other physicians in group, Part D beneficiaries, Part D beneficiaries under the age of 65, low-income subsidy claims, female beneficiaries, female beneficiaries, black beneficiaries, beneficiaries on Medicare and Medicaid (dual), generic+patented marketing, generic-only marketing.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table 3: Effect of Opioid Marketing Interactions on Generic Opioid Claims (2014-2017)

opioid industry on a doctor's generic opioid claims. The results inform about whether direct-to-physician marketing of patented opioids has any spillover effects on generic opioid prescribing. All specifications suggest that such spillovers are indeed present, with opioid industry interactions positively affecting physicians' generic (non-patented) opioid claims. Column 1 shows that each interaction is associated with an average increase of 28 generic claims per year, or about 6% of the average generic claims. When control variables and interacted zip code by year fixed effects are added to the model in columns 2 and 3, respectively, the coefficient measuring the effect of industry interactions falls to about 12 claims. The average effect of an interaction declines further to 5.3 (or 1% of the average) when physician fixed effects are added to the model in column 4. This suggests that physician-specific heterogeneity is an important consideration. Because in rare instances generic opioids were listed as being part of the promotion of patented drugs, it may be a concern that generic promotion could be driving the spillover effect on generic prescribing. To address this potential issue we examine the effect promotions that did not involve any generic opioids.[22] The results, presented in column 5, are very similar those in column 4, indicating that the spillovers are not the result of generic-related marketing.

The estimates in Table 3 suggest that the direct-to-physician marketing of patented opioids has significant and substantial spillover effects on generic opioid prescribing, with doctors increasing their generic opioid claims by 3.6% per year[23] as a result of pharmaceutical interactions related to patented opioids. Therefore, doctors are prescribing more generic opioid drugs instead of switching patients away from generics when they learn about the new patented (and in some cases safer abuse-deterrent) opioid medications.

While 94% of the promotional interactions in our dataset are detailing visits (proxied by the "Food & Beverage" category), other types of promotional activities may nevertheless influence physician prescribing behavior. To see whether the effects differ depending on the type of interaction, we disaggregate the *Interactions* variable into the number of detailing interactions (*Food & Beverage Interactions*) and the number of other types of

[22]In this specification, the control variables include the number of generic opioid-related interactions.
[23]Based on the 3.19 interactions per year average.

promotional interactions (*Other Interactions*).[24] Additionally, in order to test whether the value of the payment matters, we include the payment amount received by the physician for an opioid-related interaction. The results are presented in Table 4.

	Patented Claims	Generic Claims
Food & Beverage Interactions	0.627***	6.354***
	(0.0898)	(0.752)
Food & Beverage ($)	0.00957*	0.0184
	(0.00529)	(0.0341)
Other Interactions	0.230	2.545
	(0.344)	(2.060)
Other Interactions ($)	0.000117	-0.00431**
	(0.000380)	(0.00219)
Mean Dep Var	17.66	463.92
Zip Code x Year FEs	Yes	Yes
Physician FEs	Yes	Yes
N	177,227	177,227
R^2	0.935	0.969

Robust standard errors in parentheses. Clustered at zip code level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table 4: Effect of Opioid Marketing Interactions (2014-2017)

The coefficient estimates on detailing visits do not substantially differ from the main specification results, with each detailing visit increasing patented prescribing by about 0.6 claims and generic prescribing by about 6.4 claims per year. These estimates imply that the primary results in Tables 2 and 3 are primarily driven by detailing pharmaceutical visits. This finding is not particularly surprising given that the sole objective of pharmaceutical detailing is to induce physicians to prescribe the advertised drug, unlike other types of interactions.

The results produced by Grennan et al. (2018) suggest that while receiving a meal leads to an increase in claims for the promoted drugs, there are no marginal returns to

[24]See Table A2 in the appendix for more information on the types of interactions in the dataset.

higher-value meals. However, our results suggest that after controlling for promotional visits, higher value meals do increase patented claims more than lower-value detailing. We find that for every $1 increase in the meal value, the doctor will generate 0.01 more patented claims. The average spending on promotional detailing is $48.29 per physician per year in our dataset, and each doctor has 3 detailing visits per year on average. This implies that the average detailing visits combined with the money spent on food and beverages will increase physician's patented claims by about 2.34 or by about 13.3%.[25]

The results indicate that non-detailing interactions such as education-related speaking, consulting, travel-related activities, and gifts do not have a statistically significant effect on opioid prescribing. Although column 2 indicates that higher-paid activities related to patented opioids induce physicians to prescribe fewer generics, the magnitude is extremely small - a $1 increase in the amount paid to the physician decreases generic prescribing by 0.004 claims (or 0.00001% of their average generic claims). This implies that the average non-detailing payments to physicians ($187.96) will decrease generic prescribing by 0.81 opioid claims or 0.2% of the physician's average generic claims. In these non-detailing interactions physicians are likely spending some time on researching and preparing materials related to newer and safer opioid drugs, so the slight negative effect on unsafe generic prescribing may be expected.

Prior direct-to-physician advertising literature indicates that the effects of promotion on prescribing generally go away within two years. To shed light on the persistence of promotional effects, Table 5 presents the coefficient estimates for equation 2. The first column estimates suggest that the effect of patented promotion on patented opioid claims dissipates after about two years, consistent with prior literature's findings. While current-year interactions increase current-year patented opioid claims by about 0.7 claims, the interactions from one year ago increase patented claims by about 0.2, and interactions from two years ago have no statistically significant effect on patented prescribing. On the other hand, the generic spillover effects remain persistent over the years. The results in

[25] 0.00957(48.29)+0.627(3)=2.343.

the second column indicate that current-year interactions increase current generic claims by 3 claims per year, interactions from one year ago and two years ago increase current generic opioid prescribing by about 2 claims. These estimates suggest that not only are doctors prescribing more unsafe generic opioids as a result of patented marketing, but that these effects continue to linger over the years.

	Current Patented Claims	Current Generic Claims
Current Interactions	0.659***	3.136***
	(0.110)	(0.553)
Interactions 1 Year Ago	0.237***	2.159***
	(0.0794)	(0.537)
Interactions 2 Years Ago	0.0579	1.981***
	(0.0599)	(0.445)
Mean Dep Var	16.82	473.38
Zip Code x Year FEs	Yes	Yes
Physician FEs	Yes	Yes
N	75,048	75,048
R^2	0.972	0.991

Robust standard errors in parentheses. Clustered at zip code level. Mean Interactions=3.43.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table 5: Effect of Marketing Interactions on Opioid Claims (2014-2017)

One explanation for positive generic spillovers is that doctors who want to prescribe ADF drugs as a result of direct-to-physician ADF marketing must first prescribe generic opioids because of "fail-first" insurance policies, leading to positive spillovers on generic opioid claims. On the other hand, physicians may not face stringent insurance constraints when they are prescribing non-ADF drugs. It is also possible that physicians who are initially induced to prescribe more ADF drugs, as they learn about their safer properties from the sales representatives, end up switching their patients to generics as a result of patents' unwillingness to deal with ADF drugs' high cost and difficulty with access. To examine in more detail the heterogeneity of the direct and spillover effects for ADF vs.

non-ADF interactions, we estimate equation 3. Figure 2 present the results.[26]

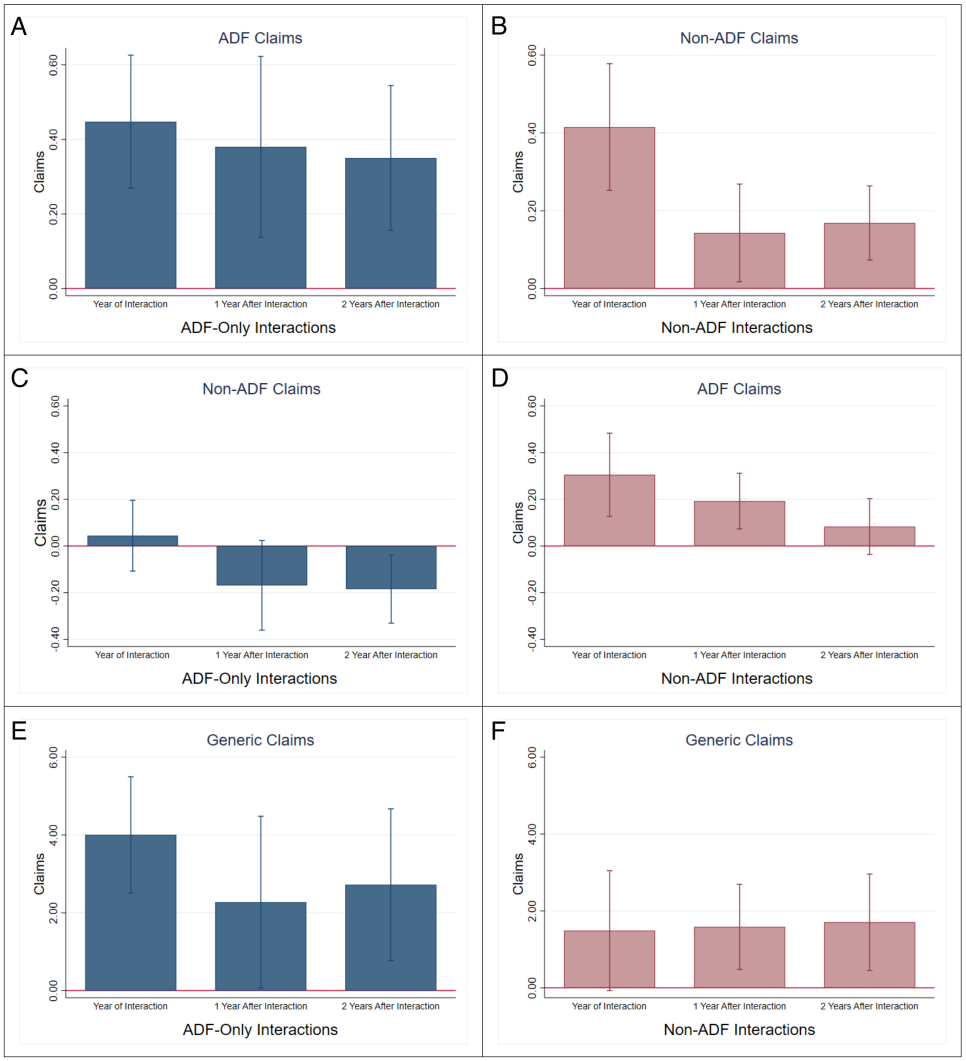

Figure 2: Effects of ADF and non-ADF Marketing Interactions

Panels A and B of Figure 2 show the effect of promotional interactions on the claims of the drugs that are being promoted. The results shown in Panel A indicate that each current-year interaction involving discussion of only ADF opioids increases current-year ADF claims by about 0.45 and interactions from one and two years ago increase ADF claims by 0.38 and 0.35, respectively. These results suggest that the effects of ADF-only marketing are very persistent throughout the time-frame of the study. On the other hand, non-ADF patented promotion does not display the same persistence, as shown in Panel B.

[26]Full set of coefficient estimates is available in Table A3 in the appendix.

While each current-year non-ADF promotional interaction increases non-ADF prescribing by 0.42 claims per year, the effects of past interactions on current claims are substantially reduced. For example, non-ADF promotions from one and two years ago increase current year non-ADF claims by only 0.14 and 0.17, respectively.

Panels C and D of Figure 2 display the non-generic spillover effects of each type of marketing. The results suggest that ADF marketers are able to dissuade doctors from prescribing non-ADF patented opioids. Panel C shows that current ADF-only marketing does not have any effect on current non-ADF claims. Additionally, past ADF-only marketing reduces the likelihood that a non-ADF opioid is prescribed, with promotions taking place one year and two years ago decreasing current non-ADF prescribing by about 0.2 claims per year. These estimates suggest that doctors may be learning about the safety features of abuse-deterrent opioids from the pharmaceutical sales reps, choosing to prescribe less patented drugs which do not prevent misuse. On the other hand, non-ADF patented promotion is not as successful in preventing doctors from prescribing ADF drugs. As Panel D shows, each current non-ADF-related interaction increases current ADF claims by 0.3 on average. This spillover effect tapers off over time, with non-ADF interactions from a year ago increasing current ADF claims by about 0.2, and non-ADF promotions from two years ago appearing to have no effect on current ADF claims.

Panels E and F of Figure 2 show the spillover effects of ADF and non-ADF patented marketing on generic prescribing. Coefficient estimates suggest that ADF-only marketing has bigger spillover effects on current abuse-prone generic prescribing relative to non-ADF interactions - current ADF-only interactions increase current generic claims by about 4, while current non-ADF promotions increase generic prescribing by only 1.5 claims per year. In addition to having higher current spillover effects on non-safe prescribing, ADF-only marketing spillovers are also more persistent through the years. ADF-only interactions from one and two years ago increase generic prescribing by 2.3 and 2.7 generic opioid claims, respectively, while past non-ADF interactions increase current generic opioid prescribing by 1.6 and 1.7 claims.

Together the figures imply that, first, ADF-only marketing is more effective than non-ADF promotion. ADF-only interactions have a highly persistent impact on ADF claims, while the effect from non-ADF marketing on non-ADF claims does not appear to be as lasting. Furthermore, ADF-only promotion appears to be successful in persuading doctors to prescribe ADF drugs and avoid non-ADF patented opioids. Second, according to the estimates, ADF marketing may come with unintended adverse consequences on public health. ADF-only opioid promotion has greater and more persistent spillover effects on unsafe generic opioid prescribing. This result is consistent with the fact that ADF prescribing involves insurance access restrictions such as "fail-first" policies that encourage substituting toward cheaper generics. It appears that physicians are substituting away from the traditional patented formulations and toward ADF opioids as a result of ADF-only marketing, which likely emphasises to physicians the relative safety of abuse-deterrent formulations. However, because abuse-deterrent opioids are subject to limited insurance plan coverage and plan-specific rules that require trying generic opioids before an ADF is covered, the ADF-related interactions also produce larger spillover effects on generic claims relative to other types of opioid interactions.[27] We find further evidence for this hypothesis using 2017 formulary data. Results suggest that broader formulary coverage of ADFs reduces generic spillovers (for details, see Appendix B).

Table 6 reports a causal forest average partial treatment effect estimate of 1.235 that is significant ($p<0.01$) and positive in magnitude along the lines of our previous analysis. Furthermore, the overall distribution of these treatment effects indicate the presence of considerable treatment effect heterogeneities across providers.[28]

Next, we explore these heterogeneities across provider specialties, provider gender, and provider geographies, within Figure 3. Looking at quadrant A of Figure 3 we note sizable treatment effect differences across providers with a primary speciality in internal medicine, family practice, orthopedic surgery, and all other. Out of these we note the highest effects

[27] Non-ADF patented opioids may also be subject to limiting insurance policies, however, not to the same extent as ADF opioid drugs.

[28] See Figure A1 in the appendix. The presence of significant heterogeneity was further supported by an omnibus test ($p < 0.001$) which indicates a significant presence of heterogeneity within the data.

among internal medicine providers (mean: 2.25) and the lowest for orthopedic surgery specialist (mean: 0.54). The same trends are illustrated using histograms within quadrant B of Figure 3, and when checking for mean differences across these specialty groups we note significant differences (p<0.0001, for two-way t-tests). These results suggests that doctors most commonly seen by an average patient (such as internal or family physicians) are likely to be more responsive to opioid promotion than specialists. Quadrant C, on the other hand, illustrates the coefficient plot (with 95% confidence bars) for regressing the treatment effect on our specialty groupings across provider gender (note: the omitted specialty is the "all other" specialties category). Here we see that there are notable gender differences across providers with a specialty of internal medicine or family practice, with male providers on average having a larger treatment response than female providers. In the case of providers with a speciality of internal medicine, the average treatment effect for male providers is measured at 2.32, while the average treatment effect for females is significantly (p<0.0001) lower at 2.06. Lastly, Quadrant D plots the average state-level treatment effect across the state-level average number of patented interactions. We note considerable variability between states across both of these dimensions, with particularly high average treatment effects seen within Alabama (mean: 2.15), Mississippi (mean: 2.04) and Florida (mean: 2.00).

Treatment Effect	**Estimate**
Average Partial Treatment Effect	1.235***
	(0.052)
Controls	Yes
State FEs	Yes
Year FEs	Yes
N	177,227

Standard errors that were clustered at zip code level are reported in parentheses.
Estimates based on an ensamble of 2,000 trees.
Controls are physician-level variables that include the number of: non-opioid claims, other physicians in group, Part D beneficiaries, Part D beneficiaries under the age of 65, low-income subsidy claims, female beneficiaries, black beneficiaries, beneficiaries on Medicare and Medicaid (dual), generic+patented marketing, generic-only marketing.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table 6: Conditional Average Treatment Effect Estimates Obtained from Causal Forest

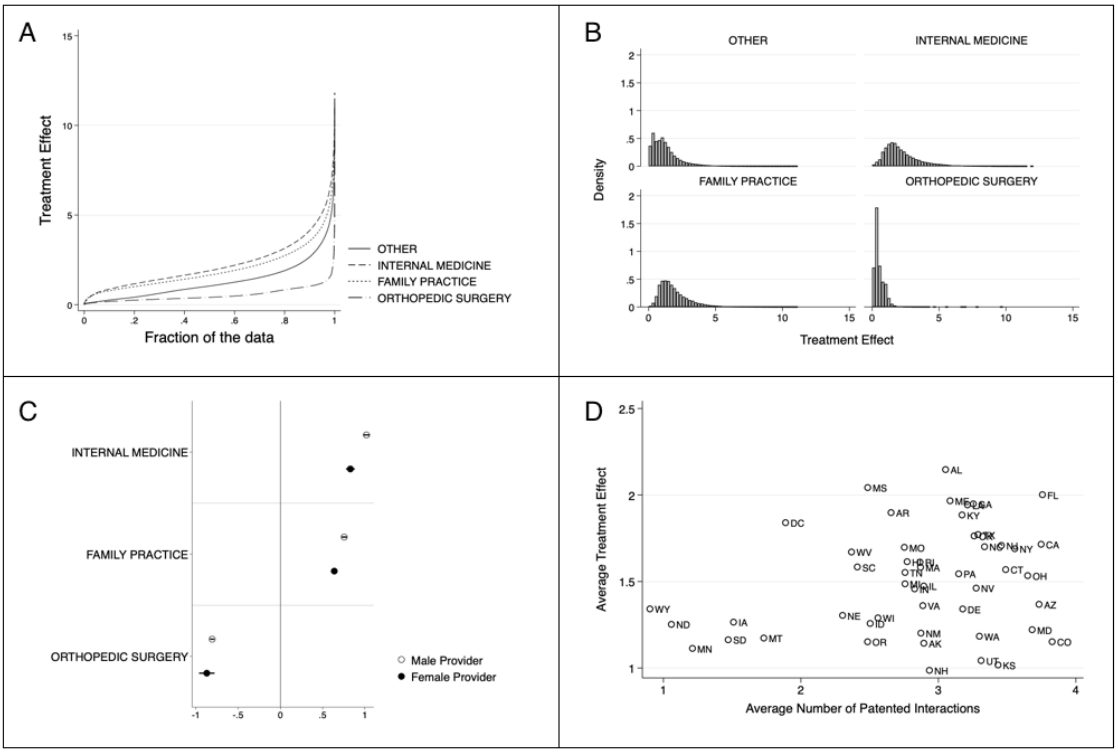

Figure 3: Heterogeneous Treatment Effects Across Provider Specialty, Gender, and State

6 IV Identification Strategy and Other Robustness Checks

Including physician and zip-code-by-year fixed effects in our main specification allows us to account for observable and unobservable physician characteristics that may lead to selection, as well as to control for time-varying local opioid demand shocks that may affect the prescribing behavior of doctors and the number of pharmaceutical interactions. However, the fixed effects strategy may not fully account for the endogeneity if a doctor experiences a physician-specific opioid demand shock that is unrelated to changes in demand at the zip code level and is at the same time correlated with the pharmaceutical marketing. For example, this could occur if a physician experiences a sudden increase in demand for opioids that is not encountered by any other physician in the same zip code and that induces a visit from an opioid sales representative. Then, the physician-specific

increase in demand could be wrongly attributed to the promotional visit. However unlikely such a scenario may be, we check our main specification results by employing an instrumental variable approach. Additionally, we estimate equation 1 on several different samples of physicians as well as by firm in order to increase confidence that the results are not driven by outliers.[29]

The instrumental variable model identification strategy is similar to the approach taken by Grennan et al. (2018) and relies on the fact that drug manufacturers allocate their marketing budget based on certain aggregate market characteristics. For example, markets with many opioid-prescribing providers and larger pain-prone population are more likely to have bigger direct-to-physician marketing budgets allocated to them.[30] The firms' marketing models are based on detailed data that includes physicians' prescribing history, physician and practice characteristics, and past history of physician's interactions with the pharmaceutical firms (Campbell, 2008). Once the budgets are allocated and pharmaceutical representatives are assigned to their respective regions, it is up to the individual sales reps to target "high-value" physicians. Thus, after conditioning on characteristics that make a given physician likely to be targeted by the sales representative, the characteristics of other physicians in the geographic market (attractiveness of other physicians to the pharmaceutical reps) can serve as instruments for the physician's interactions with the pharmaceutical company, and should not affect the given physician's prescribing directly. We conduct the analysis using a full sample of physicians. Equations 6 and 7 present the first and the second stages of the IV approach.

$$\text{1st stage: Interactions}_{i,z,t} = \gamma Interactions_{z,t(-i)} + \delta X_{i,z,t} + v_z + \tau_t + \theta_i + e_{i,z,t} \tag{6}$$

[29]Tables with coefficient estimates are available in the appendix.

[30]Pharmaceutical sales regions are defined by geography and other categories such as therapeutic area (Campbell, 2008).

$$\text{2nd stage: Claims}_{i,z,t} = \phi \widehat{Interactions}_{i,z,t} + \delta X_{i,z,t} + v_z + \tau_t + \theta_i + u_{i,z,t} \quad (7)$$

We use zip code level variables ($Interactions_{z,t(-i)}$) to serve as instruments for opioid-related interactions with the pharmaceutical firm . The instrument set includes the total number of opioid-related interactions in physician i's zip code (excluding i's opioid-related interactions) and the total value of payments made to other physicians in i's zip code by any pharmaceutical or medical device firm. These zip code level instruments should be correlated with physician i's opioid-related interactions, but should not affect i's opioid claims directly after controlling for i's practice and patient characteristics. Instead of using within-physician, within zip code differences to identify the effect of pharmaceutical marketing (our main specification), the advantage of using this strategy is that the source of identifying variation comes from the other physicians within the zip code. This estimation strategy does not allow for zip code by year fixed effects, since this is the variation we depend on. However, zip code fixed effects (v_z), year fixed effects (τ_t), and physician fixed effects (θ_i) are included separately. Vector $X_{i,z,t}$ contains covariates defined in the main specification.

Table 7 present the Two-Stage Least Squares (2SLS) results. The first stage F statistic of 84.0 suggests that the instruments are strong and Hansen J test of overidentifying restrictions implies that they are also valid. The second stage coefficient estimate for the effect of interactions on patented claims is 0.702, which is identical to the preferred specification in Table 2 (column 4). The average effect on generic claims is 6.837, compared to a slightly lower coefficient estimate of 5.3 from Table 3 (column 4). Overall, the IV coefficient estimates provide confidence in the results of the preferred, fixed effects specification shown in Tables 2 and 3.

In order to check whether the results are driven by outliers, we estimate equation 1 on samples of physicians that exclude extreme values, since doctors who have a very

high number of yearly interactions with opioid marketers (or ones with high payment amounts) may be induced the most to prescribe more opioids. The coefficient estimates remain virtually unchanged from the main, suggesting that the main results are not driven by physicians receiving large opioid payments or by prescribers with unusually high frequency of industry interactions.

Additionally, in order to check if the results may be driven by any one opioid-producing firm's ability to market drugs to doctors, we separate the *Interactions* variable into the number of interactions for each firm present in our data. The coefficient estimates suggest that while the effects vary from firm to firm, the results are not driven by just a few opioid producers.

	Patented Claims	Generic Claims
Interactions	0.702***	6.837***
	(0.271)	(1.949)
Mean Dep Var	3.2	112.2
Year FEs	Yes	Yes
Physician FEs	Yes	Yes
First-stage estimates:		
Zip Code Interactions$_{-i}$	0.0018***	
	(0.0001)	
Zip Code Total Payments$_{-i}$	-3.34e-09	
	(3.05e-09)	
N	1,632,008	1,632,008
First-stage F	84.0	84.0
Hansen J (*p-value*)	0.48	0.57

Robust standard errors are clustered at the zip code level and reported in parentheses. Instruments (zip code level, exclusing physician i): total number of opioid interactions, total value of marketing payments.* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table 7: Effect of Marketing Interactions on Opioid Claims (2014-2017) Full Sample

7 Conclusion

This study informs the direct-to-physician marketing literature by examining the effect of promotional industry interactions related to patented opioid drugs on patented and generic opioid prescribing patterns while fully exploiting physician level longitudinal data for years 2014-2017. We control for high-prescriber selection into marketing interactions by utilizing physician fixed effects, while zip-code-by-year fixed effects account for any time-varying regional opioid demand shocks that may affect both prescribing patterns and opioid marketing strategies. The results indicate that direct-to-physician patented opioid marketing increases opioid prescribing. These effects are driven by detailing visits and appear to be increasing in the value of meals provided to physicians during the sales pitch. The findings suggest that the average number of detailing visits together with the average cost of the meal induces physicians to generate 13.3% more patented opioid claims per year. Moreover, we show that these effects are heterogenous - they vary considerably across provider specialty, in some cases provider gender, and with geography. While future research is necessary to further examine the extent and the source of these heterogeneities, our results indicate that high-contact doctors (such as family physicians) tend to experience a greater prescribing response to promotion than some specialists such as orthopedic surgeons.

Not only do the results indicate the presence of positive and statistically significant effects on patented opioid claims, but they also show that patented promotion causes positive and persistent spillover effects on abuse-prone generic prescribing in Medicare Part D. Instead of substituting away from unsafe prescribing, doctors end up increasing their generic claims by about 3.6% per year as a result of patented direct-to-physician advertising.

The caveat of these findings may be that the effects are pertinent to physician-industry promotional interactions in the market for opioid drugs and not relevant for other pharmaceuticals. Nevertheless, the results carry important implication for nation-wide policy strategies used in the battle with opioid misuse and addiction. According to the estimates

in this study, the supply of both patented and generic opioids may be increased by the direct-to-physician marketing of opioids, undermining the current federal and state efforts to reduce opioid prescribing. Importantly, the promotion of safer abuse-deterrent opioid drugs may come with unintended consequences in the form of wider prescribing of generic, abuse-prone medications which could have a detrimental effect on public health. Using data for 2017 we provide some results that suggest that broader formulary coverage of ADFs by insurers may counteract these spillovers. Therefore, the FDA's encouragement to pharmaceutical companies urging them to produce and develop more abuse-deterrent opioid drugs must go hand-in-hand with broadened formulary coverage and insurance plan removal of "fail-first" requirements along with other restrictions that induce riskier opioid consumption. Alternatively, it may be in the interest of society to restrict detailing promotion of opioid drugs and to encourage prescriber education about opioid medications through "academic detailing" where information diffuses through a channel that does not pose a potential conflict of interest.

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Appendix

A Additional Tables and Results

Name	Firm	ADF
Arymo ER	Egalet	yes
Butrans	Purdue Pharma	-
Dilaudid	Purdue Pharma	-
Hysingla ER	Purdue Pharma	yes
OxyContin	Purdue Pharma	yes
Exalgo	Mallincrodt	-
Xartemis	Mallincrodt	-
Abstral	Galena Biopharma/Sentynl	-
Subsys	Insys Therapeutics	-
Conzip	Vertical Pharma	-
Fentora	Teva Pharma	-
Lazanda	Depomed	-
Nucynta	Depomed/Janssen	-
Nucynta ER	Depomed/Janssen	-
Belbuca	Endo Pharma	-
Opana	Endo Pharma	-
Opana ER	Endo Pharma	-
Avinza	Pfizer	-
Embeda	Pfizer	yes
Oxecta	Pfizer	-
Zohydro ER	Pernix/Zogenix	-
Xtampza ER	Collegium Pharma	yes
Morphabond ER	Daiichi Sankyo	yes

Table A1: Patented Prescription Opioids (2014-2017)

Nature of Interaction	**Total Number ($ Value)**	**Average Per Doctor**
Total Interactions	565,892 ($41.9 Million)	3.19 ($236.25)
Food & Beverage	530,799 ($8.56 Million)	3.00 ($48.29)
Faculty/Speaker Services	15,551 ($26.5 Million)	0.09 ($149.36)
Continuing Education Services	4 ($9,000)	0.00002 ($0.05)
Consulting	945 ($2.5 Million)	0.005 ($14.10)
Education	9,053 ($184,301)	0.05 ($1.04)
Travel & Lodging	8,843 ($2.85 Million)	0.05 ($16.06)
Gift	38 ($7,508)	0.0002 ($0.04)
Honoraria	659 ($1.3 Million)	0.004 ($7.31)

Table A2: Opioid Interactions by Nature of Interaction (2014-2017)

	ADF Patented Claims	Non-ADF Patented Claims	Generic Claims
ADF-Only$_t$	0.448***	0.0444	4.003***
	(0.0911)	(0.0773)	(0.761)
ADF-Only$_{t-1}$	0.380***	-0.169*	2.275**
	(0.124)	(0.0979)	(1.126)
ADF-Only$_{t-2}$	0.350***	-0.185**	2.721***
	(0.0992)	(0.0744)	(0.995)
Non-ADF$_t$	0.305***	0.415***	1.489*
	(0.0909)	(0.0831)	(0.796)
Non-ADF$_{t-1}$	0.192***	0.143**	1.586***
	(0.0609)	(0.0640)	(0.565)
Non-ADF$_{t-2}$	0.0833	0.169***	1.707***
	(0.0611)	(0.0486)	(0.639)
ADF+NonADF$_t$	0.558***	0.862***	7.251***
	(0.176)	(0.148)	(1.479)
ADF+NonADF$_{t-1}$	0.410***	0.353***	4.383***
	(0.134)	(0.112)	(1.374)
ADF+NonADF$_{t-2}$	-0.0499	-0.122	1.093
	(0.137)	(0.0878)	(1.287)
N	75,048	75,048	75,048
R^2	0.967	0.957	0.991

Robust standard errors in parentheses. Clustered at zip code level.* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table A3: Effect of Marketing Interactions on Opioid Claims (2014-2017)

	Patented Claims	Generic Claims
Interactions	0.548***	6.553***
	(0.0484)	(0.464)
Mean Dep Var	13.76	429.18
Percent Change	4.0%	1.5%
Zip Code x Year FEs	Yes	Yes
Physician FEs	Yes	Yes
N	173,633	173,633
R^2	0.926	0.970

Robust standard errors in parentheses. Clustered at zip code level.
Mean Interactions=2.2. * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table A4: Effect of Marketing Interactions on Opioid Claims (2014-2017) - Excluding Doctors with Top 1% Interactions (>48 visits)

	Patented Claims	Generic Claims
Interactions	0.648***	7.364***
	(0.0587)	(0.478)
Mean Dep Var	14.83	442.62
Percent Change	4.4%	1.7%
Zip Code x Year FEs	Yes	Yes
Physician FEs	Yes	Yes
N	173,733	173,733
R^2	0.931	0.971

Robust standard errors in parentheses. Clustered at zip code level.
Mean Interactions=2.4. * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table A5: Effect of Marketing Interactions on Opioid Claims (2014-2017) - Excluding Doctors with Top 1% Opioid Payments (>$951.36)

	Patented Claims	Generic Claims
Purdue Pharma	0.855***	6.557***
	(0.0865)	(0.706)
Insys	0.782***	1.966***
	(0.134)	(0.724)
Galena	2.429*	15.00*
	(1.265)	(8.373)
Vertical Pharma	0.498**	3.900***
	(0.227)	(1.317)
Mallincrodt	0.635***	-1.698
	(0.185)	(1.238)
Teva	0.247	1.159
	(0.311)	(1.622)
Depomed/Jannssen	0.772***	3.818***
	(0.123)	(1.156)
Endo Pharma	0.464***	4.635***
	(0.173)	(1.041)
Pfizer	0.404***	6.253***
	(0.131)	(0.893)
Pernix/Zogenix	0.989***	2.996
	(0.248)	(2.119)
Collegium Pharma	0.926***	5.994***
	(0.210)	(1.377)
Sentynl	0.338	17.26**
	(1.107)	(7.254)
Egalet	-0.152	3.241
	(0.196)	(2.035)
Daiichi Sankyo	1.256**	25.84***
	(0.509)	(6.375)
N	170,397	170,397
R^2	0.939	0.970

Robust standard errors in parentheses. Clustered at zip code level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table A6: Effect of Marketing Interactions on Opioid Claims (2014-2017)

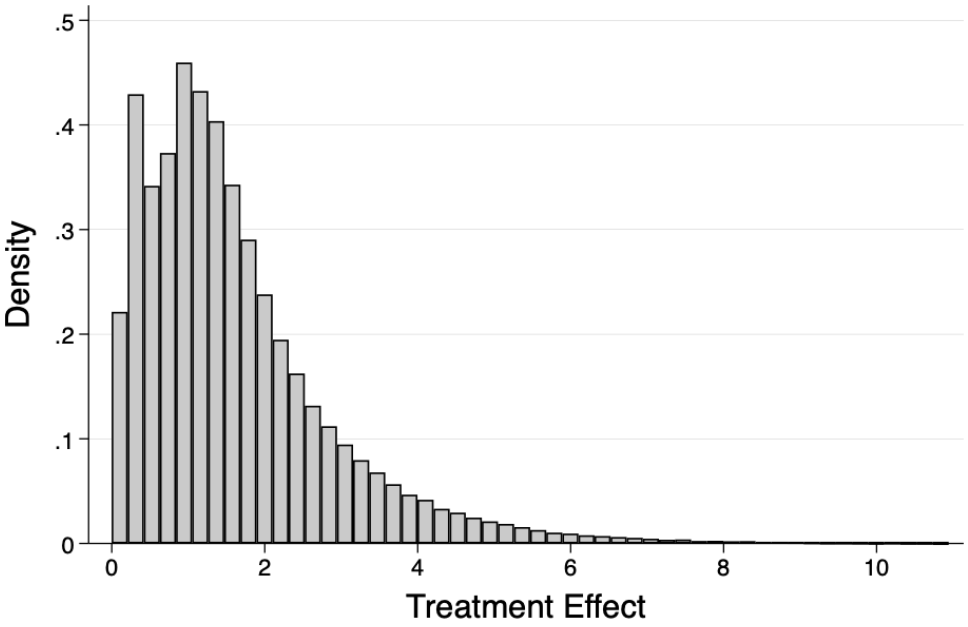

Figure A1: Distribution of Causal Forest Treatment Effects

B Exploration of the ADF Spillover Hypothesis

As part of a limited secondary analysis, we use 2017 data with information on provider's insurance network participation and the formulary details for these plans across all exchange, off-exchange and Medicare Advantage plans that we source from Vericred in order to explore the validity of our hypothesized link between physician ADF coverage and observed spillover effects from patented detailing onto generic prescribing. We do this by examining the following regression specification:

$$Claims_{i,z} = \beta Interactions_{i,z} + \gamma ADFCoverage_{i,z} + \phi Interactions_{i,z} * ADFCoverage_{i,z}$$

$$+ \delta X_{i,z} + \xi_z + \kappa_s + u_{i,z}, \tag{B1}$$

where $Claims_{i,z}$ denotes the number of generic opioid claims of provider i in zip-code/state z, $Interactions_{i,z}$ captures the number of patented opioid market interactions that the provider experiences, $ADFCoverage_{i,z}$ denotes the providers level of ADF coverage, $X_{i,z}$ captures other controls as previously defined, ξ_z denotes zip-code/state fixed effects and κ_s is a provider specialty fixed effect. Our physician specific ADF coverage is obtained by computing the coverage of each plan that a physician is affiliated with and then averaging across all plans to establish an overall (physician specific) average coverage level. As such, our specification allows us to examine whether ADF coverage matters for generic prescribing, and furthermore if the degree to which ADF coverage matters varies with the intensity of patented interactions.

Table B1 reports the results from this analysis. Here we find that the average ADF coverage varies considerably across physicians, with an average level of 71% coverage and standard deviation of 14%. Moreover, Table B1 indicates that greater ADF coverage is associated with lower generic opioid prescribing–a finding that is robust to the inclusion of zip-code as well as specialty fixed effects (see Columns (2) and (3)). While this analysis is limited to a cross-sectional analysis for 2017, we believe that these finding lend some qualitative support to the hypothesis that physicians who are part of insurance networks

with greater ADF coverage tend to exhibit lower spillover effects from patent drug specific detailing onto generic opioid prescribing. When we further restrict our attention to physicians that are within the 90th percentile in terms of ADF coverage we note that the spillover effect is reduced further, and also that there appears to be a negative interaction between the ADF coverage level and patented interactions.

	(1)	(2)	(3)	(4)	(5)	(6)
Interactions	32.99***	32.21***	32.21***	28.42***	28.06***	28.06***
	(7.765)	(7.734)	(7.734)	(1.583)	(1.583)	(1.583)
ADF Coverage (%)	-1.188***	-1.263***	-1.263***			
	(0.0820)	(0.0824)	(0.0824)			
Interactions × ADF Coverage (%)	-0.0722	-0.0658	-0.0658			
	(0.109)	(0.108)	(0.108)			
1(ADF Coverage > p90)				-27.84***	-30.23***	-30.23***
				(1.983)	(2.034)	(2.034)
Interactions × 1(ADF Coverage > p90)				-6.873*	-6.624*	-6.624*
				(3.948)	(3.905)	(3.905)
nonADF Coverage (%)	1.574***	1.567***	1.567***	0.743***	0.692***	0.692***
	(0.0862)	(0.0876)	(0.0876)	(0.0492)	(0.0499)	(0.0499)
	(8.197)	(9.175)	(9.175)	(8.395)	(9.378)	(9.378)
Controls	Yes	Yes	Yes	Yes	Yes	Yes
State FEs	Yes	No	No	Yes	No	No
Zip Code FEs	No	Yes	Yes	No	Yes	Yes
Specialty FEs	No	No	Yes	No	No	Yes
N	364,634	361,823	361,823	364,634	361,823	361,823
R^2	0.415	0.444	0.444	0.416	0.444	0.444

Robust standard errors in parentheses. Clustered at zip code level.
Controls are physician-level variables that include the number of: non-opioid claims, other physicians in group, Part D beneficiaries, Part D beneficiaries under the age of 65, low-income subsidy claims, female beneficiaries, black beneficiaries, beneficiaries on Medicare and Medicaid (dual), generic+patented marketing, generic-only marketing.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table B1: Effect of Patented Opioid Marketing Interactions and Average ADF formulary coverage on Generic Opioid Claims (2017)