

# Pharmaceutical payments to physicians may increase prescribing for opioids

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## ABSTRACT

**Background and Aims** Given the recent complete suspension of opioid-related promotional activities aimed at physicians, interest has renewed in understanding the role of promotion in the US opioid crisis. The present analysis aimed to measure associations between such interactions and opioid prescribing. **Design** Data on all promotions by pharmaceutical companies directly to physicians were linked to physician-level data on opioid prescriptions filled in a federal insurance program and analyzed using multivariate regression. **Setting** United States. **Participants** A total of 865 347 US physicians, with prescriptions filled in Medicare Part D, that might receive payments from pharmaceutical promotional activities from 2014 to 2016. **Measurements** The outcome variable was days' supply dispensed by each prescriber, by year, for all opioids (collectively) and separately for the following opioid classes: hydrocodone, oxycodone, fentanyl, tapentadol, morphine and a catch-all 'other opioids'. The independent variables were receipt of any payments and dollar amounts of payments received by each prescriber by year for all opioids and separately for opioid categories. **Findings** Prescribers who received opioid-specific payments prescribed 8784 opioid daily doses per year more than their peers who did not receive any such payments ( $P < 0.001$ ). Recipient of hydrocodone-related payments was associated with 5161 additional daily doses of hydrocodone ( $P < 0.001$ ). Recipient of oxycodone-related payments was associated with 3624 additional daily doses of oxycodone ( $P < 0.001$ ). Prescribers receiving any fentanyl-specific payments prescribed 1124 daily doses per year more than their peers ( $P < 0.001$ ). Among recipients of opioid-specific payments (63 062 physicians), a 1% increase in amount of payments was associated with 50 daily doses of opioid prescription ( $P < 0.001$ ). **Conclusions** In the United States, physicians who receive direct payments from providers for opioid prescribing tend to prescribe substantially larger quantities, particularly for hydrocodone and oxycodone.

**Keywords** Detailing, direct-to-physician marketing, Medicare Part D, opioids, opioid prescription, physician payments.

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## INTRODUCTION

Globally, 190 900 drug-related deaths were estimated in 2015, the majority attributable to the use of opioids [1]. Opioid-related mortality has increased rapidly in the United States since the early 2000s, with devastating consequences for families and communities. According to the official estimated fatality counts from CDC WONDER (Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research), in 2016 there were 19 354 overdose deaths involving prescription opioids (excluding non-methadone synthetics which is dominated by illicit fentanyl) in the United States, and 19 413 deaths were attributable to synthetic-opioid overdoses [2].

Remarkably, Ruhm emphasized that the official counts in all opioid categories were 21–35% lower than the corrected counts [3]. Mortality is the tip of the iceberg; academic research estimates that prescription disbursement has been the pathway to misuse for two million opioid-addicted individuals [4].

There is much concern that provider-directed payments from opioid manufacturers influence prescribing. Beginning in the mid-1990s, two significant changes occurred in the culture of pain management. First, Oxycontin was approved by the Food and Drug Administration (FDA) and was heavily marketed as having a lower potential for abuse than existing (short-acting) opioids [5]. This proved to be the first of a wave of new self-

administered opioids in easy-to-take pill forms to enter the market. Secondly, the medical community, increasingly recognizing the historical under-treatment of pain, began to define pain as the ‘fifth vital sign’ [6–8]. During the early 2000s opioid prescribing grew rapidly, increasing from 148 million prescriptions in 2005 to 206 million prescriptions by 2011 [9]. Given the recent announcement by Purdue Pharma that they will cease opioid promotional activities aimed at physicians and the massive number of recent lawsuits in connection with these activities against opioid makers, there is renewed interest in understanding the role of promotional activities in the opioid crisis. Surprisingly, however, little is known about the actual link between direct pharmaceutical manufacturer payments to physicians and opioid prescribing. Hadland *et al.* has been the first and only paper examining the association between any payments and all opioid prescribing for 2014–2015 [10].

The current study quantifies the association between opioid-specific direct-to-physician promotion and physician opioid prescribing in order to advance more comprehensive evidence on the role of opioid-related promotional activities than previous literature in several important aspects. First, our study explores details of how the association varies by two key measures of opioid detailing (the extent and intensity of payments). Secondly, this paper provides insight into the role of marketing directed to physicians by the type of opioids, where we find significant heterogeneity in the associations. Thirdly, the study also analyzes the characteristics of physicians who received promotional payments compared to physicians who received no such promotion. Lastly, we are able to conduct longitudinal analysis of physician behavior, extending the current literature which is cross-sectional in nature.

## METHODS

### Design

The Sunshine Act’s Open Payments data from the Centers for Medicare and Medicaid Services (CMS) 2014–16 were linked to the CMS Medicare Prescriber Public Use Files (Prescriber PUFs) and county-level data in this longitudinal analysis of physician behavior. Medicare Part D provides out-patient prescription drug coverage for eligible individuals, those who are 65 years and older as well as patients who qualify as disabled. As of 1 August 2013, the Sunshine Act mandates all manufacturers and group purchasing organizations of covered drugs, devices and biological and medical supplies to disclose annually all payments and other transfers of value that they make to physicians and teaching hospitals for all their products, with certain exceptions. We begin our analysis with 2014 because that is the first full year of the Open Payments data. All provider-directed payment records, which mentioned at least one opioid prescription drug, were extracted and

collapsed to the physician level in order to merge with Prescriber PUF data.

The list of opioid drugs was created from two sources: the Prescriber Drug Category List for opioids of the CMS 2014–16, which was based upon drugs included in the Medicare Part D Overutilization Monitoring System [11]; and the Ambulatory Care Drug Database System of the CDC [12]. All methadone and buprenorphine products were excluded from the analysis because they may also be used for substance abuse treatment, and the prescribing rules for each are complex. As with a number of prior studies, we limited this study to non-research, non-equity, drug-related payments to physicians, herein referred to as promotional payments [13–15]. Chiropractors were also excluded from the analysis because their primary approach (chiropractic manipulation) is distinct from medication.

The Open Payments and Prescriber PUF data were linked using physician name and ZIP code following previous literature and CMS recommendations regarding merging Prescriber PUF data to other public data sets [13,16,17]. Providers in the Prescriber PUF data without any reported payments were assumed to receive no payments from opioid makers; this is a reasonable assumption, as reporting is legally mandated. Physicians in the Open Payments data without any reported drug claims and profile information in the Prescriber PUF data were excluded from the analysis as they are assumed to not to have received any reimbursement for Medicare provided services; the PUF contains a census. All regressions control for observable characteristics of the prescriber from Prescriber PUF data, county-level characteristics from the Robert Wood Johnson Foundation (RWJF) County Health Rankings file [18], and the status of the ‘must access’ provision of prescription drug monitoring programs (PDMPs) was collected from the Prescription Drug Abuse Policy System [19].

### Measures

#### *Outcome variable*

The dependent variables were the number of days’ supply dispensed by each prescriber in the Prescriber PUF each year for all opioids (collectively) and then separately for opioids in the following classes: hydrocodone, oxycodone, fentanyl, tapentadol, morphine and a catch-all ‘other opioids’ category.

#### *Key predictors*

The first measure of pharmaceutical direct-to-physician marketing activities is receipt of opioid-related payments, which is an indicator variable for whether a prescriber is linked to any opioid-related payment record in Open Payments data each year. Receipt of payments is one

measure of direct-to-physician marketing activities. The second measure is the amount of payment the prescriber received each year that reflects the intensity of these marketing activities among targeted recipients. This variable takes log-transformed values in the regression because the distribution of payments is heavily skewed.

#### *Covariates*

The associations between the outcome variable and the key predictors were adjusted for state opioid control policy, local socio-demographic characteristics and physician-level characteristics. All county and state policy information is year-specific.

Specifically, whether or not the state has a 'must access' prescription drug monitoring program was controlled for several reasons. PDMPs have received the most attention as one leading state policy response to restrict the flow of opioid prescriptions, although findings have been mixed [20]. Some studies find modest improvements in outcomes related to PDMP implementation [21–23]; however, other studies find no differences in opioid-related mortality or abuse rates associated with PDMPs [24,25]. Most recently, authors have distinguished between PDMP laws that mandate access compared to those that do not, and find significant effects of reduced opioid use in the former but not the latter [26].

Local socio-demographic characteristics include the county population; the county unemployment rate; % of the county that is male; % of the county aged 65 years or older; % of the county that is non-Hispanic African American; % of the county that is Hispanic; and % of the county that is non-Hispanic Caucasian. Physician-level characteristics include number of unique Medicare opioid prescription beneficiaries by physician, physician's gender, years of practice under their National Provider Identifier (NPI) and specialty.

#### *Statistical analysis*

As a preliminary assessment of the association between the amount of payments to clinicians from pharmaceutical manufacturers and opioid prescribing, a series of unadjusted *t*-tests were conducted. Particularly, simple difference in means for prescribing, for all opioids and opioids by class, by recipients and non-recipients and the differences in prescribing for the top 25th percentile recipients of pharmaceutical payments to the bottom 75th percentile for all opioids and by class of opioids were calculated.

As unadjusted differences in means fails to account for both observable and unobservable differences among prescribers that may be correlated with the volume of opioid prescribing, we estimate the association between opioid prescribing and payment receipt using multivariate

linear regression in Stata (version 15.1) while controlling for the important predictors of opioid prescribing. We estimate two models: (1) regress days' supply on receipt of payment for all prescribers with completed information; (2) regress days' supply on the annual amount of payment variable for prescribers who received any opioid-related payment. In each model, PDMPs, county population, county unemployment rate, % male, % aged 65 or older population, % Hispanic, % non-Hispanic African American, % non-white other races, physician gender, years of practice, number of Medicare patients and their specialty were controlled for. Each regression also includes a full set of county and year fixed effects to control for temporal and geographic unobserved factors. We also controlled for within-cluster error correlation within state and provided cluster-robust confidence intervals and corresponding *P*-values.

## RESULTS

The Open Payments data show that \$50.3 million in opioid-related payments were made by opioid makers to 77 085 physicians from 2014 to 2016. The aggregate amount of payments increased from \$15.1 million in 2014 to \$20.5 million in 2015, and declined to \$14.8 million in 2016. In order to verify this study's opioid-specific payment identification strategy, the aggregate amount of opioid-related payments (including oxycodone, hydrocodone, fentanyl, tapentadol, morphine and other opioids, but excluding buprenorphine and methadone) from August 2013 to 2015 was compared to results in Hadland *et al.* [15], the first published paper to look at payments for opioids. Hadland *et al.* [15] identified \$41.01 million in opioid-related payments while this study found a very close \$40.93 million in opioid-specific payments.

The bivariate comparisons in the outcome measures, the number of days' supply dispensed by each prescriber each year for all opioids and each separate opioid class, between prescribers with at least a receipt of payments (63 062 physicians with complete data) and non-recipients are reported in Table 1. On average, prescribers who receive any payments are observed to prescribe more than 13 070 daily doses per year more than non-recipients from 2014 to 2016 ( $P < 0.001$ ). Interestingly, the magnitude of the association between opioid detailing and Medicare days' supply for opioid increased over time, 10 740 additional daily doses were associated with receipt of payments in 2014 ( $P < 0.001$ ) while 15 050 additional daily doses were associated with receipt of payments in 2016 ( $P < 0.001$ ).

Of all promotional activities from 2014 to 2016 related to opioids in this study, fentanyl, hydrocodone and tapentadol promotion accounted for a plurality of the overall promotions (fentanyl: 37.4% or \$18.8 million;

**Table 1** Opioid days' supply for Medicare beneficiaries and opioid detailing, 2014–16.

	Recipients	Non-recipients	Differences, <i>t</i> -test			
	Mean	Mean	Mean	95% CI	<i>P</i> -value	Number of recipients
Opioid day supply (2014–16)	14.3	1.23	13.070	12.9, 13.2	< 0.001	63 062
Opioid day supply 2014	12.1	1.36	10.740	10.6, 11.1	< 0.001	36 700
Opioid day supply 2015	14.9	1.2	13.700	13.3, 13.9	< 0.001	34 881
Opioid day supply 2016	16.2	1.15	15.050	14.7, 15.3	< 0.001	31 479
Hydrocodone day supply (2014–16)	5.22	0.48	4.740	4.67, 4.80	< 0.001	27 219
Oxycodone day supply (2014–16)	3.92	0.24	3.680	3.63, 3.75	< 0.001	40 450
Morphine day supply (2014–16)	1.31	0.087	1.223	1.20, 1.25	< 0.001	17 199
Fentanyl day supply (2014–16)	0.79	0.049	0.741	0.73, 0.76	< 0.001	12 510
Tapentadol day supply (2014–16)	0.049	0.0007	0.048	0.046, 0.051	< 0.001	13 949
Other opioid day supply (2014–16)	3.00	0.38	2.620	2.60, 2.66	< 0.001	12 163

The row measures were created by taking Medicare Part D Prescriber data 2014–16 at the physician level, and averaging annually by whether the physician has accepted any promotional spending (versus not). Unit of day supply is thousand of daily doses. Information on a physician's receipt of promotional spending is gathered from the CMS Open Payments Data 2014–16 matched to the same physicians in our Part D Prescriber Data. Providers in the Part D data without any reported payments were assumed to receive nothing from opioid makers. Physicians in the Open Payments data without any reported drug claims in the Part D data were excluded from the analysis. Opioid-related payments were identified based on each payment record's up-to-five listed drug names and a comprehensive list of opioid drugs from CMS and CDC. The data set is restricted to prescribers who had a valid NPI and were included on both Medicare Part D and in the Open Payments Data. CI = confidence interval.

**Table 2** Physician characteristics by recipients versus non-recipients of opioid detailing, 2014–16.

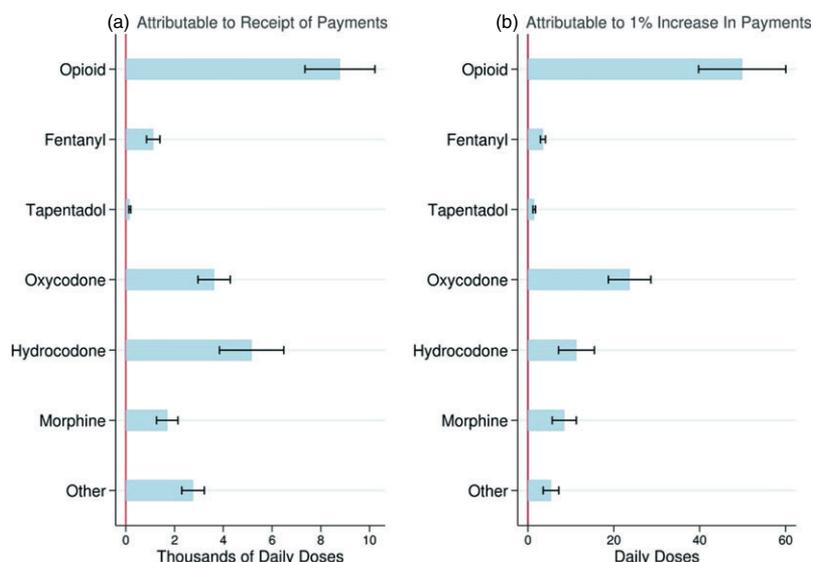
	Recipients	Non-recipients	Differences, <i>t</i> -test		
	Mean	Mean	Mean	95% CI	<i>P</i> -value
Number of Medicare patients	335.7	147.6	188.1	186.5189.9	< 0.001
Year of practice	8.63	7.62	1.01	1.02, 1.00	< 0.001
% Male physician	77.7	68.8	8.9	8.59, 9.11	< 0.001
Residents per square mile in practicing county	1940.2	3460.5	–1520.3	–1562.7, –1477.9	< 0.001
% Rural population in practicing county	16.4	13.1	3.3	3.16, 3.42	< 0.001
% Non-Hispanic white population in practicing county	64	60.2	3.8	3.67, 3.92	< 0.001
% Mandatory access PDMPs in practicing state	30.5	31.5	–1	1.29, –0.71	< 0.001

Physician-level characteristics were created by taking profile information in the Prescriber PUF data 2014–16 at the physician level, and averaging annually by whether the physician has received any promotional spending (versus not). County-level characteristics were extracted from RWJF County Health Rankings. Mandatory access prescription drug monitoring programs (PDMPs) is a binary indicator whether prescribers are required to check with PDMP for at least some patients, which were mainly collected from the Prescription Drug Abuse Policy System (<http://pdaps.org/datasets/prescription-monitoring-program-laws-1408223416-1502818373>). Unlike PDAPS, we code Delaware to have a 'must access' PDMP based on 16 Del. C. 4798(u). CI = confidence interval.

hydrocodone: 21.7% or \$10.9 million; tapentadol: 12.4% or \$6.2 million). However, the payments related to fentanyl dramatically declined from \$9.2 million in 2014 to \$7.2 million in 2015 and to \$2.5 million in 2016. Results in Table 1 indicate that the associations between payments and prescribing are largest for hydrocodone and oxycodone and smallest for fentanyl and tapentadol. Receipt of hydrocodone-specific payments is associated with prescribing 4740 additional daily doses of hydrocodone ( $P < 0.001$ ); receipt of oxycodone-related payments is associated with 3680 additional daily doses of oxycodone ( $P < 0.001$ ). Prescribers who receive any fentanyl-specific payments prescribe 741 daily doses per

year more than their peers ( $P < 0.001$ ) and receipt of tapentadol-related payments is associated with 48 additional daily doses.

The characteristics of physicians who received promotional payments compared to physicians who received no such promotion as well as the role of state opioid control policy are analyzed in Table 2. The bivariate comparisons in these characteristics indicate that prescribers who receive any payments are observed to have over 188 Medicare patients more than non-recipients ( $P < 0.001$ ). Prescribers with more years of practice under their NPI tend to be more involved in pharmaceutical direct-to-physician marketing activities. Male physicians are more



Notes: Figure 1 (a) presents the adjusted difference (bar) and its 95% confidence interval (in error bars) in days' supply attributable to receipt of each drug-related payment for 7 separate regression models. The outcome variable was the number of days supply dispensed by each prescriber each year for all opioids (collectively) and then separately for opioids in the following classes: hydrocodone, oxycodone, fentanyl, tapentadol, morphine and a catch-all "other opioids" category. The dataset represents one observation per physician per year, over the period of 2014-2016. This analysis is restricted to all prescribers who had a valid NPI and were included on both Medicare Part D and in the Open Payments data. Figure 1 (b) presents the adjusted difference (bar) and its 95% confidence interval (in error bars) in days' supply attributable to 1% increase in each drug-related payment for 7 separate regression models. This analysis is restricted to aforementioned prescribers with receipt of drug-related payments.

**Figure 1** Relationship between physician opioid prescribing and promotions. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

likely to receive these payments. The results also show significant differences in practice community characteristics: population density, rural population and race ratios. On average, recipients of the payments tend to operate in less densely populated counties, more residents in rural areas and counties with a higher percentage of non-Hispanic white population. Additionally, mandatory access PDMP is negatively associated with receipt of opioid-related payments.

Figure 1 visualizes the results of multivariate regression models by presenting the adjusted difference and its 95% confidence interval in days' supply attributable to two distinct measures of opioid detailing: the extent of opioid detailing, measured by the likelihood of receiving of any opioid-specific payments (Fig. 1a) and the intensity of opioid detailing, measured by the dollar amount of these payments (Fig. 1b). Supporting information, Table S1 provides full results of regression models regressing days' supply for opioid and hydrocodone on receipt of payments. Prescribers who are male, more experienced or prescribe for a larger number of unique Medicare patients tend to prescribe more daily doses of opioids ( $P < 0.001$ ). Providers in states with a mandatory access prescription drug monitoring program do not prescribe statistically significantly different amounts of opioids than in states with no policy, although the coefficient sign would imply that it is less.

Figure 1a reinforces the unadjusted association between Medicare prescribing for opioid and receipt of opioid detailing. Particularly, prescribers who receive any opioid-specific payments prescribe 8784 daily doses per year more than their peers who are not involved in any opioid-specific, direct-to-physician promotions ( $P < 0.001$ ). As expected, we found heterogeneous and statistically significant associations with promotion for each opioid class. The associations between payments and prescribing are largest for hydrocodone and oxycodone and smallest for fentanyl and tapentadol. Holding other predictors constant, recipients of hydrocodone-specific promotion tend to be high-volume hydrocodone prescribers with approximately 5161 additional daily doses per physician than non-recipients ( $P < 0.001$ ). Providers with oxycodone-specific, direct-to-physician marketing (predominantly from Purdue Pharma for Oxycontin) are associated with 3624 additional daily doses of oxycodone prescription by a physician ( $P < 0.001$ ). Prescribers who receive any fentanyl-specific payments prescribe 1124 daily doses per year more than their peers ( $P < 0.001$ ) and receipt of tapentadol-related payments is associated with 49 additional daily doses ( $P < 0.001$ ).

Figure 1b demonstrates the association of the intensity of pharmaceutical payments relative to the extent of opioid prescriptions in Medicare Part D. We estimated that among

recipients of opioid-specific payments, a 1% increase in the amount of payments is associated with approximately 50 daily doses of opioid prescription ( $P < 0.001$ ). We found heterogeneous and statistically significant associations with the intensity of promotion for each opioid class, which are slightly different from the associations with the extent of promotion. Particularly, the associations between the dollar amount of payments and prescribing are largest for oxycodone. A 1% increase in the amount of oxycodone-specific payments is associated with approximately 24 daily doses of oxycodone prescription ( $P < 0.001$ ), while a 1% increase in the amount of hydrocodone-specific payment is only associated with 11 daily doses of hydrocodone prescription ( $P < 0.001$ ). A 1% increase in the amount of fentanyl-specific payments only increased oxycodone prescriptions for Medicare patients by three daily doses ( $P < 0.001$ ).

## DISCUSSION

In 2007, Purdue Pharma agreed to pay \$109 million to the United States federal government and \$214.6 million to state governments to settle the allegations of mislabeling its product Oxycontin. Nevertheless, Purdue Pharma was the largest marketer to physicians among opioid makers in 2015; it paid \$0.2 million for 14 432 Oxycontin-specific interactions, \$4.8 million for 36 837 Hysingla (extended release) related promotion events and \$1.5 million for Butrans (buprenorphine) promotions. In 2018, Insys Therapeutics was accused in five lawsuits related to the marketing of Subsys, a newer and highly potent fentanyl approved in 2012 for the treatment of persistent breakthrough pain in adult cancer patients. The federal government alleged that physicians were wrongly encouraged to prescribe Subsys for patients who did not have cancer by Insys, which also had employees who misrepresented patients' diagnoses so that they could increase reimbursement for Medicare patients [27]. Given the massive number of recent lawsuits against opioid makers (for example, more than 800 lawsuits brought by cities and counties in the United States alone) [28], there is renewed interest in understanding the role of promotional activities in the opioid crisis.

Remarkably, there is little literature that investigates the association between opioid detailing and prescribing. Hadland *et al.* [10] has been the first and only paper examining the association between any payments and all opioid prescribing for 2014–15. Although our work initially discloses similar conclusions regarding the pharma–physician relationship in respect to opioid prescriptions, our paper advances more comprehensive evidence on the role of opioid-related promotional activities in several aspects. Our study explores details of how the association varies by two measure of opioid detailing (the extent and intensity of

payments), the type of opioid, physician-level and local socio-economic factors. Additionally, we also extended the analysis to include newly released 2016 data. Medicare Part D is large and worthy of study in its own right. A Kaiser Family Foundation survey indicates that 93% of primary care doctors accept Medicare patients, so Medicare Prescriber PUFs cover most prescribers in the United States [29]. Medicare Part D accounts for a large share of all US drug spending (30%) [30]. The Medicare population has the highest and fastest-growing prevalence of opioid use disorder [31]. Meara *et al.* [32] also estimate the rate of death due to prescription-opioid overdose in their sample of disabled Medicare beneficiaries, and suggest that nearly one in four nation-wide prescription overdose deaths in 2008 was a disabled patient.

Medicare patients were prescribed approximately 4.2 billion of daily doses from 2014 to 2016. The most frequently prescribed opioids are hydrocodone (1.6 billion daily doses) and oxycodone (0.9 billion daily doses). The Open Payments data, however, show that fentanyl makers were the largest payors to US physicians in order to promote these synthetic opioids, which possess high potency and the associated risk of fatal overdose.

Both the bivariate comparisons and multivariate regressions provide evidence on the substantial and significant association between opioid detailing and opioid prescribing in Medicare Part D. This study is the first work, to our knowledge, exploring the heterogeneous associations between opioid detailing and prescribing by opioid class. It is important to note that the heterogeneity in effectiveness of marketing practices by opioid class depends on the measure of opioid detailing. Using any receipt of payments as an indicator of extent of direct-to-physician marketing activities, we found that the associations between payments and prescribing are largest for hydrocodone and oxycodone and smallest for fentanyl and tapentadol. On the extensive margin, therefore, we see that physicians are statistically significantly more likely to respond to any payment related to oxycodone and hydrocodone (which are themselves not statistically distinct from each other) by increasing prescribing than for other opioid classes.

We also examined the associations between on the intensive margin of payment (that is, the amount of money paid to physicians, given that they have received any payment) and prescribing by opioid type. We found positive associations for all opioid types, suggesting that a 1% increase in dollar payments were associated with statistically significant increases in prescribing for all types of opioids. Regarding the 'any payment' models, we observed statistically significant differences in the association by opioid type. The observed association of the intensity of pharmaceutical payments (the dollar amount of payments) relative to the extent of opioid prescriptions in Medicare Part D, however, is largest for oxycodone (and statistically

difference from the associations with the other opioid types). This result is intriguing, given the substantial attention that oxycodone has received from the public at large and from the public health community.

Finally, this study also analyzed the characteristics of physicians who received opioid-related promotional payments compared to physicians who received no such promotion. Our findings are consistent with prior studies which have examined the characteristics of physicians with a financial tie to pharmaceutical companies [14,33]. Recipients of opioid-specific payments are more likely: to serve more Medicare patients; to have acquired more years of practice; to be male-gendered; and to practice in locations with more rural and white populations. Specialists such as pain management, anesthesiology and physical medicine and rehabilitation physicians had greater ties than general practitioners. Interestingly, mandatory access PDMP is significantly and negatively associated with receipt of opioid-related payments, which may indicate some deterrent, spill-over effect of mandatory access PDMP on opioid detailing which indicates a potential avenue for future research. The significant differences in these physician- and county-level characteristics between physicians who received promotional payments compared to physicians who received no such promotion suggest that it is necessary to control these factors in order to isolate the association between opioid detailing and prescribing. Particularly, the adjusted difference in days' supply for opioid attributable to receipt of payments was approximately two-thirds of the unadjusted difference (8780 daily doses versus 13 070 daily doses). Controlling for the physician- and county-level predictors of opioid prescribing is an additional step to examine the relationship between opioid detailing and prescribing compared to the only other previous work in this area, by Hadland *et al.* [10], which adjusted only for physician specialty and prior prescribing.

The quantified association between opioid manufacturer payments and the subsequent volume of opioid prescriptions provided by individual physicians in this paper has several important policy implications. This paper adds more extensive insight into the role of marketing directed to physicians in the intensity of opioid prescribing to previous literature. Our findings support the significance of ongoing efforts to enhance transparency and efficient regulation regarding pharmaceutical marketing.

Personal detailing to physicians by pharmaceutical companies' sales representatives is a widely used competitive marketing practice in the prescription drug industry [34]. In a national survey of 3167 physicians between 2003 and 2004, as many as 94% reported relationships with industry through research funding, consulting fees, medical education expenses and gifts [33]. In the 2000s, there were a number of calls by states and medical

organizations for transparency and increased regulation regarding these promoting activities [35]. For instance, Massachusetts enacted a law requiring public disclosure of personal detailing to health-care providers in 2008. As a part of the Affordable Care Act (ACA) of 2010, a provision known as the Physician Payments Sunshine Act was established to provide greater transparency of physician and hospital relationships with private industry in all 50 states. Policymakers should consider policies restricting the strategies utilized by pharmaceutical companies to manipulate physician prescribing. For instance, pharmaceutical companies might track prescription by purchasing prescription records from information distribution companies [36]. Regulations restricting the dissemination of such records to profit-driven entities could aid in limiting illegitimate influence.

The study has several limitations. First, and most significantly, the findings of this paper should be interpreted as the association between opioid manufacturer payments and the volume of opioid prescriptions by individual physicians, rather than causality. Pharmaceutical companies may strategically target high-volume prescribers for payments, thus there is probably a degree of endogeneity of payment receipt in our regressions. Additionally, while we have a near-census of Medicare Part D prescribers our data cover a relatively short panel, from 2014 to 2016. Future research could utilize a longer series of longitudinal data merging the Open Payments data and Prescriber PUF data for 2014–17 (Prescriber PUF 2017 is not yet available at this time), as well as a rigorous identification strategy to address this endogeneity concern.

Secondly, as we are using Medicare Part D data, it is possible that clinicians prescribe differently to patients in other plan types (e.g. Medicaid or private insurance) because of differences in the underlying patient populations and formularies although, even so, Medicare Part D is large and worthy of study in its own right. The Medicare Prescriber PUF file provides the only publicly available data to capture prescribing in a way that is linkable to the Open Payments data. Thirdly, we rely upon the pharmaceutical manufacturers' self-reports of which drugs were linked (marketed) to each payment, thus measurement error is distinctly possible. For instance, there is a limit of five drug mentions per record. Non-listed opioids in the records might lead to some measurement error. Additionally, illicit provider-directed payments such as 'under-the-table' kickbacks might not be reported in the Open Payment data.

Lastly, while our data are at the individual physician level, and hence on that dimension are not subject to the ecological fallacy that bedevils many aggregate studies, we want to emphasize that our associations cannot speak directly to what is happening with individual patients [37,38]. It would be an ecological fallacy to infer that

because prescribing rises for the average physician this means that there are more individual patients receiving opioids. Additional research, using different data, is needed to understand patient-level associations.

In conclusion, receipt by physicians of either any provider-directed payments or greater dollar amounts of payments from opioid manufacturers were both associated with substantially higher opioid prescribing. The association between payments and prescribing varies by drug and is largest for hydrocodone and oxycodone, the most frequently prescribed opioids among Medicare patients. These associations persist after adjusting for a range of physician characteristics, local socio-demographic predictors and state opioid control policies. These findings support the significance of ongoing efforts to enhance transparency and efficient regulation regarding pharmaceutical marketing.

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### Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1** Regression Results: Relationship between Physician Opioid Prescribing and Promotions.