Association between payments from manufacturers of pharmaceuticals to physicians and regional prescribing: cross sectional ecological study
Online Supplement

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Supplement Methods Details

Source and processing of payment data

The publicly-available payment data was obtained on 6/30/15, the day of its release, from the CMS Open Payments website.[1] CMS released updated data on 1/15/2016 but this only affected 854 or 0.03% of the 2,486,152 unique payments studied. Each payment is associated with a physician by way of a unique "physician profile ID". We used a non-publicly available CMS crosswalk to link the physician profile ID to National Provider Identifiers (NPIs). We excluded 3437 payments that were verified by CMS, but were not linked to an NPI. The payments were then merged with National Provider & Plan Enumeration System (NPPES) data to obtain physician practice location and specialty. We used the July 2015 full-release NPPES file[2] for both payment and prescribing data.

We identified the credentials and specialties of providers based on NPPES data, and we included payments to allopathic and osteopathic physicians, and excluded payments to academic medical centers and to non-physician providers. We also excluded payments for research and royalties, or reports of ownership or investments. We relied on CMS' definition of research, from the U.S. Public Health Service Act, defined as payment related to a "systematic investigation designed to develop or contribute to generalizable knowledge relating broadly to public health, including behavioral and social sciences research. This term encompasses basic and applied research and product development."[3] Based on this definition, manufacturers designated payments as research or non-research, and CMS then released the research and non-research payment data in separate files; we only analyzed non-research payments.

For payments related to oral anticoagulants, we excluded 2,015 payments (0.2% of all payments) that were not linked to an NPI and 12,795 payments (1%) that had recipient zip codes not assigned to a HRR, mainly zip codes in Puerto Rico and other outlying territories. For payments related to non-insulin oral diabetes drugs, we excluded 1,422 payments (0.08%) that were not linked to an NPI and 22,864 payments (1%) that had recipient zip codes not assigned to a HRR.

Source and processing of prescribing data

Prescribing data were obtained from the CMS claims database on 12/15/15. We obtained line-item claims data for all drugs classified as "anticoagulants" (group 83 in the Master Drug Database [MDDB] classification system, which CMS uses to categorize drug claims). For diabetes drugs, claims with drugs classified as "anti-diabetic" (MDDB group 27) were obtained. We then excluded claims for non-study drugs such as clopidogrel, aspirin, and insulins, as described in in the manuscript. Data were obtained at the prescription-level in order to obtain the total number of patients and physicians studied, and were then aggregated to HRR level using the prescribing physician's practice zip code from the same NPPES file used for payment data.

For prescriptions related to oral anticoagulants, we excluded 281,004 prescriptions (1.6% of all prescriptions) that were not linked to an NPI, and 160,874 prescriptions (1%) that had recipient zip codes not assigned a HRR, mainly zip codes in Puerto Rico and other outlying territories. For prescriptions related to non-insulin oral diabetes drugs we excluded 427,797 prescriptions (1.2%) that were not linked to an NPI, and 1,254,427 prescriptions (3.8%) that had recipient zip codes not assigned to an HRR.

We used "prescription days filled" as the measure of prescribing. This number is calculated by the pharmacy filling the prescription based on the prescribing physician's instructions, and is thus an equivalent measure among drugs with different dosages and/or treatment regimes. For example, patient A filling a 30-pill prescription for a once-a-day drug, and patient B filling a 60-pill prescription for a twice-a-day drug, will both be reported to have filled 30 days-worth of the prescribed drug.

Within each class, drugs were categorized as marketed or non-marketed (Table); a marketed drug was defined as any drug for which there were 100 payments or more during the study period. For each drug class and for each HRR, we calculated the market share (i.e. the percentage) of prescription days filled of marketed drugs from all drugs in class. For example, among oral anticoagulants, dabigatran, rivaroxaban, and apixaban were considered marketed drugs, while generic warfarin was considered non-marketed. So an example calculation is as follows: HRR 1 had 9,437,948 prescription days filled of all anticoagulants, and 2,733,737 prescription days filled of marketed oral anticoagulants. The market share for marketed anticoagulants was therefore 2,733,737/9,437,948 = 28.97%.

Determination of physician specialty and categorization of specialists

We used specialty-designation data from the NPPES. Each NPPES record can contain up to 15 specialty designations. We used taxonomy designations in the first 5 fields to identify specialists. We used a taxonomy code-specialty crosswalk from the National Uniform Claim Committee[4] to match taxonomy codes to specialties. For oral anticoagulants, cardiologists and hematologists were categorized as specialists, and all other physicians as non-specialists. For non-insulin diabetes drugs, endocrinologists were categorized as specialists, and all other physicians as non-specialists.

Source of processing of model covariates

Covariates for age, sex, race, income and Hierarchical Condition Category risk scores (HCC) were obtained from the Chronic Condition Data Warehouse 2014 beneficiary file.[5] HCC scores are used by CMS to adjust payments to Medicare Advantage insurers according to beneficiaries' risk. Of note, while HCC scores are only used for Medicare Advantage patients, they are generated for all Medicare beneficiaries. The covariates for age, sex, race and HCC were obtained at the beneficiary level for all Part D enrollees. We then calculated averages of age and HCC scores, and proportions of female sex and minority race at the HRR level, and these were used as covariates in all HRR-level models. For income, since actual income numbers were not available, we instead calculated HRR-level proportions of beneficiaries eligible for Part D subsidies as a surrogate marker of income. CMS determines eligibility for subsidies for each beneficiary on a monthly basis. We therefore calculated the average proportion of Part D enrollees eligible for subsidies for each HRR during calendar year 2014.

We obtained estimated median household income for 2014 from the US Census' American Community Survey.[6] Thee estimates are only provided at the zip code tabulation area level (ZCTA), which usually include more than one zip code.[7] We used a ZCTA to zip code crosswalk[8] and a zip code to HRR cross walk[9] to link the data to HRRs. We then aggregated the estimated median household income to the HRR level using weighted means, similar to prior-published analyses.[10] We also calculated aggregate weighted medians and used it in a sensitivity analysis compared to weighted means and the results did not differ significantly.

Analysis and interpretation of coefficients

We used linear regression models fitted using ordinary least squares to analyze for associations between payments and prescribing. All analyses were performed at the HRR level. Because Part D populations vary substantially among the HRRs, the dependent variable was the number payments per 1000 person-years of coverage. The main predictor variable was the market share (percentage) of marketed drugs in-class, from among all drugs in class. The coefficients thus were interpreted as: for each 1 increase in the number payments per 1000 person-years of coverage, there is an associated X increase in market share for marketed drugs. We then translated the coefficients into per-payment prescribing associations using the following calculation:

Additional days filled by increasing payments per 1000 person-years by 1 divided by the number of person-years of coverage in thousands.

In other words:
prescription days filled per payment = $((B_0 + B_1)$(RxDaysClass) – (RxDaysMark))/(pycovg/1000)

where:
B_0 = baseline market share of marketed drugs
B_1 = regression coefficient = the additional market share for an increase of 1 in payments per 1000 person-years of Part D coverage
RxDaysClass = N days filled of all drugs in class
RxDaysMark = N days filled of all marketed drugs in class
pycovg = person-years of coverage

The full calculation then is:
prescription days filled per payment = ((actual market share of marketed drugs + regression coefficient)(total prescription days filled for drug class)) - (actual prescription days filled of marketed drugs) /(person years part D coverage/1000)

Subgroup analysis – specialist vs non-specialist, and by payment type
For these subgroup analyses, we analyzed the association of payments to the study target on overall market share – e.g., we analyzed the association of payments to specialists on the overall market share, including prescriptions written both by specialists and non-specialists, and so on. For both of these subgroup analyses, we analyzed linear regression models for each of the two subgroups, then used the "suest" procedure in Stata,[11] which uses a Wald test to test coefficient differences between the groups for significance.

Subgroup analysis – number of payments vs average value of payment
To briefly review, here we answer the following question: what drives the observed payment-prescribing association, the number of payments or the dollar value of those payments? We answer this by comparing the payment-prescribing association of the number of payments in a region to the payment-prescribing association of the average dollar value of those payments. Since we are comparing variables with different units, we calculated equivalent payment-prescribing associations as detailed below using oral anticoagulants as an example:

1. On an HRR level, we analyzed an adjusted linear regression with marketed oral anticoagulant market share as the dependent variable, and N payments per 1000 person-years, log average dollar value of payment, and adjustment variables as covariates.
    a. The resulting coefficients read: for each 1 unit increase in the number of payments per 1000 person years, there is 0.25% increase in market share, and for each 1 unit increase in the natural log of average payment, there is a 1.11% increase in market share.

2. We then calculated the dollar value change for each average payment that would be equivalent to increasing N payments by 1 unit:
    a. Average number of payments/HRR = 26
    b. Average value of each payment = $54
    c. $54/26 = $2.08
    d. $2.08/$54 = 0.039 or 3.9%

In other words, increasing N payments by 1 is equivalent to increasing the average value of each payment by $2.08 or 3.9%.

3. Increasing the average payment by 3.9% is approximately equivalent to increasing the log average payment additively by 0.039. Thus the effect on market share is 0.039*1.11% = 0.04%. So while increasing N payments by 1 is associated with a 0.25% market share increase, increasing the average value of payments by an equivalent amount, is only associated with a 0.04% market share increase.

Supplement Table 1. Drugs studied, their associated payments and prescription days filled. A marketed drug was defined as any drug for which there were 100 payments or more during the study period

Drug Marketed Name (Generic)	No. Payments	Prescription days filled
Oral anticoagulants		
warfarin	0	868,531,775
Xarelto (rivaroxaban)	450,374	128,599,387
Eliquis (apixaban)	327,798	33,543,322
Pradaxa (dabigatran)	199,235	75,938,757
Totals	**977,407**	**1,106,613,241**
Non-insulin diabetes drugs		
Victoza (liraglutide)	491,924	39,765,307
Invokana (canagliflozin)	351,732	13,071,299
Tradjenta (linagliptin)	238,634	3,407,8713
Bydureon (exenatide extended-release)	256,267	7,937,679
Januvia (sitagliptin)	106,511	224,952,640
Jardiance (empagliflozin)	100,939	89,686
Farxiga (dapagliflozin)	94,101	1,341,015
Janumet Xr (sitagliptin-metformin)	83,126	10,030,642
Janumet (sitagliptin-metformin)	82,912	57,063,657
Oseni (alogliptin-pioglitazone)	78,182	382,665
Nesina (alogliptin)	77,882	376,411
Kazano (alogliptin-metformin)	67,117	175,312
Onglyza (saxagliptin)	56,310	36,184,252
Tanzeum (albiglutide)	39,863	65,264
Jentadueto (linagliptin-metformin)	36,488	3,170,805
Glumetza (metformin)	13,479	2,966,649
Invokamet (canagliflozin-metformin)	4,973	45,113
Trulicity (dulaglutide)	3,444	6,784
Symlin (pramlintide)	1,593	1,072,418
Byetta (exenatide)	855	12,183,981
Kombiglyze Xr (saxagliptin-metformin)	824	9,440,242
Actos (pioglitazone)†	130	148,059,082
Duetact (pioglitazone-glimepiride) †	31	876,590
Avandia (rosiglitazone)	1	143,782
acarbose	0	11,449,259
chlorpropamide	0	183,494
glimepiride	0	362,827,560
glipizide	0	542,231,121
glipizide-metformin	0	20,315,775
glyburide	0	105,153,148
glyburide-metformin	0	40,075,121
metformin hcl	0	1,676,482,227
miglitol	0	759,428
nateglinide	0	17,246,815
pioglitazone-metformin	0	14,032,457
repaglinide	0	18,550,385
repaglinide-metformin	0	90,802
rosiglitazone-glipizide	0	7,410
rosiglitazone-metformin	0	37,098
sitagliptin-simvastatin	0	46,242
tolazamide	0	384,943
tolbutamide	0	209,225
Totals*	**2,187,286**	**3,413,562,498**

*For the non-insulin oral diabetes drugs, many payments were associated with more than one drug, hence the totals here represent the number of "associations" as opposed to unique payments. The study analysis examined all non-insulin diabetes drug as a group, and used the unique number of payments for all diabetes drugs, not the number of associations.
†These two drugs were the only drugs counted as "non-marketed" which had any reported payments: Duetact (pioglitazone-glimepiride) had 31 total payments for a total of $46,283; Avandia (rosiglitazone) had 1 payment for $4.85.

Supplement Table 2. Comparison of regression analysis using 2013-2014 data vs using payments from 2014 alone. Changes in market share of marketed anticoagulants and the association of regional prescribing with all payments, payments to specialists vs non-specialists, food and education payments vs speaker and consulting payments, and the number of payments compared to the sum value of payments.

	Oral Anticoagulant 2013 -2014 payments			**2014 payments only**		
	Market share change (95% CI)*	*P value*	*Days filled per payment† (95% CI)*	*Market share change* (95% CI)*	*P value*	*Days filled per payment† (95% CI)*
All payments to all physicians	0.32 (0.26-0.38)	<0.001	94 (76-112)	0.43 (0.34-0.51)	<0.001	93 (74-111)
Physician Type						
Payments to non-specialists	0.32 (0.23-0.41)	<0.001	100 (68-123)	0.42 (0.29-0.55)	<0.001	91 (63-119)
Payments to specialists	0.71 (0.58-0.84)	<0.001	212 (174-250)	0.98 (0.80-1.16)	<0.001	213 (174-251)
P value for difference between groups		<0.001			<0.001	
Payment Type						
Payments for food and beverage, gifts, or educational materials	0.32 (0.23-0.41)	<0.001	96 (77-114)	0.43 (0.35-0.52)	<0.001	94 (75-113)
Payments for speaker fees, consulting fees, honoraria, travel costs, and non-research grants	1.09 (0.21-1.98)	0.016	326 (62-590)	1.94 (0.48-3.40)	0.009	421 (104-738)
P value for difference between groups		0.17			0.063	

*Percent change in market share for one additional payment per 1000 person-years of Part D coverage in an HRR.
†Number of additional prescription days filled during the study period of the marketed drug associated with an increase of one payment in a region. The lower numbers for the 2014-only analysis reflect the shorter study period.

Supplement Table 3a. Payment characteristics for the two drug classes studied for all physicians. Median and interquartile ranges (IQR) are reported because the data was not normally distributed. Some of the payments overlap, as they were related to both an anticoagulant and a diabetes drug.

	Oral anticoagulants			Non-insulin diabetes drugs		
Type of Payment	*N (% of total)*	*Sum (% of total)*	*Median payment (IQR), $*	*N (% of total)*	*Sum, (% of total)*	*Median payment (IQR), $*
Speaker fee	18,709 (1.9)	37,418,181 (61.3)	2,125 (1500-2500)	32,491 (1.8)	56,913,144 (52.5)	1,750 (1300-2050)
Consulting Fee	1,485 (0.2)	2,871,851 (4.7)	1,650 (1000-2250)	10,068 (0.6)	11,748,901 (10.8)	500 (125-1595)
Journal articles/books	20,510 (2.1)	798,714 (1.3)	12.5 (3-83)	30,170 (1.7)	1,121,850 (1.0)	30 (5-74)
Food and Beverage	923,619 (94.5)	16,453,862 (27.0)	12.7 (10-16)	1,683,335 (94.2)	29,818,312 (27.5)	13 (10-17)
Gift	11 (0.0)	3 (0.0)	0.3 (0-0)	11 (0.0)	3 (0.0)	0.3 (0-0)
Honoraria	87 (0.0)	225,048 (0.4)	2,850 (690-4000)	266 (0.0)	283,348 (0.3)	741 (200-1020)
Travel and Lodging	12,986 (1.3)	3,258,481 (5.3)	118 (37-310)	31,543 (1.8)	8,532,058 (7.9)	104 (31-356)
Total	**977,407 (0.0)**	**61,026,140 (100.0)**	**12.9 (10-17)**	**1,787,884 (100.0)**	**108,417,616 (100.0)**	**13.2 (10-18)**

Supplement Table 3b. Payment characteristics for oral anticoagulants to non-specialists and specialists.

	Non-specialists			Specialists		
Type of Payment	*N (% of total)*	*Sum (% of total)*	*Median payment (IQR), $*	*N (% of total)*	*Sum (% of total)*	*Median payment (IQR), $*
Speaker fee	5,466 (0.6)	10,662,589 (17.5)	2,000 (1500-2500)	13,243 (1.4)	26,755,593 (43.8)	2,125 (1500-2500)
Consulting Fee	569 (0.1)	117,9099 (1.9)	1,500 (900-2400)	916 (0.1)	1,692,752 (2.8)	1,800 (1000-2005)
Journal articles & books	9,981 (1.0)	360,425 (0.6)	12.5 (4-79)	10,529 (1.1)	438,289 (0.7)	12.5 (3-85)
Food and Beverage	65,0173 (66.5)	11,298,753 (18.5)	12.5 (10-16)	273,446 (28.0)	5,155,108 (8.4)	13.1 (10-17)
Gift	11 (0.0)	3 (0.0)	0.3 (0-0)	-	-	-
Honoraria	43 (0.0)	117,732 (0.2)	3,150 (1275-3600)	44 (0.0)	107,316 (0.2)	1,890 (500-4000)
Travel and Lodging	4,363 (0.4)	1,234,992 (2.0)	132 (40-340)	8,623 (0.9)	2,023,489 (3.3)	111 (36-295)
Total	**670,606 (68.6)**	**24,853,593 (40.7)**	**12.6 (10-16)**	**306,801 (31.4)**	**36,172,546 (59.3)**	**13.6 (11-19)**

Supplement Table 3c. Payment characteristics for non-insulin diabetes drugs to non-specialists and specialists.

	Non-specialists			Specialists		
Type of Payment	*N (% of total)*	*Sum, $ (% of total)*	*Median payment (IQR), $*	*N (% of total)*	*Sum, $ (% of total)*	*Median payment (IQR), $*
Speaker fee	7,903 (0.4)	13,095,195 (12.1)	1,700 (1040-2000)	24,588 (1.4)	43,817,949 (40.4)	1,750 (1400-2150)
Consulting Fee	6,138 (0.3)	5,386,185 (5.0)	125 (125-1200)	3,930 (0.2)	6,362,716 (5.9)	1,400 (465-2194)
Journal articles & books	27,187 (1.5)	1,034,080 (1.0)	30 (5-74)	2,983 (0.2)	87,770 (0.1)	30 (3-40)
Food and Beverage	1,537,986 (86.0)	26,130,698 (24.1)	12.9 (10-17)	145,349 (8.1)	3,687,614 (3.4)	14.4 (10-20)
Gift	11 (0.0)	3 (0.0)	0.3 (0-0)	-	-	-
Honoraria	113 (0.0)	96,753 (0.1)	200 (175-713)	153 (0.0)	186,595 (0.2)	778 (625-1250)
Travel and Lodging	9,064 (0.5)	2,774,553 (2.6)	119 (35-377)	22,479 (1.3)	5,757,504 (5.3)	96.9 (30-344)
Total	**1,588,402 (88.8)**	**48,517,467 (44.8)**	**13 (10-17)**	**199,482 (11.2)**	**59,900,148 (55.2)**	**17.5 (12-97)**

References

1. Centers for Medicare & Medicaid Services. Open Payments: Dataset Downloads. 2014. http://www.cms.gov/OpenPayments/Explore-the-Data/Dataset-Downloads.html (accessed 2 Aug 2016).

2. Centers for Medicare & Medicaid Services. NPI Files. 2015. http://download.cms.gov/nppes/NPI_Files.html (accessed 2 Aug 2016).

3. Title 42: Public Health - Transparency Reports and Reporting of Physician Ownership or Investment Interests. 42 C.F.R. § 403. http://bit.ly/1VVM9sG (accessed 2 Aug 2016).

4. National Uniform Claim Committee. 2016. http://www.nucc.org/ (accessed 2 Aug 2016).

5. Chronic Conditions Data Warehouse. 2016. https://www.ccwdata.org/ (accessed 2 Aug 2016).

6. US Census Bureau. American Community Survey. 2014. https://www.census.gov/programs-surveys/acs/ (accessed 2 Aug 2016).

7. US Census Bureau. ZIP Code Tabulation Areas (ZCTAs). https://www.census.gov/geo/reference/zctas.html (accessed 2 Aug 2016).

8. UDS Mapper. ZIP Code to ZCTA Crosswalk. 2014. http://www.udsmapper.org/zcta-crosswalk.cfm (accessed 2 Aug 2016).

9. The Dartmouth Institute for Health Policy and Clinical Practice. The Dartmouth Atlas of Health Care. http://bit.ly/28zQV46 (accessed 2 Aug 2016).

10. Aneja S, Ross JS, Wang Y, Matsumoto M, Rodgers GP, Bernheim SM, et al. US cardiologist workforce from 1995 to 2007: modest growth, lasting geographic maldistribution, especially in rural areas. Health Aff 2011;30:2301–9. doi: 10.1377/hlthaff.2011.0255

11. Weesie J. Seemingly unrelated estimation and the cluster-adjusted sandwich estimator. Stata Tech Bull 1999;STB-52:34–46.