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ORIGINAL ARTICLE

Receipt of Promotional Payments at the Individual and Physician Network Level Associated with Higher Branded Antipsychotic Prescribing Rates

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Abstract
Pharmaceutical promotion can lead to market size expansion, which is beneficial if previously untreated patients access treatment but deleterious if it leads to overuse, an area of concern for second generation antipsychotics (SGA). We contribute to a growing body of work suggesting that networks of social and professional relationships shape prescribing behavior. We examined 88,439 Medicare Part D prescribing physicians, finding that promotion is associated with SGA market size expansion (elasticity: 0.062) and that network-level promotional activity is associated with network members' branded product prescribing. Research on the effects of promotion should account for its effects in prescribers' networks.

Keywords Medicare · Physician behavior · Pharmaceutical promotion · Social network analysis

Introduction

Pharmaceutical manufacturers spend billions annually on direct-to-physician marketing (e.g. gifts, samples, speaker fees, medical organization funding, travel, meals, lodging, etc.). (Centers for Medicare and Medicaid Services 2015) Promotional efforts may serve to educate physicians on important developments, new drugs, and side effects. However, conflicts of interest arising from these interactions can influence physician decisions regarding drug choices, leading to higher costs and potentially inappropriate prescribing (Borkowski et al. 2012). Numerous policies have been implemented by professional bodies, hospitals and healthcare organizations, states, and the federal government, to reduce the risk of negative effects from promotion (Lo and Field 2009; Mitka 2010; Office of the Inspector General 2003). The American Medical Association issued guidelines regarding gifts from industry in 1992, and in 2002 the federal government issued a guidance statement that threatened anti-kick-back prosecution for companies offering gifts intended to promote prescription drug sales (McMurray et al. 1991; Office of the Inspector General 2003). In 2012, the Affordable Care Act required documentation and annual publication of all promotional payments from manufacturers to prescribers, which the Centers for Medicare and Medicaid Services (CMS) publishes in their 'open payments' data set.

Evidence for associations between physician-directed promotion and prescribing behavior is found in both the health and health economics literature. For example, Yeh et al. shows higher odds of brand-name statin prescribing in physicians who received payments from industry (Yeh et al. 2016) and receipt of promotional payments is shown to be associated with higher per-patient prescribing costs (Perlis and Perlis 2016). In the health economics literature, findings are consistent, but there is also an attempt to distinguish between substitution vs. market size expansion effects. That is, are physicians simply switching generic to brand, brand to brand, or are there new prescriptions, that otherwise would not have occurred. Examining the drug famciclovir (Datta and Dave 2017) find evidence only for substitution effects, whereas others have found evidence for both substitution and market expansion effects when studying different drug classes (David and Richards-Shubik 2010; Rizzo 1999; Windmeijer et al. 2006). Prior research, however, has focused on the individual physician in isolation, ignoring any additional impacts exerted through peer interactions.

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Professional and Peer Influences

Because physicians do not work in independent silos, their prescribing decisions may not just be a reflection of their own preferences—in fact, there is evidence that the opinions and knowledge prevailing in their professional networks also influences their prescribing decisions (Bae et al. 2015; Barnett et al. 2012; Barnett et al. 2011; Cunningham et al. 2012; Fattore et al. 2009; Gabbay and le May 2004; Iles 2001; Keating et al. 1998; Landon et al. 1998, 2013; Ong et al. 2017; Senge 1990).

Modern physicians practice alongside other actors (e.g. physician colleagues, nurses, healthcare administrators, payers, pharmaceutical representatives), where any activity may be regarded as a "reaction" to an "action" somewhere else in a complex network of interrelationships (Iles 2001; Senge 1990). Landon et al. developed a conceptual model of the effects of health care organizations on health care quality. One of their four proposed domains for organizational attributes that directly influence physician practice behavior was the normative environment (e.g. information sharing, group norms and common practice styles developed through interactions with colleagues) (Landon et al. 1998). The literature on diffusion of innovations highlights similar factors. For example, seminal work by Becker (1970) and Coleman et al. (1967) in the 1970s demonstrated the significance of social networks and the influence of local peers on medical technology diffusion. These insights—that provider behavior is strongly influenced by group norms, common practice, and peer interactions—motivate the growing interest in applying social network analysis to answer health services research questions (Bae et al. 2015; Barnett et al. 2011, 2012; Cunningham et al. 2012; Fattore et al. 2009; Gabbay and le May 2004; Keating et al. 1998; Landon et al. 2013; Meltzer et al. 2010; Ong et al. 2017). The term social network used is used broadly in the literature and incorporates both social relationship (e.g. friendship networks), as well as professional networks (e.g. physician shared patient networks). Two systematic reviews synthesized evidence demonstrating social networks' role in shaping clinical decision-making behavior (Bae et al. 2015; Cunningham et al. 2012). Some studies showed that interactions with and experiences of colleagues, patients, opinion leaders, and pharmaceutical representatives heavily influence clinical decision-making (Gabbay and le May 2004; Keating et al. 1998); others found that more dense within-network linkages are useful for improving organization-wide communication (Meltzer et al. 2010). Several studies have explored issues pertaining to direct to consumer advertising on social network websites (Greene and Kesselheim 2010; Tyrawski and DeAndrea 2015), but none that have examined direct to physician marketing.

Network Analysis

This literature has typically operationalized networks using surveys and qualitative methods. A validated approach to identify networks using observational data involves the use of shared patient and referral relationships—it has been shown that the likelihood of a true professional relationship between physicians grows with the number of patients shared (Barnett et al. 2011; Landon et al. 2013). In a sufficiently large patient network, pre-existing communities, i.e., naturally occurring local networks not bound by geography or delivery systems factors, can be identified with clustering algorithms (e.g. Louvain community detection algorithm) and used in analysis. Although we are not aware of a scientific literature focused on social networks and drug promotion, there are indications that industry marketing strategies are data-driven with network analyses being used to inform which physicians to target for promotion. For example, Voxx Analytics, which contracts with 19 top manufacturers, highlights the use of social network analysis to identify key relationships, influencers, and opinion leaders, which would then allow pharmaceutical companies to embark on data-driven promotional campaigns (VOXX Analytics 2017).

Second Generation Antipsychotics

The influence of pharmaceutical promotion on prescribing behavior is of interest for second generation antipsychotics (SGAs). After entering the U.S. market in the 1990s, SGAs saw a dramatic uptake—they are now used in over 90% of all antipsychotic related visits (Alexander et al. 2011). A known contributor to the steep rise in SGA utilization is off-label use—in fact, estimates suggest that half of all SGA scripts are used for off-label indications (Driessen et al. 2016). The frequent and growing use of antipsychotic polypharmacy, i.e., the concurrent use of two or more antipsychotics for extended periods of time, a practice lacking evidence of effectiveness (Barnes and Paton 2011; Galling et al. 2017; Marchand and Grignon 2007), has also contributed to the growth in SGA utilization. Because at best, these two practices constitute an inefficient use of resources and at worst their potential for harm exceeds their likely benefit, they are examples of overuse (Orszag 2008). Hence, it is critical to elucidate the role of pharmaceutical promotion on their growth (Kreyenbuhl et al. 2007; Larkin et al. 2014; U.S. Department of Health and Human Services 2011).

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Current Study

We examined the association between direct-to-physician pharmaceutical promotion and branded SGA prescribing considering both physician-level and network-level effects. We focused on the branded product of the SGA aripiprazole (proprietary name: Abilify), hereafter aripiprazole^{BN}, one of the costliest drugs overall for Medicaid, and one of the most heavily promoted SGAs. In the U.S. in 2015, Medicaid spending on aripiprazole^{BN} totaled over $2 billion, second only to the combination drug ledipasvir/sofosbuvir (Centers for Medicare and Medicaid Services 2015), and promotional payments were more than $4 million (Centers for Medicare and Medicaid Services 2017). This study contributes to the literature in two important ways. First, we studied representative drug products from an important drug class: SGAs which are understudied in the context of pharmaceutical promotion. At the physician level, we explored both substitution and market expansion effects. This distinction has not traditionally been a focus of the health literature; however, it is key in attempting to determine whether promotional efforts might lead to harmful prescribing practices such as overuse. For SGAs, overuse would show up primarily in market expansion effects as opposed to substitution. Second, we capitalized on a unique dataset using social network analysis to expand individual-level models to the physician network-level.

Methods

We conducted a cross-sectional exploratory analysis linking publicly available Medicare prescriber data, pharmaceutical promotion data, and shared patient networks, in the United States in 2015; the final sample consisted of 88,439 physicians.

SGA Prescriber Cohort

We defined the study cohort as physicians who prescribed one or more of the following SGAs, billed to a Medicare Part D plan, in 2015: *Generic (Brand)*: aripiprazole (Abilify), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon), paliperidone (Invega). These data were available at the provider, drug, year level and included information on prescriptions such as the quantity, total cost, days supplied, etc. The data set was publicly available as the Part D Prescriber Public Use File (PUF) which was derived from CMS's Chronic Conditions Data Warehouse, and included records submitted by Medicare Advantage Prescription Drug plans as well as by stand-alone prescription drug plans (CMS Office of Enterprise Data and Analytics 2019). The data included patients in long term care facilities, a setting frequently targeted with SGA promotion (Pimentel et al. 2015). We refer to this as the *SGA prescriber cohort*.

U.S. healthcare providers are required to obtain a unique 10-digit NPI which identifies them throughout the industry. The CMS National Plan and Provider Enumeration System (NPPES) database tracks active NPIs and includes information such as specialty and practice geography (zip-codes); prescribers include both physician and non-physicians (e.g. nurse practitioners). Because eligible prescribers were drawn from the NPPES, we required members of the SGA prescriber cohort to have a record in the NPPES. We restricted the SGA prescriber cohort to physicians because they are the primary targets of pharmaceutical promotion.

We included non-institutional NPIs in the 50 States. We linked the SGA prescriber cohort to the pharmaceutical promotion data using physician first name, last name and city of practice (the promotional data do not have NPIs). To avoid ambiguous name matching, we removed records where two or more NPIs shared the same first name, last name and city. Analysis of physicians who were excluded for ambiguous name locations revealed some statistically significant differences in specialties, sex and region of provider. We refer to the NPPES NPI population after exclusions as the *provider study population*. The "physician compare" file assembled by CMS was used to obtain gender and medical school graduation year for physicians. We obtained rurality based on zip-codes from CMS, and zip-code income and population from the US Census Bureau.

Shared Patient Networks

We used the Care Set Labs 2015 Root NPI graph to generate a complete set of shared patient networks, and then ran clustering algorithms (described below) to identify naturally occurring local networks within the full graph. Similar approaches have been used before, and shared patient networks are a validated means of approximating meaningful physician social networks (Barnett et al. 2011; Landon et al. 2013). As with the SGA cohort, we required members of shared patient networks to have a record in the NPPES. However, unlike the SGA prescriber cohort, we made no restriction on provider type for the creation of networks and thus as a result, nurse practitioners and physician assistants were eligible. While we were interested only in the effects on physicians; we hypothesized that other provider types would still have some network level influence. We linked the shared patient networks to the pharmaceutical promotion with the same method used for the SGA prescriber cohort as described above.

The Root NPI graph was developed using counts of all Medicare beneficiaries shared between two NPIs during 2015; the relationships include both implicit and explicit

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referrals between physicians, and other provider types (Trotter 2017). We assumed undirected edges so that the relationship between provider A and B was the same as between provider B and A. Once the full network was formed, we used the Louvain community detection algorithm, a method designed to efficiently identify communities in large networks, to group physicians into mutually exclusive local networks (Blondel et al. 2008). We first partitioned the graph at the state level for two reasons: first, most meaningful professional relationships among physicians are unlikely to occur over state lines due to differences in state and payer policies and insurance plans. Second, doing so allowed for parallel processing to improve computational efficiency when running the clustering algorithm. We also considered a more direct measure of network influence, that is, the promotional activity occurring for a physician's immediate network neighbors (i.e. directly sharing patients). Communities identified by the Louvain algorithm are mutually exclusive and so do not require that each member is directly connected.

To avoid small cell count estimation issues, we excluded physicians who were the only member of the SGA prescriber cohort in their community (i.e., physicians with no naturally occurring network) and those whose communities were too small (operationalized as $n = 2$). Inspection of physicians excluded for small community size vs. the final sample, showed statistically significant differences for all characteristics. We used the term 'community' to refer to the local clusters identified by the Louvain community detection algorithm.

Pharmaceutical Promotion

We obtained information on payments made by manufacturers to providers from the publicly accessible CMS Open Payments Data Program under which applicable group purchasing organizations and manufacturers are required to submit data about financial relationships, payments, and other transfers of value made to providers (Centers for Medicare and Medicaid Services 2017). The unit of observation in the Open Payments data was the transaction, i.e., a payment from a manufacturer to a provider that was associated with one or more promoted drugs. These data were available for the entire calendar year 2015.

Our primary drug of interest was aripiprazole^{BN}; we sought to identify the influence of promotional payments for aripiprazole^{BN} on aripiprazole^{BN} prescribing rates. The FDA approved generic aripiprazole at the end of April 2015, i.e. in the fourth month of our follow up period. We also replicated the analyses using branded quetiapine^{BN} product (Seroquel), another heavily promoted and widely prescribed SGA. We matched the promotion data to the prescriber cohort and shared patient networks at the provider (physician name and city), drug, and year levels. Similar approaches to matching have been used previously with these data (DeJong et al. 2016; Singh et al. 2017).

Measures

Outcome Measure

Count of aripiprazole^{BN} prescriptions (*branded* aripiprazole only; both 'new starts' and refills) filled by each physician in 2015. We analyzed the total number of fills first which picks up both substitution and market size effects. We then conditioned on the total number of all SGAs (branded and not) filled by each physician in 2015.

Key Independent Variables

Primary We created three measures reflecting the number of promotional payments:

(i) Count of aripiprazole^{BN} related promotional payments received by each physician, during 2015. Evidence from the literature suggests diminishing returns to promotion, so we also included a quadratic term.
(ii) Count of immediate network neighbors (i.e. directly sharing one or more patients) who received aripiprazole^{BN} related payments. We also included a quadratic term here.
(iii) At the community level, we determined the average number of payments received (where a community was determined by the Louvain community detection algorithm). We considered community level effects as both continuous (mean number of payments), categorial (quartiles), and binary (some payments in the community vs. none).

Adjustor Variables Physician-level variables: sex, year of medical school graduation, region (Midwest, Northeast, South, West), rural practice, practice zip code: (1) median income, (2) population, and physician specialty. We also calculated the unweighted degree (how many physicians they shared patients with) of each physician to capture network centrality. This measured how densely a physician is connected within a given network which is shown to be important for information sharing within a network (Meltzer et al. 2010).

Community-Level Variables Proportion of male physicians, average graduation year, practice specialty proportions, mean total prescription claim counts.

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Statistical Analysis

We calculated summary statistics for the SGA prescriber cohort, and community level variables for aripiprazole^{BN} prescribers using frequencies and means. We estimated a hierarchical Poisson regression model to account for the community level clustering. We modeled the log of the expected aripiprazole^{BN} prescribing rate as a function of the key independent variables and adjustors, as well as a community-specific random effect. We assumed a normally distributed (mean 0 and unknown variance) random effect.

We presented four models for each drug, two which capture both market size and substitution effects, and two which can be interpreted as substitution only effects. The difference being that we control for total SGA fills in the latter models. We first assessed physician level exposure in isolation and then ran models which included community level exposure and immediate network neighbor exposure. We calculated elasticities as $((\exp(\ln(1.01)*\beta)-1)*100)$ for easier comparison with the health economics literature and we estimated effects for four promotional payments vs. zero which is slightly above the non-zero mean.

We used SAS proc glimmix to estimate the hierarchical Poisson regression models. We imputed missing values for physician graduation year, median zip-code income and zip-code population using a normally distributed random variable with the sample mean and standard deviation of the respective variables. An 'NA' category was included for missing values of sex.

This study was approved by the RAND Human Subjects Protection Committee.

Results

The final study sample included 88,439 physicians nested within 1776 communities. Details of the study cohort creation are shown in Fig. 1.

SGA Prescriber Cohort Characteristics and Shared Patient Communities

Of the 88,439 physicians in the final cohort, 21,434 (24.2%) were aripiprazole^{BN} prescribers, and 4001 (5%) received promotional payments for aripiprazole^{BN}. More than half of the prescribers were female, and just under 20% of physicians graduated after 2005 (Table 1). More aripiprazole^{BN} prescribers were psychiatrists relative to the non-aripiprazole^{BN} prescriber group. The communities contained a median of 296 providers, and a median of 33 physicians belonging to the SGA prescriber cohort. Roughly 62% of the communities received some aripiprazole^{BN} payments; with a mean community payment dollar amount of $4.72 (range $0–$828). The average of the mean number of

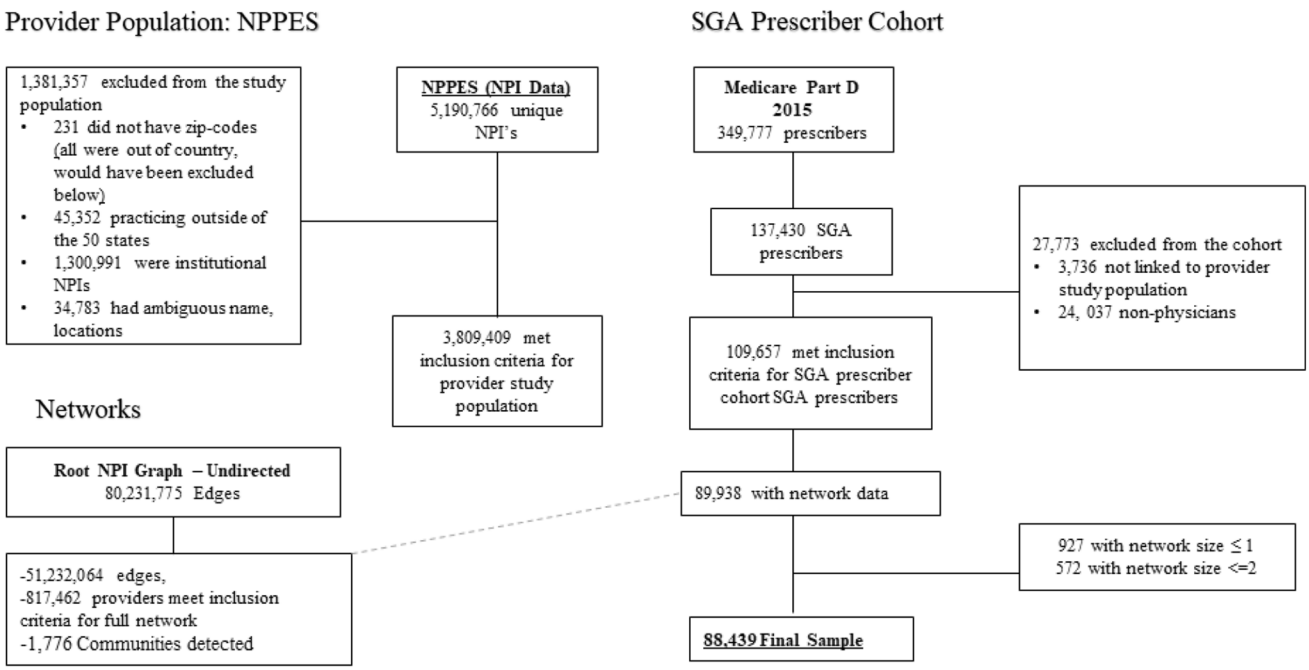

Fig. 1 Cohort creation flow chart. Note: an 'edge' is defined as the link between two physicians who are directly connected in the shared patient network

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Table 1 Physician level characteristics stratified by aripiprazole^{BN} prescriptions filled in 2015 and community characteristics

Variable	Value	Did not prescribe aripiprazole^{BN} ($n=67,005$)	Prescribed aripiprazole^{BN} (n=21,434)	p Value
Individual level				
Sex	Female	42,879 (64%)	13,883 (65%)	<0.001
	Male	17,779 (27%)	5061 (24%)	
	NA	6347 (10%)	2490 (12%)	
Med school graduation year > 2005		11,897 (18%)	3686 (17%)	0.062
Region	Midwest	16,408 (24%)	5904 (27%)	<0.001
	Northeast	13,962 (21%)	4915 (23%)	
	South	23,743 (35%)	7596 (35%)	
	West	13,250 (20%)	3233 (15%)	
Rural		10,004 (15%)	3869 (18%)	<0.001
Specialty description	Internal	23,905 (36%)	4997 (23%)	<0.001
	Family	29,055 (43%)	6369 (30%)	
	Neurology	4720 (7.0%)	224 (1.0%)	
	Psychiatry	3827 (5.7%)	8165 (38%)	
	Other	5498 (8.2%)	1679 (7.8%)	
Income, $1000 (practice zip-code)	Median (IQR)	52 (41, 70)	50 (39, 68)	<0.001
Total SGA prescribing costs	Mean (SD)	2613 (7451)	92,991 (1.6e+05)	<0.001
Total SGA scripts	Mean (SD)	544 (465)	881 (796)	<0.001
Received payment for aripiprazole^{BN}		1046 (1.6%)	2955 (14%)	<0.001
Received payment for quetiapine^{BN}		1012 (1.5%)	2184 (10%)	<0.001
Number of payments (>0) for aripiprazole^{BN}	Mean (SD)	2.7 (6.4)	5.3 (8.7)	<0.001
Number of payments (>0) for quetiapine^{BN}	Mean (SD)	2.3 (7.3)	4.1 (6.9)	<0.001
Unweighted degree, mean (SD)	Mean (SD)	85 (100)	90 (115)	<0.001
Neighbor was paid for aripiprazole^{BN}		11,821 (18%)	7623 (36%)	<0.001
Mean number of neighbor payments	Mean (SD)	0.77 (2.55)	2.22 (5.23)	<0.001
Neighbor was paid for quetiapine^{BN}		12,160 (16.28%)	4399 (32%)	<0.001
Mean number of neighbor payments	Mean (SD)	0.64 (2.2)	1.7 (4.2)	<0.001
Community level				
Number of networks		1776		
Community size: full, median (IQR)		296 (90–640)		
Community size: SGA prescriber cohort, median (IQR)		33 (12–72)		
Received any aripiprazole^{BN} payments		1100 (62%)		
Received any quetiapine^{BN} payments		933 (53%)		
Mean $ amount paid aripiprazole^{BN}, mean (SD)		4.72 (33)		
Mean $ amount paid quetiapine^{BN}, mean (SD)		1.80 (22)		
Mean $ amount paid other drugs, mean (SD)		2830 (5653)		
Mean # payments aripiprazole^{BN}, mean (SD)		0.05 (0.22)		
Mean # payments quetiapine^{BN}, mean (SD)		0.03 (0.13)		
Median graduation year of physicians, mean (SD)		1995 (1994–1997)		
Proportion of male physicians, mean (SD)		0.59 (0.11)		
Proportion internal medicine, mean (SD)		0.09 (0.07)		
Proportion psychiatry, mean (SD)		0.03 (0.10)		
Proportion cardiology, mean (SD)		0.02 (0.02)		
Proportion family medicine, mean (SD)		0.11 (0.10)		
Mean prescription cost for aripiprazole^{BN}, mean (SD)		92 (211)		
Mean prescription cost for any SGA, mean (SD)		233 (610)		
Mean prescription cost for quetiapine^{BN}, mean (SD)		27 (67)		
Mean prescription cost for other drugs, mean (SD)		3922 (2191)		

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community level aripiprazole^{BN} payments was 0.05 (SD: 0.22), quetiapine^{BN} 0.03 (SD 0.13).

Physician Level Effects

Aripiprazole^{BN} promotion had a positive and significant association with aripiprazole^{BN} prescribing rates, with a diminishing effect (negative quadratic term). A one percent change in the physician level number of aripiprazole^{BN} promotional payments during the year was associated with 0.061% higher prescribing rates (Table 2: Model 0). The prescribing rate of physicians with four promotional payments was 27% higher than those with 0 (Table 2: Model 0). Once we constrained the model by total number of SGA promotions (i.e. isolating the substitution effects), the magnitudes were smaller; we saw physicians with four or more promotional payments prescribing aripiprazole^{BN} at a rate that was 12% higher than those with no promotional payments (Table 2: Model 3). The effect of promotion on prescribing rates was also significant for quetiapine^{BN} where rates were 51% higher for physicians who received four or more quetiapine^{BN} promotional payments compared to those with no payments (Table 3: Model 0). We saw a similar shift between the market size and substitution effects with quetiapine^{BN} (Table 3: Model 0, Model 3). Adding network level promotion variables to our models did not change individual level estimates.

Network Level Effects

The effect of immediate network neighbor aripiprazole^{BN} promotion followed a similar pattern to the direct to physician effects: prescribing rates were 45% higher for physicians with four immediate network neighbors receiving aripiprazole^{BN} payments vs. physicians with no network neighbors receiving aripiprazole^{BN} payments, and the effect was diminishing (negative quadratic term). Communities with some aripiprazole^{BN} promotional activity vs. communities with none were associated with higher aripiprazole^{BN} prescribing rates (~30% higher) (Table 2: Model 1). For the community level effects, the continuous specification was not significant, and there was no discernible dose response pattern for categorical formulations. Network level quetiapine effects were also significant; odds of prescribing quetiapine were 49% higher for physicians with four network neighbors receiving quetiapine payments compared to physicians with no network neighbors receiving payments.

Discussion

Linking three national data sets, we quantified the association between pharmaceutical payments to physicians and physician SGA prescribing, focusing on aripiprazole^{BN} and quetiapine^{BN}, two costly SGA products prone to overuse. We found evidence for both substitution and market

Table 2 Poisson regression: aripiprazole

Variable	N = 88,439 Rate ratio (exp(B)) (95% CI)			
	Market size + substitution effects		Substitution effects	
	Model 0	Model 1	Model 2	Model 3
Individual level				
Aripiprazole^{BN} payment count during year	1.06 (1.06, 1.06)	1.06 (1.06, 1.07)	1.03 (1.03, 1.03)	1.03 (1.03, 1.03)
Aripiprazole^{BN} payment count during year squared	0.999 (0.999, 0.999)	0.999 (0.999, 0.999)	0.999 (0.999, 0.999)	0.999 (0.999, 0.999)
Payment count evaluated at 4 vs. 0	1.27 (1.27, 1.27)	1.27 (1.27, 1.28)	1.12 (1.12, 1.13)	1.14 (1.13, 1.14)
Total SGA scripts (per 100)	–	–	1.10 (1.10, 1.10)	1.10 (1.10, 1.10)
Elasticity (at 1 vs. 0)	0.061	0.062	0.03	0.033
Network level				
# of network neighbors receiving aripiprazole^{BN} payments	–	1.14 (1.14, 1.14)	–	1.04 (1.04, 1.05)
# of network neighbors receiving aripiprazole^{BN} payments squared	–	0.991 (0.991, 0.991)	–	0.995 (0.995, 0.995)
Sum of network neighbor payments: 4 vs. 0, exponentiated	–	1.45 (1.44, 1.46)	–	1.10 (1.09, 1.10)
Any network member received aripiprazole^{BN} payment	–	1.32 (1.19, 1.46)	–	1.49 (1.35, 1.66)
Sigma (SE)	0.831 (0.034)	0.745 (0.031)	0.727 (0.031)	0.759 (.032)

Note All models controlled for sex, years since graduation, region, specialty, degree, rurality, zip-code: population, median income, community level: sex, specialty, claim counts, graduation year, random intercept. Model 1 and Model 3 controlled for network level effects

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Table 3 Poisson regression: quetiapine

Variable	N = 88,439 Rate ratio (exp(B)) (95% CI)			
	Market size + substitution effects		Substitution effects	
	Model 0	Model 1	Model 2	Model 3
Individual level				
Quetiapine^{BN} payment count during year (95% CI)	1.11 (1.11, 1.11)	1.10 (1.10, 1.10)	1.08 (1.08, 1.08)	1.08 (1.08, 1.08)
Quetiapine^{BN} payment count during year squared (95% CI)	0.999 (0.999, 0.999)	0.999 (0.999, .999)	0.999 (0.999, 0.999)	0.999 (0.999, 0.999)
Total SGA Scripts (per 100)	–	–	1.09 (1.09, 1.09)	1.09 (1.09, 1.09)
Payment count evaluated at 4 vs. 0	1.51 (1.50, 1.51)	1.47 (1.46, 1.47)	1.36 (1.36, 1.37)	1.35 (1.35, 1.36)
Elasticity (at 1 vs. 0)	0.105	0.097	0.079	0.078
Network level				
# of network neighbors receiving quetiapine^{BN} payments	–	1.16 (1.15, 1.16)	–	1.06 (1.06, 1.07)
# of network neighbors receiving quetiapine^{BN} payments squared	–	0.989 (0.989, 0.989)	–	0.994 (0.994, 0.994)
Sum of network neighbor quetiapine^{BN} payments: 4 vs. 0	–	1.49 (1.48, 1.51)	–	1.16 (1.14, 1.17)
Any network member received quetiapine^{BN} payment	–	1.55 (1.37, 1.75)	–	1.70 (1.51, 1.91)
Sigma (SE)	1.23 (0.052)	1.10 (0.047)	1.17 (0.050)	1.05 (0.045)

Note All models controlled for sex, years since graduation, region, specialty, degree, rurality, zip-code: population, median income, community level: sex, specialty, claim counts, graduation year, random intercept. Model 1 and Model 3 controlled for network level effects

size expansion. This is an important finding for researchers and policymakers as it signals potentially inappropriate prescribing of SGAs. We also provided the first evidence showing higher prescribing rates when members of a physician's professional networks were receiving payments, independent of the physicians own relationship with industry. As policymakers grapple with strategies to limit harmful effects of pharmaceutical marketing, understanding how professional networks propagate these effects can facilitate devising effective solutions.

Our physician level findings were in line with the prior literature. In the range of 0.03–0.1, our elasticity estimates come in slightly lower than the summary effect of 0.18 derived in a meta-analysis of 373 econometric estimates of pharmaceutical detailing elasticities (Sridhar 2014). Our estimates were closer to those found by Datta and Dave (2017) who used physician level data to study famciclovir detailing, with elasticities from fully specified models closer to 0.05. An important difference is they concluded no evidence for market size expansion—only substitution effects. The most comparable study in the health literature, which used the same Open Payments data, examined substitution effects only (DeJong et al. 2016). They found stronger magnitudes of effect for branded olmesartan (≥ 4 payments vs. 0: Odds Ratio (OR) 2.26), branded desvenlafaxine (≥ 4 payments vs. 0: OR: 2.47), and branded nebivolol (≥ 4 payments vs. 0: OR 2.42); their estimates for branded rosuvastatin were more consistent with ours (≥ 4 payments vs. 0: OR 1.34).

The responsiveness of prescribing to promotional efforts, and whether physician prescribing modifications are socially beneficial, neutral, or harmful, depend on drug specific considerations. Unlike direct to consumer advertising which generates new demand by prompting patients to seek new treatments (Chintagunta 2004), with direct to physician promotion, market size increases must come from more prescriptions with the patient population held constant. This raises important questions around the appropriateness of the additional prescriptions, for example, whether promotional relationships lead to greater disease awareness and new scripts are written accordingly or whether physicians are using the drugs for new indications, e.g. off-label, or in combination e.g. polypharmacy. Off-label prescribing can be problematic when the evidence for efficacy and safety of the off-label conditions has not been rigorously established, which is the case for SGAs (Maher et al. 2011). In a review of off-label prescribing designed to inform policymakers of the most problematic practices, four of the top fifteen drugs identified were SGAs (Walton et al. 2008).

Promotion for off-label indications is always illegal; in the 2000's there were three major settlements between SGA manufactures and the federal government for illegal off-label SGA promotion (Pollack et al. 2014; United States Department of Justice 2009; Wilson 2010). Under

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these considerations, our findings of a robust market size expansion effect of SGA promotion is concerning given the frequent overuse of SGAs, mainly in the form of off-label and antipsychotic polypharmacy prescribing (Barnes and Paton 2011; Carton et al. 2015; Driessen et al. 2016). These practices present a significant burden to our healthcare system. The estimated direct drug costs of off-label use in 2008 was US$6.0 billion; (Alexander et al. 2011) polypharmacy prescribing also represents a financial drain on the system (Valuck et al. 2007). These dollars could be put to better use by budget-constrained public payers. Moreover, these practices put patients at unnecessary risks of serious side-effects including serious cardiometabolic morbidity (Meyer et al. 2008). Some researchers and policy-makers have hinted at the potential influence of pharmaceutical promotion on overuse but the hypothesis is yet to be tested empirically (Kreyenbuhl et al. 2007; Larkin et al. 2014; U.S. Department of Health and Human Services 2011). While our current analysis does not explicitly answer questions regarding overuse, it provides a strong motivation for further research, as the question of whether physician directed promotion leads to inappropriate prescribing behavior, is still unanswered. It is worth noting that since these data were collected, the SGAs studied in the current analysis have gone off patent, which is generally followed by a substantial drop in promotional activity. While this may limit the immediate policy implications of our study as it relates to these particular drugs, the findings are nonetheless important as an illustration of network influences on physician practice behavior.

Physicians' practice behavior is a reflection of both their individual preferences and their normative practice environment which includes factors such as peer and social influence and group norms prevailing in their professional networks (Bae et al. 2015; Barnett et al. 2011, 2012; Cunningham et al. 2012; Fattore et al. 2009; Gabbay and le May 2004; Iles 2001; Keating et al. 1998; Landon et al. 1998, 2013; Ong et al. 2017; Senge 1990). Physicians who work together are shown to have more similar practice styles than those who do not (DeJong et al. 2003). For example, when examining variation in hospital length of stay among physicians working at multiple hospitals, De Jong et al. found that physician decisions changed with respect to the norms of the hospital under consideration (DeJong et al. 2006).

Another pathway for shaping normative changes in a network is local opinion leaders who are used to help disseminate evidence based practices and shape shared practice behaviors, where informal education delivery is a key mechanism at play (Flodgren et al. 2011). The services of opinion leaders are also enlisted by pharmaceutical companies and public relations agencies for marketing purposes, sometimes with controversial results. For example, opinion leaders in psychiatry have issued media statements aimed to reassure physicians about the benefits of antidepressants and the hazards of under prescribing (American College of Neuropsychopharmacology 2004; Jureidini and McHenry 2009). Our analysis uncovered several new insights as to how physician networks might amplify associations between pharmaceutical promotion and prescribing.

Our regression models included several variables meant to capture professional network related influences of promotion. The first set, and the strongest predictors of physician level SGA prescribing was the promotional activity of immediate network neighbors, that is, two physicians who were immediately connected in the graph (sharing patients directly). The number of immediate neighbors receiving SGA promotion was significantly related to SGA prescribing rates, and, like the individual level effects, the quadratic term was negative implying diminishing returns. When we analyzed the promotional activity of any 'community' members (i.e. the local clusters identified by the Louvain clustering algorithm), the effect was less apparent. After accounting for the effects of immediate neighbors, the only significant relationship identified was higher SGA prescribing rates for physicians in 'communities' with *some* promotional activity vs. physicians in communities with none.

Importantly, the addition of the network effects had virtually no impact on our estimates of physician's own promotional activity, as evidenced by the similar physician-level coefficients in models 0 and 1 and models 2 and 3. This suggests an additional mechanism at play beyond what occurs when physicians take payments directly. Because we are not aware of prior research on the prescribing effects of pharmaceutical promotion mediated by prescribers' professional networks, we cannot directly compare these findings to extant evidence. However, our results are consistent with evidence on the effects of physicians' normative environment on their prescribing behavior. For example, using administrative data, Fattore et al. (2009) found that general practitioners working in a collaborative arrangement had similar prescribing behavior. Ong et al. found that improved care cohesion within networks lowered dangerous prescribing (Ong et al. 2017). Moreover, our findings were consistent with literatures that have evaluated the effects of social networks on a broad array of behaviors, for example, obesity spreading through social ties (Christakis and Fowler 2007), and network structure being significantly associated with a hospital's patterns of patient care (Barnett et al. 2012). When interpreting network level effects, it should also be noted that we were unable to differentiate 'new start' prescriptions from refills. A physician might see a *new* patient who was previously started on an SGA by a different physician in their community and they would likely maintain the treatment regime at least initially. If physicians in communities with heavy SGA promotion were more likely to be switching patients in this manner, this could be another mechanism apart from normative influences that effect prescribing.

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Limitations

Our analyses had several limitations. First, our data were cross-sectional, and aggregated to the physician –drug—year—level, and thus, our findings should be interpreted as associative and not causal. Additionally, we could not parse out temporal confounding. For example, the FDA approved aripiprazole for generic marketing at the end of April 2015; consequently, the number of aripiprazole^{BN} scripts filled during the year dropped by around 17,000 compared to 2014 (CMS part D data). Promotion for aripiprazole^{BN} trailed off during the year as well (5398 promotions in January 2015 vs. 1878 in Dec 2015). This may reduce the expected magnitude of effect, as well as the policy relevance of the finding as it relates specifically to aripiprazole$^{BN;}$ though the patterns unveiled by this analysis are still highly relevant for other SGAs, and potentially other drug classes. Additionally, if a physician writes a prescription for a branded drug, certain pharmacists have the authority to substitute the branded product with a generic alternative; as such, the number of scripts we see filled in 2015 for aripiprazole^{BN} are likely less than the number of scripts written. Since our analysis only picks up filled scripts, we might expect to see regression to the mean and diminished effect sizes. The effect of promotion, therefore, may be underestimated in this study for aripiprazole^{BN} since physicians may have been nudged by promotion to prescribe aripiprazole^{BN} but subsequently had a pharmacist substitute the generic formulation, which would not count as an outcome in our study. In addition, unmeasured confounding variables may have biased our results and since name and location were used to match payments data, there is still the possibility of matching inaccuracies. The clustering algorithm was applied once using standard parameters; parameter tuning might be a productive exercise for future research. Next, the study reflects the effects of promotion on SGA prescribing for Medicare beneficiaries by Medicare-billing physicians and thus, the generalizability to Medicaid or commercial insurance is uncertain; further research on network level effects of pharmaceutical promotion using Medicaid and commercial claims populations could provide valuable information on both replicability and generalizability of our findings. Additionally, while medication in outpatient and long-term care settings is covered under part D, short term nursing homes (SNF), inpatient, and hospice settings involve different billing schemes, so generalization to these settings should also be done with caution. Our estimates represent a pooled analysis of these prescribing settings; future researchers might attempt to disentangle differential effects of pharmaceutical promotion between settings. Lastly, aripiprazole was originally found to have a lower metabolic risk than other SGAs (Vancampfort et al. 2015), and marketed as such. Switching to aripiprazole for this reason has been studied as a strategy to reduce morbidity (Stroup et al. 2011). As such, a portion of our observed substitution effects may be attributable to physicians attempting to follow an evidence-based strategy for reducing morbidity which would not, at least in spirit, be a form of inappropriate prescribing. However, aripiprazole is not the only SGA in the low risk category; a recent study that simulated switching from higher to lower metabolic risk SGAs included aripiprazole as well as ziprasidone (generic as of 2012), along with several first-generation antipsychotics in the lower-risk category (Mulcahy et al. 2017).

Conclusion

Research on the effects of pharmaceutical promotion on physician prescribing behavior may underestimate, or misattribute, the influence of promotion on physician prescribing decisions by not considering the residual effects of promotion in physicians' professional networks. This highlights the importance of physicians' normative environments and implies that efforts to improve prescribing quality might not need to reach all members of a network.

Budget-constrained payers such as Medicaid and Medicare looking to lower drug costs should consider further action to limit pharmaceutical promotion. They should also consider the role of physicians' normative environments and the diffusion of influence through professional networks as they attempt to modify prescribing behavior. If governing bodies were to implement policies to limit promotional interactions with industry, focusing first on the most tightly connected physicians in a professional network may be an efficient strategy. Future research on physician prescribing decisions might also consider the network-level effects demonstrated in this study.

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Compliance with Ethical Standards

Conflicts of interest The author declare that he has no conflict of interest.

Research Involving Human Participants and/or Animals/Informed Consent This study uses publicly available, secondary data and was approved by the RAND Human Subjects Protection Committee.

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