Informational Shocks, Off-Label Prescribing and the Effects of Physician Detailing

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Abstract

The relationship between pharmaceutical detailing and off-label prescribing has been the subject of considerable regulatory scrutiny, with more than $12 billion in regulatory settlements for off-label promotion since 2004. Using a physician panel combining detailing data with patient chart information, I study how detailing causes physicians to prescribe for on-label versus off-label uses for the branded anti-psychotic drug, Seroquel. Between 2001 and 2006, Seroquel received two informational shocks in the form of good news about its side effect profile relative to other treatments. These shocks were each immediately followed by large increases in detailing to primary care physicians. I exploit the gap between the incidence of the shock and the first detailing visit to separate the direct effect of the information, such as reading the journal articles, from the incremental effect of the detailing. While detailing was indeed targeted at many physicians who never prescribed on-label, I find the effect of detailing on off-label prescriptions is small in both absolute and relative terms. Detailing on net tilts the prescribing distribution toward on-label. KEYWORDS: Detailing, Off-Label Prescribing, Pharmaceutical Promotion

1 Introduction

In the healthcare industry, physicians control nearly $3 trillion of largely price-insensitive dollars.[1] As such, it should come as no surprise that pharmaceutical firms use advertising directly to physicians, or detailing, as their primary marketing tool to increase profits. In 2012, pharmaceutical firms spent roughly $15 billion on detailing activities.[2] This type of promotion has been the subject of considerable regulatory scrutiny, as regulators would like to ensure firms provide scientifically justifiable information. Indeed, promoting a drug for any use that has not been approved by the Food and Drug Administration (FDA) ("off-label" uses) is illegal, and regulators have vigorously pursued such promotional activities. Since 2004, 31 federal cases alleging off-label promotional activities of pharmaceutical firms have settled for more than $12 billion.

Regulators are primarily interested in two questions with regards to the promotion of drugs and how it interacts with off-label prescribing. First, did pharmaceutical firms engage in promotional efforts designed to convince physicians to prescribe more off-label? Second, did these efforts by firms actually cause more off-label prescriptions? It is clear the regulator cares about the first question, as directly promoting off-label use is illegal and has been the subject of considerable litigation. While the content conversations between sales reps and physicians is not observable in data, suspicious patterns in which physicians are visited is potentially detectable in the data. Whether or not these visits actually caused off-label prescriptions is directly addressable in the data. The regulator and the firm should be particularly interested in the effect of detail visits on off-label prescriptions. Regulators must choose how to allocate scarce time and resources, and they might only find off-label promotion worth prosecuting if it actually has an economically significant effect on the amount of off-label prescriptions being written by physicians. From the manager's perspective, if such promotion has only a small effect, it might be in the firm's interest to avoid any activities that are suggestive of off-label promotion. Conversely, if the effect of detailing on off-label prescriptions is very high, regulators might want to increase the attention and scrutiny they put on detailing.

This paper addresses these questions in the context of anti-psychotic drugs. These drugs are used to treat severe psychosis, particularly schizophrenia and bipolar disorder. Not only is the anti-psychotic class important for treating a serious illness, it is also a multi-billion dollar category that has drawn substantial regulatory attention. Branded anti-psychotics have brought in at least $3.5 billion in revenue every year since 2001, and in 2013, the highest grossing drug in the United States was the anti-psychotic Abilify, which grossed over $7 billion by itself. In the meantime, the category has faced nearly $5 billion in regulatory fines from charges of marketing products off-label in addition

[1] https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/nationalhealthexpenddata/nationalhealthaccountshistorical.html

[2] http://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients

to more than $2 billion in fines for failure to disclose adverse effects. Most evidence surrounding firms' efforts to promote off-label has come from whistle-blowers within firms and time-intensive investigations rather than from detailing data, and despite the enormous regulatory fines, there is little existing empirical evidence of the effects of promotional activities on off-label prescribing.

Using a novel data set that connects patient chart data, including diagnosis codes, with physician-level detailing data, I show that physicians with very high shares of off-label prescriptions are detailed just as much as those with low off-label shares. Even physicians who never record a prescription on-label are visited a considerable number of times by sales reps. While this evidence is not definitive, as I cannot observe the content of the conversation, it is consistent with the whistle-blower evidence obtained by the United States Department of Justice.

To estimate the effect of detailing on prescribing behavior in the anti-psychotic category, I use the panel nature of the data to employ a within-physician approach. As previous literature (Manchanda et al. 2004) has documented, pharmaceutical firms tend to employ decile rules, where the number of detail visits a physician receives is determined by the volume of his or her prescribing in the category relative to peer physicians. Additionally, I make use of two information shocks that drive a large push in detailing for the branded drug Seroquel to primary care physicians. These two shocks take the form of clinical studies showing that the side effect profile of Seroquel was superior to other popular treatments for psychosis. In the first information shock, the market leader, Zyprexa, was found to be significantly worse than the rest of the category in terms of adverse effects, generating a positive shock for the other products, particularly AstraZeneca's brand, Seroquel. Next, the Clinical Anti-psychotic Trials of Intervention Effectiveness (CATIE) study found that Seroquel had main effects comparable to and a side-effect profile superior to the rest of the products. Upon receiving this good news, AstraZeneca sharply increased detailing to primary care physicians, presumably to spread the good news. These shock-driven detailing visits are useful in a few ways. First, they provide a significant amount of within-physician variation in detailing to primary care physicians that was not present prior to the first shock. Second, using the shocks allows me to estimate an informative upper bound on the effect of the shock-driven detailing. It is an upper bound because independent of detailing, these positive information shocks may also have direct positive effects on physician prescribing of Seroquel. Further, I am able to separate the direct effect of the shocks from the promotional effect for most of the physicians in the sample, as sales representatives are only able to visit a fraction of the physician population in any given month. Much of the reason for this difference in timing is random. Sales reps often unsuccessfully attempt visits at practices and find the physician too busy to be seen. I confirm this intuition by allowing the detailing effect to vary based on the month of first visit following a shock, and find that those detailed later are no less responsive to detailing. For those physicians who are unable to be reached by sales representatives in the month of the shock, I am able to observe their prescribing behavior after the shock was made

known and prior to being visited by a sales rep in order to quantify the direct effect of the shock. Finally, I use the diagnosis codes in the chart data to attribute a share of the detailing effect to off-label prescriptions.

This analysis gives several interesting findings. First, I find no evidence that the information shocks lift prescriptions prior to detailing. Following the first detailing visit after the shock, detailing has a modest effect. After the first shock, detailing lifts prescribing by about 0.07 prescriptions per detail per month, though that effect is not significant, and most of that effect can be attributed to off-label prescriptions. Following the second shock, detailing lifts prescriptions by about 0.15 prescriptions per detail per month, which is significant and almost entirely attributable to on-label prescriptions. The 'upper bound' effects on the physicians who are detailed in the month of the shocks are not distinguishable from the detailing effects estimated for the other physicians. This provides some evidence that the physicians may not internalize the good news of the shocks until they have been detailed. Overall, these effects are quite small in magnitude. Additionally, over the course of the sample, off-label prescribing accounts for between 31% and 39% of the total detailing effect, while off-label prescriptions make up about 42% of the total prescriptions in the data, suggesting that detailing has disproportionately benefited on-label prescriptions. Taken together, these estimates provide evidence that regulators may wish to use less of their scarce time and resources pursuing an activity that has a minimal nefarious effect, even if it has ill intent. Secondly, these results suggest that managers should be especially careful to avoid activities that even suggest the possibility of illegal activity, as the size of the potential fine is very large while the gain from the promotion is very small. Finally, the fact that the information shocks have no direct effect without detailing suggests that managers should exert effort to spread good news if they wish for it to increase prescriptions.

The primary contributions of this paper are substantive in nature. First, I document that physicians who prescribe a very large share of anti-psychotics for off-label, including many who never prescribe on-label, receive a significant number of detailing visits. While I cannot definitively identify what was said during those detail visits, the fact that some physicians who do not ever prescribe an anti-psychotic for approved uses still get detailed a significant amount in the data is consistent with the smoking gun evidence that firms are attempting to push these drugs for non-approved uses. Second, I am able to quantify the effects of those detailing visits on actual off-label prescriptions using the high level of detail in the patient chart data. These substantive points add to the literature at the intersection of advertising and regulation, relevant to firms and policy makers alike. Off-label prescribing is a popular topic in regulatory circles, but the academic research speaking to off-label promotional concerns is especially sparse.

As a secondary contribution, I estimate these effects using a new identification strategy combining within-physician variation to control for persistent differences in physician willingness to prescribe with exogenous changes in scientific knowledge to generate additional variation in detail visits.

While the information shocks by themselves only provide an upper bound on the treatment effect of detailing, the fact that there is a delay between the incidence of the shocks and the first detail visit after the shock allows me to separate the direct information effect from the detailing effect for most of the population. Although the exact methodology using these specific studies is special to this application, other drug classes have had discrete changes in information that might also affect detailing levels, making this approach potentially useful for other applications.

The main contribution of this study is to examine the interaction of advertising and regulation in a particularly important category. Most industries are allowed to speak as they wish in their advertisements, conditional on avoiding false claims. Rao (2015) examines the effects of false claims on sales and finds they are extremely useful even after paying settlements or stopping their advertisements. Liu et al. (2014) show combination therapies in HIV/AIDS can drive positive spillovers of detailing onto other drugs, and argue such spillovers can cause strange incentives in the presence of regulation. Larkin et al. (2013), Stremersch (2009), and Anderson et al. (2015) all look directly at changes in detailing regulations and their effects on demand, and all find reasonably different effects depending on the exact context of the policy changes. The size of the fines levied on the anti-psychotic category for off-label promotion indicates how important the question is to regulators. In particular, regulators are worried that a large portion of off-label prescribing of anti-psychotics is to seniors in nursing homes with insomnia and dementia (Ray et al. 1980, Gurwitz et al. 2000). These populations are seen as particularly vulnerable to adverse effects and might be less able to decline treatment. Although off-label prescribing need not be welfare reducing (Bradford et al. 2015), firms are not legally allowed to promote such uses, and empirical evidence on the question is scarce.

This study is also related to a literature that thinks about the effects of publicity and clinical studies on drug demand. Ching et al. (2015) find evidence that news coverage on drug efficacies might have interesting interactions with detailing, depending on the complexity of the information. Azoulay (2002), Ching & Ishihara (2010) and Sood et al. (2015) also look at the role of clinical studies, how they could change the return of detailing, and the implications. This paper is related to these studies in that it shows how detailing changes come as a result of new information and allows detailing effects to vary with each new major information shock. It adds to this literature by documenting that many of these details are directed at physicians who prescribe mostly off-label and by finding the effect of these details on actual off-label prescriptions, a parameter of interest to both firms and regulators.

Finally, this paper adds to a very large literature about the effects of detailing on demand. In addition to documenting a detailing elasticity for an additional class of drugs, this study uses an identification strategy leveraging shifts in the scientific knowledge surrounding these drugs. Identifying the causal effects of detailing is challenging largely because it is individually targeted by a presumably profit-maximizing firm. Individual targeting creates both significant opportunity and

significant challenges for firms: opportunity in the ability to influence the influentiable without wasting money on those who are not, but challenges in estimating the effects of firm actions and optimally allocating sales forces. Previous literature has attempted to address this challenge using three main approaches: structural approaches (Manchanda et al. 2009, Dong et al. 2011, Montoya et al. 2010, Iyengar et al. 2011, and many others), instrumental-variable approaches (Berndt et al. 1995, 1997) and panel methods with fixed effects (Datta et al. 2011, Mizik et al. 2004). A final approach to dealing with the endogeneity of detailing is to use aggregate data with control variables (Ching et al. (2015)). Another stream of literature examines the effects of policy changes relating to detailing on prescribing behavior (Stremersch et al. 2009, Larkin et al. 2013, Anderson et al. 2015) without explicitly estimating a detailing effect. In this paper, I leverage the introduction of new scientific information in the form of a comparative effectiveness study. In addition, the data are a physician-level panel, allowing the study to control for unobserved physician-specific factors that lead to prescriptions.

2 The Setting – Anti-psychotics

2.1 Psychosis and Background of the Class

The specific setting of anti-psychotic drugs will be important as a vehicle for identifying the effects of detailing, but it is also a large and important market per se, as well as the category most scrutinized by regulators for off-label promotional practices. Anti-psychotics are approved to treat psychosis, in particular schizophrenia and bipolar disorder. Figure 1 shows that the anti-psychotic market is huge in terms of revenue per year. The top five branded anti-psychotic drugs, Zyprexa, Rispderdal, Seroquel, Abilify, and Geodon, represented approximately $3.5 billion in 2001 and grew to over $7 billion by 2006. In addition, this market has undergone shifts in preferences particularly driven by scientific discovery in the mid 2000s. Figure 2 shows the revenues of the top five brands between 2001 and 2006. The market leader at the beginning of the sample, Zyprexa, lost favor to surging shares from Seroquel and Abilify. Each of these drugs, with the exception of Geodon, were among the top 20 highest-grossing drugs at various points, and Seroquel, Zyprexa, and Abilify were among the top 10. By 2013, Abilify was the overall top grossing drug, bringing in more than $7 billion on its own even though many of the other popular drugs had become available in cheaper generic form. In addition, because these drugs are "small molecules" in capsule and tablet form, the marginal cost of production is miniscule.

Prior to the invention of these new, highly successful brands in the late 1990s, psychosis was largely treated with what are called "typical" anti-psychotics. Typical anti-psychotics were first introduced in the 1950s and all have long since lost patent protection. As such, they are inexpensive and widely available from numerous generic manufacturers. These drugs were largely considered to be very

risky in terms of adverse effects. In particular, use of the drugs is associated with both metabolic syndrome (weight gain) and anti-pyramidal side effects (difficulty controlling body movements). Some studies even linked the drugs to the development of diabetes and heart disease (Arana 2000).

The first "atypical" anti-psychotic to be discovered was Clozapine in 1971, but it was quickly removed from the market because of adverse effects. It later returned to the market, but never to the kind of commercial success that the newer generation of drugs attained. Atypical anti-psychotic drugs were introduced with the hopes of reducing the adverse effects associated with the treatment of psychosis. In 1993, Janssen Pharmaceuticals won FDA approval for Risperdal as a treatment for psychosis, followed in 1996 by Eli Lilly's Zyprexa, in 1997 by AstraZeneca's Seroquel, in 2001 by Pfizer's Geodon, and in 2002 by Otsuka's Abilify, which was jointly marketed in the United States with Bristol-Myers Squibb. These drugs were all thought to have better side-effect profiles than typical anti-psychotics while still being effective for treating psychosis. Although the revenues they generated were enormous, the quantities dispensed were not quite as impressive, because the category is characterized by very high prices. From 2001-2006, manufacturers charged between $225 and $380 on average per prescription for atypical anti-psychotics. According to the drugs.com top100 list, the average price per prescription that Otsuka received for Abilify in 2013 was $650. Although Abilify was the highest grossing drug that year, it was only the 23^{rd} most prescribed.

2.2 Regulatory Controversy

As these drugs became more popular, physicians sometimes prescribed them to treat illnesses for which the drugs were not indicated. A drug receives an indication by clinically testing its efficacy against a placebo in a randomized controlled trial registered with the Food and Drug Administration. A positive outcome of that trial are required for ultimate marketing approval by the FDA. Any prescription for a drug being used to treat a condition for which it did not receive FDA approval is considered an "off-label" prescription. Although physician can legally prescribe a drug off-label, a pharmaceutical manufacturer cannot legally market the drug as effective in treating something for which it is not approved by the FDA. In addition, the welfare effects of off-label prescriptions are not clear and could be positive (Bradford et al. 2015). Anti-psychotics became popularly used off-label, primarily for treating dementia and insomnia. Although no cases ever came to trial, firms have paid numerous fines to settle charges that they illegally promoted these off-label uses. In September 2007, Bristol-Myers Squibb (BMS) agreed to pay over $515 million to resolve a wide variety of illegal marketing charges. In particular, "the Government alleged that, from 2002 through the end of 2005, BMS knowingly promoted the sale and use of Abilify, an atypical anti-psychotic drug, for pediatric use and to treat dementia-related psychosis, both "off-label" uses."[3] In fact, the FDA had even mandated that Abilify carry a "black box" warning against its use in treating dementia. The FDA

[3] http://www.justice.gov/archive/opa/pr/2007/September/07_civ_782.html

has approved Abilify to treat adult schizophrenia and bi-polar disorder, but has not approved its use for children and adolescents or for geriatric patients suffering from dementia-related psychosis. Further, the Department of Justice (DOJ) charged, "BMS also created a specialized long term care sales force that called almost exclusively on nursing homes, where dementia-related psychosis is far more prevalent than schizophrenia or bipolar disorder." In April 2010, the DOJ fined AstraZeneca $520 million for off-label promotion. According to a DOJ statement, "the company recruited doctors to serve as authors of articles that were ghostwritten by medical literature companies and about studies the doctors in question did not conduct. AstraZeneca then used those studies and articles as the basis for promotional messages about unapproved uses of Seroquel."[4] In 2009, Eli Lilly pleaded guilty to a criminal misdemeanor charge of illegally promoting Zyprexa off-label, and paid a fine of $1.4 billion.[5] In 2013, Johnson & Johnson, Janssen's parent company, paid more than $2.2 billion to settle several cases charging off-label promotion of Risperdal.[6] In particular, authorities emphasized that Janssen focused its off-label detailing practices on the "most vulnerable" populations: elderly nursing home residents, children, and individuals with mental disabilities. This settlement was one of the largest to date in a drug-marketing case. These fines, accounting for nearly $5 billion, were all imposed for the messages contained in physician detail visits, allegedly encouraging physicians to prescribe off-label. With the total settlements for all drug classes being around $12 billion, the anti-psychotic class was clearly the most heavily scrutinized and fined, largely due to the fear that the adverse effects made inappropriate prescribing especially costly.

In addition to the off-label promotion controversy, firms were also fined for failing to disclose severe side effects discovered during clinical trials, notably, metabolic side effects including weight gain and the onset of diabetes. Between 2006 and 2007, Eli Lilly spent $1.2 billion to settle over 26,000 lawsuits from patients who claimed to have developed diabetes or other diseases while taking Zyprexa. In April of 2012, a jury found Johnson & Johnson guilty of downplaying several risks of the drug Risperdal, and a judge fined the company $1.2 billion, though the Arkansas Supreme Court later reversed this fine.[7]

Although the data in this study cannot speak to whether sales reps hid risks, they can speak to the question of off-label marketing. In particular, because diagnosis code is observable in the data, I can speak to the effect detailing had on prescriptions for off-label use.

[4] http://www.justice.gov/opa/pr/pharmaceutical-giant-astrazeneca-pay-520-million-label-drug-marketing

[5] http://www.nytimes.com/2006/12/18/business/18drug.html?_r=0

[6] http://www.justice.gov/opa/pr/johnson-johnson-pay-more-22-billion-resolve-criminal-and-civil-investigations

[7] http://www.nytimes.com/2014/03/21/business/arkansas-court-reverses-1-2-billion-judgment-against-johnson-johnson.html?_r=0

3 Data

The data for this study come from AlphaImpactRx, a pharmaceutical market research company. The data follow a monthly panel of 1,762 primary care physicians (PCPs) from 2001 through 2006 and 239 psychiatrists from 2002 through 2006 and include physician identifiers. AlphaImpactRx recruits this panel largely from those physicians in the 40^{th} percentile or higher of anti-psychotic prescribing. The reason for this non-representativeness is that physicians below the 40^{th} percentile are highly unlikely to be detailed. These physicians record the number and types of interactions with sales reps on a daily basis. In addition, the data include the number of minutes spent on the product and the other products promoted in that visit.

The physician panel and detailing data are connected with patient treatment information. All patient visit information for each physician is recorded for two days each week. The specific days are rotated across time to prevent day-of-the-week effects from skewing the treatment data. Included in each visit observation is information about the patient diagnosis in the form of an ICD-9 code. In addition, each observation includes patient race, age, insurance status, and diagnosis severity (though without any patient identifiers). Further, the data include whether or not the PCP gave a prescription, the drug the prescription was written for, and whether the diagnosis was new or recurring. Because physicians are not restricted to prescribe for only on-label diagnoses, the data include every diagnosis code for which an anti-psychotic was ever written. As such, whether a prescription was on-label (used to treat schizophrenia or bipolar disorder) or off-label (used to treat anything else) is observable in the data.

Two main challenges of the data are measurement error and representativeness. Because treatment data are only observed for two days per week for each physician, the measure of "total prescriptions" is 2.5 times the observed number of prescriptions. This measurement error may over- or understate the true number of prescriptions. Because prescriptions will be a left-hand-side variable throughout the study, measurement error will reduce the precision in estimation but will not induce bias. In terms of representativeness, physicians who are above the 40^{th} percentile in prescribing are overrepresented in the data. Further, because AlphaImpactRx recruited the panel, selection on willingness to participate in market research might exist, which might be correlated with treatment effects. To the extent that these items are a concern, they will affect how best to think about the counterfactuals. That is, increasing detailing to those below the 40^{th} percentile should not necessarily have the same effects as estimated here. Similarly, those willing to participate in the sample might have a higher or lower sensitivity to marketing activities than the general population of physicians.

Table 1 shows summary statistics before and after the informational shocks for both PCPs and psychiatrists. Note that PCPs have a large distinct jump in detailing and an increase in prescribing as the shocks occur. There is no corresponding distinct jump for psychiatrists. Table 2 shows

summary stats for PCPs on the types of prescriptions they are writing, including on-label versus off-label and distributions by age, severity of illness, and insurance status.

Figure 3 presents psychiatrist prescribing of branded Seroquel, and for comparison, generic perphenazine, and the difference between the two. As can be seen, perphenazine is prescribed at a very low rate, and overall Seroquel prescriptions have a modest upward trend. By contrast, Figure 4 presents PCP prescribing of the same products. As with the psychiatrists, PCPs rarely prescribe perphenazine; however, there is a strong upward trend in PCP prescriptions of Seroquel.

3.1 Did Sales Reps Target Off-Label Prescriptions?

A primary question of interest to regulators is whether or not the firm attempted to push the off-label use of a drug with detailing. This question is of direct interest, as such promotion is explicitly illegal. However, it is very difficult for the regulator to tell whether this kind of behavior has happened. In general, they rely on intensive investigations including the testimony of whistleblower type witnesses. As is clear from the DOJ press release, such witnesses were present in the Seroquel case. Here, I add some suggestive empirical evidence that is consistent with the witness testimony.

While the exact nature of the conversation between sales rep and physician is not observable, other patterns are available in the data. For example, as the data contain a diagnosis code for each prescription which is linked to a particular physician, it is possible to measure how frequently each physician prescribes off-label relative to his or her total prescriptions in the category. In this section, I assign each physician a 'type'; which is simply the total share of off-label prescriptions of Seroquel that physician wrote over the course of the sample. As this is a share of total Seroquel prescribing, values range from 0 to 1. Table 3 contains descriptive statistics for the types, as binned into six groups: a group that has zero off-label prescription share, one with between 0 and 0.25, one with between 0.25 and 0.5, one between 0.5 and 0.75, one between 0.75 and 1, and one with an off-label prescription share of 1, indicating that he or she has only prescribed off-label over the course of the sample.

The striking result of the descriptive statistics is that there are 244, or about 14% of the physicians in the sample, that only ever prescribe off-label. While these physicians are detailed slightly less often than others, all of them are detailed at least once and average one sales rep visit every 10 months. Additionally, the average month of first detail for this group is not significantly later than any of the other groups. In particular, it is the same as for the group that never prescribes off-label. In fact, the group that, on average, gets the earliest first detail in the sample is the group with off-label share between 0.75 and 1, which is a very high share of off-label prescribing. This group is detailed just as much as every group except for the one with off-label share between 0 and 0.25. While none of this is definitive proof that the messages contained in the visits were pushing off-

label, it is suggestive evidence that sales reps spent considerable energy on physicians who primarily prescribed their drug for off-label use, and that regulators might choose to pursue a smoking gun.

Additionally, I bin psychiatrists in the same way without such a clear picture. On average, psychiatrists prescribe about 22% of their anti-psychotics off-label, but the dispersion is quite different. Only one of the 239 psychiatrists in the data prescribes only off-label, and 221 of the psychiatrists prescribe both on-label and off-label in significant quantities. Figure 5 shows side-by-side histograms of PCP and psychiatrist types. The distribution of psychiatrists is much more tightly centered around 22% off-label and is less obviously suggestive of nefarious activity by the sales reps, but it is not definitive, as I do not observe the conversations. However, psychiatrists are potentially less concerning from a regulatary perspective. They are more likely to have extensive experience with these drugs and be aware of the risks of prescribing them off-label than PCPs.

4 The Effect of Detailing on Off-Label Prescribing

4.1 The endogeneity problem and previous literature

The individually targeted nature of detailing makes for significant managerial opportunities, but also provides challenges in terms of estimating the effects of detailing. In particular, not only is detailing set at the individual physician level, it is also not random. A firm optimally targeting its details would necessarily direct more detailing activities to those who provide the most potential profit: those who are most responsive and those who prescribe the most. As documented in previous literature (Manchanda et al. 2004) and learned in informal conversations with managers, decile rules play a significant role in detailing allocation. That is, sales reps tend to work independently and can visit physicians as many times as they please. However, the firm provides them with recommendations of how often to visit each physician, often generated by a third-party analytics firm, while putting pressure on reps to make a minimum total number of physician contacts. The physician's volume of prescribing in the class of drugs, and in particular, the physician's decile of category prescribing, strongly influence these recommendations. Given this information, sales reps decide whom to visit, and the firm attributes sales to visits and rewards the sales reps with bonuses based on performance. Given this structure, physician-specific characteristics must be controlled for as much as possible, preferably with a physician fixed effect. Otherwise, the researcher runs the risk of attributing sales to detailing when that prescriber would have prescribed with or without the sales rep visit.

Solving this type of endogeneity problem in aggregate data is also difficult. Some authors (Berndt et al. 1995, 1997) employ instrumental-variable methods, using time until patent expiration as an excluded instrument. Firms advertise less as the patent expiration date approaches. The difficulty in this approach is that a number of supply and demand changes happen at the same time as patent

expiration approaches, so disentangling these effects is difficult. Another approach (Ching et al. 2015) is to employ numerous control variables for the potential confounds. The limitation in this approach is that it requires the researcher to obtain every possible variable that might be correlated both with prescriptions and detailing, which can be a rather difficult task. The most common approach to controlling for the endogeneity of firm detailing decisions is a structural approach (e.g., Dong et al. 2009, Kalra et al. 2011, Montoya et al. 2010, Manchanda et al. 2004, Stremersch et al. 2013) whereby the researcher writes down the firm's objective function and requires that the firm optimize it. If the theory is correct, the structural approach will control for the factors that determine detailing decisions that might contaminate the estimated demand effects. This approach requires reasonably strong assumptions on both the objective function of the firm and the firm's sophistication in maximizing that objective function. This difficulty is especially present in aggregate data, but is also a complication in physician-level data without using physician fixed effects. Using fixed effects can be computationally unattractive in complicated non-linear estimation problems, but failing to account for unobserved physician-specific characteristics might induce significant positive bias.

A smaller literature has used physician-level data and fixed effects to assess the effects of detailing. One strand of such literature looks at the effects of policy changes involving detailing on physician behavior (Anderson et al. 2015, Larkin et al. 2013, Stremersch et al. 2009). Using these policy changes, directionally signing the strategies that are being outlawed is possible, but without detailing data, extracting managerially meaningful implications is difficult. In particular, Anderson et al. (2015) show that conflict-of-interest disclosure policies have no significant effect on the prescribing of anti-psychotics, whereas Larkin et al. (2013) show that direct restrictions on detailing activities decreased anti-psychotic prescriptions to all populations. Two other papers use physician fixed effects together with physician-level detailing data (Datta et al. 2014, Mizik et al. 2004). These approaches can control for a strict application of decile rules and rely on the timing of detail visits being random. If sales reps can anticipate when demand will be high, they might detail more during those months, which would induce an upward bias, even with physician fixed effects. However, such anticipation might be very difficult. Indeed, those studies with the smallest point estimates on detailing elasticities are those that employ physician-level fixed effects, suggesting physician characteristics play a large role in the allocation of detailing; in particular, those who would prescribe the most in the absence of detailing are the ones who are detailed the most.

This study will employ a within-physician design similar to that of Datta et al. (2014) and Mizik et al. (2004), controlling for persistent physician-specific factors that drive prescribing independent of detailing. Additionally, changes in scientific knowledge provide significant within-physician variation to primary care providers in detailing visits. Separating the direct effects of the information shocks from the detailing effects relies on the fact that there is a gap between the timing of the shock and

the timing of the first post-shock detail visit for most of the physicians in the sample.

4.2 Informational Shocks and Anti-psychotic Prescribing

This study will leverage exogenous informational shocks that caused one branded product, Seroquel, to detail much more to primary care physicians. To separate the direct effect of the information shock from the effect of the shock-driven detail visit, I will primarily rely on the fact that the shocks and the first post-shock detail visit are not coincident for 90% of the physicians after the first shock and 82% of the physicians after the second shock. I will refer to these physicians as the 'non-coincident' physicians. I will further exploit the panel nature of the data using physician-specific fixed effects to control for unobserved physician-specific factors that lead to prescribing. Prior to the information shocks, only 4% of physician-months and 18% of physicians in the data had at least once detail visit. The information shocks drove a significant increase in the amount of within-physician variation in detailing. As such, the period prior to the information shocks will be especially helpful in pinning down physician fixed effects and the periods following the information shocks will provide significant variation in detailing. The period following the shock but preceding the first detail visit will pin down the direct effect of the information that is unrelated to detail visits. Here, I rely on randomness in the timing of the first detail visit following the information shocks. I test the assumption by allowing the estimated effect of detailing to vary based on the date of initial post-shock detailing visit. Those physicians who are detailed later are no less likely to prescribe post detail than those who are detailed sooner, giving credibility to that assumption. For those physicians who are detailed in the same month as the information shock (I will refer to these physicians as 'coincident' physicians), I will be unable to separate the information effect from the detailing effect. However, the estimated effect on these physicians could be viewed as an upper bound, as some of the lift in their prescriptions could be due to the positive information and some could be due to the detailing.

When atypical anti-psychotics were first discovered and widely used in the late 1990s, they were thought to be significantly better than the older-style typical anti-psychotics in terms of their side-effect profiles. In particular, the atypicals were thought to carry a significantly lower risk of metabolic side effects: significant weight gain and development of diabetes. However, these beliefs about comparative effectiveness and side effects were not clinically proven. As time progressed, the scientific community learned more about how these drugs compared with each other and with the older typical anti-psychotics. In February of 2004, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity in the journal, *Diabetes Care,* released a consensus statement. The statement was meant to summarize the results of a consensus-development conference that took place in November of 2003. In particular, the statement said, "Clozapine and

olanzapine [generic name for Zyprexa] are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia. Risperdione [Risperdal] and quetiapine [Seroquel] appear to have intermediate effects. Aripiprazole and ziprasidone are associated with little or no significant weight gain, diabetes, or dyslipidemia, although they have not been used as extensively as other agents." The guidelines recommended both metabolic baseline screening and follow-up monitoring of patients who were prescribed a second-generation anti-psychotic. This information was a positive shock for all products other than Clozapine and Zyprexa, because Zyprexa was previously the market leader in anti-psychotics and received clear negative news. Indeed, Figure 2 shows Zyprexa revenues took a significant hit in 2004 and beyond, losing its status as a market leader, while other products gained ground.

Although the consensus statement provided some information about the comparative effectiveness and side effects of these products, it was well short of definitive in setting the standard of care. It was not the culmination of a randomized control trial, but rather the summation of a number of other studies, some more suggestive than others. The field went a bit further in commissioning "The Clinical anti-psychotic Trials of Intervention Effectiveness" (CATIE) in the early 2000s. The purpose of CATIE was to compare four new atypical anti-psychotics (Zyprexa, Seroquel, Risperdal, and Geodon) and one old typical anti-psychotic (perphenazine) on the dimensions of tolerability, efficacy, and side-effect profiles. Note that none of these products are molecularly equivalent: they are therapeutic substitutes. The study was conducted from January 2001 through December of 2004 and the results were disseminated in early 2005, to be published in the *New England Journal of Medicine* in September of that year. The study found the big winners to be branded Seroquel and generic perphenazine. The products were big winners not in the sense that they were clearly safer and more efficacious than other products, but rather that neither performed significantly worse than the rest of the products on any of the adverse effects. Both products had the lowest incidence of metabolic and anti-pyramidal side effects while having similar efficacy and tolerability to other treatments. The market leader, Zyprexa, was found to have better tolerability than other products, but that tolerability was offset by severe adverse effects, particularly, weight gain that was far worse than any of the other products. Rispderdal performed poorly on the dimension of insomnia and had adverse sexual side effects.

Given that the information for a very inexpensive generic and a very expensive brand was more or less equal, perphenazine would seem likely to take over as the first-line medication for psychosis. Indeed, the National Institutes of Mental Health published a press release following the publication of CATIE explaining that the study showed the conventional wisdom that the older-generation drug would have a worse side-effect profile was false, and that physicians should take that information into account when making treatment decisions.[8] That perphenazine was not significantly affected by the

[8] http://www.nimh.nih.gov/funding/clinical-research/practical/catie/phase1results.shtml

clear good news combined with NIMH publicity is a bit of a puzzle, as previous studies have shown that publicity can affect prescriptions in the statin market (Ching et al. 2015). However, the lack of positive effect on perphenazine might also be seen as evidence of the limitation of good information and publicity without an accompanying firm response to spread the good news. Analysis of the effect of the information shocks on perphenazine prescribing is available in the appendix.

These information shocks were met with a sharp marketing response by Seroquel. Figure 6 shows the average number of Seroquel detail visits received by each PCP in the sample after partialing out physician fixed effects. Distinct jumps occur in the amount of detailing in February of 2004 and January of 2005. Presumably these jumps in detailing were to help spread the good news, or said differently, the perceived marginal returns to detailing had increased, consistent with the story in Ching & Ishihara (2010) and Venkataraman & Stremersch (2007). Figure 7 shows the average number of Seroquel detail visits for psychiatrists per month, partialing out physician fixed effects. Interestingly, no such distinct jump occurs in marketing activities to psychiatrists. The lack of a detailing response to psychiatrists suggests reasons orthogonal to this particular new scientific information likely explain the large number of visits to psychiatrists. Indeed, it is entirely possible that psychiatrists know the news well before its publication and as such, the marginal benefit of detailing to psychiatrists has not changed with the new information. With no distinct jumps at the dates of information revelation to psychiatrists, the main portion of this study will focus on PCPs, because the research design taking advantage of the shock-driven detailing increase will not work for psychiatrists. However, to the extent that firms use decile rules to target detailing, a fixed-effects design will still be valid for psychiatrists, under the assumption that the timing of visits is as good as random. Making this assumption, a fixed-effects analysis of psychiatrists is provided in the appendix. There is significant within-physician variation in detailing to psychiatrists throughout the sample period.

Are PCPs an important target for anti-psychotics? Figure 8 shows the total number of detail visits in the sample inflated to represent the number of PCPs and psychiatrists in the United States. After the release of the CATIE study, more than half of all detail visits appear to be going to PCPs. This finding suggests that, at least to the firm, PCPs are an important target. PCPs represent about a third of the anti-psychotic prescriptions in this sample, though this sample is slightly skewed toward PCPs. Additionally, non-traditional prescribers of anti-psycotics, primarily PCPs, were the focus of the regulator concern regarding off-label promotion.

4.3 The Effects of Information Shocks

4.3.1 Reduced Form Effects

While there were overwhelming jumps in physician detailing following these information shocks, these jumps were not met with an overwhelmingly obvious jump in prescribing behavior. Corresponding regressions show the significant effect of the information shocks on detailing PCPs and the associated increase in prescriptions. Interestingly, while the increase in detailing is sharp and significant, the increase in Seroquel prescriptions following each shock is modest. The next section will dissect these results more carefully. Figure 9 plots the Seroquel prescriptions per physician per month after partialing out physician-specific fixed effects. Although a jump could occur, it is not as clear as the distinctive jump in detailing. To more clearly see whether the prescribing of Seroquel increased significantly with the different information regime, I estimate

$$SeroquelRx_{it}^{g} = \alpha_i + \gamma * time + \beta_1 Shock1_t + \beta_2 Shock2_t + \epsilon_{it},$$

for $g \in \{TotalRx, OfflabelRx\}$. To further evaluate how much of this effect could come from detailing versus the direct effect of the shock, I take advantage of the fact that many physicians are not detailed at exactly the time of the shock, the 'non-coincident' physicians. Figure 10 illustrates exactly which types of physicians are identifying the effects of interest. In each panel, there is the time series of detail visits for a single physician. Each of these physicians receives three detail visits over the course of the sample, which is the median. In panel (a) is an example of a 'non-coincident' physician for both shocks. After each shock, there is a lag before a sales rep reaches this physician. The time before the detail visit but after the shock will pin down the information effect, while the time after the detailing visit but prior to the next shock will pin down the detailing effect. Meanwhile, in panel (b) is an example of a physician who is a 'coincident' physician for shock 2, as this physician was visited in the exact month of the information shock. For this physician, I will not be able to separate the direct effect of shock 2 from the detailing effect associated with the shock 2-driven detailing activities. I quantify this systematically in the sample with the equations

$$\begin{aligned} SeroquelRx_{it}^{g} &= \alpha_i + \gamma * time + \beta_0 * PreShocks_t + \sum_{j=\{shock1,shock2\}} [\beta_{j1} Shock_{j,it}^{coincident} \\ &\quad + \beta_{j2} Shock_{j,it}^{non} + \beta_{j3} Shock_{jit}^{non} * PostDetail_{it}] + \epsilon_{it}. \end{aligned}$$

for $g \in \{TotalRx, OfflabelRx\}$. The pre-shock period will serve as the reference period and as such will not provide an estimate of β_0. In this case, β_{11} and β_{21} will provide the composition effect between the information and the detailing for the coincident physicians. As these physicians are

never observed in periods where the information shock has happened and they have not yet been detailed, it is impossible to separate those two effects. These physicians make up about 11% of the sample for the first shock and 18% of the sample for the second shock. These can be viewed as upper bounds on the total effect of the positive shock-driven detailing for these physicians. For all other physicians, β_{12} and β_{22} will give the direct effect of the information shock prior to any detailing activities and β_{13} and β_{23} will give the effect of the shock after the first detail visit they receive, providing the incremental effect of the detailing over and above the shock by itself. If physicians all read the studies and take the information as a reason to prescribe more Seroquel, this will show up inβ_{12} and β_{22}. To the extent that physicians need to be informed of the shocks by sales reps, it will be reflected in β_{13} and β_{23}.

This analysis assumes that β_{13} and β_{23} are the same no matter which month the physician is first detailed in after the shock. This essentially amounts to the assumption that conditional upon receiving a post shock visit, the timing of the first visit to each physician is essentially random with respect to the effect of detailing on that physician. There is reason to think this is a reasonable assumption. Conversations with experienced sales reps indicate two sources of randomness in the timing of visits. First, they often set the sequence of their visits to minimize the distance they have to drive in a given day. Unless the highly responsive physicians are all located together, this pattern will lead to randomness in timing with respect to detailing responsiveness. Second, the sales reps are often turned away at practices due to the physician being too busy. The sales rep then comes back at a different time, hoping to find the physician available. The random timing assumption might not be reasonable if the firm targets the most responsive physicians earlier than the less responsive physicians. I test the assumption by allowing β_{13} and β_{23} to have heterogeneous effects based on the time elapsed between the shock and the first detail. This requires the much less restrictive assumption that each physician who receives his or her first post-shock visit in the same month has the same response. If firms visit the most responsive physicians first, then the interaction term between $Shock_{j,it}^{non} * PostDetail_{it}$ and time elapsed between shock and detail will be strongly negative. As will be shown in the results, this interaction term is very small and insignificant, which provides support for the random timing assumption.

An additional concern is that independent of both detailing and the initial release of the scientific information, there might be publicity in the news or other sources in a given month that leads to further prescriptions, as is considered in Ching et al. (2015). One way to deal with this concern is to add in month fixed effects to control for any particular event that occurs for all physicians in a particular month. A limitation in this approach is that many of the variables above only vary at the month level, so are not distinguishable from month fixed effects. However, the variable, $Shock_{j,it}^{non} * PostDetail_{it}$, which generates the main variable of interest, varies both by physician and by month, as different physicians get their first detail visits at different times following shocks. As

such, the parameter on that variable can be separately distinguished from the month fixed effects. As will be shown in the results, the parameter of interest is unchanged by the inclusion of month fixed effects, which should address concerns of publicity biasing the results.

I run these analyses for both total prescriptions of Seroquel and off-label prescriptions of Seroquel, using the detailed nature of the prescribing data. It might be hypothesized that since the detail visits are driven by the clinical studies and the clinical studies themselves were in part motivated by investigating efficacy on the main effect, an effect of these detail visits on off-label prescriptions should not be expected. However, the studies did not illuminate any statistically significant differences between the treatments with respect to on-label efficacy. All of the significant differences that affected Seroquel were about the side effects, which should apply equally to both on-label and off-label uses. Additionally, according to a Department of Justice press release, they were worried about the effects of detailing on off-label prescribing, particularly in the time period between 2001 and 2006 and to primary care physicians. If it were obvious and unsurprising that these details had no effect on off-label prescribing, it would be rather peculiar for the DOJ to fine AstraZeneca $520 million for off-label promotion. Their April 2010[9] press release reads (emphasis added):

> The United States alleges that AstraZeneca illegally marketed Seroquel for uses never approved by the FDA. *Specifically, between January 2001 through December 2006*, AstraZeneca promoted Seroquel to psychiatrists and other physicians for certain uses that were not approved by the FDA as safe and effective (including aggression, Alzheimer's disease, anger management, anxiety, attention deficit hyperactivity disorder, bipolar maintenance, dementia, depression, mood disorder, post-traumatic stress disorder, and sleeplessness). These unapproved uses were not medically accepted indications for which the United States and the state Medicaid programs provided coverage for Seroquel.
>
> According to the settlement agreement, AstraZeneca targeted its illegal marketing of the anti-psychotic Seroquel towards doctors who do not typically treat schizophrenia or bipolar disorder, such as physicians who treat the elderly, *primary care physicians*, pediatric and adolescent physicians, and in long-term care facilities and prisons.

Further, as per the previous section, the data in this study show that AstraZeneca sales reps visited physicians with a high propensity to prescribe off-label nearly as frequently and intensely as those who had low propensity to prescribe off-label, including many visits to physicians who never recorded an on-label prescription. They also visited just as promptly after the information shocks. Both the descriptive evidence from these data and the direct historical evidence from the Department of Justice suggest that the regulator cares a great deal about whether or not these particular detail visits produced a significant number of off-label prescriptions.

[9] http://www.justice.gov/opa/pr/pharmaceutical-giant-astrazeneca-pay-520-million-label-drug-marketing

It must also be noted that a finding of a positive effect of detailing on off-label prescribing need not imply criminal behavior by the firm. The firm may simply report the side effects and in doing so increase off-label prescriptions by physicians who now feel more comfortable that the drug is more safe. If that were the case, the fraction of the detailing effect attributable to off-label prescriptions should be similar to the total off-label share of prescriptions. However, the converse, that detailing has little or no effect on off-label prescribing, might suggest to the regulator that even if the firm is illegally attempting to push off-label uses, the fact that it does not have much effect might make it not worth spending scarce resources investigating and prosecuting the case. In either case, how promotional activity affects off-label prescriptions is a useful piece of information to consider in thinking about how to most efficiently regulate promotion. Additionally, this effect is an important input for firms. If it turns out that their detailing efforts have minimal effect on off-label prescriptions, they might be wise to avoid any activity that is even suggestive of promoting off-label, as it would not be worth the risk of a large settlement. If such settlements are seen as a cost of doing business, it is important to the manger to know whether or not the activity in question was worth the punishment.

One additional way to consider separating the direct effect of information from the promotional effect would be to consider the effect of the information shocks on the generic drug, perphenazine, which, as noted previously, also received positive information indistinguishable from the news received by Seroquel, though without an associated increase in detailing. If it did not have an associated increase in prescriptions without the detailing that Seroquel received, it would be some evidence that detailing is necessary to spread good news, as PCPs are unlikely to find the news on their own. Indeed, I find this to be the case, and details of the analysis are provided in the appendix. As perphenazine is working from a much smaller prescription base from Seroquel, it is not a perfect comparison group. However, it does provide some evidence of the limited power of even strong clinical study information that is not accompanied by a firm response.

4.3.2 Reduced Form Results

Table 5 presents regressions looking only at the effects of the shocks on detailing and prescribing. Column 1 confirms the intuition from Figure 6, that the information shocks caused large and significant increases in detailing to PCPs. Columns 2 and 3 show that the corresponding effect on total and off-label prescriptions are very small and insignificant. Interestingly, prescriptions for Seroquel among PCPs did not rise at all in the period following the first shock and only increased a small, statistically insignificant amount following the second shock. Meanwhile, off-label prescriptions of Seroquel decreased in the periods following each shock, though neither effect is not distinguishable from zero. Following the logic that using the information shocks as instruments would present an upper bound on the effect of detailing, these very small reduced-form results suggest that any de-

tailing effect must be small. However, it is possible to gain significant precision as well as separation of the information and the detailing effect with the data.

Table 6 presents the reduced form regressions separating out the coincident and non-coincident physicians to separate the information effect from the detailing effect. The coefficients on $Shock1^{coincident}$ and $Shock2^{coincident}$ correspond to β_{11} and β_{21} above and are the composition effect of the direct information shock and detailing for the coincident physicians. There are 198 of these physicians for the first shock, and they make up roughly 11% of the physicians in the sample. There are 322 of these physicians in the sample for the second shock, making up 18% of the physicians in the sample. The coefficients on $Shock1^{non}$ and $Shock2^{non}$ correspond to β_{12} and β_{22} and are the intercepts for the period following the information shock but prior to the first detail visit for the non-coincident physicians. There are 490 of these physicians following the first shock and and 1171 following the second shock. This means that many physicians are not detailed at all during the period of the information shock for each shock and a separate intercept is allowed for these physicians. Finally, the coefficients on $Shock1^{non} * PostDetail$ and $Shock2^{non} * PostDetail$ correspond to β_{13} and β_{23} and are the effect of the information shock following the first detail visit.

Columns 1 and 2 show a small and insignificant combined effect of Shock 1 and detailing to the coincident physicians, both for total and off-label prescribing. Meanwhile, non-coincident physicians in the period after Shock 1 and prior to the first detail also show small, negative, but insignificant changes to their prescribing of both total and off-label prescriptions. After their first detail following Shock 1, these physicians now show a positive effect on prescribing, but it is small, at about 0.05 prescriptions per month and insignificant. A similarly small effect is is present for off-label prescriptions that is marginally significant, at 0.035. Overall, Shock 1 appears to have had no overall effect to either total or off-label prescriptions, while detailing seems to have a small effect that is mostly attributable to off-label.

The story shifts considerably after with Shock 2. There is a positive and significant composition effect for the coincident physicians of about 0.16 prescriptions, and a very small and insignificant 0.007 effect on off-label prescriptions. The shock and the detailing combine for these physicians to generate 0.16 prescriptions, none of which are off-label. After Shock 2, there is a very small and insignificant effect of 0.005 on the total prescriptions to the non-coincident physicians prior to a detail visit, and a similarly insignificant effect on off-label prescriptions. However, following their first detail the effect increases to a significant 0.066 for on-label prescriptions while remaining small and insignificant for off-label prescriptions. While the first information shock seems to have had little effect either directly, or through detailing, the second shock appears to have had a significant effect on total prescriptions, none of which can be attributed to off-label prescriptions. Also interestingly, the period before a physician gets detailed but after Shock 2, there is no increase in prescriptions, suggesting that it is the detailing rather than the direct information driving the

increase in prescriptions. This is consistent with physicians not necessarily learning the information unless a detail visit provides them with the information.

Recall that these results assume that firms are not first visiting physicians who are more responsive to detailing, as some physicians are first detailed in the second month after the shock while others are first detailed in the fourth or fifth, and the above results pool those into one coefficient. Columns 3 and 4 provide a relaxation of the assumption by allowing the $Shock1^{non} * PostDetail$ effects to vary by the month of first detail. If firms are visiting the most responsive physicians the earliest, the interaction term $Shock1^{non} * PostDetail * FirstMonth$ should be negative and significant. All of the interaction terms are both small and insignificant, giving some support to the assumption that within physician, the timing of each detail is as good as random. As mentioned before, this is perhaps unsurprising given the fact that firms are known to employ simple decile rules. Additionally, this is consistent with the fact that many sales reps report being turned away from practices only to return in a subsequent visit and try again.

While aggregate time effects are incorporated into all of the above analysis using a linear time trend, it remains possible that detailing effects could be confounded by discrete news stories that are independent of the initial release of information. Such a story would be consistent with Ching et al. (2015). To address this concern, columns 5-6 contain month fixed effects to control for any news story that might lift the prescriptions of all physicians at the same time. As many of the variables in this analysis vary only at the month level, the month fixed effects will make the estimation of those impossible. However, the main variable of interest, $Shock_j^{non} * PostDetail_{it}$, varies at the individual and the monthly level, as different physicians receive their first detail visits at different times. Additionally, the $Shock_j$ effect can only be identified for one of the two physician types and will represent the difference between them in that time period. Columns 5-6 show that the main variables of interest are not changed significantly with the addition of the month fixed effects, alleviating the concern that publicity and news stories could be causing the lift in prescriptions for all physicians in a particular month. This is perhaps unsurprising because unlike statins, which Ching et al. (2015) study, anti-psychotics are not taken by as large of a patient base and that base may be less responsive to news stories about the drugs they take due to the nature of the condition that is treated.

4.3.3 Scaling the Results

While the previous section is designed to show the effect of the different regimes (Post Shock 1 Pre Detail, Post Shock 1 Post Detail, Post Shock 2 Pre Detail, Post Shock 2 Post Detail) on prescribing behavior, I would ideally like to estimate a detailing effect so prescriptions may be attributed to each detail visit as opposed to the regime as a whole. This simply requires scaling each estimate by the propensity to be detailed during each regime. Again, for those physicians who are detailed in

the same month as the informational shock, the direct information effect is not separable from the detailing effect, but since the information is positive, the estimated effect on these physicians can be interpreted as an upper bound on the true effect.

$$\begin{aligned} SeroquelRx^{g}_{it} &= \alpha_i + \gamma * time + \beta_0 * PreShocks_t * SeroquelDetail_{it} + . \\ &\quad \sum_{j=\{shock1,shock2\}} [\beta_{j1} Shock_{j,it}^{coincident} * SeroquelDetail_{it} + \beta_{j2} Shock_{j,it}^{non} \\ &\quad + \beta_{j3} Shock_{jit}^{non} * PostDetail_{it} * SeroquelDetail_{it}] + \epsilon_{it}, \end{aligned}$$

for $g \in \{TotalRx, OfflabelRx\}$. The reduced form results will be scaled in two ways. First, I will use the flow of detailing as the scale variable. Second, I will assume that detailing accumulates as a stock to allow past detailing to affect present prescriptions. I build this stock using the formula,

$$SeroquelStock_{it} = \sum_{\tau=0}^{t} \delta^{t-\tau} SeroquelDetail_{i\tau},$$

and assuming a decay parameter of $\delta = 0.6$. The use of the geometric decay and assumed decay parameter is consistent with previous literature (Narayanan et al. 2004), and I calibrate the δ parameter using a non-parameteric analysis assessing the effects of lagged detailing on prescriptions following the second shock. Details of this calibration are in the appendix.

As with the reduced form analysis, I include a specification testing to see if the detailing effect differs by the date of first detail following the information shock. This is also effectively a test of the assumption of randomness in the timing of first visit with respect to detailing effect. If firms visit those physicians who are more responsive sooner, then the parameter on this interaction term will be significantly negative. Also analogous to the reduced form analysis, I include a specification including month fixed effects to control for potential confounds in publicity that all physicians might receive in a given period.

From these estimates, a number of deductions are possible. First, it is possible to see to the extent to which detailing affected off-label prescriptions to PCPs in absolute terms in the periods following each shock. The magnitude of the off-label effect is important in itself, as a small effect might indicate a low level of regulatory concern about details to PCPs of this nature. However, as mentioned before, a finding that detailing increases off-label prescriptions does not necessarily implicate firms in illegal activity. Sharing good news about adverse effects could cause physicians to prescribe more off-label even if the sales rep did not try to push that specific course of action.

To further assess whether detailing might have pushed off-label uses, the fraction of the total detailing effect comes from off-label prescriptions can be informative. If that fraction is larger than the overall fraction of off-label prescriptions in the populations, the regulator might be more likely to infer that detailing messages were geared towards off-label prescribing. To assess this

question, I compare $\frac{\hat{\beta}_{offlabel}}{\hat{\beta}}$ to $\frac{SeroqueRx_{offlabel}}{SeroquelRx}$. These quantities can then be compared for the different scalings of the detailing effect and separately for the periods following each shock. As there are a considerable number of physicians for whom the information effect is not separable from the detailing effect, this comparison will be limited to those physicians for which the two can be separated. Finally, I weight these ratios for each period by the total number of details during that time to see how the total impact of detailing influenced the distribution of on-label versus off-label prescribing over the course of this sample, 2001-2006, which was exactly the period the DOJ referenced in its press release.

Before proceeding to the main results of interest, I note here that across all specifications, detailing in the period preceding both shocks is small and not distinguishable from zero. It also has no exogenous shock generating the variation. Indeed, the estimated effect is extremely imprecise. There are limited data from which to estimate this effect, as less than 4% of physician-months in this period contain a detail visit and only 18% of physicians are visited. The fact that very few physicians are visited might indicate the firm believes the effect of detailing in this period is low.

The results scaled by flow are in Table 6, and the stock-scaled results are in the appendix. For each, I will focus on the preferred specifications, which are in columns 1 & 2 and corresponds to columns 1 & 2 of Table 5, as the results are all consistent with each other. Following Shock 1, β_{11} corresponds to the 'upper bound' effect of detailing on coincident physicians, as it cannot be separated from the direct information effect. β_{11} indicates that at most, details have a positive, though insignificant, effect on total prescriptions of about 0.03 and off-label prescriptions of about 0.02 to coincident physicians following Shock 1. Not only are these small and insignificant, but they are not separable from the direct effect of the information, which is presumably positive. Meanwhile, the detailing effect on total prescriptions for the non-coincident physicians is larger at about 0.08, though it is not significant. However, the effect on off-label prescriptions is about 0.07 and statistically significant, making up nearly all of the detailing effect following the first shock. It seems as though there is a small detailing effect of the Shock 1-driven details that is mostly attributable to off-label prescriptions. While it might be concerning to the regulator that the share of the detailing effect attributable to off-label prescriptions is far higher than the share of off-label prescriptions (0.42) in the data for this time period, it is worth noting that these effect sizes are quite small.

Following Shock 2, the combination detailing and information effect, β_{21}, is about 0.18 per detail for the coincident physicians. This is a much more sizable effect and confirms what was found in the reduced form, though it must be emphasized that this should be thought of as an upper bound on the detailing effect. It corresponds with an elasticity with respect to detailing of about 0.12, which is on the very low end of what has been found in the literature, even with it being viewed as an upper bound on the true effect. The corresponding effect on off-label prescriptions is considerably smaller,

at about 0.04 and statistically significant. This makes up less than one fourth of the effect on total prescriptions and would represent a shift in the prescribing distribution towards more on-label treatments. For the non-coincident physicians, the detailing effect on total Seroquel prescriptions following Shock 2 is a positive and significant 0.15. Meanwhile, the effect on off-label prescriptions is quite a bit smaller, at about 0.05 and significant. This effect makes up only about one third of the detailing effect for this group, which is smaller than the share of off-label prescriptions in the data, which is 0.42. The estimated detailing effect for the non-coincident physicians is only slightly smaller than and not statistically distinguishable from the upper bound of the detailing effect on the coincident physicians, suggesting that the firms are not visiting more responsive physicians sooner. Furthermore, the effect for the period prior to the first detail remains small and insignificant and, in fact, negative for the non-coincident physicians. All of these results together suggest that the direct information effect of the shock in the absence of a detail visit is either very small or zero. This is also consistent with the fact that the generic drug receiving good news, perphenazine, sees no increase in prescriptions following the shocks. The lack of a large direct effect is consistent with physicians not having much time to read clinical studies, instead relying on detailing to provide them with the information. Given that the information they receive through is from a firm that only wishes to maximize its own profits, it is unsurprising that they might not share the good news about the generic as well.

Columns 3-6 provide the same validity and robustness checks as in the reduced form, while also controlling for detailing activities of rivals. In columns 3 & 4, I allow detailing to have a heterogeneous effect by the date of first detail following each shock, while also including rival detailing. The interaction terms, as with the reduced form, are very small and insignificant, showing no evidence that firms are visiting more responsive physicians sooner. Additionally, rival detailing shows no significant effect, nor does it alter the coefficients of the variables of interest. Columns 5 & 6 include month fixed effects to control for the fact that there might be various types of publicity beyond the initial release of information that could be correlated with both prescriptions in a given month overall and detailing to each individual physician. Again, the time invariant covariates are no longer identified, but the parameters of interest remain unchanged.

Discussion of the results scaled by detailing stock may be found in the appendix, as they are entirely consistent with the results on flow.

The above results show some very interesting patterns in detailing effects surrounding these significant information shocks. Overall, it must be noted that the magnitude of the estimated detailing effects are exceptionally small. Assuming an average price of Seroquel of $217, which is the average price in 2006[10], and assuming that these detailing patterns extend to the population of PCPs, these estimated effects imply total incremental revenues from detailing to PCPs from 2001-2006 which

[10] http://www.drugs.com/top200_2006.html

are on the order of $40 million. While this assumes past detailing has no effect, the results using the stock conception of detailing imply incremental revenues on the order of $80 million. These numbers likely over-state the incremental revenues, as this sample over-samples physicians in the 40th percentile of prescribing who are more likely to be detailed. This includes all prescriptions, on and off-label, and is significantly smaller than the regulatory fine of $520 million.

In addition to the absolute magnitude, the relative share of the total effect attributable to on and off-label prescriptions is of interest. While detailing after Shock 1 has an effect which is almost entirely attributable to off-label prescriptions, that effect is tiny, and the number of detail visits was small compared with those following Shock 2. To make this comparison more precise, here, I compare the total prescriptions caused by detailing with the total off-label prescriptions caused by detailing over the course of this sample, 2001-2006. I believe this to be an informative comparison for two reasons. First, 2001-2006 was exactly the time period the DOJ referenced in their settlement with AstraZeneca over Seroquel detailing. Next, while this sample is not representative of the entire population, the non-representativeness stems from the fact that these physicians were more likely to be detailed than the average physician in the population.

I compute the total number of prescriptions and total number of off-label prescriptions caused by detailing analogously:

$$\begin{aligned} SeroquelRxCaused^g &= \hat{\beta}^g_{13}\Big(\sum_{i,t\in Shock1} Shock1^{non}_{it} * PostDetail_{it} * SeroquelDetail_{it}\Big) + \\ &\quad \hat{\beta}^g_{23}\Big(\sum_{i,t\in Shock2} Shock2^{non}_{it} * PostDetail_{it} * SeroquelDetail_{it}\Big), \end{aligned}$$

for $g \in \{TotalRx, OfflabelRx\}$. This will only add up the total and off-label prescriptions caused for the non-coincident physicians over the course of the sample. However, the quantity of interest is the ratio of these two numbers and how it compares with the share of off-label prescriptions in the data. Using these formulas, I find that for this group of physicians, off-label prescriptions account for about 39% of the total prescriptions caused by detailing, which is below the 42% of off-label prescriptions in the data. This suggests that overall, over the time frame 2001-2006, detailing caused the distribution of prescribing to move slightly toward on-label prescriptions. This helps to provide an overall picture to go along with the shock-by-shock picture of the share of the off-label effect.

I similarly calculate the total and off-label prescriptions caused using all physicians in the sample. For those that are detailed in the same month of the shock, I assume that the estimated composition effect of detailing and the direct information is the detailing effect. This is not ideal, as this is an upper bound on the true effect. As the quantity of interest is a ratio, the direction of the bias depends on whether or not there was a bigger direct information on total or off-label prescriptions.

The estimation did not provide evidence of a direct effect on either total or off-label prescriptions for the other physicians, but this ratio should be taken with the limitation in mind. For the full sample, it appears as though off-label prescriptions account for about 31% of the total detailing effect over the course of the sample. That is again well below the 42% off-label share of Seroquel prescriptions in the data. Analogous calculations were done using the detailing stock measure and estimates, with nearly identical results.

4.3.4 Boundary Conditions

It is a useful exercise to think about the boundary conditions of this approach. First, a clear limitation is that for the share of the physicians that is detailed exactly at the point of each information shock, I cannot separate the effect of direct information from the detailing effect. As the information is positive, the bias resulting if we were to consider the composition a detailing effect would be in the upward direction. Additionally, bias due to sample selection could be present. Only physicians that receive detailing during the sample period enter into the estimation. It could be the case that the firm only visits those physicians who are most affected by detailing rather than a level shift in all detailing across physicians.

If this is the case, the estimated effect will still represent a "treatment effect on the treated" (TOT), as long as the timing of the shocks is as good as random to each physician, because with fixed effects, the estimation controls for the fact that some physicians might be more likely to prescribe in any case. This TOT will be larger than the "average treatment effect" (ATE) in the population, because the physicians who are not being visited are the ones who are less affected. Given this concern, we may not want to interpret these treatment effects as what would happen if the firm increased detailing to include physicians who were never detailed in this sample.

However, the regulator should be interested in the estimated TOT rather than the ATE. That is, the regulator is concerned about whether the firm's *observed promotions actually lead to* off-label prescriptions rather than about how much they would have affected prescriptions if they had detailed differently. Similarly, this is the treatment effect the firm would be interested in if it wanted to evaluate the return of its past detailing effort. However, if the firm wished to maximize future profits considering the potential effect of detailing to all physicians, it would want to know something about the treatment effect on those physicians who were not treated, a question about which this estimation would be less informative. It would not be entirely uninformative, as we can view this TOT as a weak upper bound for the relevant ATE, with equality binding when those not detailed had the same treatment effect as those detailed.

An additional concern could be that the diagnosis codes might be mis-measured. Because physicians self-report the diagnosis codes, we might be worried physicians might have an incentive to under-report off-label prescribing if there were some fear of consequences for prescribing off-label. Such an

incentive would not bias the estimation of $\beta_{offlabel}$ as long as the incentive to under-report did not change in a way that was correlated with the information shocks. We have no compelling reason to believe any of these incentives have changed because of a change in the scientific knowledge about adverse effects. However, any incentive to under-report could bias the measure of the average fraction of off-label prescriptions in the data, $\frac{SeroquelRx_{offlabel}}{SeroquelRx}$. Because thinking an under-reporting rather than an over-reporting incentive would be present, $\frac{SeroquelRx_{offlabel}}{SeroquelRx}$, should potentially be thought of as a lower bound on the average share of off-label prescriptions. Although under-reporting is potentially a concern, roughly 44% of the prescriptions in the data are classified as off-label. If an incentive to under-report exists, a huge fraction of prescriptions for these drugs is still reported as off-label.

4.3.5 Regulatory and Managerial Implications

At first glance, it appears as though firms made a concerted effort to visit physicians who primarily prescribe off-label, which is a warning sign to regulators, as pushing drugs for off-label uses is not legal. While visiting these physicians is not definitive proof that firms were behaving in an illegal way, it may signal to regulators that it is worth further investigating the issue. The effects of these visits are also very important to regulators, as what they seek to avoid is illegal promotional activity which leads to inappropriate off-label prescribing.

Overall, the effects of post-shock detailing appear to be small on all types of prescriptions. As mentioned previously, the fact that there is an effect of detailing on off-label prescriptions need not implicate firms in illegal activity. Indeed, I find that there is a positive effect of detailing on off-label prescriptions. However, it appears as though overall through the time period, detailing did not disproportionately affect off-label prescriptions. It appears to have increased total prescriptions roughly proportionately, slightly pushing the distribution of prescriptions toward on-label. Behind the overall effect is the finding that detailing following the first shock, the consensus statement, appears to have caused primarily off-label prescriptions. However, this effect is very small, with each visit only pushing off-label prescriptions by 0.07 per month and only a fraction of the physicians being detailed during this time period.

The results presented here are suggestive that there was some illegal activity by the firm that generated some of the results that regulators might be concerned about, but the magnitude of those results was exceptionally small, and the balance of the effect over the time period did not tip the scale to off-label. Given these facts, the regulator might not want to spend quite as much time and resources in pursuing these types of cases.

Meanwhile, there are strong managerial implications. Given the threat of extremely large fines combined with the small estimated effects of detailing, managers should avoid any behavior that is even suggestive of nefarious activity, even if that suggestive behavior is not definitive. Additionally,

as the results here suggest no direct information effect without detailing, managers may need to spread the good news from studies themselves rather than relying on physicians to learn the good news on their own.

5 Conclusion

In this paper, I study detailing in the anti-psychotic industry, which was the category most implicated in off-label promotion litigation by the federal government, and how it relates to off-label promotion and prescribing. I first show that physicians who primarily prescribe anti-psychotics for non-approved uses get detailed a significant amount, though a bit less than their colleagues who precsribe more on-label. Even physicians who never prescribe on-label at all receive detail visits. This is consistent with the United States Department of Justice finding that AstraZeneca targeted physicians who were unlikely to have schizophrenic patients.

Next, I examine whether or not those detailing efforts actually caused off-label prescriptions in a way that pushed the distribution of prescriptions more towards off-label. Two scientific informational shocks to the anti-psychotic category provide significant within-physician variation in post-shock detailing. I use the fact that most physicians are not visited in the month of the information shock to separate the direct effect of the shock from the detailing effect. I find the short-term marginal effect of detailing to PCPs is about 0.08 prescriptions following the first shock, most of which can be attributed to off-label prescriptions and is about 0.16 following the second shock, most of which can be attributed to on-label prescriptions. These magnitudes are modest, and over the time period, these marginal prescriptions are disproportionately likely to be on-label rather than off-label prescriptions. Additionally, I find small and insignificant direct effects of the information shocks, as measured by the period after the information shock and before the first detail received by a physician. Consistent with the lack of a direct information effect, I find that the information shock did not lift prescriptions of the generic drug, perphenazine, which received equally good news from the shock.

Meanwhile, the lack of any effect of the informational shocks on detailing to psychiatrists suggests those visits are orthogonal to this particular scientific information. Although that finding may not be surprising, because psychiatrists might likely know the information pre-release, they receive significant numbers of sales rep visits both before and after the informational shocks. The intention and effects of those visits are less clear and are certainly worthy of further research.

References

[1] Anderson, T. S., Huskamp, H. A., Epstein, A. J., Barry, C. L., Men, A., Berndt, E. R., ... & Donohue, J. M. (2015). anti-psychotic Prescribing: Do Conflict of Interest Policies Make a Difference?. Medical care, 53(4), 338-345.

[2] Arana, G. W. (2000). An overview of side effects caused by typical anti-psychotics. Journal of clinical psychiatry, 61(8), 5-11.

[3] Arcidiacono, P., Ellickson, P. B., Landry, P., & Ridley, D. B. (2013). Pharmaceutical followers. International Journal of Industrial Organization, 31(5), 538-553.

[4] Arrow, K. J. (1963). Uncertainty and the welfare economics of medical care. The American economic review, 941-973.

[5] Berndt, E. R., Bui, L., Reiley, D. R., & Urban, G. L. (1995). Information, marketing, and pricing in the US antiulcer drug market. The American Economic Review, 85(2), 100-105.

[6] Berndt, E. R., Bui, L., Reiley, D. R., & Urban, G. L. (1997). The roles of price, quality, and marketing in the growth and composition of the antiulcer drug market. The economics of new goods (NBER Studies in Income and Wealth, vol. 58), Bresnahan, T. F., & Gordon, R. J. (Eds.). (1997), (Vol. 58). University of Chicago Press., pp. 277-322.

[7] Berndt, E. R., Pindyck, R. S., & Azoulay, P. (2003). Consumption externalities and diffusion in pharmaceutical markets: antiulcer drugs. The Journal of Industrial Economics, 51(2), 243-270.

[8] Bradford, W. D., Turner, J. L., & Williams, J. W. (2015). Off-label use of pharmaceuticals: a detection controlled estimation approach. Available at SSRN: http://ssrn.com/abstract=2230976 or http://dx.doi.org/10.2139/ssrn.2230976

[9] Ching, A., Clark, R., Horstmann, I. & Lim, H. (2015). The effects of publicity on demand: the case of anti-cholesterol drugs. Forthcoming, Marketing Science.

[10] Ching, A., & Ishihara, M. (2010). The effects of detailing on prescribing decisions under quality uncertainty. Quantitative Marketing and Economics, 8(2), 123-165.

[11] Chintagunta, P. K., & Desiraju, R. (2005). Strategic pricing and detailing behavior in international markets. Marketing Science, 24(1), 67-80.

[12] Chintagunta, P. K., Goettler, R. L., & Kim, M. (2012). New drug diffusion when forward-looking physicians learn from patient feedback and detailing. Journal of Marketing Research, 49(6), 807-821.

[13] Conti, R. M., Huskamp, H. A., & Berndt, E. R. (2011). The Effect of FDA Advisories on Branded Pharmaceutical Firms' Valuations and Promotion Efforts (No. w17528). National Bureau of Economic Research.

[14] Datta, A., & Dave, D. M. (2013). Effects of Physician-Directed Pharmaceutical Promotion on Prescription Behaviors: Longitudinal Evidence (No. w19592). National Bureau of Economic Research.

[15] David, G., Markowitz, S., & Richards, S. (2009). The effects of pharmaceutical marketing and promotion on adverse drug events and regulation (No. w14634). National Bureau of Economic Research.

[16] Dong, X., Manchanda, P., & Chintagunta, P. K. (2009). Quantifying the benefits of individual-level targeting in the presence of firm strategic behavior. Journal of Marketing Research, 46(2), 207-221.

[17] Dong, X., Chintagunta, P. K., & Manchanda, P. (2011). A new multivariate count data model to study multi-category physician prescription behavior. Quantitative Marketing and Economics, 9(3), 301-337.

[18] Ellison, G., & Ellison, S. F. (2011). Strategic entry deterrence and the behavior of pharmaceutical incumbents prior to patent expiration. American Economic Journal: Microeconomics, 1-36.

[19] Fischer, M., & Albers, S. (2010). Patient-or physician-oriented marketing: what drives primary demand for prescription drugs?. Journal of Marketing Research, 47(1), 103-121.

[20] de Frutos, M. A., Ornaghi, C., & Siotis, G. (2013). Competition in the pharmaceutical industry: How do quality differences shape advertising strategies?. Journal of health economics, 32(1), 268-285.

[21] Gönül, F. F., Carter, F., Petrova, E., & Srinivasan, K. (2001). Promotion of prescription drugs and its impact on physicians' choice behavior. Journal of Marketing, 65(3), 79-90.

[22] Gurwitz, J. H., Field, T. S., Avorn, J., McCormick, D., Jain, S., Eckler, M., ... & Bates, D. W. (2000). Incidence and preventability of adverse drug events in nursing homes. The American journal of medicine, 109(2), 87-94.

[23] Huckfeldt, P. J., & Knittel, C. R. (2011). Pharmaceutical use following generic entry: Paying less and buying less (No. w17046). National Bureau of Economic Research.

[24] Iyengar, R., Van den Bulte, C., & Valente, T. W. (2011). Opinion leadership and social contagion in new product diffusion. Marketing Science, 30(2), 195-212.

[25] Janakiraman, R., Sismeiro, C., & Dutta, S. (2009). Perception spillovers across competing brands: a disaggregate model of how and when. Journal of Marketing Research, 46(4), 467-481.

[26] Janakiraman, R., Dutta, S., Sismeiro, C., & Stern, P. (2008). Physicians' persistence and its implications for their response to promotion of prescription drugs. Management Science, 54(6), 1080-1093.

[27] Kalra, A., Li, S., & Zhang, W. (2011). Understanding responses to contradictory information about products. Marketing Science, 30(6), 1098-1114.

[28] Kolsarici, C., & Vakratsas, D. (2010). Category-versus brand-level advertising messages in a highly regulated environment. Journal of Marketing Research, 47(6), 1078-1089.

[29] Larkin, I., Ang, D., Avorn, J., & Kesselheim, A. S. (2014). Restrictions On Pharmaceutical Detailing Reduced Off-Label Prescribing Of Antidepressants And anti-psychotics In Children. Health Affairs, 33(6), 1014-1023.

[30] Lieberman, J. A., Stroup, T. S., McEvoy, J. P., Swartz, M. S., Rosenheck, R. A., Perkins, D. O., ... & Hsiao, J. K. (2005). Clinical anti-psychotic Trials of Intervention Effectiveness (CATIE) Investigators Effectiveness of anti-psychotic drugs in patients with chronic schizophrenia. N Engl J Med, 353(12), 1209-1223.

[31] Liu, H., Liu, Q. & Chintagunta, P.K., Advertising spillovers: drug detailing in combination therapy (2014). Available at SSRN: http://ssrn.com/abstract=2406363 or http://dx.doi.org/10.2139/ssrn.2406363

[32] Majumdar, S. R., Almasi, E. A., & Stafford, R. S. (2004). Promotion and prescribing of hormone therapy after report of harm by the Women's Health Initiative. Jama, 292(16), 1983-1988.

[33] Manchanda, P., Rossi, P. E., & Chintagunta, P. K. (2004). Response modeling with nonrandom marketing-mix variables. Journal of Marketing Research, 41(4), 467-478.

[34] Mizik, N., & Jacobson, R. (2004). Are physicians "easy marks"? Quantifying the effects of detailing and sampling on new prescriptions. Management Science, 50(12), 1704-1715.

[35] Montoya, R., Netzer, O., & Jedidi, K. (2010). Dynamic allocation of pharmaceutical detailing and sampling for long-term profitability. Marketing Science, 29(5), 909-924.

[36] Moon, S., Kamakura, W. A., & Ledolter, J. (2007). Estimating promotion response when competitive promotions are unobservable. Journal of Marketing Research, 44(3), 503-515.

[37] Nair, H. S., Manchanda, P., & Bhatia, T. (2010). Asymmetric social interactions in physician prescription behavior: The role of opinion leaders. Journal of Marketing Research, 47(5), 883-895.

[38] Narayanan, S., & Manchanda, P. (2009). Heterogeneous learning and the targeting of marketing communication for new products. Marketing Science, 28(3), 424-441.

[39] Narayanan, S., Manchanda, P., & Chintagunta, P. K. (2005). Temporal differences in the role of marketing communication in new product categories. Journal of Marketing Research, 42(3), 278-290.

[40] Narayanan, S., Desiraju, R., & Chintagunta, P. K. (2004). Return on investment implications for pharmaceutical promotional expenditures: The role of marketing-mix interactions. Journal of marketing, 68(4), 90-105.

[41] Ray, W. A., Federspiel, C. F., & Schaffner, W. (1980). A study of anti-psychotic drug use in nursing homes: epidemiologic evidence suggesting misuse. American Journal of Public Health, 70(5), 485-491.

[42] Rao, A., & Wang, E. (2015). Demand for "healthy" products: false claims in advertising. University of Chicago working paper.

[43] Ross, J. S., Nazem, A. G., Lurie, P., Lackner, J. E., & Krumholz, H. M. (2008). Updated estimates of pharmaceutical company payments to physicians in Vermont. JAMA, 300(17), 1998-2000.

[44] Shapiro, B.T. (2015). Positive spillovers and free-riding in advertising of prescription pharmaceuticals: the case of antidepressants. University of Chicago working paper.

[45] Sood, A., Kappe, E., Stremersch, S. (2014) The commercial contribution of clinical studies for pharmaceutical drugs. International Journal of Research in Marketing, 31(1), 65-77.

[46] Stremersch, S., & Lemmens, A. (2009). Sales growth of new pharmaceuticals across the globe: The role of regulatory regimes. Marketing Science, 28(4), 690-708.

[47] Stremersch, S., Landsman, V., & Venkataraman, S. (2013). The relationship between DTCA, drug requests, and prescriptions: Uncovering variation in specialty and space. Marketing Science, 32(1), 89-110.

[48] Venkataraman, S., & Stremersch, S. (2007). The debate on influencing doctors' decisions: Are drug characteristics the missing link?. Management Science, 53(11), 1688-1701.

[49] Zoltners, A. A., & Sinha, P. (2005). Sales territory design: Thirty years of modeling and implementation. Marketing Science, 24(3), 313-331.

Tables and Figures

Figure 1: Revenues over Time

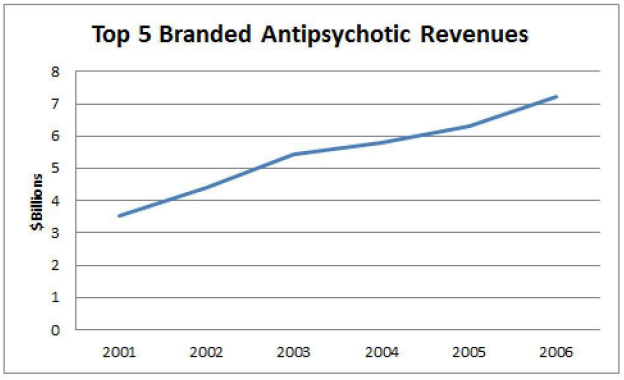


Figure 2: Revenues over Time by Firm

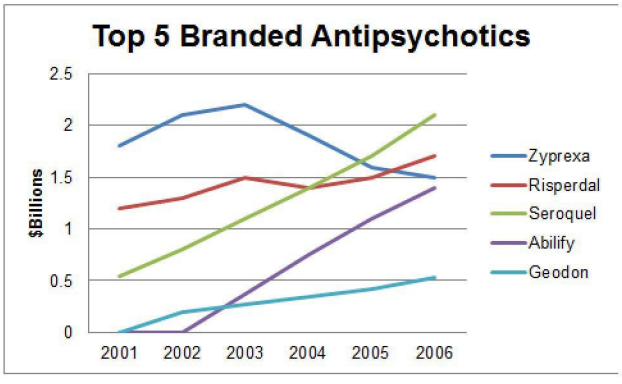


Figure 3: Psychiatrist Prescribing

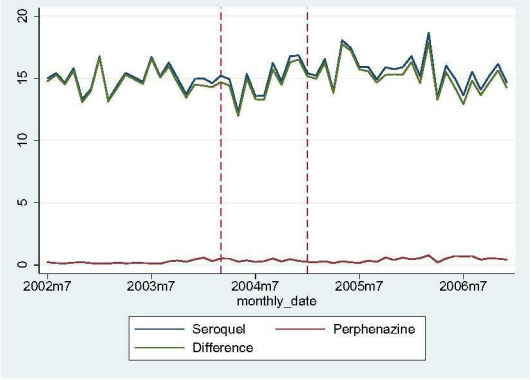
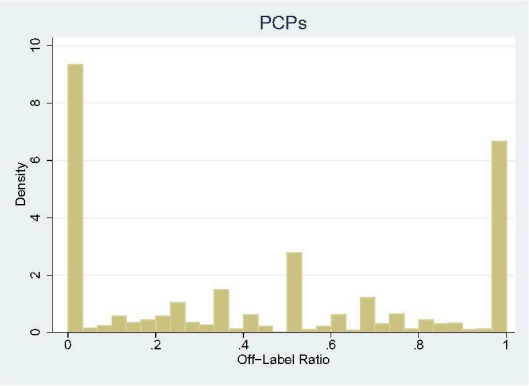


Figure 5: Physician Types by Specialty

(a)



(b)

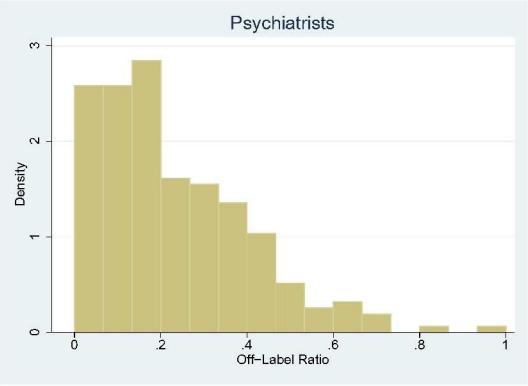


Figure 4: PCP Prescribing

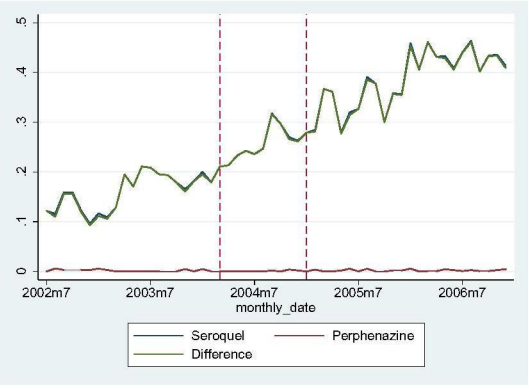


Table 1: Summary Statistics Pre and Post Information

	PCP		Psychiatrist	
Visits/Month				
Pre 2004 Announcement	0.0466	(0.2281)	0.8551	(1.0510)
Between 2004 and CATIE	0.1814	(0.4651)	0.9502	(1.1430)
After CATIE	0.4310	(0.7571)	0.7803	(1.0420)
Seroquel Rx/Month				
Pre 2004 Announcement	0.1178	(0.8920)	13.9525	(16.0525)
Between 2004 and CATIE	0.2328	(1.2065)	14.8670	(16.5225)
After CATIE	0.4020	(1.4983)	16.0445	(16.9425)

Standard deviations in parentheses

Table 2: Summary Statistics: PCP by Type of Rx

	Mean	(SD)
Label		
On-Label Rx	0.1629	(0.8620)
Off-Label Rx	0.1281	(0.8143)
Insurance		
Medicaid	0.0571	(0.4981)
Medicare	0.1000	(0.6890)
Third Party Payer	0.1172	(0.6755)
Uninsured	0.0140	(1.2065)
Severity		
Mild	0.0266	(0.2933)
Moderate	0.1984	(1.0322)
Severe	0.0661	(0.5266)
Age		
<18	0.0091	(0.2063)
>=18, <=60	0.1850	(1.0040)
>60	0.0969	(0.6545)

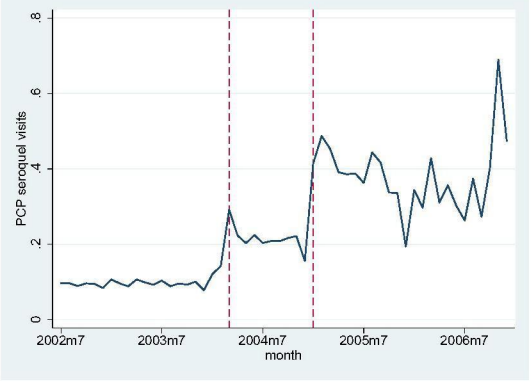
Standard deviations in parentheses

Table 3: Detail Visits By Propensity to Prescribe Off-Label

Off-Label Share	Number of Physicians	First Detail Date	Average Visits Per Month	Months Visited
$= 0$	339	12/2004	0.158	6.398
		(11.921)	(0.209)	(6.351)
$\in (0, 0.25]$	127	9/2004	0.286	10.205
		(12.573)	(0.351)	(8.677)
$\in (0.25, 0.5]$	217	10/2004	0.175	7.060
		(11.798)	(0.213)	(6.873)
$\in (0.5, 0.75]$	115	9/2004	0.166	6.817
		(12.351)	(0.201)	(6.570)
$\in (0.75, 1)$	56	7/2004	0.160	7.232
		(13.784)	(0.160)	(6.630)
$= 1$	244	12/2004	0.094	4.176
		(11.256)	(0.111)	(3.875)

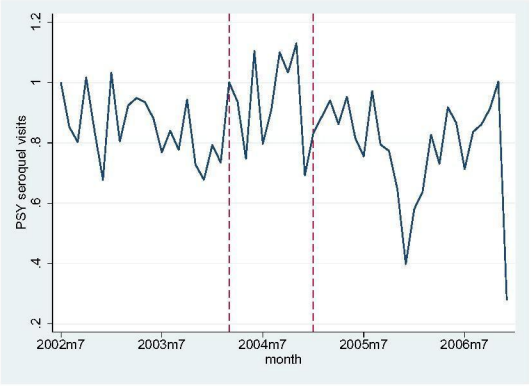
Standard deviations in parentheses.

Figure 6: Probability of Seroquel Detail Visit for PCP



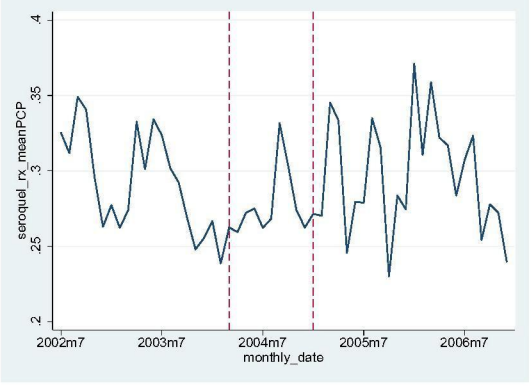
Physician fixed effects partialed out

Figure 7: Probability of Seroquel Detail Visit for PSY



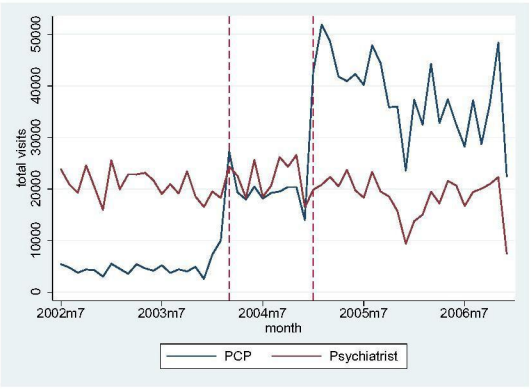
Physician fixed effects partialed out

Figure 8: Seroquel Prescriptions for PCP



Physician fixed effects and time trend partialed out

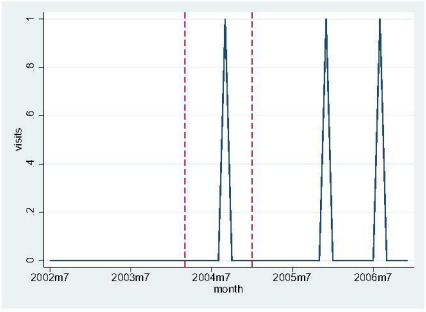
Figure 9: Total Detailing Visits by Specialty



Detailing from this sample extrapolated to population of physicians

Figure 10: Separating Information from Promotion: Example

(a) 'Non-Coincident' Physician: Identification Good



(b) 'Coincident' Physician for Shock 2: Not Separable

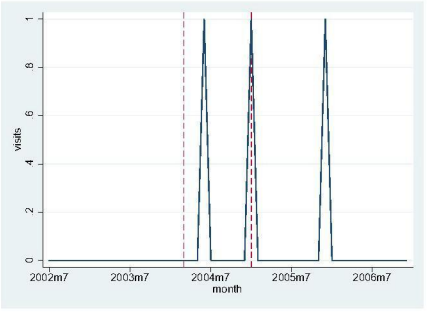


Table 4: Information Shocks, Detailing and Prescribing Response

VARIABLES	Detail Visits	Total Rx	Offlabel Rx
	(1)	(2)	(3)
PostShock1	0.1812***	0.0022	-0.0023
	(0.0105)	(0.0204)	(0.0145)
PostShock2	0.3911***	0.0410	-0.0091
	(0.0193)	(0.0314)	(0.0229)
R-squared	0.289	0.323	0.277
Observations	62,849	62,849	62,849

*** p<0.01, ** p<0.05, * p<0.1

Physician clustered standard errors in parentheses. Physician fixed effects and time trend included in all specifications.

Table 5: Reduced Form Results

VARIABLES	Total Rx	Offlabel Rx	Total Rx	Offlabel Rx	Total Rx	Offlabel Rx
	(1)	(2)	(3)	(4)	(5)	(6)
$Shock1_{coincident}$	0.0144	0.0086	0.0135	0.0083	0.0072	0.0189
	(0.0377)	(0.0223)	(0.0378)	(0.0223)	(0.0528)	(0.0303)
$Shock1_{non}$	-0.0008	-0.0123	-0.0029	-0.0135		
	(0.0349)	(0.0211)	(0.0360)	(0.0222)		
$Shock1_{non} * PostDetail$	0.0513	0.0356*	0.0706	0.0522	0.0580	0.0483
	(0.0407)	(0.0193)	(0.0797)	(0.0457)	(0.0792)	(0.0470)
$Shock1_{non} * PostDetail * FirstMonth$			-0.0060	-0.0051	-0.0071	-0.0055
			(0.0159)	(0.0102)	(0.0168)	(0.0101)
$Shock2_{coincident}$	0.1613***	0.0069	0.1549***	0.0052	0.1610***	0.0333
	(0.0514)	(0.0349)	(0.0513)	(0.0349)	(-0.0500)	(0.0281)
$Shock2_{non}$	0.0051	-0.0195	-0.0109	-0.0230		
	(0.0381)	(0.0276)	(0.0400)	(0.0292)		
$Shock2_{non} * PostDetail$	0.0657***	0.0107	0.1018***	0.0179	0.0941**	0.0276
	(0.0268)	(0.0170)	(0.0429)	(0.0256)	(0.0479)	(0.0287)
$Shock2_{non} * PostDetail * FirstMonth$			-0.0055	-0.0011	-0.0052	-0.0017
			(0.0044)	(0.0025)	(0.0047)	(0.0027)
Time Trend	x	x	x	x		
Month Fixed Effects					x	x
R-squared	0.323	0.277	0.323	0.277	0.324	0.278
Observations	62,849	62,849	62,849	62,849	62,849	62,849

*** p<0.01, ** p<0.05, * p<0.1

Physician clustered standard errors in parentheses. Physician fixed effects included in all specifications. Separate dummies included for Shock1 and Shock2 for physicians who never receive a detail in the respective time period.

Table 6: Main Results: Flow

VARIABLES	Total Rx	Offlabel Rx	Total Rx	Offlabel Rx	Total Rx	Offlabel Rx
	(1)	(2)	(3)	(4)	(5)	(6)
$Visits0$	-0.0146	0.0383	-0.0208	0.0266	-0.0130	0.0294
	(0.0927)	(0.0615)	(0.0907)	(0.0592)	(0.0910)	(0.0597)
$Visits1_{coincident}$	0.0341	0.0197	0.0319	0.0210	0.0339	0.0241
	(0.0437)	(0.0201)	(0.0452)	(0.0209)	(0.0470)	(0.0210)
$Shock1_{non}$	-0.0113	-0.0090	-0.0447	-0.0245		
	(0.0280)	(0.0161)	(0.0310)	(0.0165)		
$Visits1_{non}$	0.0788	0.0684**	0.1160	0.0850	0.1201	0.0854
	(0.0523)	(0.0279)	(0.1147)	(0.0657)	(0.1159)	(0.0658)
$Visits1_{non} * FirstMonth$			-0.0095	-0.0023	-0.0108	-0.0028
			(0.0250)	(0.0164)	(0.0254)	(0.0164)
$Visits2_{coincident}$	0.1842***	0.0374***	0.1768***	0.0359***	0.1814***	0.0355***
	(0.0368)	(0.0116)	(0.0362)	(0.0120)	(0.0364)	(0.0121)
$Shock2_{non}$	-0.0408	-0.0346	-0.0790*	-0.0316		
	(0.0380)	(0.0275)	(0.0409)	(0.0235)		
$Visits2_{non}$	0.1507***	0.0531***	0.1655**	0.0522	0.1657**	0.0491
	(0.0388)	(0.0194)	(0.0674)	(0.0332)	(0.0682)	(0.0335)
$Visits2_{non} * FirstMonth$			-0.0069	-0.0011	-0.0074	-0.0009
			(0.0073)	(0.0039)	(0.0075)	(0.0039)
Rival Visits			x	x	x	x
Time Trend	x	x	x	x		
Month Fixed Effects					x	x
R-squared	0.326	0.278	0.353	0.317	0.354	0.318
Observations	62,849	62,849	62,849	62,849	62,849	62,849

*** p<0.01, ** p<0.05, * p<0.1

Physician clustered standard errors in parentheses. Physician fixed effects included in all specifications. Separate dummies included for Shock1 and Shock2 for physicians who never receive a detail in the respective time period.

Appendix A – The Direct Effect of Information Shocks on Perphenazine

Are the direct effects of the information shocks large, as measured by the trend break in take-up of perphenazine at the information-shock times? I first address this question by estimating the following:

$$PerphenazineRx_{it} = \alpha_i + \gamma * time + \beta_1 Shock_1 + \beta_2 Shock_2 + \epsilon_{it}.$$

Table X presents the results of estimating this equation including only the first shock, using both shocks, and including Seroquel detailing. Neither shock induces a trend break in the prescribing of perphenazine by PCPs, even though the information shocks contain information that is beneficial to perphenazine. A concern might be that this lack of an information effect is coming from the increase in competitor Seroquel's detailing. However, as seen in the third column, including Seroquel detail visits into the estimation does not change the finding of no trend break in perphenazine prescribing. The result is consistent with the pictures in Figures 4, which shows PCPs rarely prescribe perphenazine. Given this result, I will continue under the assumption that a direct-information effect without detailing is not influencing PCP demand for Seroquel. To the extent that an informational effect exists that is not detected by a product that receives identical news, it will lead to an overstatement of the detailing effect, because the estimated effect will be a composition of the detailing effect and the direct effect of the information shock.

Table 7: Effects of Informational Shocks on Perphenazine Demand

VARIABLES	*PerphenazineRx*	*PerphenazineRx*	*PerphenazineRx*
	(1)	(2)	(3)
*PostShock*1	-0.00125	-0.00115	-0.00101
	(0.00087)	(0.00086)	(0.00084)
*PostShock*2		0.00101	0.00117
		(0.00156)	(0.00158)
SeroquelVisits			-0.00077*
			(0.00034)
Physician FEs	x	x	x
Time Trend	x	x	x
R-squared	0.0851	0.0851	0.0852
Observations	62,849	62,849	

*** p<0.001, ** p<0.01, * p<0.05

Physician clustered standard errors in parentheses. All specifications include physician-specific fixed effects, and time trends.

Appendix B – Stock Measure of Detailing

B.1 Constructing the Persistence Factor

In this section, I calibrate the persistence factor in the geometric decay of detailing stock. To do this, I focus on the period following the second shock for the non-coincident physicians, as this is the period with the cleanest variation to identify the effects.

$$SeroquelRx_{it}^{non} = \alpha_i + \gamma * time + \beta_0 SeroquelDetail_{it} + \beta_1 SeroquelDetail_{i,t-1} + ... + \beta_5 SeroquelDetail_{i,t-5} + \epsilon_{it}.$$

The results are provided in Table 8. It appears we can reject that past detailing is useless. The detailing effect appears to taper off completely by three months after the visit. This magnitude of decay is roughly consistent with a geometric persistence parameter of 0.6.

Table 8: Depreciation Parameter Results

VARIABLES	Seroquel Rx
$Visits_t$	0.08971***
	(0.0270)
$Visits_{t-1}$	0.05081**
	(0.0237)
$Visits_{t-2}$	0.03678*
	(0.0253)
$Visits_{t-3}$	-0.0125
	(0.0285)
$Visits_{t-4}$	-0.02683
	(0.0273)
$Visits_{t-5}$	0.01662
	(0.0283)
R-squared	0.404
Observations	20,993

*** p<0.01, ** p<0.05, * p<0.1

Physician clustered standard errors in paranetheses. Pysician fixed effects and time trends included.

B.2 Stock Scaled Results

In this section, I scale the reduced form results by detailing stock, with detailing decay assumed to be geometric with decay parameter $\delta = 0.6$. Table 9 presents the results, but I will focus on the preferred specification, columns 1 & 2, as the parameters of interest to do not change across specifications. First, for the physicians who have detailing visits in the same month as the information shock, there is a very small and insignificant detailing stock effect on both total and

off-label prescriptions for the first shock. For the second shock, there is a positive and significant effect on total prescriptions, but no significant effect on off-label prescriptions. Overall, the point estimate of about 0.13 for the second shock corresponds to a total of about 0.325 prescriptions caused by each detail visit over time, with a very small elasticity of detailing flow of less than 0.1. For this group, there is no evidence of any effect of detailing on off-label prescriptions. Note again that for this group, the estimated detailing stock effect represents a composition of the detailing stock effect and the direct effect of the information, which cannot be separated.

Next, for the physicians for whom I can separate the direct information from the detailing using the months between the release of the shock and the first detail, there is a positive and significant effect of detailing stock following the first shock of about 0.11, about 0.10 of which can be attributed to off-label prescriptions. This is consistent with the flow results and corresponds to about 0.275 prescriptions over time from each detailing visit. Again, their direct information effect is negative, but small and insignificant for both on- and off-label prescriptions. Following the second information shock, the detailing stock effect is slightly larger, at 0.13, only 0.04 of which can be attributed to off-label prescriptions.

In column 3, all of these results hold up to the validity test, allowing the detailing effect to vary by month of first post-shock visit. The interaction term is tiny and not significant. In column 4, the parameters of interest are unchanged by the addition of month fixed effects in an effort to control for publicity effects.

Appendix C – Effects of Detailing on Psychiatrist Off-Label Prescribing

As shown in Figure 6, the informational shocks do not affect detailing to psychiatrists. As such, the proposed identification strategy using the informational shocks to generate quasi-exogenous timing in detail visits will not have power to identify the effects of detailing on psychiatrist prescribing. However, if we are willing to accept that the timing of visits to psychiatrists is essentially random, as would be the case if firms were employing a decile rule or if sales reps were routinely turned away, we could implement a simple fixed-effects estimator for psychiatrists to obtain an estimate of the effectiveness of detailing for driving prescriptions, both on- and off-label. In this section, I explore the effects of detailing on psychiatrist prescribing using only a fixed-effects approach. Most of the directional conclusions are similar as with the PCPs, noting the identification requires the additional assumption of random timing of detail visits.

Table 9: Main Results: Stock

VARIABLES	Total Rx	Offlabel Rx	Total Rx	Offlabel Rx	Total Rx	Offlabel Rx
	(1)	(2)	(3)	(4)	(5)	(6)
$Stock0$	0.0532	0.1136	0.0461	0.097	0.0513	0.1007
	(0.1365)	(0.1056)	(0.1319)	(0.1006)	(0.1326)	(0.1015)
$Stock1_{coincident}$	0.0258	0.0266	0.0256	0.0292	0.0273	0.0303
	(0.0462)	(0.0196)	(0.0484)	(0.0208)	(0.0488)	(0.0208)
$Shock1_{non}$	-0.0338	-0.0330*	-0.0583*	-0.0429**		
	(0.0319)	(0.0175)	(0.0345)	(0.0190)		
$Stock1_{non}$	0.1124**	0.0994***	0.1906*	0.1538***	0.1831*	0.1388***
	(0.0554)	(0.0275)	(0.0978)	(0.0464)	(0.0961)	(0.0464)
$Stock1_{non} * FirstMonth$			-0.0268	-0.0174*	-0.0273	-0.0186*
			(0.0199)	(0.0095)	(0.0221)	(0.0105)
$Stock2_{coincident}$	0.1305***	0.0246***	0.1303***	0.0234***	0.1323***	0.0231**
	(0.0278)	(0.0088)	(0.0289)	(0.0090)	(0.0290)	(0.0091)
$Shock2_{non}$	-0.0623	-0.0292	-0.0975**	-0.0254		
	(0.0427)	(0.0304)	(0.0442)	(0.0225)		
$Stock2_{non}$	0.1392***	0.0441***	0.1372***	0.0463*	0.1387***	0.0475*
	(0.0314)	(0.0152)	(0.0499)	(0.0244)	(0.0502)	(0.0244)
$Stock2_{non} * FirstMonth$			-0.0008	-0.0004	-0.0012	-0.0006
			(0.0068)	(0.0041)	(0.0069)	(0.0041)
Rival Visits			x	x	x	x
Time Trend	x	x	x	x		
Month Fixed Effects					x	x
R-squared	0.342	0.289	0.365	0.330	0.366	0.331
Observations	62,849	62,849	62,849	62,849	62,849	62,849

*** p<0.01, ** p<0.05, * p<0.1

Physician clustered standard errors in parentheses. Separate dummies included for Shock1 and Shock2 for physicians who never receive a detail in the respective time period.

Table 10: Effects of Informational Shocks on Perphenazine Demand for Psychiatrists

VARIABLES	*PerphenazineRx*	*PerphenazineRx*
	(1)	(2)
*PostShock*1	-0.0272	-0.0491
	(0.140)	(0.137)
*PostShock*2		-0.184*
		(0.0755)
Physician FEs	x	x
Time Trend	x	x
R-squared	0.247	0.248
Observations	7,520	7,520
*** p<0.001, ** p<0.01, * p<0.05		

Physician clustered standard errors in parentheses. All specifications include physician-specific fixed effects, and time trends.

Table 10 shows the effects of the two informational shocks on psychiatrist prescribing of the generic drug, perphenazine. Similar to the PCPs, the informational shocks do not drive psychiatrists to prescribe the effective and inexpensive drug. If anything, following the CATIE study, psychiatrists appear to in fact to prescribe *less* perphenazine. Table 10 provides the basic fixed-effects results, pooling all detailing to have one common effect. Unlike in the PCP case, including rival detailing makes a significant difference for psychiatrists, perhaps because psychiatrists are highly likely to be detailed by many companies, whereas PCPs are more likely to be detailed by only one. Rival detail visits appear to be positively correlated with Seroquel prescriptions. That is, detailing to psychiatrists appears to be category expansive and provide a positive spillover to rivals, as has been found in DTCA for antidepressants (Shapiro 2015). The positive competitor detailing effect could also be driven by non-random timing of visits to each physician. If sales reps were able to predict the months with high levels of prescribing and visit in those months, prescribing would be positively correlated with both own and rival detailing, even if the correlation were not causal. To interpret these effects as causal, we need to assume such non-random timing does not occur.

Tables 11 and 12 provide the off-label analysis for psychiatrists. Before any regression analysis, note that psychiatrists prescribe a much smaller share off-label than do PCPs, at about 22% of prescriptions as opposed to 43% by PCPs. Even so, detailing still provides a disproportionately large effect on on-label prescriptions, tilting the distribution toward on-label.

C.1 Discussion and Policy Implications

Although the marginal effect of detailing on psychiatrists is higher than it is for PCPs (as should be expected with their higher base rate of prescribing), the detailing elasticity remains low. Although the identification of these effects is not as clean due to the potential for non-random timing, the potential bias here would likely bias the effect upward. These main effects are much smaller than

those found elsewhere in the literature. Given the small overall effects, regulators might find the social returns on their litigation disappointing. They will have spent time and energy that could have been employed elsewhere, while potentially causing distortions in the product market. Conversely, managers might find the returns on their detailing efforts to be disappointing. Perhaps the growing influence of payers and the inherent knowledge of the physicians have lowered the influence of sales reps.

Most of the small detailing effect is attributable to on-label prescribing. In fact, off-label prescribing is much lower for psychiatrists than PCPs, and detailing shifts the distribution even more toward on-label prescriptions. This finding makes the regulatory concern about off-label promotion leading to off-label prescriptions to those most vulnerable even smaller and reinforces the managerial implication that although trying to promote off-label use through sales reps might seem attractive, the return is almost surely not worth the expected cost of litigation.

Table 11: Baseline Results - Psychiatrists

VARIABLES	*SeroquelRx*			
	(1)	(2)	(3)	(4)
Visits	2.382***	1.478***	1.504***	0.961***
	(0.508)	(0.237)	(0.234)	(0.203)
Rival Visits				0.736***
				(0.113)
Physician FEs		x	x	x
Time Trend			x	x
Implied Elasticity	0.126	0.080	0.080	0.051
R-squared	0.0229	0.535	0.535	0.548
Observations	7,520	7,520	7,520	7,220

*** p<0.01, ** p<0.05, * p<0.1

Physician clustered standard errors in parentheses. Elasticities are computed at the sample means and are with respect to advertising flows.

Table 12: Effects of Detailing on Off-Label Prescribing

VARIABLES	Off-Label Rx	On-Label Rx
	(1)	(2)
Visits	0.181*	0.750***
	(0.0760)	(0.181)
% of Total Effect	19.5	80.5
% of Rx	22.2	77.8
R-squared	0.444	0.559
Observations	5,976	5,976

*** p<0.001, ** p<0.01, * p<0.05

Physician clustered standard errors in parentheses. Seroquel visits are depreciated stocks with persistence parameter 0.6. All specifications include physician-specific fixed effects, rival detail visits, and time trends.